Historical Perspective of Rabies in Europe and the Mediterranean Basin

A testament to rabies by Dr Arthur A. King

By A.A. King, A.R. Fooks, M. Aubert and A.I. Wandeler, eds

BIOGRAPHY OF DR ARTHUR A. KING

Dr Arthur Alfred King was the principal editor of the book entitled ‘Historical Perspective of Rabies in Europe and the Mediterranean Basin’. Sadly, Arthur died on 22 June 2002 and did not witness the completion of his book.

Arthur was born on 14 March 1931 in London and during the war was evacuated to Chertsey, Surrey, where he was later educated at Woking Grammar School. On 12 May 1952, Arthur began working at the Central Veterinary Laboratory of Weybridge in the United Kingdom and by 1977 had been promoted to Principal Scientific Officer.

Arthur was a founder member of The Department of Virology and worked mainly on swine fever virus and rabies virus and was a recognised expert in the field of fluorescent microscopic techniques. He was responsible for the laboratory diagnosis of swine fever virus during its eradication in the 1960s, but it was in the field of rabies that he made his scientific reputation. In the early 1980s, Arthur became involved in the international rabies research forum. He played a significant role in not only the characterisation of rabies virus isolates from different parts of the world using monoclonal antibody technology, but possibly in the exchange of virus isolates between laboratories namely the Wistar Institute, the Centres for Disease Control in the US and the Federal Research Institute for Animal Virus Diseases in Tuebingen, Germany. In recognition of his scientific work and his service to the UK Ministry of Agriculture, Fisheries and Food (MAFF); currently The Department for Environment, Food and Rural Affairs, he was awarded the Imperial Service Order in 1991.

When Arthur retired from the Central Veterinary Laboratory, he collaborated with colleagues at the Onderstepoort Veterinary Institute in South Africa. He met up with George Bishop from the Allerton Laboratory outside Pietermaritzburg, and together they organised the first meeting of what became known as the ‘Southern and Eastern African Rabies Group (SEARG)’, with an interest in studying rabies in Africa. The group was a great success, thanks largely to Arthur’s enthusiasm and commitment. The first meeting was in Zambia in 1992, and subsequent meetings were held in South Africa, Zimbabwe, Kenya, Uganda, Malawi and Swaziland. Arthur also developed strong links with the World Health Organization (WHO) and was eminent in advising on rabies control policies throughout the world, especially in rabies-endemic regions, specifically in Africa and Asia.

Biography of Dr Anthony R. Fooks

Anthony Fooks obtained his Ph.D. in 1994 on a study to investigate immunity to viral infections and was more recently appointed a Fellow of the UK Institute of Biology. In 2000, Dr Fooks joined the Veterinary Laboratories Agency (an executive agency of the UK Department for Environment, Food and Rural Affairs) as Group Head of the Rabies Research and Diagnosis Group (the UK National Reference Laboratory for rabies). In 2001, he was appointed director of a World Health Organization Communicable Disease Surveillance and Response Collaborating Centre for the characterisation of rabies and rabies-related viruses.
Biography of Dr M. Aubert

Michel Aubert has an M.Sc. and a Ph.D. from the University of Nancy in France. He joined the ‘Centre d’études sur la rage’ of Nancy-Malzéville (France) in 1972, and investigated rabies with Louis Andral and Jean Blancou. When he was appointed director of this laboratory in 1990, he defined his goal: ‘No rabies case in France after the year 2000!’. The last fox rabies case was recorded in France in December 1998. After the laboratory became an EU reference institute involved in alternative measures to quarantine, he moved to another laboratory, where his main activities are now sheep and honey bee disease control. However, he is still involved in several scientific works on rabies and in providing consultancy on rabies to the French authorities.

Biography of Dr Alexander I. Wandeler

Alex Wandeler has an M.Sc. and a Ph.D. from the University of Berne in Switzerland. He joined the Swiss Rabies Centre at the Veterinary School in Berne in 1966 and was appointed the Center’s director in 1975 after returning from postdoctoral studies with J.B.Henson at Washington State University. Together with the late Franz Steck he investigated, and ten years later, applied oral rabies vaccines for wildlife. In 1989, he accepted a position with Agriculture Canada. At present he is leader of the Center of Expertise for Rabies at the Canadian Food Inspection Agency in Ottawa, which also serves as the WHO Collaborating Centre for Control, Pathogenesis and Epidemiology of Rabies.
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FOREWORD

The aim of this book is to provide scientists, veterinarians and policy-makers with an expert analysis of rabies from ancient times to today. The principal objectives are to summarise our knowledge of the history of rabies in Europe and the Mediterranean Basin and to describe the various strategies that have been used to eliminate (terrestrial) rabies from reservoir populations. This has required the co-operation of animal health specialists from many countries and the assistance of international groups such as the World Organisation for Animal Health (OIE), the World Health Organization (WHO) and the European Union (EU). In this first edition, leading experts in the field describe the policies that have been used to eliminate rabies from different parts of Europe throughout the 20th Century, with the aim of providing information which can be adapted for future global rabies control programmes. Having this knowledge available for reference is important, especially in regions of the world where rabies control is still neglected and where rabies remains endemic, largely as a result of financial limitations and poor infrastructure.

In recent years, previously un-identified rabies virus strains have emerged, new reservoirs have been established in Europe (e.g. bats), and control strategies have been improved. Our understanding of rabies is advancing and in such a dynamic field it is important to establish a source of current knowledge and information for future reference.

Dr Bernard Vallat
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INTRODUCTION

‘Historical Perspective of Rabies in Europe and the Mediterranean Basin’

A testament to rabies by Dr. Arthur A. King

Edited by Arthur A. King, Anthony R. Fooks, Michel Aubert and Alex Wanderler

As many parts of Europe are now free of rabies, it seems timely to publish a historical review of the history of rabies in Europe and countries of the Mediterranean Basin. Since the successful development of the first human rabies vaccines in 1885 by Louis Pasteur, significant developments have been made in reducing the burden of one of the most feared human diseases. Despite these major advances rabies is still endemic in many countries, largely as a result of financial limitations and poor infrastructures. In some countries of Europe and the Mediterranean Basin, rabies remains a ‘neglected’ disease.

The principal author of this overview of rabies in Europe was Dr Arthur King (formerly of the Central Veterinary Laboratory-Weybridge, United Kingdom), however Arthur died in June 2002 before his book was completed. Arthur and his co-editors originally entitled the book ‘Rabies in Europe and the Mediterranean Basin’. This title was changed in 2004 to reflect the historical content of the book. The goal of the book ‘Historical Perspective of Rabies in Europe and the Mediterranean Basin’ is to provide scientists, veterinarians and policy makers with an historical perspective and expert analysis of rabies in Europe from ancient times to more recent episodes. This should enable those of us currently involved in the control of rabies to share knowledge, to learn from past experience and to adopt ‘best practice’.

The book covers historical aspects of the disease in different chronological divisions, pre-Pasteur and Negri, Pasteur to the end of World War II and WWII to the end of the 20th Century. The reasons for these divisions are to show how the disease changed from one largely of domestic dogs to one almost exclusively adapted to wildlife and to disclose how wildlife disease was controlled and, in many geographical areas, eliminated by the immunisation of particular wildlife reservoir species. The first part of the book is focused on both the historical and geographical aspects of rabies. The overview describing rabies in the ancient world up until the 19th Century is followed by country reports of rabies from the United Kingdom, Ireland, Iceland, Norway, Sweden, Finland, Estonia, Latvia, Lithuania, the European parts of Russia, Belarus and Ukraine, Poland, the Czech Republic, the Slovak Republic, Germany, Denmark, Austria, Hungary, Italy, Yugoslavia, Croatia, Bosnia, Slovenia, Macedonia, Albania, Greece, France, the Netherlands, Belgium, Luxembourg, Switzerland, the Iberian Peninsula, Turkey, Cyprus, Syria, Lebanon, Israel, Jordan, Algeria, Egypt, Libya, Malta, Tunisia and Morocco. From 1990 onwards, we have witnessed the elimination of rabies from terrestrial mammals (principally the red fox) in many western European countries: the Netherlands (1991), Switzerland (1999), France (2000), Belgium and Luxembourg (2001) and the Czech Republic (2004) resulting in these countries being declared ‘rabies-free’. Re-introductions have resulted in extensive media coverage. Whilst rabies cases are decreasing in many western European countries there is a greater need to incorporate the control strategies for rabies-endemic countries. The second part of the book concentrates on the analysis and interpretation of the epidemiology of rabies. This section includes an account of different epidemiological models of rabies especially dog rabies and the epidemiology and ecology of fox rabies using a computer analysis of the fox-rabies epidemic.

We would like to thank all those contributors for their patience and to commend them on the high scientific standard and of their respective chapters. More importantly, the patience of all contributors is appreciated.

Numerous people whose joint efforts, especially since the death of the principal editor Dr Arthur King, have enabled this book to be completed. We would like to express our sincere gratitude to members of the World Organisation for Animal Health (OIE), particularly Bernard Vallat (Director General of the OIE), Alejandro Schudel and Raymond Dugas, and to the staff of the OIE Publications Department.
The editors must especially thank the director of the Veterinary Laboratories Agency, Steve Edwards, and members of the VLA team who have assisted in the proof-reading and the editorial changes required for publication. The editorial assistance of Mrs Christina Yeung has been essential and was gratefully appreciated. Assistance in proof reading is credited to Sharon Brookes, Nicholas Johnson and Lorraine McElhinney.

Lastly, the editors wish to acknowledge the support from numerous individuals from around the world who have given their time and provided the impetus to complete this book on behalf of Arthur. These include: John Bingham, Jean Blancou, David (Dai) Edwards, Brian Mahy, Francois X. Meslin, Paul-Pierre Pastoret, Charles Rupprecht, Gavin Thompson, Noël Tordo and Henry Wilde.
CHAPTER 1
RABIES IN THE ANCIENT WORLD

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Summary

Much of what came from the ancient world remained the accepted wisdom for most of the middle ages — and often in garbled form at that. Galen was known in Latin, translated from Arabic versions of the Greek original, and some of Aristotle's works were studied in even more distant versions, such as Latin translations from Arabic versions of Syriac commentaries on the Greek original.

Yet despite this indirect transmission, the authority of ancient medical writers remained exceedingly high. Dante quotes Galen and Hippocrates as first among medical writers in his catalogue of eminent men. His familiarity with Chaucer's Doctour of Physik is attested to by his knowledge of Dioscorides, Rufus, Hippocrates and Galen — four of the first five medical writers he quotes are ancient.

The university system perpetuated this situation: lectures in mediaeval universities consisted of the senior academic expounding (Latin profateor, professus — hence professor) on the works of ancient writers, excerpts from which were quoted by his assistant, the 'lector' (reader) who read from those classical texts.

Finally, lest we should become too supercilious about the irrational in ancient medical practice, at least as late as 1929 copies of the Missal included the exorcism of St. Hubert for those bitten by a rabid dog.

Keywords: Aetius of Amida, Alexander Aphrodisiensis, Andreas of Carystos, Antoines, Arataeus, Aristotle, Cassius Felix, Celsius, Columella, Dioscorides Pedanus, Hippocrates, Lyssa, Lucian of Samosata, Galen, Philumenus, Oribasius, Paul of Agina, Pelagonius, Pliny the Elder, Plutarch, pre-Galenic writers, Scribonius Largus, Vegetius

Lyssa

The Greek word for rabies is 'lyssa' (variously transliterated 'lussa', 'lutta' or 'lytta'), a word of unknown derivation. Ancient etymologists suggested its root was either lysis, meaning 'loosing, dissolving' (as in hydrolysis and other -lysis compounds in English), because it led to loss of rational faculties, or lykos, meaning 'wolf' (English lycanthropy) which suggests an animalistic belief that the madness derived from absorption of a bestial nature. In this respect, it would closely parallel our English word 'berserk', which probably derives from Old Norse words meaning 'bear shirt'.

The word 'lyssa', however, was not used exclusively for rabies. Like our word 'berserk' it was used for wild, irrational madness. In the earliest of Greek authors, Homer, it is used to describe furious martial rage — as indeed was 'berserk', originally a wild Norseman fighting in furious frenzy. After Homer, the word was used to describe madness generally: Plato (36) uses it to describe erotic passions, and a lyric poet sings of a 'lyssa' for sexual intercourse (39).

Hence, there are difficulties in establishing the earliest reference to rabies: when the word 'lyssa' occurs, does it refer to rabies specifically or madness generally? On the one occasion (23) when Homer uses the word to refer to a dog (when Ajax states 'I cannot kill this raging dog', meaning Hector), can this be taken as evidence of the existence of rabies in Homer's time? For Caelius Aurelianus (a Numidian medical writer of the 5th Century AD) it could: he mentions Homer's line as the earliest written reference to rabies (6), and tries to corroborate the point by stating that Homer clearly had the sufferings of a hydrophobic person in mind when he describes the torment of Tantalus in Hades, always having drink before him but never being able to drink it. Various other fanciful allusions to rabies are seen in ascriptions of the disease to Hekabe (widow of Priam, allegedly transformed into a mad dog), Hecate and the howling hounds of
Hell, and the monstrous Hydra which devoured all. In this respect, it would be interesting to interpret
Hercules’ actions of overpowering the dog Cerberus and bringing him back from the Underworld as an
allegory for the scientists’ hopes of conquering rabies! Other literary records remain equally tantalising:
when Xenophon, in Anabasis, writes ‘They were afraid that some madness had come upon them, as it
does upon dogs’, is he specifically referring to rabies? He may be – but we cannot be certain (47).

Before looking at the specific treatments recommended by ancient authors, we should take brief note of
the importance attached by various Greek scientists to isolating the first known reference to the disease.
Underlying this insistence was another fundamental question: ‘Have all diseases always existed, or do new
diseases suddenly or spontaneously arise?’ The learned Plutarch (c.46-120 AD) devotes a whole dialogue
(37) to this question, concluding that new diseases can arise and old ones die out, partly through change of
lifestyle over the years and partly through contact with new civilisations. Furthermore, he argues, diseases
thought to be new may well have existed earlier but not been identified: he quotes the Homer reference
already mentioned as evidence that rabies did exist in Homer’s time. Although we may disagree with
Plutarch’s conclusion, attempts to establish the origins of the disease are an important aspect of the Greek
contribution to scientific development.

**Hippocrates (c.460-377 BC)**

Although Hippocrates is known as the ‘Father of Medicine’, none of the surviving works bearing his name
can be confidently ascribed to Hippocrates’ own lifetime. Many of them seem to have been edited and
assigned to him by the librarians at Alexandria in the 4th Century BC. Hippocrates nowhere refers directly
to rabies, although in his discussion of frenetics he mentions that they drink little, are disturbed by every
sound and afflicted with trembling; elsewhere (22) he calls them ‘small-drinkers’. Some have deduced from
this that Hippocrates was referring to the sufferings of an hydrophobic, but such a conclusion is at best
uncertain. Others maintain that the absence of any specific mention in Hippocrates indicates that rabies
had not reached Europe by the 5th Century BC: but an *argumentum ex silentio* is always dangerous – and is
especially so when we do not know exactly what Hippocrates wrote.

**Aristotle (384-322 BC)**

The encyclopedic writings of Aristotle have provoked much controversy among scholars, partly because
of their range and partly because of their presentation. It is particularly the latter aspect which has proved
perplexing. His extant works are often terse to the point of obscurity, leading to suggestions that what we
have are either Aristotle’s own lecture notes, or the notes of one of his students taken during the course of
his lectures. In all of these voluminous writings, rabies is specifically mentioned in only one section, where
he says: ‘Dogs are susceptible to three diseases: rabies, distemper and hard-pad. Rabies makes the animal
mad... It is fatal to the dog itself, and to any animal it bites... Distemper is also fatal to dogs, and few
recover from hard-pad.’ (4). I quote most of this section, partly to illustrate the manner in which Aristotle
deals with his material and partly to indicate his terseness: note especially the economy of the description.

Elsewhere (5), Aristotle discusses madness and frenzy more generally, ascribing its causes to the heat of
the bile which, when it comes near to the seat of the mind, induces the insanity. Important too for later
ideas about rabies was Aristotle’s insistence upon treating many irrational phenomena, what we would call
psychological disturbances, by teaching the supremacy of reason, i.e. the idea that man has a rational
faculty which he can use to override all physical and psychological problems. For that reason, it should be
noted that Aristotle, unlike most who wrote later, includes no remedies or cures for rabies.

**Andreas of Carystos (3rd Century BC)**

Of Andreas we know little except that he was the author of a treatise on the subject of rabies. His early
date would thus make him the first author of a work devoted entirely to the disease.
Other writers of the pre-Christian era

We know the names of many medical writers from the second and 1st Century BC, but our information about them derives entirely from later sources. Medical theorists tended to subscribe to one of two opposing approaches: the Dogmatists taught that the causes of disease were frequently hidden and must be discovered through the application of reason, whereas the Empirical sect rejected much theoretical speculation and concentrated upon what had been proven to work in practice.

Two names usually quoted together are Eudemus and Themison, about whom many contradictory facts are recorded. Eudemus is mentioned by Tacitus (42) as being the friend and physician of Livia, wife of the Emperor Augustus, and again as being the physician of Livilla, helping her to murder her husband Drusus (son and heir apparent of the Emperor Tiberius).

Eudemus was a pupil of Themison, a name that, (as was common practice), seems to have been that of several doctors. One of these doctors called Themison was reputed to have been the only person to have cured rabies, though two different accounts of his exploit are recorded! Not only that, another writer (38) states that Themison would treat all diseases except rabies! According to Philumenus (late second/early 3rd Century AD), Themison caught the disease either from the bite of a rabid dog or from the bite of a friend already afflicted with the disease: he treated himself and made a complete recovery (44). In Caelius Aurelianus’s account, Themison contracted the disease, successfully worked out a remedy which he began to put into practice, but suffered a relapse and died before he had the opportunity to record his treatment (45).

Themison was said to have been a pupil of Asclepiades, another name adopted by a number of physicians, the most celebrated of whom probably dates from the 1st Century BC. To him is attributed the first attempt at a more precise definition of the disease. In trying to assess which part of the body is affected by rabies, he came to the conclusion that it was the membrane enclosing the brain, to which he attributed all diseases causing mental confusion (45).

A slightly younger contemporary was Marcus Artorius, friend and physician to Octavian (later the Emperor Augustus), whom he attended at the Battle of Philippi. According to Artorius, hydrophobia affected the oesophagus primarily, producing hiccoughs, vomiting and an insatiable desire for drink. The membrane around the brain was also affected, causing raging madness.

Finally, from the same century comes our first recorded attempt at defining the cause of rabies and prescribing treatment. This comes in a poem entitled ‘On Hunting’ by Grattius Faliscus, a contemporary of Ovid (43 BC-18 AD):

‘Rabies is very common among young dogs, and if not dealt with promptly causes death. It is thus safer to apply the remedies early and deal with its primary causes. A malignant and pestilential nuisance occurs in the part where the tongue is attached by strong bonds; they call it a little grub. When it penetrates deep into the intestines, it vibrates with flaming heat causing fevers, inducing flight and shunning its bitter seat. Of course the dogs, driven on by this movement and powerful stimulation, become rabid. So they cut out the root cause and origin of the malady while still young. Nor is there any long treatment for the wound made: sprinkle it with pure salt and wipe the wound with light olive oil. Before night returns and completes its shadows, the dog will have forgotten the wound and be fawning at the table wanting food.’ (20). This practice of ‘worming’ young puppies was still carried out early in the 20th Century.

Celsius

Of the encyclopedia compiled by Aulus Cornelius Celsius during the reign of Tiberius (14-37 AD), only the medical sections survive. Included among this part of the work are some detailed instructions for the treatment of bites from poisonous animals or rabid dogs (8). Celsius, like all ancient medical writers, regarded the two as similar, in that the bites of both contained something poisonous which, unless treated, would prove fatal. For this reason, Celsius stressed that the wound must be attended to as soon as possible by using cupping glasses to draw out the poison, or by cauterisation. To ensure that as much blood was
withdrawn as possible, thereby increasing the chance of removing the poison, he suggested that the wound be enlarged by making incisions around and across it.

Interestingly, the ‘poison’ (for which Celsus uses the normal Latin word ‘virus’) affected a person only if it entered the bloodstream. In describing how some people suck the poison from wounds, Celsus warned against anyone doing so if they had any open sores on their gums or palate, through which the poison could enter their blood. He clearly saw some connection between poison in the blood and the digestive system: not only did he recommend emetics to supplement his treatment of rabies, but he also believed that snakebites were more harmful when either serpent or man was hungry.

In default of cupping glasses or anyone to suck the poison from the wound, Celsus recommended the cutting of a live chicken and its immediate application to the wound. It is not clear whether this was to be done to effect suction to remove the poison, or to prevent the wound from becoming cold. Most poisons, Celsus believed, caused death by inducing cold. Finally, if none of these remedies had been done, the patient could become hydrophobic, tortured by craving for and dread of water. In this case, the patient should be thrown into a pond and, if he could swim, be periodically pushed under the water; if he could not swim, then he should be lifted occasionally. In both instances, he should be left until he had been forced to drink his fill of water, and this would overcome the hydrophobia. It should be observed that Celsus does not, as do later authorities mentioning this method, claim that rabies would be cured by this treatment.

An alternative method, practiced in ancient times and surviving until the last century, was to tie the patient in a sack and lower him into a well, keeping him there until he had drunk enough water to overcome the hydrophobia.

Scribonius Largus

Scribonius Largus was a surgeon practising during the reign of Claudius (41-54 AD): we know from his extant treatise on medicine that he accompanied Claudius on his expedition to Britain, presumably in the role of army surgeon. Scribonius mentions a number of herbal remedies, and also relates that at great expense he had acquired a piece of hyena skin wrapped in cloth, supposedly a powerful prophylactic against rabies. He reports that he has never had occasion to use this artefact, and expresses the hope that he will never have to do so. He also quotes recipes for various poultices to be applied to the wound (41).

Columella

Extant is a work of 12 books on practical and scientific farming by Lucius Junius Moderatus Columella, which is thought to have appeared c.60-65 AD. Part of the work deals with the care and treatment of dogs; yet somewhat surprisingly he does not mention rabies specifically. However, there is one possible reference when he discusses feeding, ‘the liquid of boiled beans should be given only lukewarm, for if given boiling hot it causes madness/rabies’ (10).

Antaeus

Of Antaeus (no known relation of the giant killed by Heracles) we have no reliable information: he was, however, reported to have developed a pill to cure those afflicted with the bite of a mad dog. The pill itself he compounded from the skull of a hanged man (35).

Pliny the Elder (23-79 AD)

Pliny’s voluminous Natural History, comprising 37 books and requiring 10 volumes in the Loeb Classical Library, contains references to rabies scattered throughout. Pliny was a rather uncritical collector of facts and theories: in Peter Green’s cruel but accurate description, ‘His work gives the impression of having been shovelled together by some delirious magpie.’ (21).
Pliny mentions several ways in which rabies can be transmitted. Dogs can become rabid by tasting the menstrual blood of a woman, and are particularly susceptible to rabies whilst the Dog Star is shining. Human beings can also contract the disease during that same period, the disease being so virulent that even treading upon the urine of a rabid dog can lead to infection, especially if the foot has open sores (35).

The cures that Pliny mentions belong much more to the magical than the medical tradition. Dogs can be protected from rabies, during the time of the Dog Star when they are most at risk, by including chicken droppings in their food. Another effective cure was the root of the wild rose, *cynorrhodon* or dog rose: this latter term has survived even if its original sense of an antidote to rabies has been lost (35). Human beings may protect themselves against being bitten by a rabid dog by carrying the worm from a dead dog, bitch's menstrual fluid, a dog's tongue placed in the shoe under the big toe, or a weasel's tail – provided the weasel has survived and been released again into the wild. Remedies for those bitten include the liver (raw or cooked) of the dog that bit the patient, pounded-up coxcombs, poultry dung in vinegar or the ash of a shrew mouse’s tail, provided that the animal has been set free alive (35).

**Dioscorides Pedanius**

Dioscorides, who lived during the reign of Nero (54-68 AD), is best known for his manual of herbal remedies, although he wrote other works including a treatise on theria (on which see below). To him we owe our earliest mention of a cure which subsequently became a classic: ‘The ash of burnt river-crabs: two spoonfuls, with a spoonful of gentian root, taken in wine for three days, actively helps those bitten by a rabid dog. With boiled honey it soothes cracks on the feet and fingers, chilblains and sores. Ground up raw and drunk with asses’ milk it helps against the bites of snakes, venomous spiders and scorpions... The ash of sea crabs is less effective.’ Elsewhere he cites garlic as a cure, repeats Pliny’s dog-liver remedy, and adds that some people carry the canine tooth of a dog, tied in a pouch attached to the wrist, as a prophylactic against being bitten (11).

**Other pre-Galenic writers**

Very influential were two medical authorities from Ephesus, Rufus and Soranus. The former wrote many works; perhaps his most lasting influence was in the naming of parts of the eye. His terminology is in use today. The latter wrote over twenty treatises, although only one is extant in its entirety: a gynaecology, and easily the best available until little more than a century ago. For both, we have to rely upon later authors to learn what they had to say about rabies: Philumenos relied heavily upon Rufus, and Caelius Aurelianus transmitted many of Soranus’s ideas. Among their contributions, we learn that Rufus believed rabies was also sexually transmissible and that Soranus recorded a baby afflicted with rabies as being terrified of its mother’s breast.

George Sarton is most emphatic that Soranus was the original author of the two treatises ascribed to Caelius Aurelianus: ‘Let us repeat aloud, very loud, that those great medical treatises were written in Greek by Soranus of Ephesus; Caelius was only the translator of them into Latin; he took liberties with the original, abridging it and even making a few additions, but no matter how many liberties he took, these texts did not become his own.’ (41). As it is impossible to be certain how much Caelius added/subtracted from the Greek originals, which do not survive, in what follows, the work is summarised as though by Caelius himself.

Caelius begins by stressing how extremely contagious rabies is: not just through the bite of a rabid dog, or of a human being suffering from rabies, but also through the breath or even the claws of a rabid dog. To illustrate just how contagious it could be, Caelius relates the story of a needlewoman mending the garment of a man who had been bitten by a rabid dog. As she sewed, she chanced to bite through the thread she was using, at the same time putting the garment torn by the rabid dog to her lips. She contracted rabies from this contact and subsequently died.

Symptoms include general feverishness and lethargy, accompanied by violent frenzy and painful breathing, sometimes involving sweating or even involuntary ejaculation. Above all, there is the fervent fear of water, sometimes accompanied by a passionate craving for it as well: Soranus’s story of the terrified baby has
already been noted above. The disease itself is a rapid one, the patient dying fairly quickly after being bitten.

Rabies is a physical, not a mental disorder: not only is it the actual physical body that feels the cravings but the source of the disease, the bite itself, is the physical contact causing the distress. The area of the bite itself is first affected, then gradually the whole body and finally the brain, after which the disease is invariably fatal. Nor is rabies a new disease: it has existed since Homer's time (see above). For treatment, try first to relax the patient; give him thin, watery foods to get him used to the idea of liquids, then get him to suck liquids whilst blindfolded. For the wound itself, use cupping glasses and poultices. Getting the patient used to liquids can also be done by giving an enema of warm water and olive oil. If the liquid is retained, then relief has been achieved; unlike remedies such as dropping the patients into water or tying them into a sack and lowering into a well, which try to force the patient to drink, rather than encourage the desire to do so. Nor are many of the herbal remedies – hellebore, castoreum, rose oil etc., of any real help in the treatment of rabies (6).

For many other first/early 2nd Century writers, we depend upon snippets from later authors. Thus we learn that Archigenes (a Syrian from Apamea who practised in Rome during the reign of the Emperor Trajan (98-117 AD), used a concoction of olive oil, myrrh and terebinth (16); that Straton made a poultice from burnt calf bones with pitch or honey or both; and that Theodorus's poultice used burnt pig dung dissolved in olive oil (34).

Galen quotes many of his predecessors' remedies: among these were those of Aelius Gallus, Aeschrian, Andromachus, Antoninus of Cos, Asclepiades, Democrates, Heras and Pelops. Although many of these are merely names to us, we do learn that Heras concocted a remedy from filbert nuts (14) and that Antoninus of Cos used the flower of alyssum (12), a plant owing its very name to rabies (a- is the normal Greek negative prefix + 'lyssa'). Pliny had already mentioned its efficacy as a cure 'if taken in vinegar and worn as an amulet' (35). Andromachus, in a lengthy eulogy of theriac, also mentioned another classic cure, castoreum (12). Both of these topics really demand a paragraph to themselves.

‘Theriac’, or ‘treacle’, was a general name for a concoction of a variety of different substances used for medicinal purposes. Nicander of Colophon (mid-2nd Century BC) wrote a poem, ‘Theriaca’ dealing with its efficacy against bites of poisonous animals. It was defined in 1853 as ‘a name given by the ancients to various compositions esteemed efficacious against the effects of poison, but afterwards restrained chiefly to what has been called Theriaca Andromachi, or Venice treacle, which is a compound of sixty four drugs, prepared, pulverised and reduced by means of honey to an electuary.’

‘Castoreum’ was regarded as ‘an excellent remedy for’ virtually any malady. It was concocted from pulverised beavers’ testicles: we owe to Pliny the information that these obliging little creatures, when hunted, tear off their own testicles, realising the reason for their pursuit (35). Modern castor oil is a vegetable substitute, preserving the name (but not the ingredients) of ancient ‘castoreum’.

Plutarch (c.45-120 AD)

Plutarch has been mentioned above. Although not specifically a medical authority, he was a prolific writer, perhaps most famous for his Parallel Lives of distinguished Greeks and Romans (11 volumes in Loeb Classical Library), and his numerous other essays generally known as Moralia.

When discussing the efficacy of various herbs, Plutarch mentions alyssum, but without specific reference to rabies, commenting that those who picked it, or even looked at it, were relieved of hiccoughs. Yet he was clearly familiar with rabies, as his above reference to Homer demonstrates. He also remarks that it is the mental faculty in dogs that is affected, ‘as we can see no such disturbance in their powers of sight and hearing.’ (38). This stress upon the mental faculty being affected, deriving ultimately from Aristotle, was destined to have some very interesting developments in later thought.
Lucian of Samosata (c.120-180+ BC)

Lucian, a satirical writer whose works have had to be heavily bowdlerised in translation, (in Nigrinus) makes a pleasant link between supposed remedies and what was to become a proverbial expression:

Friend: A person bitten by a rabid dog not only goes mad himself but also infects with madness anyone whom he bites whilst still rabid. The disease thus passes on from one to another through a long succession of people.

Lucian: Do you then admit to some weakness?

Friend: I do, and I beg you to think of some remedy for both of us.

Lucian: We should take our cue from Telephus.

Friend: How do you mean?

Lucian: We need the hair of the dog that bit us.

Galen (129-199 AD)

It is almost impossible to overestimate the importance of Galen in the history of medicine. Aristotle may be regarded as the fount of all wisdom in many areas, but Galen was the ultimate medical authority throughout the Middle Ages and almost until within living memory. Until 1833 candidates at Oxford for the degree of Doctor of Medicine had to present lectures upon Galen, and even after the reforms of 1833 Galen figured very prominently among the authors to be studied in detail. Part of the reason for this pre-eminence was the fact that medicine had made little progress after Galen. We may perhaps regard an earlier assessment that ‘After Galen there is a thousand years of darkness, and biology ceases to have a history’ as exaggerated, but there was little advance in medical knowledge from Galen up to approximately a couple of centuries ago.

It is not difficult to see why Galen achieved such a dominant position in later assessments. He was a prolific writer on a wide variety of subjects including philosophy and philology, although only his medical works survive today. The ‘only’ there perhaps concealing that the full text of his medical writings extends to 20 volumes each of 500+ pages in the edition by C. Kuhn (25): Greek text with (sometimes very unreliable) Latin translation. In view of his importance for later science generally, it is perhaps surprising that so few of his works have been translated. He acknowledged allegiance to none of the general schools of medicine of his time, preferring an eclectic approach. He comes closest to rejecting the dogmatists in asserting: ‘If there is any effective remedy, either taken internally or applied externally, for those bitten by a rabid dog, it is impossible to know by reason alone.’ (19): to this extent he accepts the approach of the empirical school.

Inherited from the Hippocratic tradition was another fundamentally important practice; that of recording in detail symptoms and treatment with results. With Aristotle (above), Galen believed that all mental disorders were the result of an imbalance in the rational faculty: ‘All deliria, arising from the movement of the guiding forces, come from harmful humours or an intemperance of the membranes surrounding the brain’. As a result of these mental disorders, people fear death, then begin to wish for it (15).

Somewhat surprisingly, Galen believed only dogs and men were susceptible to rabies: ‘No other animal is affected by rabies, dogs alone being susceptible to it. So great does the corruption of their humours become that their spittle alone, if it falls upon a man, can make him become rabid.’ Elsewhere, he draws attention to the problem of diagnosis: ‘The poison of a rabid dog causes no distinctive symptom on the body before the person bitten becomes rabid’, and again ‘Even though there may be no immediate signs in the affected area, after four or six months or even longer the poison destroys the man...I have even known someone who lapsed into the condition known as hydrophobia a whole year after being bitten. All doctors are agreed that an extreme dryness arises in the solid parts of the animal, increasing its natural warmth and turning to fever. The canine poison produces this affliction over a long period of time, that is, gradually; and is for this reason more difficult to treat, because the substance of the solid parts is altered.’ (15, 13, 18). Yet the rabid dog is more easily discernible: ‘If you hear that the dog is wasted in body, dry and red in the eyes; with tail hanging limp, saliva flowing from its mouth, tongue hanging out and bile-coloured; bumping into people it meets, irrationally running then stopping, and biting with furious rage people it has never seen before; then you may be sure the dog is rabid.’ (17).
Galen laid stress upon identifying the dog because any treatment, he insisted, must be promptly given if it is to be effective: 'Cut the flesh all around the bite, opening it up in a large circle so that it cannot easily scab but will keep the flow of blood open. Keep the wound open for a minimum of forty days so that the poison may come out. I generally use cauterisation and apply such medicaments as are likely to extract the poison and not allow it to remain in the wound'. The aim of prompt – and from the sound of it pretty vicious – cauterisation seems to have been to prevent the poison from entering deeper into the body, for if it does so, ‘it causes a fierce fever inside and makes the mind delirious’. In this aspect of rabies, Galen would concur with Aristotle; that the effect upon the mind derives from heat coming too close to the seat of reason. He further illustrates that the power of the mind has a powerful influence. (ibid)

Galen favoured two remedies above all others. He quotes his own teacher Pelops’ reasons for preferring river to sea crabs’ ash ‘He used to say that river crabs are more beneficial than sea crabs because through their contact with salt, which is a desiccating agent, sea creatures cannot as well protect against the opposite in rabies’ – that is, hydrophobics need water, not a desiccating agent. His second preferred remedy was theriac, also mentioned above, particularly one which he tells us was specifically favoured by ‘the divine Marcus’, the Emperor Marcus Aurelius who reigned 161-180 AD (16). Galen mentions many other remedies, but usually without comment.

Besides their use as remedies against poison, many concoctions enjoyed high esteem as prophylactics: Galen (as Juvenal before him) refers to the story of Mithridates (King of Pontus and prototype Rasputin). ‘It is reported that the great warrior Mithridates took not theriac, for it did not then exist, but some other mixture, from which it was called by his name, and from the strong constitution of his body, increased by this mixture, could not die by poisoning. When he waged war against the Romans led by Pompey, and was reduced to the direst extremities, he drank poison copiously but was unable to die – his daughters however, who were anxious to die at the same time as their father, as soon as they drank the poison immediately fell down dead’. (24, 17)

**Aretaeus (c.150-200 AD)**

Aretaeus, a native of Cappadocia, wrote a treatise on diseases generally, in eight books which are still extant. His style is terse and elliptical; his one reference to rabies reads ‘Even from the tongue of a dog merely breathing onto the breath, not biting, a man becomes rabid’. Within the context – he is arguing that diseases can be spread by breath alone, not necessarily by any physical contact – the meaning is clear enough. (3).

**Philumenus (c.180 AD)**

Philumenus was an Alexandrian zoologist, author of several works; including one on gynaecology (which has not survived) and one on poisonous animals. Amongst poisonous animals, Philumenus includes rabid dogs, explaining at the outset: ‘The section on bites of rabid dogs I have placed first, because the animal is very common, shares our homes and is particularly susceptible to rabies. This makes the disease hard to control, and the danger from it is very great, unless one applies many medicaments’. After a brief description of the clinical symptoms of a rabid dog, he goes on to detail the effect upon those bitten: ‘The disease is accompanied by spasms and frenzy, the whole body, particularly the face, turning red; with much sweating and listlessness. Some of those suffering from hydrophobia shun the light, some are constantly exhausted; some even bark like dogs, attacking and biting people and thereby spreading the disease itself’. (34).

Philumenus then goes on to describe various remedies, especially the river-crab ash + gentian mentioned above (‘This is the best remedy for bites of rabid dogs; it alone has helped some people – use it with confidence’), accompanied by laceration of the wound itself, cauterisation and the use of cupping-glasses. Cauterisation he recommends for all poisonous bites: ‘For fire is more powerful than any other remedy; at one and the same time it destroys the poison, preventing it from being conveyed deeper inside the body, and renders the affected part harmless. One should also take great care with the diet of those bitten by a rabid dog: in this the consumption of theriac plays an important part, with white hellebore and rennet, the curdled milk obtained from an animal’s stomach’ (34). After his own recommendation for the treatment
of those bitten, Philumenus repeats several of the other remedies already mentioned. He also adds one diagnostic: ‘Make the patient stare at himself in a mirror; if he can recognise himself, then he will live’. Clearly this was meant to be a test of the rational faculty, and as such ultimately derives from Aristotle. (34).

**Cassius Felix (3rd Century AD)**

Cassius was the author of a work entitled *Medical Questions and Problems*, which he presented in the form of a question followed by his answers/solutions. I quote his problem 73 in full:

‘Why do hydrophobics fear water, extend their genitals together with their abdomen, tremble, have convulsions and thrash about to such an extent that they even howl like dogs? They have convulsions and tremble because the stomach is held together with sinewy parts. For the same reason they also extend their genitals. The reason for their hydrophobia is a constriction in the belly and the stomach. They thrash about because disordered matter is distributed against the belly and stomach, and part of this is vaporised into the membrane. Settling around these, it causes loss of senses: these become deranged when drinking because the disturbances are accomplished around small passages. When they drink, the water, being composed of small particles, steals into the small passages and increases the constrictions. Hence they are not disturbed by solid food’. The same disturbances, we later gather, can occur even if the water is not drunk: in their delirious state, they imagine that it is, so the same constrictions occur.

**Alexander Aphrodisiensis (3rd Century AD)**

Roughly contemporary with Cassius Felix was the prolific Alexander from Aphrodisias in Caria. He wrote many commentaries upon Aristotle, which were translated into Latin and were much studied during the Renaissance; several other works survive in the original Greek, and still others are preserved in Arabic translations. Alexander also wrote in the question-and-answer format: Problem reads (1): ‘Why do dogs alone become rabid in summer? It is because of the preconception of their dry constitution; for they are by nature dry, and are more so in the heat. When they become warm and dry, the moisture in them and their whole constitution is burnt up, with the result that they rage like delirious people. For the same reason, even their saliva becomes poisonous and dry. Only the driest dogs become rabid, not all. Some say that the Dog Star contributes to their inclination to become rabid’.

**Oribasius (c.325-400 AD)**

Another native of Asia Minor was Oribasius, who acquired a reputation at an early age as being one of the leading medical authorities of his time. He moved to Rome, where he became a close friend of the future emperor Julian, better known as Julian the Apostate (Emperor 360-363 AD), who instructed Oribasius to compile the *Collecta Medicinalia*, about half of which is still extant. It became a most important manual of the practice of medicine.

Much of Oribasius’ work is derivative, and thereby invaluable to us in preserving the opinions of earlier writers whose works have not survived. Some of his remedies for bites of rabid dogs contain familiar elements, but others are less well-known: ‘A salve for those bitten by a rabid dog. Pitch is boiled with very sharp vinegar until the vinegar is absorbed, then gum of opopanax hispidus (Hercules’ woundwort) pounded up with a little vinegar is added. This prevents the wound from scabbing over... After fomenting the wounds with garlic, apply the salve. When the scab has fallen, treat the wound with the recommended medicament, such as walnuts, pounding them up carefully and applying to the wound. The following day, remove the salve and give it as a food to a hen, and initially she will not touch it. If she is forced by constraints of hunger and eats it, she will die. The next and subsequent days do the same. When the hen which eats it does not die, then allow the wound to scab over as the patient is out of danger’. (29).

A recipe for desiccating powder, to encourage scabbing after the poison has been removed from the wound, included salt, rock alum, squill (*urginea maritima*) fresh rue, violet and horehound (*marrubium vulgare*). For internal consumption, Oribasius recommended the familiar river-crab ash + gentian (advising that the crabs be burnt ‘on twigs of bryony’), adding that an alternative modification to the remedy was to
add partridge blood, and that ‘the crabs should be caught when the moon is waxing, just before dawn’. Elsewhere: ‘They should be burnt after the rising of Sirius, when the Sun is in Leo and the moon 18 days old’ (29, 30).

Another internal remedy: ‘Sea horse, to the amount of one teaspoon, drunk with hydromel’ (a mixture of honey and water) ‘is believed to put an end to the craving for water in those bitten by a rabid dog. Also suitable for such patients is the antidote from sweet bay, frogs boiled in a soup and drunk, or bear’s bile (one teaspoonful in water). The theriac which Mark the teacher used for those bitten by a rabid dog: equal quantities of clover-seed smeared with pitch, wild rue, meal of bitter vetch (\textit{vicia ervilia}) and round aristolochy. Make it into small balls and administer in wine mingled with olive oil. Single common potions: for general use, make potions from a mixture of castoreum or rosemary with either bryony root or the juice of horehound or myrrh or cinnamon or aristolochy or chaste-tree seeds or cypress berries or hartwort (\textit{tordylium officinale}) or black peppers or river-crabs, boiled or roasted’. (29).

Oribasius’ full medical works must have been voluminous: we have an abridgement, in nine books, of the complete text. For the treatment of bites he recommends cauterisation, with ‘a decoction of salvia (\textit{salvia triloba}) or Hercules’ madwort, which they also call alyssum, because it alone can help’, and the river-crab ash + gentian remedy, adding ‘If one uses this remedy, one always saves those bitten by rabid dogs’. (30, 31).

These detailed remedies, deriving from earlier sources, had by the 4th Century clearly acquired some mystique of their own – note the specification of bryony twigs and the precise time at which the crabs should be caught. These careful details add to the whole process an aura of mystery and arcane lore, both to deter amateur imitators and to increase the fees due to the doctor himself for his expertise. They also no doubt provided an excuse to explain unsuccessful treatment. Was the moon waxing? Was it too soon after dawn? Greeks and Romans had the same attitude in religious matters: in the event of a sacrifice not being favourably received by the gods, some fault or blemish in the animal accompanying the sacrifice was accounted the cause. Similarly, when so many medical writers recommend the river-crab ash + gentian remedy with such phrases as ‘this always works’, there was clearly a need to explain non-success: although an admission that the concoction was imperfectly prepared might impugn the doctor’s professional competence, it would not totally destroy his credulity.

**Pelagonius (4th Century AD)**

Pelagonius was a veterinary surgeon rather than a medical writer; the only treatise of his which has survived is one on horses, which includes the following potion for rabid horses: ‘Clean laurel berries, grind them up with olive oil, mix with warm wine and insert through the nostrils’ (33).

**Vegetius (4th Century AD)**

Another veterinary surgeon, Vegetius was roughly contemporary with Pelagonius. He too deals with rabies in other animals: ‘Sometimes beasts of burden fear water, and are said to be hydrophobic. The signs of this are: the animal will have all veins extended, will sweat with eyes suffused and will tremble and gnash its teeth. It will strike itself against walls, and from these sufferings usually goes mad. One can cure this as follows: let blood from its thighs, keep it away from fodder, place it in an enclosed space so that it cannot see the light, and with as little noise as possible pour water into a bucket or trough, ensuring that it cannot hear the sound. Grind up a handful of rue, fifteen laurel berries, a pound of rose oil, mix in one ounce of vinegar, and then very carefully anoint its head and nostrils, and it will be cured’. (46).

**Aetius of Amida (late 5th Century/early 6th Century AD)**

Aetius was the author of sixteen books on medicine, of greater importance as evidence for works now lost than as an innovator. Hence much of what he has to say on rabies is frankly derivative: there are some new ideas/theories, however.
Aetius adds further refinements to Orribasius’ modifications of the original river-crab ash + gentian remedy. He stipulates that the dish in which the crabs are cooked must be made of copper, the crabs should be cooked alive, in the month of August when the moon is eighteen days old. (3). This clearly takes the ‘professional caution’, or whatever reason we may attribute to it, considerably further. It should also be noted that these refinements are in addition to those of Orribasius and equally, quickly became part of the general lore concerning rabies, repeated again and again by subsequent writers.

The importance that Aristotle placed upon irrational phenomena as psychological disturbances also reached classic proportions in Aetius, as demonstrated by two explanations frequently reappearing in later authorities. The first sought an explanation for the fear of water: ‘Their (the ‘hydrophobics’) perturbation becomes greater when they see water or anything shiny… It is possible, as some say, that they imagine they see in the water the image of the dog that bit them, and when they see the shape of the dog, great fear grips them’ (3).

In further elucidation of this idea, Aetius quotes an anecdote oft-repeated by subsequent authors: ‘Once a philosopher, who had been bitten by a rabid dog, resisted the disease through the nobility of his intellect. Finding that a dog illogically appeared in his bath — for this appeared to him as it does to others suffering from the disease — he pondered about it, then said to himself: ‘What has a dog to do with a bath?’ In this way he overcame the disease and took delight in washing and drinking fearlessly’ (3).

To the already formidable list of herbal remedies, Aetius adds pimpernel, chamomile and sorrel. The river-crab ash + gentian remedy can be made even more efficacious by using it alongside the nut remedy — ‘Two measures of sagapene (\textit{\textTrade{ferula persica}}), two of Theban opium, one of saffron, one of Indian holly-fern (\textit{aspidium lonchitis}) and twenty measures of nut kernel. Administer it with warm rain-water towards night, after the peak of the fever’ (3). Just try getting everything right in that one!

Other innovations include the liver of the shearwater bird; sea-horses, not only taken internally, but also rubbed with sharp vinegar and applied to the wound; and the skin of a bear, seal or especially hyena placed beneath the patient. Ever since Pliny, there had been a particular mystique attached to the hyena. ‘Most people believe that the hyena is bisexual, becoming male and female in alternate years... Many other remarkable qualities are attributed to it, the most astonishing being that it can simulate human speech, outside shepherds’ cottages, to call out the shepherds and tear them to pieces... Additionally, when its shadow passes over a dog, the dog becomes dumb, and by certain magical arts every animal which it looks at three times becomes rooted to the spot’ (35). Hyena skin could also be burnt and the ashes sprinkled on a drink for the patient, and ‘this stops the sufferings of hydrophobia’. (3).

Paul of Aegina (7th Century AD)

Paul was a celebrated medical writer born in Aegina but probably spending much of his professional life in Alexandria, during the latter part of the 7th Century. His seven books on medicine are largely derivative (the major source being Orribasius) but do contain some original material. On the clinical signs of rabid dogs and their immediate treatment, Paul quotes Orribasius in the main, though he does add that ‘some people, thinking that the dog that bit them was not rabid, were in a hurry to let the wound heal and thereby became transmitters of the disease’ (32). River-crab ash + gentian is also mentioned (one might be tempted to add ‘Of course!’ so common did it become), complete with the refinements of Orribasius and Aetius.

It becomes apparent from reading these later authorities that the medical practitioners were prepared to try virtually anything. The common core of remedies becomes not only repeated, (complete with any additional refinements), but also circumscribed with yet more precautionary measures. It is difficult not to see evidence of almost panic entering the writings. When so many ‘sovereign’ remedies were available, and recommended with such \textit{encomia} as ‘this never fails to be effective’, yet none of them actually worked in practice, then physicians retreated within their professional cliques, claiming that the ‘specific’ was ‘sovereign’ but the execution imperfect.
CONCLUSION

There have been claims of instances of rabies from the time of Homer (ca. 8th Century B.C.) onwards, yet the fact that Hippocrates make no mention of it earliest suggests it had not reached Greece by then (5th Century B.C.) – although we must be cautious as not all of his works are extant. Hence the first attested appearance of the disease was in 4th Century B.C. and even then more precise diagnosis is not recognisable until 1st Century B.C. Various remedies were attempted, often with increasingly arcane methods as time went on (e.g. specifying shearwater liver, when any bird – even a chicken or animal – liver would have suffice, or insisting upon the precise collection/preparation of gentian + river crabs) in herbal remedies; in cauterisation and in “treatment”. Later medical writers, in large quantities, by and large adopted a “pick and mix” approach which persisted well into the mediaeval period and beyond.

Claims of success in “curing” the disease must have been at best economical with the truth or more likely faulty in the diagnosis of rabies.

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CHAPTER 2
RABIES IN EUROPE AND THE MEDITERRANEAN BASIN:
FROM ANTIQUITY TO THE 19TH CENTURY

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Summary

The history of rabies in ancient times is without doubt one of the most fascinating subjects of all for anyone interested in the epidemiology of animal and human diseases. Indeed, it is the disease for which there exists the greatest number of ancient documents, and we are fairly certain that the disease which they describe actually corresponds to rabies as we know it today. Evidence to support this idea comes both from recent discoveries in molecular epidemiology, which date the origin of some strains of the rabies virus to several thousand years ago (4) and from certain clinical and epidemiological characteristics of rabies that are pathognomonic in both human and veterinary medicine. The research for this chapter was greatly facilitated by the fact that it is in Europe and the Mediterranean Basin that the most ancient and most detailed rabies observations can be found.

This chapter is confined to the period before the 19th Century and will deal successively with all of the various aspects of the history of rabies (clinical and epidemiological observations, control methods, treatment, etc.) in each of the countries in the region, even though the borders of these countries have changed considerably over the course of history.

Keywords: Europe, History, Mediterranean Basin, Rabies

COUNTRIES OF THE MEDITERRANEAN BASIN

This study of the different Mediterranean Basin countries begins with those for which we have the most ancient information (Chapter 14, H. Matter et al.; Chapter 16, A. Mantovani et al.).

Egypt

Historians are divided about whether or not rabies infections did actually occur in ancient Egypt. Leca (22) believed that the following passage, from a book of spells written in the 3rd Century AD, applied to rabies: ‘O dog, ye which are one of the ten dogs belonging to Anubis, his own son, remove your poison with spells, take now away from me your saliva. If you do not remove your poison with spells and if you do not take now away from me your saliva, I shall bring you to the courtyard of the temple of Osiris.’ In those days, the treatment of a person who had been bitten by a dog consisted of applying crushed garlic to the wound (22). Other historians thought that the ‘poison’ referred to in this text could have been another pathogen that contaminates through bites.

However, a Coptic text from the 4th Century AD is much more convincing, as demonstrated by the following account: ‘Now Saint Tarabon met a rabid dog and the drool was dripping from its mouth and it was staggering around like a cripple, staring hither and thither, and its eyes were glittering like gold and it resembled a drunken man (in the way it was walking).’

In the 12th Century, human rabies was so common in Egypt that Chief Judge El-Fadel asked Maimonides (Moses ben Maimon) to write a short popular treatise offering practical advice to people who had been bitten by stray dogs (8). In the 15th Century, the Egyptian author, Sidi Siouti, gave an account of the disease ‘Addat-el-Kalb’ which was rampant among dogs at the beginning of winter (‘due to an excess of bad humours’). He described these dogs as having arched backs, wagging heads, an abstracted air and tongues that hung out, he also said that they were disposed to bite and that the biting transmitted the
disease to humans, leading to hydrophobia after 40 days of incubation. The fox and stone marten were also known to display similar clinical signs and they too could contaminate humans through their bite (24).

Another anonymous treatise, written in Egypt in 1467, reported cases of rabies in camels and horses, and described the rabid dog as drooling, with a lowered head, red eyes, blurred vision, tail between its legs, and biting anything that got in its way. The author even proposed a treatment for the animal (inhalaion of *Helleborus niger* and applications of cucumber boiled in wine), which were efficacious, ‘God willing...’ (22).

Although the disease was absent, or very rare, during the 18th Century, it was common in Alexandria and Cairo at the end of the 19th Century according to Pruney and Piot-Bey (6). There appears to be no doubt, then, that in the region now known as Egypt, urban and sylvatic rabies have coexisted since very ancient times.

**Greece**

The terms ‘rabies’ and ‘rabid’ have been employed on several occasions in various texts from Ancient Greece, notably in Homer’s *Iliad* (9th Century BC) where Teucros called Homer a ‘rabid dog’. Moreover, historians believe that Homer was referring to rabies when he stated that Sirius (the constellation of the dog) had a detrimental effect on human health, a belief that was also widespread in Egypt (21).

However, an in-depth study of numerous medical works subsequent to this period convinced Théodoridès that human rabies could not have been known to either Hippocrates or the authors of the Hippocratic corpus, although this in no way proves that animal rabies did not exist in Greece. Indeed, in Volume VIII, Chapter 21 of his *History of Animals*, written in the 4th Century BC, Aristotle does specify that: ‘Dogs are subject to three diseases, namely rabies, quinsy and gout. One of these diseases, rabies, produces raging madness and if the patient bites, all of the animals that are bitten, with the exception of man, become rabid.’ (1).

By contrast, an apocryphal document from the 1st Century, entitled *Letters from Hippocrates to Democritus*, confirmed the possibility of rabies being transmitted to humans, and other cases of rabies were mentioned in dogs, as well as in jackals, lions, wolves and other animals ‘which are distinguishable by excessive heat’ (22). In the 3rd Century, Philumenos described canine rabies, for which, though the disease was always fatal, he nevertheless proposed a treatment based on a powder made from crayfish and gentian root dissolved in old wine (Chapter 1, J. Neville), a remedy that was already being advocated by Discorides as far back as the 1st Century. Subsequent anonymous texts describe the anorexic rabid dog, frothing at the mouth and with an abstracted look (22) and, in the 5th Century, Caelius Aurelianus reported that canine rabies was very common in Crete (24). All of these texts clearly suffice to confirm the existence of canine rabies as an enzootic disease in Greece at least 2,000 or 3,000 years ago, and the concomitant existence of secondary outbreaks (or of a reservoir of virus?) among wild carnivores.

**Israel, the Lebanon, Malta, Palestine, Syria**

Curiously, biblical texts, which frequently refer to dogs, do not expressly mention canine rabies (Chapter 13, B.A. Yakobson et al.), although they do allude to the danger of attacks by wild beasts (19). This is surprising, particularly as rabies had already been mentioned in very ancient times in neighbouring regions, especially in Mesopotamia (Iraq) in the *Eshunna Code*, written 23 centuries BC, and in Persia (Iran) in the *Avesta*, written seven centuries BC.

By contrast, the various versions of the *Talmud* (fourth and fifth centuries) do mention this subject on several occasions and, in particular, give an excellent description of a rabid dog: ‘Its jaws are open, it froths at the mouth, its ears are lowered, its tail is between its legs, it walks to the side of roads, and is so hoarse that its bark cannot be heard.’ (22). The ‘Talmud also reports that about the 2nd Century AD a German slave was bitten by a rabid dog in Galilee and died in spite of the usual treatment recommended in this time: consumption of the diaphragm of the biting dog (19). In those days, controlling canine rabies involved slaughtering affected animals. However, as dogs were considered to be unclean, they had to be
killed without being touched. For the same reason, the treatment of infected people by making them eat liver from a biting dog was condemned by the rabbis (22).

In the 9th Century, Jahiah-Ibn-Serapion from Syria treated people who had been bitten with honeyed water (7). In the 12th Century, Sultan Saladin’s physician (Maimonides) estimated the incubation period of rabies in humans to be at least seven days. His book, *Treatise on Poison*, reported an experimental method for diagnosing canine rabies: to give bread, soaked in blood from the bite, to a healthy dog, which would refuse it if the biting dog were rabid (22). Also in the 12th Century, Al-Quazmini reported the existence in a village in the province of Alep (Syria) of a ‘dog well’: people who had been bitten by a rabid dog could escape death if they drank water from this well no more than 40 days after being bitten (22). During the same period, in Israel, Moshe ben Nackman recommended isolating anyone who had been bitten by a rabid dog (8).

When, in the 16th Century, a rabid dog entered the Oman Mosque in Jerusalem, the Cadi ordered each Jew and Christian in the city to bring a dog and have it sacrificed (at their own expense), in exchange for a receipt testifying that they had complied with their duty (8). In 1847, canine rabies appeared in Malta, supposedly for the first time (21).

As with other countries in the eastern Mediterranean Basin, canine rabies therefore clearly appears to have been prominent in the four above-mentioned territories, even if its existence prior to the Christian era remains difficult to establish.

**Italy**

Greek and Roman authors mentioned rabies in the Roman Empire on several occasions (Chapter 16, A. Mantovani *et al.*), although Galen (2nd Century) mistakenly wrote that it affected only dogs and man. As early as the 1st Century the term rabies ‘virus’ (but in the sense of poison or venom) was used by Celsus, and Pliny stated that dogs were especially prone to rabies during hot weather. He proposed making them eat hen droppings in order to prevent the disease! Like the Greeks, Pliny attributed canine rabies to the existence of a small worm (‘lyssa’), situated under the frenum of the dog’s tongue, the removal of which prevented the disease. Like Columella, Pliny also proposed another means of prevention: to cut the tail of puppies at 40 days of age (22).

Shortly before the beginning of the Christian era, Ovid in *Metamorphoses* and Virgil in the *Georgics* mentioned the disease in humans and animals (12). Seribonius Largus (1st Century) reported that Sicily was frequently beset by rabid dogs (24), affirming that the disease was always fatal in man (12).

In the 13th Century, Pietro d’Abani, a teacher from Padua, spoke of a rabid dog that was walking along with its tongue hanging out and its tail between its legs, howling hoarsely. He proposed treatment by scarification, cupping (drawing blood to the surface of the skin by forming a partial vacuum over the infected area using a glass cup which has been heated) and sea bathing to save people who had been bitten (22). In the 15th Century, Ferrari reported the case of a Venetian lord who died from rabies after having probed the mouth of a rabid dog (22).

In 1546, Fracastor stated that rabies was common in both Italy and France, often caused by wolf bites (14). He studied the disease closely and attributed it to germs (‘semina’) ‘creeping slowly, which resemble organs such as nerves’ (22). In 1557, Cardamos affirmed that the saliva of a rabid dog had the power to infect (21). In 1610, Codronchi described cases of equine rabies and estimated that the incubation of human rabies could vary from 40 days to... 40 years (22). In 1691, then again in 1693, a major epidemic of animal rabies (especially among dogs) was reported in several Italian provinces (17, 10). In 1779, a number of people and domesticated animals were bitten in the district of Bellumo by a mad wolf, and many died (7). It was in Italy in 1799 that Eusebio Valli proposed the first anti-rabies vaccine (for human and veterinary use), which was composed of the saliva from a rabid dog, neutralised using the gastric juice of a frog (22).
Canine rabies has therefore been well known and feared in Italy for at least two thousand years. Secondary outbreaks must also have existed in wild animals up to the 19th Century: in 1804, a rabid wolf came down from the mountains into the town of Crema and bit thirteen people, nine of whom died of rabies (2).

**Turkey**

There is a wealth of information about this region, as Greek and Byzantine authors transferred knowledge of Greek and Roman medicine to the region for over one thousand years (Chapter 12, N. Akkoca et al.). In the 4th Century, Priscianus described the rabid dog as panting, ravenous and thirsty, with its ears lowered and no longer able to recognise its master. Posidonius proposed treating people who had been bitten by making them eat the liver from the biting dog, with salt and oil (22). During the same period, both Apsyrté (veterinary surgeon to the armies of the Emperor Constantine) and Eumelos provided good descriptions of equine rabies, for which they recommended local treatments (cauterisation) or general treatments (blood-letting, castration, etc.).

In the 5th Century, Timotheus of Gaza described hydrophobia in rabid humans, which he advised treating by administering a pill made from the flesh of the right-hand flank of a hyena (22). During the same period, Caelius Aurelianus reported canine rabies in south-eastern Anatolia (24). He also cited rabies in wolves, foxes, leopards, bears, donkeys and even birds. Vegetius described cases of rabies in cattle and horses that had been bitten by rabid dogs, which he treated by cauterisation and the administration of nitre or bitumen in wine (25).

In the 6th Century, Aetius of Amida reported cases of hydrophobia in rabid dogs, and also treated exposed people by administering the liver from the biting dog, as well as hyena hairs, cat intestine, etc. He was the first to describe a diagnostic method which would be taken up again over the centuries (and was even proposed to the French Academy of Science in the 18th Century!). It consisted of sponging the dog-bite wound with a homogenate of walnuts, which was then administered to hens that died from it only if the dog was indeed rabid (24). In the 13th Century, Actuarius, a renowned Byzantine physician, attributed rabies to overheated bile (24).

Animal rabies was therefore very common in Asia Minor during the early centuries of the Christian era and appears to have subsequently continued to be prevalent among both dogs and wild carnivores. For example, on 7th July 1852, a rabid wolf entered the town of Adalia in Anatolia and in one day and one night bit or wounded 135 people and massacred 85 sheep (3).

**Portugal and Spain**

Rabies was reported by Pliny in Lacetania (Spain) in the 1st Century AD (Chapter 11, C. Abellan Garcia et al.), where he told the story of a Roman praetorian guard who had been saved from rabies after having drunk the juice of a wild rose tree (24). In the 6th Century, Isidore, archbishop of Seville, believed that humans could contract rabies simply through contact with the drool of a rabid dog (22). In the 11th Century, Avenzoar, a physician in Islamic Spain, mentioned cases of rabies in mules (already reported by Avicenna in the previous century). He described the signs observed in a rabid animal thus: ‘Its madness is a sort of frenzy. After this has lasted for some time and has arrived at crisis point, it avoids water and very soon dies. This disease affects all animals, especially wild beasts and dogs: it also sometimes affects horses and mules.’ (22).

In the 15th Century, the Catalan physician, Arnau de Vilanova, believed that a dog could contract rabies by eating infected carcasses (22) and, according to Nocard and Leclainche, the disease was very widespread in Spain around 1500 (15). In Madrid in 1763, 700 dogs were slaughtered as part of a campaign to control rabies (24).

Portugal appears to have been the only European country where the wearing of a muzzle was compulsory from the 18th Century: in 1788 dogs wandering about the town without a collar or muzzle could be slaughtered (22).
Algeria, Morocco, Tunisia

There are few documents about these countries (Chapter 14, H. Matter et al.), although canine rabies was described in the 10th Century by a Tunisian author, Ibn-Al-Jazza (22). In 1776 and 1780, travellers reported that the carcasses of wolves and foxes lay strewn about the roads in the region of Bône and La Calle, in Algeria. Some of the signs described in these animals are reminiscent of rabies: trembling, loss of the instinct of self-preservation, unsteady gait, etc. (11). In 1858, the disease was so extensive in Algeria that the Governor General issued a circular relative to preventive measures (21).

OTHER COUNTRIES

Austria, Germany

No documents attesting to the existence of animal or human rabies in these countries seem to have existed prior to the Middle Ages (Chapter 7, W. Müller et al. and Chapter 15, A. Wandeler). In the 12th Century, Hildegard of Bingen proposed a remedy (plaster of flour) for the bite of a rabid animal (22) and Albert the Great, Bishop of Regensburg, reported cases of rabies in horses (12).

In 1535, an inn-keeper from the Duchy of Wurtemberg offered his customers meat from a pig that had died from rabies: they died from rabies after having bitten each other! (24). In 1578, Fettich reported a large number of cases of vulpine rabies in the same region (24) and Bauhin reported that in 1580, near Frankurt, foxes had unearthed and eaten the carcass of a rabid pig. Bauhin gives interesting details about the epidemic and the means used for controlling it: ‘the (infected) foxes attacked and bit the other foxes to such an extent that a large number of foxes fell to the disease. In the end, the latter bit first the cattle and the mares, and then people who, after they were bitten, succumbed to a sort of hydrophobia... and several of them died wretchedly. As a result, when the magistrate had been told of this misery, he gave everyone permission to go fox-hunting, wiping out the foxes altogether: we have seen nothing of the sort since.’ (22). Outbreaks of canine rabies were reported in Austria in 1556 (21).

In the early 17th Century, Fabian of Hilden asserted that saliva, even when dry, could remain virulent, citing the case of a person who had become infected after having broken off with his teeth the thread that had been used to mend a garment torn by a rabid dog (22). From 1725 to 1726, rabies affected dogs, as well as wolves and other wild animals in Saxony and Silesia. Urban rabies, which was enzootic throughout the 18th Century, was overcome by slaughtering dogs that were rabid or suspected of being so (10).

Théodoridès (22) refers to the controversy that arose concerning an anti-rabies treatment, based on crushed cantharides, recommended by King Frederic II of Prussia in 1777, who suggested to his French friend, D’Alembert, ‘to have it administered to the English Parliament, because it would appear that some rabid dog has bitten it!’ In 1786, Vandesmonde reported the case of a person from Regensburg who had apparently contracted rabies two months after having been bitten by a dog presenting no signs of rabies on the day it bit (24). Zincke, in Jena, succeeded, in 1804, in transmitting rabies to experimental animals: dogs, cats, rabbits and even chickens, by inoculating them with saliva from a rabid dog (27).

Between 1805 and 1807, an epizootic of vulpine rabies raged in Baden-Württemberg (11) and reappeared in 1828, with secondary cases among martens (24). In the same region, several cases of rabies were reported among martens between 1810 and 1813 (24). Between 1804 and 1840, a major epizootic of vulpine rabies held sway in southern Germany and Switzerland (24). From 1838 to 1843, Vienna was invaded by a severe dog epizootic (21). From 1843 to 1844, an unusual outbreak of cattle rabies occurred in the district of Heyden (Rhine-land) and spread among animals with no evidence of dog bite (21). Between 1866 and 1872, a serious rabies epizootic hit foxes in Carinthia, leading to their virtual extinction and the contamination of numerous domestic animals (3).

In Bavaria, the number of cases of canine rabies rose alarmingly between 1871 and 1875, and many people died of rabies: 15 in 1873, 29 in 1874 and 23 in 1875. A law passed on 2 June 1876 then imposed a tax on dogs, making their identification compulsory, and rabies disappeared five years later (3).
France

According to most historians, rabies was rare in France prior to the Middle Ages (Chapter 10, M.F. Aubert et al.). However, numerous cases of the disease were reported in dogs and wild animals: towards the year 900, a rabid bear bit twenty people in Lyon, six of whom died from rabies (21). In 1271, rabies among wolves was reported in Franconia (10). Henri de Ferrières (1379) and Jacques du Fouilloux (1573) both described the various forms of canine rabies (‘desperate, running, dumb, falling, sleeping and lanke’), which were later taken up by English authors, namely Tuberville in 1576 (20). He reported an experimental method of diagnosing canine rabies, which consisted of placing the rump of a cock over the bite-wound: if the dog truly was rabid, the cock would swell up and die (22).

In 1534, Ambroise Paré considered certain clinical signs as pathognomonic of canine rabies: bristling fur, lowered head, red eyes, lolling tongue, lowered ears, anorexia, etc. (24). In 1590, Bauhin reported that rabies in wolves was raging at an enzootic level in the region of Montbéliard (10) and Paumier said it was very frequent in the 16th Century, especially among wolves (24).

In France, as in most other European countries up until the 15th Century, people suffering from rabies were considered to be incurable. The authorities therefore agreed to them being put to death by strangulation, blood-letting or suffocation (9).

There is a great deal of information about the epidemic of canine rabies that raged in France in the 17th Century. The chronicles of King Henry IV cited the case of a rabid man who, on 30 March 1602, ‘rushed at anyone whom he was able to catch in Maubert Square in Paris, and even bit a dog and the tail of a donkey’ (22).

In the 18th Century, rabies in wolves appears to have been enzootic throughout the kingdom of France. In 1739, a rabid wolf bit 70 people (50 of whom died). In 1753, a she-wolf bit 17 people near Dijon, eight of whom died, and in 1764, another wolf bit 40 more people in Auvergne (2, 22). Bonel de la Brageresu reported the result of his treatment (based on mercury) of over 500 infected people in Lozère between 1753 and 1777 (22) and Rosnay said he had treated 2,000 infected people between 1727 and 1767 in the region of Morbihan (Brittany) with a mixture of oyster shell, wild rose root and bone from a rabid dog (16).

In 1760, Andry considered that the main carriers of rabies in France were wolves, foxes, dogs and cats, and cited sheep, equidae, horses, bears, monkeys, stone martens and martens simply as victims (24). In 1768, D’Yauville published a treatise on hunting, in which he specified how to control rabies in a pack of hunting dogs: to slaughter the rabid dog and all those dogs that could have been bitten or attacked by the rabid dog, then to isolate each of the remaining dogs separately until thirteen moons had passed (23). Rey reported that, between 1811 and 1842, the number of dogs suspected of having rabies, which later died of the disease at the Veterinary College of Lyon, totalled 779 (11). An extensive fox outbreak occurred in the Jura Alps in Eastern France, from 1803 to 1835, spreading over to Switzerland and Germany (21).

In 1860, Tardieu presented an interesting statistic to France’s Advisory Committee on Public Health: of the 198 people who had been bitten by rabid animals, only 112 had contracted rabies (22). In 1881, Galtier, a professor at the Veterinary College of Lyon, succeeded in vaccinating sheep prior to exposure, using an intravenous injection of virulent saliva and, in 1885, Pasteur succeeded in protecting humans following exposure.

At the end of the 19th Century, there was an ‘explosion’ of canine rabies in France, as in other European countries: in 1878, 500 cases of canine rabies were recorded in the city of Paris alone and 24 people died. The authorities were roused to action following the death of an important figure and 4,000 dogs were slaughtered in the French capital in the space of two months (2).
Great Britain and Ireland

The first mention of rabies in Great Britain appears to date back to 1026 (Chapter 3, A.R. Fooks et al.). In that year, the *Laws of Wales*, compiled by Howel Dda (Howel the Good, who died in 950) reported that numerous dogs were suffering from ‘madness’ (7). These *Laws* therefore authorised any suspect dog to be killed, provided that clinical signs of rabies had been observed in the animal, i.e. a severely inflamed tongue and a frequent tendency to fight with other dogs or human beings (27).

Canine rabies was described by Bartholomeus Anglicus around the year 1230, and was considered to be transmissible to any other beast that was bitten (22). In 1613, Spackman wrote a complete work on rabies, entitled *A Declaration of such grievous accidents as commonly follow the biting of Mad Dogges together with the cure thereof*. Among the possible causes of canine rabies, he cited unquenchable thirst and feeding on carrion, particularly if the beast ‘has died of any murrain or rot or been struck dead by thunder or sorrow for a lost master’ (3). At the end of the 17th Century, Martin Lister noted that rabies was rather rare in England, where it was transmitted mainly by dogs. He also quite rightly observed that the risk of rabies was higher after being bitten on the face (24).

In 1709, Richard Mead described three cases of human rabies following dog and fox bites and, in 1760, in London, James published *A Treatise of Canine Madness*, in which he included the first recorded description of the characteristic bi-tonal bark of the rabid dog (22). Furthermore, he stated that, in England, the rabies virus had always been successfully destroyed in contaminated kennels by making dogs cohabit with geese! (18). Canine rabies was particularly rampant in the British Isles from 1734 to 1735, from 1759 to 1760 and in 1765 (22). The 1759 epizootic was so significant in London that a very large number of dogs had to be slaughtered, which infuriated the inhabitants so much that an essay was published on the subject, entitled *On the prevailing rage of dog-killing* (21, 22). In 1774, following an outbreak in Eccles, near Manchester, a general meeting of parishioners unanimously agreed to strike off the poor’s rate all paupers who kept dogs, and to pay five shillings for every mad dog killed in the parish (5). In 1778, John Hunter clearly stated that a rabid dog is not hydrophobic: ‘He has no fear of water, for he never avoids it’ (22) and he proposed experimentally inoculating such animals with the saliva of dogs or people suffering from rabies, in order to study the disease and its treatment more effectively (27).

In 1793, Bardsley proposed a plan for eradicating rabies in the British Isles: ‘It consists merely in establishing a universal quarantine for dogs within the Kingdom and a total prohibition of the importation of the animals during the existence of such quarantine’ (27). Forty years later, Youatt took up the same idea and fixed the duration of quarantine at eight months (27). In 1887, the British Government sent a commission to France to report back on Pasteur’s vaccination results. Pasteur himself suggested to Victor Horsley, the secretary of the commission: ‘what you have to do is to establish a brief quarantine covering the incubation period, muzzle all your dogs at the present moment and in a few years you will be free’. This was achieved in 1902 (26).

In 1832, *The Lancet* reported the story of a young man who had died from rabies after having been bitten by a pet fox (2). In 1874, the number of people dying from rabies in Great Britain totalled 74, and 47 more people died in England in 1875 (21). A further wave of rabies hit Great Britain in 1806, and then Ireland in 1807 (15). Another outbreak was reported in Roscommon, Ireland, in 1847 (21). In 1886, Lord Doneraile, who was bitten by a pet fox, refused Pasteur’s treatment and died (5).

From 1868 to 1871 a high number of cases were reported in humans and animals in England (7). A total of 1,112 people were reported to have died from rabies in England during the second half of the 19th Century, according to an official statistic (2). The British Minister for Agriculture was then charged with controlling canine rabies by means of the ‘General Rabies Order’ of 23 March 1897 and a Muzzling Order for the Metropolitan Police District covering an area within a 15 mile radius of Charing Cross. The Board of Agriculture took powers to issue such orders in any district of Great Britain. The first Importation of Dogs Order required imported dogs to be isolated at their owner’s premises for three months; this was later extended to six months and dogs had to be kept on a veterinary surgeon’s premises.
Belarus, Russia and Ukraine

Few documents are available relating to this region prior to the 18th Century, but the epizootiological situation was probably not very different from that of other European countries. In 1787, Samvilovitch proposed a new method of diagnosing canine rabies: to rub one’s gums with the grilled flesh of the biting dog and give it to another dog, which would refuse it if it contained the virus (22). In 1797, Johann Van Hildebrand reported his personal observations about rabid wolves in Russia, Poland and Lithuania. He quite rightly observed that only a rabid wolf will attack humans, usually on the face, which is particularly dangerous because it allows the infectious agent contained in the saliva to act on the nervous system more quickly (22).

Rabies was very common in Ukraine in 1813 (14 persons died from the disease), probably as a result of the disruption caused by the Napoleonic war (21). On 8 November 1855, at between four and seven o’clock in the morning, a she-wolf bit 28 people in Petersburg (on one of the Neva islands), three of whom died before 7 January (24). In St. Petersburg from 1863 to 1874, 47 people died from rabies (21). On 27 February 1886, a wolf ferociously bit 19 people in Smolensk. These people travelled to Paris to receive the anti-rabies treatment recently discovered by Pasteur, but three of them nevertheless died because the treatment had been administered too late (24).

Baltic States

Rabies in wolves was reported in Lithuania in 1797 (see above). In Estonia, human cases of rabies were regularly reported in parish registers from 1759 to 1955, with a peak of 17 cases in 1820 (Chapter 4, B. Westerling et al.).

Scandinavia

In 1815, an epidemic of canine rabies was reported in Copenhagen (11). In 1824, a major epidemic of vulpine rabies raged in Denmark, Norway and Sweden, particularly in Stockholm: other species (dogs, cats, wolves and even reindeer) were infected (11, 21). Cases of the disease in domestic and wild animals were reported in Sweden until 1886 when the last case of the disease in the country was reported (13).

CENTRAL EUROPE

An epizootic of canine rabies was reported in Hungary in 1586 (21) and another in 1722 (7). In 1711, Gensel reported another serious epizootic of rabies ‘among wild beasts’ in this country, which was transmitted to dogs and humans (11). In November 1829, a wolf bit 11 people in Marmaros (Hungary), four of whom died of rabies (24). In 1766, a rabid wolf bit 23 people near Warsaw: all died of rabies (2).

Belgium, Luxembourg and the Netherlands

Outbreaks of rabies were reported in dogs in Flanders in 1586 (21; Chapter 10, M.F. Aubert et al.). In 1660, van Helmont wrote several chapters on human rabies, maintaining that it could be transmitted simply through the odour of the tooth of the biting dog, which impregnated the garment that had been torn by the bite (22). In order to combat urban rabies, which was rampant in Belgium during the 18th Century, dog-owners were obliged to keep their dogs tied up, on pain of a fine (22).

Between the ninth and nineteenth centuries, people who had been bitten by rabid animals would go on a pilgrimage to the Belgian Ardennes, where relics of Saint Hubert were said to have the power to protect against infection. The Sorbonne condemned all these practices as superstitious by a declaration of the 10th of June 1671 (7). In 1868, two human cases were seen in Belgium (21).

In 1709, Boerhaave considered the principal carriers of rabies in the Netherlands to be the wolf and the fox, but he also cited as victims dogs, cats, donkeys, horses, mules, pigs and hens. It was his view that the disease was caused by vermin (22, 24).
Switzerland

At the end of the 18th Century, Haller wanted to make it compulsory for dogs to wear a muzzle and, in order to persuade recalcitrant dog-owners, he offered to show them a person suffering from rabies (24). From 1809 to 1812, a major epidemic of vulpine rabies raged in the Zurich region (11). The disease began in the canton of Vaud in 1804 and lasted until 1840, after having spread to neighbouring regions of southern Germany (24).

CONCLUSION

The history of rabies in Europe and the Mediterranean Basin clearly reminds us of the extent to which this disease posed a threat in these regions in ancient times. In continental Europe, dogs and wolves were initially the greatest rabies threat, and in the 20th Century fox rabies became the most important challenge, before it was eradicated by oral vaccination. In the Mediterranean Basin, dog rabies is still prevalent in many places, and, unfortunately, 120 years after Pasteur developed the rabies vaccine, the number of human deaths in some countries of this region is not very different from ancient times. This is partly because proper post-exposure treatment is not available to all, but mainly due to the fact that there is no effective control of the reservoir of dog rabies virus in these countries.

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References


CHAPTER 3
RABIES IN THE UNITED KINGDOM, IRELAND AND ICELAND

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Summary

Rabies has been reported in the United Kingdom (UK) and Ireland but the disease has never been detected in Iceland. This chapter will describe the measures used to eliminate rabies and the legislation used to ensure the rabies-free state of these island countries is maintained. The UK, Ireland and Iceland are all free from classical rabies, principally due to their island status and the enforcement of strict quarantine laws. In February 2000, changes to the quarantine laws in the UK were introduced with the creation of the Pet Travel Scheme (PETS) as an alternative to quarantine. This scheme allows for the free movement of companion animals (dogs and cats) between rabies-free countries.

Keywords: pet travel scheme, quarantine, rabies, rabies-free

THE UNITED KINGDOM

Introduction

Since 1902, the United Kingdom (UK) has been rabies-free but previously rabies had been present for most of its recorded history. Towards the end of the 18th Century, there was a growing interest in science in London and elsewhere, and Bardsley's observations on rabies and hydrophobia in 1793 were very remarkable for their time (14). Bardsley was emphatic that there was no spontaneous occurrence of either rabies in dogs or hydrophobia in man. He argued for the purely contagious nature of the disease that could be eliminated from the island by establishing a universal quarantine for dogs within the Kingdom, and a total prohibition of the importation of these animals during the existence of such quarantine. The first attempt to deal with rabies on a national basis was made in 1831 when a Bill was drafted to 'prevent the spreading of canine madness'. The Bill did not become law but local authorities were later given the power to require muzzling, to restrict the movement of dogs and to destroy strays. These methods were only partly successful, but when the Board of Agriculture assumed overall responsibility there was a marked decline in the number of rabies cases each year and the disease was eradicated in 1902.

Human rabies

In the 19th Century, canine rabies was a widespread problem and for the 16 years up to 1863 the average annual number of human deaths from hydrophobia was eight. In 1864, 12 people died of rabies in England and 7 in Ireland. In 1866, 36 deaths from the disease, 11 of them in London, were reported by the Registrar General (1). Between 1886 and 1898 over 160 human deaths from rabies were recorded (11). There were no indigenous human cases of rabies in the UK between 1902-2001. However, in November 2002, a bat conservationist died in Scotland from rabies caused by a bat-adapted rabies virus.
strain, European Bat Lyssavirus type-2 (EBLV-2), following exposure to a bat – the most plausible explanation is a bite from a Daubenton’s bat (*Myotis daubentonii*). This human death was the first recorded case of indigenous human rabies for 100 years in Great Britain (5).

Between 1977 and 2002, 11 human rabies cases were reported in Great Britain. All of them were recent immigrants and the disease was contracted abroad. All 11 cases: India (4), Pakistan (2), Nigeria (2), Zambia, Bangladesh and the Philippines gave a history of being bitten by an animal of a species that could transmit rabies (principally dogs). None of these documented cases of human rabies received PET for rabies before the appearance of symptoms. In April 2001, the first case of human rabies that year, imported from the Philippines to the UK, was recorded (12). In May 2001, a second case of human rabies was suspected in a patient who had travelled to the UK from Nigeria (6). Rabies remains widely distributed in almost all of the inhabited islands throughout the Philippine archipelago and is widespread throughout West Africa.

**Animal rabies**

One of the earliest books in the English language covering farriery and veterinary medicine was by Gervase Markham in which, in an appendix headed ‘to cure diseases in dogs’ in the sixteenth edition published in 1703, he states that ‘It is said there is Seven sorts of Madness in Dogs; the *Dumb Madness*, the *Running*, the *Falling*, the *Lank*, or *Lean Madness*, the *Sleeping*, the *Slavering*, and the *Hot Burning Madness*; and in my Opinion the best and only Cure is to knock them on the Heads for it’ (1). Markham recognised that ‘it’s the Venomous Spittle of the mad Dog that infecteth’ and ‘that it will make the Person bitten go Mad’; and that ‘some time it will be about that Day Year’ (1).

During the 18th Century numerous outbreaks of canine madness occurred in England and Scotland and in 1752, following the appearance of several mad dogs in London and other towns in England, orders were given by justices that all such dogs should be shot. In 1759 and 1760, rabies in dogs in London caused widespread alarm. Magistrates immediately issued an order that every person who kept dogs must confine them within doors for a month; beadles and other officers were ordered to destroy dogs found at large, with a reward of two shillings for each dog that was killed (1).

Rabies in dogs became more prevalent in England during the 19th Century and in 1860 Youatt, who believed firmly that rabies was a communicable disease, was one of those who gave evidence before a House of Commons committee which eventually led to the eradication of rabies from the British Isles. Coleman, a contemporary of Youatt, also gave evidence to the committee and suggested that every dog should wear ‘a collar, with the name and residence of the owner (and in the streets a muzzle)’ (1).

Between 1886 and 1903, 3,056 animals are known to have died of rabies in the UK. Rabies never became established in wildlife, although two outbreaks in deer occurred. One was near Barnsley (Yorkshire) in 1856, when 100 animals were involved and another in Richmond Park, London, in 1886 when 257 fallow deer (which were seen to bite each other), died but did not pass on the disease to red deer in the same park (11).

Great Britain appears to have been free of rabies from 1902 until a further outbreak of urban rabies occurred between 1918 and 1922, originating from dogs smuggled into the country by returning First World War servicemen. During this period there were confirmed cases in 312 dogs, eight cattle, two sheep, three swine and three horses. The disease was controlled and eliminated by muzzle and leash restrictions and the destruction of strays.

**Rabies control**

Since 1901, protection from rabies has been based on the quarantine of domestic pets on import into Great Britain. The detailed arrangements for the quarantine of animals have been altered from time to time but the basic principle of requiring six months isolation from any risk of infection has remained unchanged.
Between 1922 and 1969, there were 27 cases of rabies within quarantine: 25 dogs, one cat and one leopard. Two cases of rabies occurred in dogs after their release from quarantine. In July 1969, a collie which had arrived from India in April died of rabies in quarantine kennels. In October 1969, another imported dog died of rabies ten days after its release following six months of quarantine in the same kennels. In November 1969, a third dog showed signs of rabies, which was later confirmed by laboratory examination. Investigators concluded that there was a strong possibility that at least one of the dogs contracted rabies while in quarantine.

In 1970, a second case of rabies in an imported dog after release from quarantine kennels occurred. Signs of illness were noted three months after release from quarantine and death from rabies occurred seven days later. Following these outbreaks, recommendations to prevent cross-infection within kennels were implemented (13). The recommendations included rabies vaccination on arrival at the quarantine premises. In 1966, rabies also occurred in a rhesus monkey which had been imported 53 days earlier and been taken directly to a research establishment. Since 1972, two further cases of rabies in dogs have occurred in quarantine.

The statutory instrument governing the importation of pet and certain other animals into Great Britain is the Rabies (Importation of Dogs, Cats and Other Mammals) Order 1974; Northern Ireland, the Channel Islands and the Isle of Man have similar legislation. The system currently operating in Great Britain is as follows:

1) licencing before importation of any pet animal from anywhere other than Northern Ireland, the Republic of Ireland, the Channel Islands and the Isle of Man. Licences are obtained by sending the appropriate form, duly completed, to one of the Agriculture Departments

2) entry of the animal at designated ports and airports only

3) movement of the animal by an authorised carrier from the place of entry to an authorised quarantine premises

4) six months isolation in authorised quarantine premises. Construction and operation of quarantine premises have to be to approved standards, laid down by the Agriculture Departments to prevent escapes and contact between quarantined and other animals

5) vaccination against rabies of all cats and dogs, but not of animals of other species, on arrival at the quarantine premises.

The Rabies (Importation of Dogs, Cats and Other Mammals) Order 1974 was amended in 1994 to implement European Community law on traded animals. The amendment provided for commercially traded cats and dogs to enter Great Britain from other Member States without quarantine, provided that they:

1) have been born and have remained on a registered holding of origin since birth, with no contact with wild animals susceptible to rabies

2) have been vaccinated against rabies with an inactivated vaccine of at least one international antigenic unit (Office International des Epizooties (OIE) Standard) when at least three months of age and at least six months before export

3) have been blood tested after vaccination to show that this has resulted in an adequate level of protective antibodies against rabies

4) are accompanied by a veterinary health certificate and vaccination record and

5) are individually identified by implanted microchip; and have details of their movements notified to one of the Agriculture Departments at least 24 hours in advance.

**Changes to rabies policy in the United Kingdom**

On 26 March 1999, the UK Government announced sweeping changes to the quarantine laws. It decided to abandon quarantine for dogs and cats entering the UK from rabies-free islands and from certain
European countries, replacing it with a system based on identification, certification, vaccination and blood testing (4). The system allows UK-resident dogs and cats which meet these criteria to travel between Britain and those countries without having to be put into quarantine on their return. Pets from other countries would continue to be subject to quarantine. The government introduced the Pet Travel Scheme (PETS) on 28 February 2000. The changes are broadly in line with those recommended by the expert group chaired by Professor Ian Kennedy (9). Animals resident in a qualifying country and whose owners want them to travel, will need to fulfill the following criteria:

1) be electronically identifiable, by means of an implanted microchip
2) have been vaccinated against rabies using an approved inactivated vaccine
3) have been blood tested at an approved laboratory
4) have been issued with an official health certificate recording details of the animal, its chip, its vaccination and its blood test and
5) have been treated against exotic infections.

In addition to these changes, pet cats and dogs from other countries would still be subject to six months in quarantine and bats would be subject to quarantine for life. Other non-carnivores from qualifying countries would no longer be subject to quarantine, provided that they are accompanied by a health certificate giving assurance that the animal concerned had been resident in one or more qualifying countries for at least six months and had not been resident on a premises that had had a case of rabies within 30 days of the certificate being issued.

Changes to the United Kingdom quarantine law

The Waterhouse Report of 1971 recommended that effective measures to keep rabies out of the UK must be based on quarantine. Quarantine is easy and cheap to enforce and the system is well understood by the public. The experience of the past 75 years indicates clearly that quarantine is an effective control measure and that the UK’s freedom from rabies stems from these protective measures and from one of the Government’s most successful public awareness schemes, the ‘keep rabies out of Britain’ campaign. According to the Kennedy Report of 1998, the weaknesses of quarantine are:

1) it is expensive for animal owners
2) it has disadvantages from the point of view of animal welfare although, in this context, it should be pointed out that the Minister now has the power to make statutory provision in respect of the welfare of animals in quarantine and
3) current quarantine arrangement do not provide 100% protection because the incubation period can on very rare occasions be longer that six months.

The Kennedy Report recommended that British-resident animals returning to Britain from qualifying countries or animals which have been resident in such countries for at least six months, would have to be identified with an approved microchip, certified as having been vaccinated against rabies at or over three months of age using an approved inactivated vaccine and have a blood test in an approved laboratory following vaccination, carried out at least six months before entering or re-entering Great Britain. Where the animal was imported more than 12 months after the vaccination that preceded the blood test, it would subsequently have to be re-vaccinated annually or at intervals in accordance with the conditions of authorisation of the vaccine. In cases where the animal had not been re-vaccinated at the appropriate intervals, it would have to be re-vaccinated and a blood test taken at least six months before entry.

The Kennedy Report also recommended that animals should be checked on entering the UK, and that points of entry should be restricted to a limited number of ports and airports. It recommended that on arrival by vehicle at the port of entry, the animal owner should be required to enter a separate lane so that the animal can be checked. This lane and the associated premises would be manned by personnel, either from or under contract to, the Department of Agriculture. Similar arrangements would be made for passengers on foot at ports, and for those arriving by train or by air. Emergency kennels and catteries
would need to be available at every port of entry where animals with doubtful documentation could be held.

Any changes based on the Kennedy Report must be made with the greatest care and must improve the situation without increasing the risk. The Kennedy Report states that the difference in risk between the new system and the previous system of quarantine could only be eliminated if rabies were to be eradicated from the European Union (EU).

In the EU and the United States of America (USA), only inactivated vaccines that meet stringent safety and efficacy standards can be marketed. In a rabies endemic area it is unclear what proportion, if any, of vaccinated animals in the field situation are actually exposed to rabid animals. Vaccinated animals in urban areas are unlikely to be exposed to rabies. The efficacy of rabies vaccines has been recently assessed and it was demonstrated that all UK-licensed vaccines are fully efficacious with only a small proportion of vaccine failures (4, 10).

In Texas, between 1976 and 1990, 25 laboratory confirmed cases of rabies occurred in previously vaccinated dogs and cats (2). Between 1991 and 1996, seven pre-exposure rabies vaccination failures were recorded. Vaccine failures have been documented in 1% of rabid animals (3). A positive history of vaccination does not preclude the possibility of rabies infection.

Future success of the new system hinges on the quality of the documentation, the validity of the animals’ identities and the thoroughness with which each can be checked, both on entry to the UK and on entry to the EU. The UK Government has stated its determination that there would be no weakening of its defences against rabies; pre-entry checks with 100% coverage are to be carried out by government-approved transport operators whose operations would be audited and inspected. The UK Government believes that the cost of these new arrangements should be met by pet owners, as the cost of quarantine is now.

IRELAND

Although rabies had been recorded in Ireland in the past, no case of rabies has occurred since 1903. Under the Importation of Dogs and Cats Order, 1929-1970, all dogs and cats from places abroad (other than Great Britain, the Channel Islands and the Isle of Man) must undergo a period of at least six months’ detention in approved public quarantine premises on arrival and be subject to one anti-rabies vaccination during quarantine.

A modified form of private quarantine is available in Ireland in certain cases, depending on the country of origin. Provided that the animal has been vaccinated against rabies and has a current rabies vaccination certificate, a minimum of one month’s quarantine in the approved public quarantine premises followed by five months’ quarantine at the owners existing permanent premises (if suitable) would be considered, providing that, on post-import blood testing in the approved public quarantine facility, adequate neutralising antibodies are found to be present. The private quarantine establishment would have to be inspected and approved before use by the Department’s Veterinary Inspectorate. The facility must be escape-proof and constructed so as to prevent access by wildlife and birds. Inspection by a nominated private veterinary surgeon during the period of home quarantine in accordance with the conditions laid down, is also mandatory.

Ireland’s response to changes in rabies policy in the United Kingdom

For many decades, there have been no quarantine restrictions on dogs and cats travelling between the UK and Ireland. However, the UK has dispensed with its requirement for quarantine for dogs and cats entering or re-entering the UK from Member States of the European Union, the European Economic Area or rabies-free islands, in favour of a regime involving microchip identification, vaccination, blood testing and health certification. From the end of February 2000, the UK introduced a pilot of this scheme, the PETS pilot project, using certain approved carriers along a limited number of approved routes from EU Member States and European Fair Trade Association (EFTA) countries to the UK.
However, in order to maintain the common control area operating between Ireland, the UK, the Channel Islands and the Isle of Man, a limited adjustment has been made to Ireland’s rabies legislation. This allows pet dogs and cats entering the UK from qualifying countries to travel on to Ireland without the need for quarantine, provided that they have come along routes approved under the terms of the UK PETS pilot project and have complied with all of the other conditions of that project. Such animals may originally have travelled from Ireland to any of the countries approved under the UK pilot project, or may have originated in one of those countries. Irish travellers intending to avail themselves of the scheme will be required to have their veterinary practitioner microchip, vaccinate, blood test and certify their dogs or cats before their departure, in the manner provided for under the terms of the UK pilot project.

The Irish authorities will maintain close contact with the UK authorities in the UK during the year in relation to the operation of the PETS pilot project and any further adjustment to the Irish quarantine regime will be considered only in the light of the experience of this project and following further essential consultations.

ICELAND

Rabies has never been diagnosed in Iceland. However, the former Physician General – Dr Vilmundur Jónsson, studied all available evidence in annals and letters preserved in the National Archives of Iceland on an epizootic in dogs, foxes, sheep and cattle in eastern Iceland between 1765-1766. He compared the descriptions and signs with other epizootics in the same species in 18th Century Iceland and concluded that the 1765-1766 epizootic was almost certainly rabies while other epizootics had almost certainly not been rabies (7, 8).

The rabies epizootic of 1765-1766 was traced to the arrival of a foreign ship, which some say was English, others that it was Dutch, in the port of Nordfjördur. The disease was first noticed in dogs which attacked each other and cattle that subsequently became sick and aberrant in behaviour. At one farm, a bitch from another farm some 40 km away, entered a stable and attacked a tethered horse. The horse became sick and able to reach only its hooves, bit these to the bone and had to be destroyed. A number of cattle became sick and died after being attacked by dogs. Sheep which were bitten became demented and ran into anything in their path. Finally the epizootic in dogs began to recede, presumably partly due to the fact that in some parishes all dogs had died by this stage. On some farms all cattle had died. At this time the epizootic seemed to have been transferred to cats and arctic foxes. Cats approached people with mouths open and tongues hanging out and were easily killed. Other cats disappeared and were never seen again. One arctic fox entered a farm and was killed there. A few foxes put their heads through farm windows. Farm animals that died from the disease were generally dropped into bogs as nobody dared eat the meat. Only one human died from the disease, a young girl who was nursing a sick puppy which had bitten her.

An interesting feature of the 1765-1766 rabies epizootic was that it was confined to a small part of Iceland, probably because the area was bordered to the west and south by fast-flowing rivers and an ice cap; presumably a hindrance to fox movements for a large part of the year. The time of the first case of rabies is unknown but we can presume that it was during summer, the time of the year when most merchant ships arrived in Iceland. One letter, dated 26 September 1765, states that in Nordfjördur almost all dogs were dead from the disease. In another letter, dated 4 November 1766, it is stated that the epizootic appeared to be declining. Thus the rabies epizootic lasted more than a year, probably close to 18 months.

Clearly there was no systematic attempt to eradicate rabies during the outbreak but, when people realised the seriousness and severity of the disease, they would have taken general measures to protect themselves and their livestock, actions which one can only presume must have limited the availability of susceptible animals. This would in turn have limited the severity of the outbreak and possibly helped to bring it to an end earlier than otherwise might have happened.
Preventive measures

According to Law No. 54/1990, there is a total ban on the importation of all domestic or wild animals, including all genetic material of animal origin. However, the Minister for Agriculture can, with the recommendation of the Chief Veterinary Officer, grant import permits. Animals imported without a licence will be destroyed immediately. All animals imported with a licence are put into quarantine under the supervision of an Official Veterinary Surgeon. Law No. 25/1993, on animal diseases and their prevention provides the powers required to eradicate exotic diseases, should they occur. Law No. 290/1980, on rabies prevention provides a detailed description of the disease and instructions on actions to be taken in the case of a suspected rabid animal.

Dogs and cats

Dogs are found on most farms and in increasing numbers in towns and villages. All dogs in Iceland must be licensed and stray dogs are not a problem. Cats are very common and in recent years feral cats have become a problem in the capital.

Wild carnivores

The arctic fox is native to Iceland and for centuries these animals have been hunted to control their numbers and a bounty paid for each animal killed. The red fox is not found in Iceland. Mink were first imported from Norway in 1931 for fur farming, but they soon escaped and became feral and have now colonised the whole country. Polar bears occasionally come ashore off drift ice from Greenland and Spitsbergen. They are not native to Iceland and, as they cannot survive here, are not protected.

It is well known that the arctic fox often pursues polar bears for long distances on the drift ice, feeding on the remains of the bears’ prey. It is possible that these arctic foxes of foreign origin occasionally come ashore in Iceland and mix with Icelandic arctic foxes. They may come from countries where rabies is endemic, and are of serious concern. Cases of foxes suspected to be of exotic origin have been investigated, but rabies has never been confirmed.

Diagnosis

The techniques used to check for rabies in the past include staining for Negri bodies, infectivity tests on mice and fluorescent antibody tests. In doubtful cases and if rabies was suspected, assistance and advice were sought from Nordic State Veterinary laboratories and other reference laboratories where diagnosis of rabies is routinely made.

CONCLUSIONS

The main requirements for the elimination of rabies will be to extend the vaccination of companion animals which are moved across national boundaries and oral vaccination campaigns in wildlife species to control sylvatic rabies (especially in Eastern Europe). The objective will be to create rabies-free areas throughout Europe and to increase the number of rabies-free countries eligible to participate in a universal pet travel scheme. In Europe, this can only be achieved through the introduction of compulsory parenteral vaccination for domestic animals which are transported between countries. In addition, a widespread legislative system to control trade and restrict animal movement would be an advantage in safeguarding existing rabies-free areas. Clearly, cross-border cooperation between nations will be a necessary step towards undertaking the elimination of rabies.

In addition, the standardisation and extensive availability of uncomplicated diagnostic tools for measuring seroconversion following rabies vaccination in companion animals may assist in influencing other countries to assess their existing quarantine procedures. This would include the use of diagnostic techniques that are quick and easy to perform and include reagents that are easily obtained from manufacturers.
It would still be prudent however, to limit the number of laboratories performing rabies testing for a national pet movement scheme to government-regulated organisations. This would establish an OIE network of specialist rabies laboratories controlled by proficiency schemes and regular quality assurance.

References

**CHAPTER 4**

**RABIES IN THE BALTICS**

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**Summary**

Rabies has never been diagnosed in material originating from mainland Norway nor has there been any case of animal rabies on mainland Norway. This is in contrast to the situation in Sweden, where before the disease was eradicated, cases had occurred all over Sweden, from Jämtland in the north to the Malmöhus province in the far south. Similarly, the first described rabies epizootic in Finland started in the south-eastern part of the country where a dog, obviously incubating rabies, had been brought in from St Petersburg, Russia. Within a year the disease had spread via stray dogs to the western coast. In 1929, vaccination trials on dogs in Finland were started in the south-eastern veterinary districts and the disease was soon eradicated. Norway, Sweden and Finland remain rabies-free. In contrast, rabies is still present throughout Estonia, Latvia and Lithuania. In all three countries, the number of reported cases has continued to increase each year with peaks every three to five years. Rabies in domestic animals is commonly associated with epizootics in wildlife and shows a direct correlation with the size of the raccoon dog and fox populations. Interestingly, the number of cases in wildlife in the infected countries currently outnumbers those reported in domestic animals.

**Keywords:** Baltics, epizootic raccoon-dog, fox, rabies

**NORWAY**

According to the National Veterinary Institute established in 1891, rabies has never been diagnosed in material originating from mainland Norway and to their knowledge there has never been a case of animal rabies in mainland Norway (41, 55). However, in one report concerning the history of dog taxation in Sweden, rabies reached Norway in 1815 (45).

In the Svalbard Islands, some 600 km north of the Norwegian mainland, an outbreak of animal rabies occurred in the spring of 1980 (52), when twelve arctic foxes (*Alopex lagopus*), three reindeer (*Rangifer tarandus*) and one ringed seal (*Phoca hispida*) were diagnosed rabid. This was the first confirmed rabies outbreak in Svalbard. As control measures, all dogs and cats in Svalbard were vaccinated twice against rabies and exposed persons and persons at risk received immunoprophylactic treatment. Restrictions were applied to the transportation of animals and animal products between Svalbard and mainland Norway. The virus isolated was considered an arctic strain, owing to its positive reaction with Mab-N P41 (57). Since that time occasional cases have been recorded in the islands – two arctic foxes in 1981, two arctic foxes and one reindeer in 1987 and one arctic fox in 1990 (53). All dogs in the settlements in Svalbard are routinely vaccinated against rabies. Control of rabies in foxes by bait vaccination is considered to be unrealistic (41).

**SWEDEN**

The disease was present in Sweden as early as the Middle Ages and was prevalent in many parts of the country during the 19th Century, with wolves and dogs being the main vectors (60). A countrywide epizootic took place in 1852-1860, but the disease disappeared due to unknown reasons and the last case occurred in 1886. More detailed information was reported, based on public notifications from the 18th Century (28). In 1749, rabies raged in Medelpad, some 300 km north of Stockholm, where ‘the wild
dogs’ caused great damage to livestock. Ten years later in Halland, a similar distance to the south-west of Stockholm, a rabid cat was reported to have bitten an ox, which contracted the disease and had to be killed. During the last 30 years of that century several official notifications and decrees were passed in Stockholm with stipulations about fines for owners of unattended dogs. In August 1784, several mad dogs were reported to be running along the streets, dogs in houses and on ships were noted to become ill and unleashed dogs were to be killed, whether or not they were wearing collars.

The impact of rabies is a central issue in another report (45), concerning political conflict during the 19th Century over the introduction of a dog tax in Sweden. An outbreak of rabies had occurred in Stockholm in 1824, but officially published documentation was only available from 1852 onwards. At the end of 1851 a new epizootic occurred in Stockholm and before the end of the year 109 dogs had either died or been euthanased at the Veterinary Institute. In 1857, the disease was more or less common in nine provinces. Mentioning all incidents and places where rabies occurred is beyond the scope of this chapter, but before the disease disappeared, cases had occurred almost all over Sweden, from Jämtland in the north to the Malmöhus province in the far south. Even if the above essays concentrate on animal rabies, it becomes evident that many human lives were lost in Sweden because of rabies during the eighteenth and nineteenth centuries.

FINLAND

There is little published historical information on rabies in Finland because the country was a Grand Duchy of Russia from 1809 to 1917 and before that had belonged for centuries to Sweden. Some sources of documentation are, however, to be found in the bibliographies by Hjelt (34) and Kauppi (39) as well as in the History of the Medical Society of Finland (40).

Human rabies

It seems that the disease was not as common as has been described for Sweden in the eighteenth and nineteenth centuries. An outbreak of rabies occurred in the municipality of Virolahti, close to the present south-eastern border, in the years 1827-1828 (27). The author merely comments on an earlier dissertation, which concerned the effects of tobacco and sweating on the course of clinical rabies (46). The suffering of people who succumbed to rabies had been witnessed during the above mentioned outbreak, which motivated him to produce his dissertation. Information on the effect of the ‘beneficial’ remedies was obviously gathered by hearsay from local people. The rabid animals mentioned were wolves.

Despite this, awareness of the disease among doctors does not seem to have been substantial, (40). The Proceedings of the Medical Society of Finland include a presentation from 1852 with the title ‘To our country new epidemic disease, Rabies canina’ referring to an incidence where two people had been bitten by rabid dogs in Helsinki the same year. One Society member expressed his doubts about the existence of such a (contagious) disease, characterising it as ‘Trismus’, a condition which does not have to be explained by any specific pathogen. The history of the Society further mentions one case in 1864 in Wyborg in Carelia and one case of ‘lyssa’ in Kuopio, some 300 km further north in 1876.

The first patients from Finland arrived in Paris for Pasteur treatment in 1886 (24). They were three female servants and three children who had been bitten by a rabid dog. In Paris they were cared for, amongst others, by the Finnish painter Albert Edelfelt, who one year earlier had completed his portrait of Louis Pasteur now hanging in the Musée d’Orsay. Later, when a Pasteur Institute had been founded in St Petersburg, Finnish patients were treated there, until such an Institute was founded in Helsinki in 1916. In a paper on the prophylaxis of rabies, Murto (49) mentions an unusually high incidence of rabies that year. The need for a local Pasteur Institute seemed obvious, because as many as 1846 people were admitted to the Institute during the years 1916-1929, figures which can be compiled from the annual reports of the Collegium Medicum and its successive Institutions. Four of these patients, all of whom had been bitten by dogs, died of rabies despite treatment. According to the reports, 1,436 animals were diagnosed rabid during the corresponding period. The last case of dog-mediated rabies in a human in Finland occurred in 1934, but in 1985 a biologist who had been working with bats in several countries died of bat rabies (47; Chapter 17, A.A. King et al.). Virological screening for the virus in Finnish bats gave negative results (38).
Historical Perspective of Rabies in Europe and the Mediterranean Basin

Chapter 4

Animal rabies

The first description of a rabies epizootic in Finland was by Bärlund (25). The epizootic started in a garrison in the south-eastern part of the country where a dog, obviously incubating rabies, had been brought in from St Petersburg. Within a year the disease spread via stray dogs all the way over to the western coast. From 1897 until 1935 cases of animal rabies were recorded every year, especially in the south-eastern border areas. New infections were continuously brought in by stray dogs from Russia and later the United Soviet Socialist Republics (USSR). A total of 2,237 animals was diagnosed rabid during the years 1910 to 1935 (35). All victims were domestic animals except for one wolf and one red fox.

In 1929, vaccination trials on dogs were started in the south-eastern veterinary districts. The vaccine was produced in calves with a virus strain imported from Austria (33). Due to vaccinations and intensified dog control the disease was eradicated. In 1940-1942, during the Second World War, rabies was recorded in five dogs and three cattle, in 1952-1954 in 40 dogs, two cats and one red fox and in 1956-1959 in 12 dogs (35, 36). All these cases occurred in municipalities near the south-eastern border. As can be read in letters accompanying the specimens sent to the National Veterinary Institute by local veterinarians, some of the rabid dogs were actually seen crossing the border from the USSR. The disease was eradicated by the same means as in the 1930s and remained absent for 29 years.

Because of anecdotal evidence relating to the occurrence of sylvatic rabies in the Leningrad area and on the Carelian Isthmus, the Finnish veterinary authorities in 1981 made rabies vaccination of hunting dogs compulsory in certain municipalities along the south-eastern border. In March 1988, these authorities were alerted by a notification in the Leningradskaja Pravda concerning ‘a change for the worse in the rabies situation in wild animals’. Intensified screening for rabies was started in the south-east. On 8 April, one dog and one red fox from the area were diagnosed rabid. Without doubt the infection again entered from the south-east, but whether it was brought by wolves migrating along the coastal ice or, for example, by some animal hidden in an empty train wagon, remains unresolved. That it did not come directly over some land border was shown through screening. At an early stage it became obvious that the country faced sylvatic rabies for the first time, with the raccoon dog (Nyctereutes procyonoides) as the primary vector and victim.

In order to prevent a rapid spread of the disease the local dog population was vaccinated against rabies. The course of the epidemic was described by Nyberg et al. (51). Altogether, 48 raccoon-dogs, 12 red foxes, two badgers, two cats, one dog and one young bull were diagnosed rabid by direct immunofluorescence on brain tissue. The last case was recorded on 16 February 1989. The infected area was estimated to be 1700 km² and the isolated virus strain was typed as an arctic strain (43); that is, giving a positive reaction with Mab-N P-41 with no detectable species variation. Later, arctic rabies was reported from Estonia and the Leningrad area (59). The fact that sylvatic rabies did not occur in Finland despite epidemics in the dog population may be explained by a rather low red fox density of less than 0.5 km⁻². Deliberate introduction of the raccoon dog in adjacent areas of the USSR, leading to the establishment of a dense population in Finland by immigration from the east (29, 30), has resulted in a population of small predators dense enough to be a reservoir of sylvatic rabies.

In September 1988, a field trial of oral immunisation of raccoon dogs and foxes against rabies according to the Bavarian model (56, 58) was started. Invaluable planning and organisation of the project was provided by the late Professor Lothar Schneider and his staff in Tübingen. That autumn, 40,600 Tübingen SAD B19 vaccine-baits were distributed, mainly by local hunters, over an area of 2,600 km². In April 1989, a second campaign was carried out. This time 119,000 baits were distributed over an 8,000 km² area, including the primary field trial area and a large buffer zone (61, 62). In the autumn of 1989, the estimated infected area was baited with 30,000 baits and in June 1990, that part of it not baited in 1988, with 9,500 baits (62); on these occasions entirely by air. In March 1991, Finland was declared rabies-free. In an attempt to prevent the re-introduction of sylvatic rabies, 80,000 vaccine baits have been distributed by air every autumn since 1991 over a 20-30 km deep and 250 km long zone along the south-eastern border with Russia. For the time being, rabies vaccination of dogs used for hunting and showing is compulsory.
ESTONIA

Human rabies

Estonia has twice become independent of Russia, (from 1918 to 1940 and since 1991), although some of its early rabies history may be found elsewhere (Chapter 5, A. Botvinkin et al.). We shall document events since the Second World War only in this chapter. During the years 1947-1986, 27 cases of rabies in humans were recorded (50). Later, one case from 1989 was reported to the World Health Organization (WHO) Collaborating Centre for Rabies Surveillance and Research at Tübingen, Germany (48). The highest number of human cases (eight) occurred in 1950.

Animal rabies

The epidemiological development of animal rabies can be followed from the annual reports of the National Veterinary Laboratory in Tallinn, submitted to the corresponding laboratory in Helsinki. After the Second World War, some 300-500 cases of animal rabies were recorded annually – all in domestic animals. Mostly dogs and cats were affected, but also various other species. In 1951, vaccination of dogs against rabies became compulsory and thereafter a steep decline in the incidence of rabies occurred – in 1955 seven cases were diagnosed; in 1961, one case only. During the years 1962-1967 no cases were recorded.

In 1968, a red fox from south-western Estonia was diagnosed rabid and, in 1970, rabies was reported in 110 red foxes, 24 raccoon dogs, 10 other wild and some domestic animals. Since then the annual number of cases has varied, with peaks every three to five years, possibly consequent to fluctuations in the small rodent populations. When tested with a Mab-N panel, virus isolates from Estonia were shown to be of the arctic strain (59) and isolates from the mainland were identical with those isolated in Finland during 1988-1989. All isolates tested from the western islands, Saaremaa and Hiiumaa, however, differed from those of the Estonian mainland by their negative reaction with Mab-N W 187.5 (42, 44). Details of rabies cases in Estonia since 1992 are summarised in Table 4.1. For the time being there are no plans for the eradication of sylvatic rabies in Estonia.

Table 4.1 – Animal rabies in Estonia 1992-2001

<table>
<thead>
<tr>
<th>Year</th>
<th>Dog</th>
<th>Cat</th>
<th>Cattle</th>
<th>Others</th>
<th>Total</th>
<th>Fox</th>
<th>Raccoon</th>
<th>Dog</th>
<th>Others</th>
<th>Total</th>
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<tr>
<td>1992</td>
<td>16</td>
<td>10</td>
<td>7</td>
<td>0</td>
<td>33</td>
<td>34</td>
<td>38</td>
<td>5</td>
<td>77</td>
<td>110</td>
</tr>
<tr>
<td>1993</td>
<td>19</td>
<td>19</td>
<td>8</td>
<td>3</td>
<td>49</td>
<td>64</td>
<td>41</td>
<td>6</td>
<td>111</td>
<td>160</td>
</tr>
<tr>
<td>1994</td>
<td>15</td>
<td>16</td>
<td>4</td>
<td>1</td>
<td>36</td>
<td>52</td>
<td>14</td>
<td>6</td>
<td>72</td>
<td>108</td>
</tr>
<tr>
<td>1995</td>
<td>12</td>
<td>7</td>
<td>6</td>
<td>0</td>
<td>25</td>
<td>30</td>
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<td>1</td>
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<td>73</td>
<td>36</td>
<td>10</td>
<td>119</td>
<td>150</td>
</tr>
<tr>
<td>1998</td>
<td>17</td>
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<td>3</td>
<td>1</td>
<td>47</td>
<td>78</td>
<td>32</td>
<td>13</td>
<td>123</td>
<td>170</td>
</tr>
<tr>
<td>1999</td>
<td>11</td>
<td>15</td>
<td>5</td>
<td>0</td>
<td>31</td>
<td>52</td>
<td>29</td>
<td>8</td>
<td>89</td>
<td>120</td>
</tr>
<tr>
<td>2000</td>
<td>11</td>
<td>4</td>
<td>19</td>
<td>2</td>
<td>36</td>
<td>64</td>
<td>26</td>
<td>3</td>
<td>93</td>
<td>129</td>
</tr>
<tr>
<td>2001</td>
<td>6</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>30</td>
<td>74</td>
<td>63</td>
<td>13</td>
<td>137</td>
<td>167</td>
</tr>
<tr>
<td>Total</td>
<td>131</td>
<td>130</td>
<td>81</td>
<td>11</td>
<td>353</td>
<td>566</td>
<td>244</td>
<td>124</td>
<td>934</td>
<td>1,287</td>
</tr>
</tbody>
</table>
LATVIA

Introduction

From 1822 onwards, newspapers, magazines and calendars published in Latvian occasionally had reports and articles on rabies cases (1, 2, 3, 5, 6). They reported that domestic animals and humans, bitten by wolves, dogs and foxes, had died. In 1825, in Vidzeme (Livland) district (one of the three administrative units of Latvia included in Russia), it was reported that wolves killed 29,265 domestic animals, of which 3,084 were horses and 703 were dogs (4).

Human rabies

During the first half of the 19th Century, wildlife rabies was the epizootiological form of the disease, (there are reports that wolves were shot in Vidzeme), but during the second half of the century dog-mediated rabies became the most frequently observed. Various reports suggested that after a bite from a rabid wolf or dog, one could get a dangerous disease leading to death and that the greatest danger was in the saliva of the sick animals (7). The recommendation was to wash the wound with soap immediately, then treat it with sulphuric acid or other powerful acids, burn it with a heated iron, strew gun powder on it and set fire to it, and to take a heat sauna to cause perspiration. The articles mention many times and point out the importance of, a heat sauna to help the bitten (contaminated) to avoid getting sick (8, 9).

There are descriptions of the clinical signs of the disease, and the duration of the disease in humans was said to be five days. It is mentioned that one can get contaminated even before the clinical signs are observed. There are also reports of the clinical signs of the disease in dogs and other domestic animals (10). At that time one could get advice and help from priests and doctors. In 1864, in Vidzeme district there was one doctor per 6,724 inhabitants, one chemist per 21,923 inhabitants and a total of 13 veterinarians (11). In 1886, instructions on how to protect against rabies were published: a recommendation was to eradicate stray dogs (12). In 1892, the government published regulations on dog ownership and the eradication of stray dogs. There were mentions in the press in 1884 of the Copenhagen report by Louis Pasteur on the possibilities of post-exposure treatment, on the investigations of K. Helmanis and on the cooperation between Pasteur and Helmanis (13, 14).

A most important turning point in the history of rabies investigation was the scientific discoveries of the eminent French scientist Louis Pasteur and his collaborators. One such collaborator was the Latvian microbiologist Kristaps Helmanis (1848-1892), a graduate of the Institute of Veterinary Medicine in Tartu. He was a veterinarian specialising in microbiology who developed his investigations in St Petersburg. At the beginning of his studies in November 1885, Helmanis passaged a local dog strain in rabbits and in the summer of 1886 Pasteur sent Helmanis a passage of his ‘virus fixé’ in two rabbits for further investigation.

In 1886, Helmanis visited Pasteur at his laboratory in Paris. This was the start of a collaboration as well as correspondence between these two scientists (23, 26). They exchanged information on the results of their studies. Helmanis investigated the rate of distribution of the infectious agent in the body and sent his results to Paris (31, 32). Between 1900 and 1902, 248 persons from Vidzeme and Kurzeme (Livland and Kurland) districts were vaccinated at the St Petersburg Pasteur Station, as were 466 others bitten by sick animals during 1910-1911 (15). A notice was issued that humans bitten by rabies-contaminated dogs must go for treatment to the Institute of Experimental Medicine in St. Petersburg. Those who could not afford to pay could receive postexposure treatment without charge in St Petersburg from the local authorities with the agreement of the local governor.

In 1914, the Riga Pasteur Station was established and people bitten by rabid animals had to receive treatment there. In 1926, the Institute began to produce vaccine according to the modified ‘Hogyes’ and ‘Japanese’ methods. The vaccine was used for the post-exposure treatment of bitten animals as well as for healthy animals. The original Pasteur ‘virus fixé’ sent to Helmanis in St Petersburg was brought to Riga. Laboratory examination for Negri bodies was performed in the Latvian Institute of Bacteriology at the Latvian University.
In the interval between the two World Wars there were 10 cases of human rabies, of which seven were between 1922 and 1927 (18, 19). The most frequent source of the disease was dogs. Between 1914 and 1934, 6,920 humans received postexposure treatment, 73.77% at the Riga station and 26.23% at local medical establishments in the countryside. Local centres were supplied by the Riga Pasteur Station (37). After the Second World War the number of cases increased from 55 in 1946 to 149 in 1950, falling to 18 cases in 1959. The decrease was attributed to the compulsory vaccination of dogs against rabies. The number of persons who received post-exposure treatment (exposure caused by a confirmed rabid animal) varied between 885 (1991) and 407 (1992). From 1953 to 1996 there were 13 fatal human cases after exposure to foxes, raccoon dogs and a cat (20, 21, 22, 54).

Animal rabies

The results of the scientific investigations of rabies made it possible to draw up regulations for rabies eradication and control based on scientific data. In 1898, 'Compulsory regulations for protection from rabid dogs in Vidzeme district outside the city borders were published. On 15 November 1912, the governor of Kurland confirmed the 'Compulsory regulations for veterinary police to protect animals from lethal and contagious diseases and to eradicate these in Kurland' (16). Dog owners had to pay a special tax. The regulations stated that dogs out of doors had to wear muzzles or had to be kept on short leads, and stray dogs, rabid dogs and dogs bitten by rabid dogs had to be caught and killed. It was compulsory to report rabies cases to local authorities, police and a veterinarian. If a person had been bitten by a dog, the dog was confined or isolated and had to be observed for 10 days. If a dog was suspected to have been bitten by a rabid dog it had to be confined and observed for three months. The regulations stated that animal owners could be reimbursed for losses.

Local authorities were obliged to report on the rabies situation every year. In accordance with these reports, between 1905-1913, 1,738 cases of animal rabies were diagnosed in Vidzeme district. During the period between 1909 and 1913 species data of the cases show that of 788 cases, 678 (84%) were dogs, 76 (9.6%) were cows and 34 (6.4%) were other domestic animals.

Approximately one-third of these cases was diagnosed in Riga city (the district centre). Analysis of the rabies cases shows that, in comparison with 1905 when there were 51 animal cases, the annual number of cases increased to 325 in 1906, 326 in 1907 and 248 in 1908. The author of the report (chief veterinarian of the district) blamed the increase in cases on the negative consequences of the economic situation arising from the 1905 revolution. In the following years when these diminished there was also a decrease in rabies cases. In Kurzeme district in 1912, of 95 cases of animal rabies, 76 were dogs and 19 were domestic animals. Between 1921 and 1939 the intensity of rabies increased from 96 cases in 1921 to 403 cases in 1927, but then decreased to 68 cases in 1939. In this period the most frequently observed form was dog-mediated rabies, with 62.8% of cases in dogs and the remainder in other domestic animals (17).

When the independent state of Latvia was established, new national legislation for rabies was introduced. In 1919, instructions were published and in 1923 regulations for eradication and control were agreed. According to these it was compulsory to report all rabies cases, and to keep dogs leashed and muzzled.

After the Second World War, in 1951, the first cases of rabies in wildlife (foxes and wolves) were observed in three districts of eastern Latvia. From 1955 onwards, wildlife rabies was reported annually and the first case of rabies in a raccoon dog was observed in 1958. This species had been introduced into Latvia from Russia in 1948, the aim being to enrich fauna for hunting purposes. These soon became established and numbers increased rapidly. Over 40% of the territory of Latvia is covered by forests and the density of fox and raccoon dog populations increased to approximately twice that calculated to be optimal. By 1963 the disease had become mainly sylvatic (Table 4.2).

Between 1960 and 1970 there were 807 rabies cases and this number increased to 1,054 between 1971 and 1980. Of these, 64.9% were in wild animals: 47.2% foxes, 12.6% raccoon dogs, 5.1% others. Of the 35.1% cases in domestic animals, 15.5% were dogs, 12.6% cats and 7% others. Virus circulated between these animals and wolves, lynx, badgers, martens and domestic animals such as dogs and cats (21).
### Table 4.2 – Rabies in Latvia 1960-1980

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th>Wild animals</th>
<th>Overall total (annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dog</td>
<td>Cat</td>
<td>Others</td>
</tr>
<tr>
<td>1960</td>
<td>24</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
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<td>1964</td>
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<td>18</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>1979</td>
<td>17</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>343</strong></td>
<td><strong>213</strong></td>
<td><strong>192</strong></td>
</tr>
</tbody>
</table>

### Table 4.3 – Rabies in Latvia 1981-2001

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th>Wild animals</th>
<th>Overall total (annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dog</td>
<td>Cat</td>
<td>Others</td>
</tr>
<tr>
<td>1981</td>
<td>8</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>1982</td>
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</tr>
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<tr>
<td>1988</td>
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</tr>
<tr>
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</tr>
<tr>
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<tr>
<td>2000</td>
<td>49</td>
<td>41</td>
<td>28</td>
</tr>
<tr>
<td>2001</td>
<td>33</td>
<td>37</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>566</strong></td>
<td><strong>516</strong></td>
<td><strong>391</strong></td>
</tr>
</tbody>
</table>
Between 1981 and mid-1999, 4,135 rabies cases in animals were reported (Table 4.3). The annual number of cases peaked in 1990 at 306 cases; 39% of all cases were foxes, 26.8% raccoon dogs and 5.2% other wild animals, compared with 11.4% in dogs, 10.8% in cats and 6.8% in other domestic animals. Rabies in domestic animals is now always associated with the epizootic in wildlife and shows a direct correlation with the size of the raccoon dog and fox populations. The disease is present throughout the country.

Control policies

In 1977, ‘the regulations for domestic animal ownership’ were confirmed. They obliged owners of dogs, cats or other animals to report suspicious or fatal cases of rabies in animals, as well as wild animals that had bitten domestic animals etc. It was made compulsory to register dogs, which had to wear special metal badges; identification numbers had to be fastened to leads and it was compulsory to vaccinate dogs against rabies. In 1977, special instructions on catching and eradicating stray dogs and cats were also published, together with special agreements for bounties to hunters for the eradication of wolves, foxes and raccoon dogs. In 1983, the regulations were strengthened by government decisions regarding the ownership of domestic animals, on their transportation outside the territory of Latvia, on rabies eradication and control and also on detailed five-year plans and instructions published by certain authorities (21).

After the independence of Latvia was regained in 1991, the national legislation on rabies eradication and control was reformed. In 1994, ‘The instruction on rabies eradication and protection against it’ laid down the regulations for reporting, diagnostic requirements and for optimal populations of wild animals such as foxes, raccoon dogs and wolves. In addition, there were also regulations for the compulsory immunisation of dogs and cats, the compulsory registration of dogs and the eradication of stray dogs and cats. There were also instructions for the actions to be taken in cases of suspicious animals and the declaration of infected areas.

The surveillance and control of rabies was also regulated by the government’s rules confirmed on 5 October 1995 – ‘the regulations on keeping dogs and cats’. The owners’ obligations and responsibilities for the compulsory registration of dogs and cats and the wearing of identification badges for dogs and the compulsory immunisation of dogs and cats are clearly defined, as is the requirement for the eradication of stray dogs and cats. Today, 130,000 dogs and 12,000 cats are vaccinated annually.

Although each year an estimated 30%-35% of the fox, wolf and raccoon populations were reduced by hunting, it did not result in a significant decrease in rabies in wildlife species. Therefore, in 1991 the first oral vaccination campaign based on the experiences of other countries was conducted. It was continued in 1992, 1995 and 1997. Baits were prepared by veterinarians and distributed by specially instructed foresters and hunters twice a year, in spring and autumn. According to the national programme for 1998, oral vaccination of foxes was achieved in 14 districts in the territory of Latvia. The ‘Lysvulpen’ and Rabifox Desseau’ vaccines were used. Work on rabies eradication and control in Latvia remains a major goal.

LITHUANIA

Introduction

Rabies in Lithuania was known in ancient times but was reported inconsistently. However in 1897, a Pasteur's Station was established in Vilnius by Dr Vaclovas Orlovskis. In 1913, at the Exhibition of Hygiene the Vilnius Pasteur's station was awarded a silver medal. Today, it is one of the ten oldest Pasteur's stations in existence. Control of rabies is under the supervision of the State Veterinary Service. There are 44 administrative districts in Lithuania, each with a branch office of the State Veterinary Service. Disease occurrence is reported monthly to the Animal Health Department of the Service in Vilnius. Licensed veterinarians diagnose rabies clinically. Brain samples from suspected cases are sent to the County State Veterinary Service Laboratory or to the National Veterinary Laboratory for confirmation of the diagnosis by the immunofluorescence antibody test.
Human rabies

The last case, of fox origin, was reported in 1997 (Table 4.4). Rabies immunoprophylaxis is coordinated throughout Lithuania by the Centre of Infectious Diseases in Vilnius. The Centre has three epidemiologists. There is a Public Health Centre in every district where vaccinations against rabies are given.

As in previous years, in 1999 dogs were the major source of human exposures. Of all potential human cases, 7,579 (77.3%) were due to dog bites or dog scratches.

Of these, 2,094 persons were injured by stray dogs. Cats scratched 691 persons, more than in 1998. The increase may be explained by the increased incidence of rabies among cats, since insignificant numbers were vaccinated.

Cattle and their offspring are relatively non-aggressive, therefore people handling animals often do not suspect rabies and usually do not take appropriate safety measures in treating the animals. In 1999, 253 people, mostly in rural areas, were injured by cattle. Of these, 109 were injured by mad ‘rabid’ animals.

In 1998, 8,754 persons had some contact and/or were attacked by wild and domestic animals and sought medical assistance for rabies prevention. In 1999, the figure rose to 9,794 persons. Of that number, 5,310 (54.2%) were vaccinated against rabies. Dogs remained the major cause of human treatments, accounting for 7,579 (77.3%). Cats scratched 691 (7.0%), cattle harmed 109 (1.9%) and wild animals, mostly foxes, raccoon dogs and pine martens injured 363 (3.7%). Data shows that the threat of rabies among wildlife remains current, because the average fox density is 0.3 100 ha⁻¹ or higher, in the districts of Vilnius, Tauragė, Joniskis, Siauliai, Silalë, Silutë, Jurbarkas.

Animal rabies

Although no rabies was diagnosed in Lithuania between 1919 and 1921, it is almost certain that the disease was present, since there were 222 animal cases in 1922. In 1923, the highest numbers of animals infected with rabies were diagnosed in Kėdainiai, Raseiniai, Kaunas and Panevėžys counties, followed by 261 in 1924-1927 and 288 in 1928-1931.

During the 1940s, dogs and cats were the most frequently infected animals. For example, in 1947, 302 rabies cases were in dogs, 15 in cattle, six in horses and four in sheep. Cattle bitten by foxes seldom became infected and at that time there were no raccoon dogs in Lithuania. During the Second World War cattle were very seldom infected because they were well looked after, but dogs and cats were infected through contact with infected foxes.

It is not possible to detail the extent of rabies during the 1950s because written information is not available. However, in the 1960s there were 1,094 rabies cases of which 68% were in domestic animals and 32% in wildlife species. This was followed by 1,333 rabies cases in the 1970s, and 1,251 cases in the 1980s, with little change in the domestic/wildlife percentages.

Over the last 14 years (1986-1999), 2032 cases of rabies were registered among wild and domestic animals, from nearly all districts of Lithuania. Domestic animals accounted for 1206 of 2032 (59.3%) of all rabies cases, with cattle accounting for 736 (36.2%), dogs 217 (10.7%) and cats 221 (10.9%) of domestic animal
cases. Wild animals accounted for 826 (40.7%) of all rabies cases, with red foxes accounting for 437 (21.5%), raccoon dogs 290 (14.3%) and martens 61 (3.0%) of cases.

During the 1990s, the ratio of domestic to wildlife rabies cases began to change and overall, of the 1,433 cases, 53% were in domestic animals and 47% in wildlife species. However, the figures for 1999 show a continuation of the trend, with 25% of the 364 cases being in domestic animals and 75% in wildlife species. During the last four years the rabies situation continued to change, and there was a dramatic increase in the number of cases (Table 4.5), with cases in wildlife far outnumbering those in domestic animals. There are undoubtedly more wildlife cases than are reported, since all cases of rabies in domestic animals are registered, but most cadavers of foxes, raccoon dogs and other wild animals remain in forest caves and fields, so that exact numbers are unknown.

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th>Overall total (annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dogs</td>
<td>Cats</td>
</tr>
<tr>
<td>1992</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>1993</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>1994</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>1995</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>1996</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>1997</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>1998</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>1999</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>2000</td>
<td>43</td>
<td>58</td>
</tr>
<tr>
<td>2001</td>
<td>34</td>
<td>57</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>253</td>
</tr>
</tbody>
</table>

Another change is in the species involved. In former years rabies was common among such domestic animals as cattle, dogs and cats but now it is also diagnosed in pigs, horses, goats and sheep. Earlier, among wildlife species, rabies was more frequent in foxes and raccoon dogs but currently it is also found in martens, lynx, hares, squirrels, badgers and polecats. This may be an indication of an increase in rabies reservoir species of natural origin, although spill-over from the major hosts cannot yet be ruled out. Infection in the fox population appears to be cyclical, with peaks every three to four years; in the raccoon dog the disease peaks every four years.

Dog rabies has been relatively stable over the past 20 years. The most prominent increase in incidence was registered in 1976 (30 cases). The average annual incidence in dogs was 13.6 cases, rising to about 18.6 cases around 1987, but since 1994 it has fallen to 9-11 cases each year (Table 4.5).

The dynamics of rabies in Lithuania is related to that of other Central and East European countries. Long-term observations have shown that the occurrence of rabies cases varies in different months and seasons. Most occur in August-November or in the third and fourth quarters of the year, when 54%-70% of all rabies cases are recorded. Most rabies cases (18%-20%) occur in October. Only about 4%-5% is recorded in each of the first four months of the year.

Analysis of incidence by season is even more controversial: in summer comprises 8%-12% of the total, in spring 15% and in winter 40%. Autumn accounts for more than half of annual all-species cases. Since foxes, raccoon dogs and cattle comprise almost 75% of all registered rabies cases, they determine a seasonal epizootic situation. About 40% of all fox rabies cases occurs in September-November, 18% in March and April, with the lowest occurrence in summer. The situation in raccoon dog rabies is similar.
In dividing the territory of Lithuania according to the epizootic situation, we see that the northern districts of the country dominate. This territory is densely covered with forests and rich biotypes favourable for natural wildlife vectors abound.

**Control policy**

The Lithuanian Veterinary Services use the following scheme as guidance for rabies control: the annual vaccination of dogs and cats against rabies (starting from the third month of life); the reduction of stray dogs and cats and predators (fox, raccoon dog, wolf); the reduction of unvaccinated dogs; improved laboratory facilities and diagnostic methods (currently immunofluorescence is used in 10 laboratories in the country); the public promotion of guidelines for keeping non-productive animals (dogs, cats) and the application of oral vaccination in districts of high rabies occurrence.

Pathological materials for investigations are accepted by private (80%) or state (20%) veterinarians. The samples are sent to a district or state veterinary service and recently to a regional veterinary laboratory. There are ten county veterinary laboratories in Lithuania at which fluorescence equipment for rabies determination is available and every laboratory has an official veterinarian for the diagnosis of rabies.

The Rabies Department of the National Veterinary Laboratory, where three official veterinarians and two laboratory assistants work, coordinates rabies diagnosis. The equipment is very modern and if regions have problems with diagnosis confirmation, the samples are sent here for checking. Veterinary and medical services are notified within 24 hours following the identification of a focus of rabies. All animals in the focus are put under surveillance and vaccinated against rabies. Efforts are made to detect all unvaccinated dogs within a radius of 10 km. In the focus, predators (foxes, raccoon dogs) and stray dogs are shot by hunters to reduce their numbers. Every control and prevention measure is under the control of the State Veterinary Service.

Since 1995, the number of rabies cases in wild animals has increased. For instance, in 1995 of 80 reported cases, 41.2% were reported in wildlife and, of those cases, foxes were responsible for 66.7%. In 1999, 75% of all rabies cases were reported in wild animals and, of those cases, foxes accounted for 47.1% and raccoon dogs for 45.4%. The peak of rabies cases in domestic and wild animals occurred in August to November. The greatest number of reported cases and the highest incidence were observed in northern, north-eastern and south-eastern parts of the country.

Oral vaccination of foxes was started in 1983 with vaccine produced from the live virus strain Byelarus EVMTI-VVMKI-71 in cell cultures. Wildlife were vaccinated in spring and autumn campaigns. During this time oral vaccine was used in 13 districts in which the incidence of rabies was high. With these measures the number of cases fell by 25%-50%. In 1995, the first oral vaccination of wildlife was conducted in an area of 430 km² in Panevėžys, Pakruojis and Joniskis districts. The vaccine SAG-1 (Virbac) with a tetracycline marker in the bait was used. In 1996, the spring vaccination campaign was arranged over an area of 4000 km² in 13 northern districts, using 100,000 doses (approximately 25 baits km⁻²). The baits were delivered by hand, in forests, beneath bushes and by dens. In one district (Bir’ai) a plane was used for the purpose. In 1997, there were two vaccination campaigns, in spring (May) and in autumn (October-November) over an area of 5,349 km², and in 22 districts 250,000 baits were distributed.

In 1998, a vaccination campaign was organised over an area of 6,375-7,000 km² in 26 districts of northern and western parts of Lithuania and during this campaign 200,000 baits were distributed using the new type of vaccine ‘Lysvulpen’, Bioveta, made in the Czech Republic. In 1999, two vaccination campaigns were conducted in 29 districts in spring (April-May), and autumn (November), using the vaccine SAG-1 (Virbac) with tetracycline marker and Rabifox from Dessau-Tornau, Germany.

In accordance with instructions, foxes were hunted and their jaws were taken to the Pulawy National Veterinary Research Institute. In 1998, tetracycline was detected in 36 of 76 test samples. However, in the 1999 autumn campaign blood samples were taken from hunted foxes to examine for rabies antibody. Control data on the uptake of vaccine varied. In most cases baits had been eaten and bitten-foil capsules containing no vaccine had been discarded. This accounted for 85% of the baits and the remaining 15% were untouched baits, unbitten and even unmoved capsules, presumably unseen by the fox. When
offspring leave their dens they are certain to explore the baits. These data resemble those of research conducted in other countries.

CONCLUSIONS

The dynamics of rabies in the Baltic countries is similar to that of other Central and East European countries. Interestingly, wildlife reservoirs, especially the fox and raccoon-dog, are playing an increasingly important role in the epidemiology of rabies in the region. Oral vaccination of wildlife, although underway in some districts, requires further coordination and cooperation between neighboring countries to be fully effective. Appraisal of the vaccination results is still premature. As international practice shows, at least three vaccination campaigns should be undertaken: autumn-spring-autumn. In the following year a decrease in foci should be noticeable.

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CHAPTER 5
RABIES IN THE EUROPEAN PARTS OF RUSSIA, BELARUS AND UKRAINE

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Summary

Throughout history, rabies was widely distributed in Belarus, Russia and Ukraine. Historically, although dog rabies predominated, wolves also played an important role in the distribution of rabies in eastern Europe. The work of Louis Pasteur resulted in a network of rabies vaccination clinics (Pasteur’s Stations) throughout Russia, saving tens of thousands of human lives. In the first half of the 20th Century, wolf, fox and raccoon dog populations significantly increased. Consequently, the vector species of human rabies radically changed as fox rabies predominated. In 1966-1975, 120 people died from rabies following exposure to rabid foxes, although the dog remained the principal vector. Mass vaccination of dogs began in the early 1950s. Oral rabies vaccination of wild carnivores has not yet been widely used. However, despite international progress with regard to rabies control, it is likely that conditions for the next rabies outbreak are gradually forming against a background of economic crisis.

Keywords: habitat changes, Pasteur’s stations, vector species, sylvatic canine rabies

INTRODUCTION

Numerous monographs and overviews of rabies epidemiology (10, 26, 38, 41, 52, 56, 57, 72, 76) have been published in Russian. However, there has been no complete account in the English language of its natural history in Russia, Belarus and Ukraine. This region attracts attention because the wave of fox rabies which covered most of western Europe after the Second World War is said to have begun in this part of the world. In this chapter, we attempt to chronicle the principal rabies events which took place in this area from ancient times to the end of the 20th Century. An overview of three historical periods is presented.

PRE-PASTEUR AND NEGRI

Information about rabies in eastern Europe in ancient times, the Middle Ages and until the second part of the 19th Century is sparse and fragmentary. Systematic state records of human and animal rabies during the pre-Pasteur period were absent. In general, the situation may be reconstructed on the basis of the following sources: philology, history of the East Slavonic people, zoogeography and publications on rabies in the eighteenth and nineteenth centuries.

Philological analysis has confirmed that Slavonic people knew of rabies from antiquity. The Russian name of the disease ‘beshenstvo’ is descended from the word ‘bes’, meaning evil spirits. The Belorussian name for rabies is descended from the same root. The Ukrainian name ‘skaz’ has the same root with the verb which means ‘to spoil’, ‘to be out of order’. In all east Slavonic languages the adjective which comes from the noun ‘rabies’ has a second sense: emotional condition of extreme fury, madness or insanity. Word combinations ‘rabid dog’ and ‘rabid wolf’ are standard expressions and have been included in numerous proverbs. These expressions come from texts of invocations or exorcisms that were used by sorcerers after animal bites, before Russia converted to Christianity. In contrast, the word combination ‘rabid fox’ has no such status.
The Russian State dates from the 9th Century. Later, in the 15th Century, three emerging ethnic groups had been formed: Russian, Ukrainian and Belorussian. Constant inter-ethnic contacts with steppe nomadic peoples of Central Asia on the one hand and with Byzantine, Scandinavian and western Europeans on the other hand, had a significant influence on the formation of the East Slavs. The landscapes, populations of wild and domestic animals and other components of the biosphere had simultaneously changed according to traditions and ways of life (21). All these processes may have changed the rabies gene pool in the region and may account for differences in the extent of rabies during different historical periods. For example, penetration to eastern Europe of rabies virus strains of Asian origin probably took place during Hun and Mongol invasions. Trans-regional spread of rabies virus was very probable along the ancient trade routes connecting the Black and Baltic Seas. Present day virological methods appear to confirm this virus movement. Town settlements began to appear in the eleventh and twelfth centuries; late in comparison with western and central Europe. Only in the 19th Century did explosive urbanisation begin and the first million-strong cities appear. At this time, Russian cities were notable for their abundance of stray dogs (38, 53).

During the Holocene epoch, the most common wild canidae in the steppes and forest-steppe landscapes of eastern Europe were the wolf (Canis lupus) and the red fox (Vulpes vulpes). According to a theoretical reconstruction of wolf habitats (4), about a thousand years ago, the highest population densities were on the steppes between the Dnepr and the Don rivers, near the Volga river and in North Caucasus (Fig. 5.1). Native European steppes in many places differed sharply from those of modern times. In earlier times these steppes were more like forest-steppe or savannah with herds of wild hoofed animals (30). Wolves sporadically inhabited modern zones of broad-leaved forests and forest-steppe, but in conifer forest they were practically absent. Over time the forests in eastern Europe were gradually cut down, forest landscapes became more mosaic and steppes were ploughed and became degraded. It is important to note that this process occurred significantly later than in central and western Europe. By this time optimal wolf habitats had changed from steppe to the southern part of the forest zone (forest-field transformed landscape). In general, that is also true for the red fox.

The periods of high wolf abundance in the 19th Century were fixed about 1800, 1850 and 1875 (Fig. 5.2), despite significant hunting pressure. Today, the corsac fox (Vulpes corsac) inhabits the steppes to the east of the Don; in a small area along the Caucasus Black Sea coast the jackal (Canis aureus) is also found. Some centuries ago, the natural habitats of both these species were more widespread (18). The Russian and aboriginal populations of the White and Barents Sea coasts have hunted the polar fox (Alopex lagopus) since ancient times. This arctic animal sometimes migrates to the forest zone. In recent centuries the furthest migrations of the polar fox were recorded on the Baltic Sea coast near Riga Bay, at Pscov, Novogorod and in other provinces (40).
More than 400 Russian books and articles with information about rabies were published prior to 1885 (calculated on the basis of a bibliography [38, 50, 70]). The earliest of these articles is by Danilo Samoilovitch (51), who was one of the founders of Russian epidemiology and who attributed rabies to a contagious disease. References to rabies were made in the sixteenth and seventeenth centuries. In 1739, mad dogs entered the Tsar’s summer palace near St Petersburg. The emphasis of early publications was dedicated to searches for rabies treatment and prevention. Some of the described methods were highly exotic: Russian bath-house, bathing in ice-water, acetic acid, curare, arsenic, pox vaccine, different herbs and even May beetles.

The wide geographical distribution of cases must be emphasised – from the capital cities of Moscow and St Petersburg, to provincial towns and rural countryside and from the southern borders of Ukraine to the Baltic, Finland and Poland (Fig. 5.1). Dog rabies predominated among all described cases, although wolf rabies was quite common (about 15% of all publications concerned wolf rabies). Wolf rabies was more frequently mentioned in 1870-1875. Sabaneev (50) also cited a report of rabid bears in Mogilev province (Belarus) in 1870.

Fox rabies was also known. Eichwald and Pitzchke in 1967 (cited after 57), wrote of fox rabies epizootics in Russia in 1810, 1818 and 1824 but in the bibliography collected by Sabaneev (50), this information is absent. One of the first Russian language works to mention fox rabies is credited to Kunen in 1844 (reprinted by Shibaev in 1852) entitled ‘New remedy for treatment of hydrophobia and rabies after wolf, fox and dog bites’ (50). Professor Ravich (47) described classical signs of fox rabies in detail: ‘These animals, usually cowardly and apprehensive, appear in villages and towns in day time, run into houses and furiously attack men and animals’. We can find only one 19th Century description of human rabies following fox exposure in the Russian Empire, in Bessarabia (modern Moldova) in 1819 (3).

Thus, some conclusions may be drawn. Rabies was endemic in eastern Europe throughout history. In ancient times and the Middle Ages, the disease was probably distributed in steppe and forest-steppe zones where wild canidae predominately maintained its circulation. Undoubtedly, rabies was distributed throughout the tundra zone of Europe before the arrival of Slavonic peoples. The conditions for independent circulation of rabies virus among dogs were absent due to the low population density and dispersed human settlements. Historically, the distinguishing feature of rabies in eastern Europe was the important role of wolves in its distribution. Fox rabies was noted, but it did not attract special attention; it was probably not widely distributed, at least after the middle of the 19th Century. Landscapes changed as a result of human activity and consequently the distribution of wild canidae also changed. Rabies penetrated into forest zones following human settlement and anthropogenic activities. The rabies-affected area progressively extended northwards and probably during the eighteenth and nineteenth centuries, dog
rabies took hold in cities and urban areas. As a result, the social and economic significance of rabies increased and became of greater interest to medical and veterinary specialists. Measures for dog and wolf population reduction were carried out in some areas. However, state systems, organisations and laws for rabies prevention and control were absent. Louis Pasteur’s discovery became a stimulus for change.

FROM PASTEUR TO THE END OF THE SECOND WORLD WAR

Human rabies immunisation

Gamaleya was one of the first Russian physicians to learn Pasteur’s method of rabies treatment in Paris. He was admitted to Pasteur’s laboratory in February 1886 on the recommendation of Mechnikov. In March 1886, 35 Russian peasants bitten by rabid wolves arrived in Paris. Influenced by treatment failures (seven of the patients died, possibly as a result of treatment delays due to travel), Pasteur decided to pass on his method and virus fixē to other countries. The second Pasteur laboratory for vaccination against rabies was opened in Odessa in the south of Russia. On his return from Paris, Gamaleya commenced vaccinations on 11 June 1886 (17) and a Dr Bardakh first tried the vaccine treatment on himself. During 1886 other laboratories were set up in St Petersburg, Moscow, Samara and Kiev. The first laboratory in Belarus was opened in 1911 in Minsk. Among the first organisers of anti-rabies vaccination in the Ukraine were Mechnikov, Gamaleya, Motte, Cvitkis and Palavandov; in the European part of Russia, Golman, Krayushkin, Savateev, Khardin, Parshensky and Akker; and in Belarus, Sutin.

In Russia, laboratories for rabies treatment were called Pasteur’s Stations. The network of these stations broadened rapidly and we can have some idea of the distribution of rabies in Russia at the turn of the 20th Century by noting the distribution of Pasteur’s Stations (Fig. 5.3). Dubrovinsky (16) published a review of the work of Pasteur’s Stations to commemorate the fiftieth anniversary of Louis Pasteur’s discovery. By 1917, 28 Pasteur’s Stations were in place and by 1927 they numbered 72 with 285 branches. Pasteur’s Stations served as the centres for all rabies activities including vaccine production, laboratory diagnosis, statistics, teaching and research; some of them later transformed into Research Institutes.

Figure 5.3 – Wolf population density in eastern Europe in the 1940s; location of Pasteur’s Stations

Wolf number per 1000 squ. km: 1 = up to 1; 2 = 1-5; 3 = 5-15; 4 = over 15

The points: Pasteur’s Stations before 1927

State reconstruction and the Civil War led to a reduction in the number of persons treated during 1917-1923. In 1923-1934, 9.3% of treated persons were bitten by animals with laboratory confirmed rabies, 21.2% by animals showing clinical signs of rabies, and others by animals exhibiting suspicious clinical signs. The same proportion, with insignificant variations, was typical for all Pasteur’s Stations. Neurological complications were found in 0.18/1,000 treated persons. During the first 50 years of Pasteur’s treatment method, the dilution method of Hogyes and Fermi vaccine were used throughout Russia and the United Soviet Socialist Republics (USSR). Vaccination reduced mortality by 15-20 times and thus tens of thousands of human lives were saved (16, 52).
Human rabies

Systematic state recording of human and animal rabies in Russia began in 1886, but data from this period is not notable for its accuracy and varies from one publication to another. Data from the provinces of Russia, Belarus and Ukraine are not totally accurate. Records of rabies in the Asian part of the Empire are practically non-existent.

At the end of the 19th Century, no fewer than 300-400 cases of human rabies were reported annually in Russia, but undoubtedly there were more. In 1887, 693 people died (38) and during 1891-1896, 2,326 deaths, an annual average of 388, were reported. More precise reporting of human rabies came from Pasteur’s Stations. During 1886-1896, 403 fatal cases were reported (22). In the first quarter of the 20th Century, the annual average human death toll from rabies was about 1,000, with the highest number in 1909. Mortality sharply declined from the early 1930s and up to and during the Second World War human rabies morbidity was minimal (56, 57). However, it is clear that rabies data were fragmentary for the occupied territories. Summary data are presented in Fig. 5.2.

Animal rabies

Statistics of animal rabies are less accurate. In 1886-1896, rabies was reported from 52 provinces, more than half of all provinces of Russia. The average case numbers were: 740 dogs, 141 horses, 729 cattle and 152 sheep, totalling 1,760 rabies cases annually. Up to the beginning of the First World War, 3,000-12,000 animal rabies cases were reported annually, but in 1922-1926 it was as many as 2,000-14,000 (52, 56). According to statistical data, the ratio of human to animal rabies cases changed from 1:2 to 1:13. Despite the inaccuracies of these data, different researchers (16, 25, 52, 56) have inferred differences in the epizootic situation during 1909-1910 and again in 1920-1925 from periods of high morbidity in other European countries. By the end of the 1930s and at the beginning of the 1940s, a comparatively low level of rabies activity was marked in many areas. According to veterinary records for 1907-1924, 72% of all cases were reported in dogs, 18.2% in cattle and 9.8% in other domestic animal species. Rabies in wild animals was not subject to veterinary reporting (52).

All of the European part of Russia, excluding the lowly populated forest areas of the northeast, was affected by rabies and the government was compelled to intervene. As well as State Pasteur's Stations, some governmental edicts were issued – for example: in 1892 a circular of the Russian Ministry of Internal Affairs on rabies control; in 1897, a law about tax on dogs; in 1923, veterinary regulations with a chapter on rabies. In 1924, a free-of-charge drive to utilise Pasteur's Stations was established in the USSR. Measures on safe dog keeping were not welcome by Russians, although most peasants were aware that rabies had to be treated by injections (52).

Rabies virus vectors and reservoir species

The role of different animal species in the spread of rabies was presented in the records of Pasteur's Stations (Tables 5.1 and 5.2). Dogs were the most important vectors everywhere and although cats took second place on the list of suspected animals, they were of less importance than wolves as vectors of human rabies at all Pasteur's Stations; on average about 16% of all patients were bitten by wolves. In comparison, with the average probability of rabies following all animal bites, the probability of contracting the disease following wolf bites was 13-16 times higher, despite vaccination. Mortality in those not given treatment was 45.5% (16, 52). Fox bites were 10-100 times less frequent than wolf bites in the reports. Before 1892 only six fox bites were reported (St Petersburg Pasteur's Station). During 1902-1904, 116 such cases (0.04% of the total) were recorded and of these, 91 were reported from the Russian Pasteur's Stations of Moscow and Samara and nine from the Ukrainian Stations of Kiev and Kharkov (43, 52).

Fox bites were more rarely reported in the southern than in the northern provinces. However, the first human rabies case after fox exposure in the 20th Century was reported in Ukraine in 1925 (43). In 1927, one rabid fox was found in Raysan, a province of Russia (13). Less reliable reports of human rabies deaths following polar bear, squirrel and human exposure have also been described (38, 56). A change in biting species occurred during the Leningrad blockade of 1941-1942 (69). According to data of the Leningrad
Chapter 5

Pasteur's Station, dogs and cats had practically disappeared from Leningrad and about 70% of all patients were bitten by rats, although human rabies after rat exposure was never reported.

Table 5.1 – Number of people treated at Pasteur's Stations in Russia (USSR) (43, 52, 69)

<table>
<thead>
<tr>
<th>Location</th>
<th>Years</th>
<th>Total Number</th>
<th>Bitten by different animals (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moscow*</td>
<td>1886-1915</td>
<td>76,552</td>
<td>Dog 88.4  Cat 8.0  Wolf 1.4  Other 0.2</td>
</tr>
<tr>
<td>St. Petersburg*</td>
<td>1886-1942</td>
<td>46,195</td>
<td>Dog 71.1  Cat 17.0  Wolf 0.3  Other 11.6</td>
</tr>
<tr>
<td>Perm*</td>
<td>1897-1922</td>
<td>15,551</td>
<td>Dog 84.9  Cat 11.3  Wolf 0.5  Other 3.3</td>
</tr>
<tr>
<td>Samara*</td>
<td>1886-1911</td>
<td>18,183</td>
<td>Dog 86.7  Cat 7.1  Wolf 3.3  Other 2.9</td>
</tr>
<tr>
<td>Saratov*</td>
<td>1898-1923</td>
<td>22,980</td>
<td>Dog 88.5  Cat 6.1  Wolf 1.1  Other 3.3</td>
</tr>
<tr>
<td>Kiev**</td>
<td>Up to 1927</td>
<td>42,454</td>
<td>Dog 89.5  Cat 6.2  Wolf 0.0  Other 4.3</td>
</tr>
<tr>
<td>Kharkov**</td>
<td>1887-1911</td>
<td>30,076</td>
<td>Dog 90.5  Cat 6.4  Wolf 1.0  Other 2.1</td>
</tr>
<tr>
<td>All Russian stations</td>
<td>1887-1892</td>
<td>14,371</td>
<td>Dog 88.5  Cat 6.1  Wolf 1.1  Other 3.3</td>
</tr>
<tr>
<td>All Russian stations</td>
<td>1902-1914</td>
<td>313,843</td>
<td>Dog 88.5  Cat 6.1  Wolf 1.1  Other 3.3</td>
</tr>
</tbody>
</table>

* : in modern Russia
** : in modern Ukraine
+ : % for foxes only

Table 5.2 – Human rabies cases in Russia (USSR). Pasteur's Stations Data 1886-1914 (43, 52, 69)

<table>
<thead>
<tr>
<th>Location</th>
<th>Years</th>
<th>Total Number</th>
<th>Bitten by different animals (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moscow*</td>
<td>1886-1915</td>
<td>1,000</td>
<td>Dog 85.4  Cat 0.24  Wolf 12.1  Other 0.001+</td>
</tr>
<tr>
<td>St. Petersburg*</td>
<td>1886-1942</td>
<td>2,233</td>
<td>Dog 87.9  Cat 2.7  Wolf 9.4  Other 0.0</td>
</tr>
<tr>
<td>Perm*</td>
<td>1897-1922</td>
<td>112</td>
<td>Dog 85.7  Cat 1.8  Wolf 12.5  Other 0.0</td>
</tr>
<tr>
<td>Samara*</td>
<td>1886-1911</td>
<td>223</td>
<td>Dog 67.3  Cat 2.2  Wolf 35.0  Other 0.0</td>
</tr>
<tr>
<td>Odessa**</td>
<td>1887-1914</td>
<td>189</td>
<td>Dog 85.7  Cat 0.5  Wolf 13.8  Other 0.0</td>
</tr>
<tr>
<td>Kharkov**</td>
<td>1887-1911</td>
<td>331</td>
<td>Dog 82.8  Cat 3.0  Wolf 14.2  Other 0.0</td>
</tr>
<tr>
<td>All Russian stations</td>
<td>1887-1892</td>
<td>184</td>
<td>Dog 85.7  Cat 0.5  Wolf 13.8  Other 0.0</td>
</tr>
<tr>
<td>All Russian stations</td>
<td>1902-1914</td>
<td>1,446</td>
<td>Dog 85.7  Cat 0.5  Wolf 13.8  Other 0.0</td>
</tr>
</tbody>
</table>

* : in modern Russia
** : in modern Ukraine
+ : % for foxes only

Local outbreaks of raccoon dog (Nyctereutes procyonoides) rabies in 1942 in the Volga delta at first attracted little attention, as did fox rabies in eastern Prussia in 1939-1942. The latter was probably the first manifestation of the fox rabies outbreak that later invaded most of western Europe (68), although in the mid-1930s massive fox deaths from unknown causes were observed in the steppe zone of the European part of the USSR (18). What environmental transformation had taken place? By the end of the 1930s eastern European biota had rapidly and significantly changed. In the forest zones of Belarus and Russia, conifer forests were replaced by young deciduous forests or by arable lands over large areas. Unbroken steppes to the south of Ukraine and Russia became almost completely cultivated. The abundance of animals adapted to fields and glades near human settlements increased (30) to permit the wolf and fox to thrive. Growth of the wolf population in the early 20th Century was concurrent with the Civil War. During the Second World War the increase observed in wolf numbers in eastern Europe was significantly greater than in the previous two centuries (4). The fox population increased simultaneously, partly due to a reduction in hunting. From 1929, work on acclimatisation of the raccoon dog started in the Ukraine, Belarus and many areas of the Russian Federation (18, 40). Thus, to the end of the Second World War, the abundance and species diversity of wild canidae sharply increased, as did the range of the wolf. The theory
that the fox rabies outbreak in eastern Europe was as a result of a reduction in the number of wolves is not borne out by the facts.

FROM THE END OF THE SECOND WORLD WAR TO THE END OF 20TH CENTURY

Human rabies immunisation

In 1948-1950, Pasteur’s Stations were transferred to departments of regional Centres of Sanitary-Epidemiological Survey and since 1956 laboratory diagnoses of rabies have been carried out at veterinary laboratories. During 1965-1968, industrial production of lyophilised brain tissue vaccines was organised and local vaccine preparation ceased in 1969. By the end of 1975 human rabies immunisation had been completely transferred to polyclinics, and traumatologists and surgeons performed anti-rabies treatment (31, 57). Thus the specialist network of Pasteur’s Stations ceased to exist.

For many years the main centre for rabies prevention and research was at the Institute of Polio and Viral Encephalitides in Moscow, led by Midat Selimov. In 1961, work on cell culture rabies vaccine began in his laboratory and in 1970-1973 serial culture production, one of the first rabies cell culture vaccines, was produced from Vnukovo-32 rabies virus strain grown in hamster kidney cells. This vaccine and its concentrated analogues are still used. Since 1956, horse anti-rabies immunoglobulin has also been produced. In 1957, one of the first field trials of combined vaccine and antiserum treatment was carried out on 25 patients badly injured by a wolf in Belarus (59). At the beginning of the Pasteur’s Station reorganisation, the number of vaccinated persons in the USSR increased to almost half a million. The treatment was prescribed for 90-97% of admitted patients (57). An extremely high rate of vaccination was reported from Ukraine (Table 5.3). Naturally, the number of vaccine associated neurological complications increased. In 1956, more strict instructions were enforced and the quality of prescribed treatment was gradually improved. Before 1975, three peaks of human rabies immunisation rates were observed, in 1926, 1939 and 1954. All were connected with the intensive epizootics of dog rabies (57). The number of vaccinated people began to increase once again after 1975 (12, 58).

Table 5.3 – Human rabies immunisation in Russia, Ukraine and Belarus (8, 12, 56, 57)

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>No. people given PET</th>
<th>PET/100,000</th>
<th>% PET among admitted people</th>
<th>% exposed to Rabid animals</th>
<th>% exposed to Wild animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russia</td>
<td>1950s</td>
<td>176,000</td>
<td>160.0</td>
<td>96.0</td>
<td>7.8</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>1960s</td>
<td>99,000</td>
<td>83.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1970s</td>
<td>58,000</td>
<td>44.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1980s+</td>
<td>69,300</td>
<td>73.7</td>
<td>45.4</td>
<td>8.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Ukraine</td>
<td>1950s</td>
<td>120,000</td>
<td>290.0</td>
<td>99.0</td>
<td>3.3</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>1960s</td>
<td>52,000</td>
<td>125.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1970s</td>
<td>37,000</td>
<td>77.0</td>
<td></td>
<td>4.9</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>1980s</td>
<td>35,000</td>
<td>67.7</td>
<td>33.3</td>
<td>6.2</td>
<td>6.9</td>
</tr>
<tr>
<td>Belarus</td>
<td>1950s</td>
<td>6,000</td>
<td>75.0</td>
<td>99.0</td>
<td>16.8</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>1960s</td>
<td>4,500</td>
<td>53.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1970s</td>
<td>1,900</td>
<td>20.0</td>
<td></td>
<td>9.3</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>1980s</td>
<td>3,300</td>
<td>32.2</td>
<td>28.0</td>
<td>15.0</td>
<td>12.4</td>
</tr>
</tbody>
</table>

* : Average figure not always calculated over the 10 year period
+ : European Russia only, other figures refer to Russian Federation
PET : post exposure treatment

The efficacy of this strategy may be estimated from data for Russia (8). In the 1970s-1990s, despite very high vaccination indices, human case numbers declined slowly. Approximately one person per ten million died of rabies annually. Among all patients that died, 87% received no anti-rabies treatment and 7% were incorrectly treated. Failures of human rabies treatment did not exceed 2%. Dog vaccination remained insufficient and the reporting of animal rabies simultaneously worsened. The need to change the strategy...
of human rabies treatment in Russia and some other States of the FSU (former Soviet Union) at the end of the 20th Century was clear.

**Human rabies**

Shortly after the Second World War a very high rate of human rabies was reported in Belarus. In 1946, the morbidity index in Belarus (about 1.0/100,000) was five times higher when compared with Ukraine and fourteen times higher than that in Russia. During 1947-1949, the total number of rabies cases in Belarus fell significantly, but after 1950 the number of human rabies cases sharply increased in all three Republics. The peak was observed in 1951-1952, when the highest morbidity indices were registered in Ukraine (0.6-0.7/100,000) with somewhat lower (about 0.2/100,000) in Russia and Belarus. From 1946-1952, annual case numbers in Ukraine were also higher than in all of the Russian Federation. For example, in 1951, 278 rabies cases were reported in Ukraine, 215 in Russia and 17 in Belarus (19, 57, 76). The total number of cases declined after 1960 (Fig. 5.2). However, in 1967-1973 the annual number of human rabies cases was again higher in Ukraine than in Russia. Human rabies was registered only sporadically after 1964 in Belarus and after 1990 in Ukraine. In the last quarter of the 20th Century, 5-17 human rabies cases (not higher than 0.05/100,000) were reported annually from the European part of Russia (8, 12, 33, 58, 64). Geographical distribution of human rabies is presented in Figures 5.4 and 5.5. The picture had changed when compared with that of mid-century. Before 1968, the highest morbidity indices were observed in south-eastern European Russia (Rostov, Krasnodar, Stavropol provinces) and in the south and west of Ukraine – Donetsk, Lugansk and Vinnitza provinces (27).
Vector species of human rabies have radically changed since the Second World War. Until that time there were only two reports of human rabies following exposure to rabid foxes in the Russian Empire. However, by 1955 at least 40 people had died of rabies following fox bites in the European part of the USSR, although the dog remained the primary vector. In this period, the first cases of rabies following raccoon dog (n=10), badger (n=10) and marten (n=2) exposure were recorded (57). Human rabies cases connected with badgers were more frequently recorded in western Ukraine, with raccoon dogs in Belarus, northwest Russia and low levels of raccoon dogs in the Volga delta.

The percentage of wildlife vectors among all sources of human rabies continuously increased and for the first time (in 1950s) was higher in Ukraine, Belarus and western provinces of Russia (Table 5.4). Before the middle of the 1970s not only the rate, but also the total number of human cases following fox bites, increased as a result of the expansion of the fox rabies outbreak. In 1966-1975, no fewer than 120 people died from rabies following exposure to rabid foxes. The role of cats had simultaneously risen, but after 1960 human rabies from wolf bites did not exceed 3%-5% of the total (57).

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>Domestic Dog</th>
<th>Domestic Cat</th>
<th>Wolf</th>
<th>Fox</th>
<th>Raccoon dog</th>
<th>Other</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russia</td>
<td>1966-1975</td>
<td>48.1</td>
<td>13.3</td>
<td>0.74</td>
<td>35.6</td>
<td>0.74</td>
<td>1.4*</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>1974-1990</td>
<td>34.0</td>
<td>9.4</td>
<td>3.8</td>
<td>39.1</td>
<td>6.1</td>
<td>1.9*</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>1874-1990+</td>
<td>17.2</td>
<td>12.6</td>
<td>2.6</td>
<td>53.6</td>
<td>4.6</td>
<td>2.8*</td>
<td></td>
</tr>
<tr>
<td>Ukraine</td>
<td>1945-1955</td>
<td>87.9</td>
<td>5.4</td>
<td>1.5</td>
<td>2.6</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1966-1975</td>
<td>11.8</td>
<td>34.2</td>
<td>0.6</td>
<td>46.5</td>
<td>3.6</td>
<td>3.7**</td>
<td></td>
</tr>
<tr>
<td>Belarus</td>
<td>1949-1964</td>
<td>74.3</td>
<td>2.8</td>
<td>9.2</td>
<td>8.2</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After 1964, sporadic cases, mostly following wild animal exposure

* : corsac fox, marten, brown bear, bat

** : badger, marten, suslik (gopher)

+ : European Russia only, other figures refer to Russian Federation

It is necessary to emphasise that human rabies following exposure to wild carnivores occurred at temperate latitudes of eastern Europe. At the same time human rabies was only sporadically reported from sub-arctic regions: in the last quarter of the 20th Century only one human rabies case following a wolf bite was described, in Arkhangelsk province (74).

**Animal rabies**

The highest numbers of rabid animals during the period were reported in 1951-1954 and 1975-1976. For example, in 1976 about 7,600 rabid animals were reported in Russia, 1,900 in Ukraine and 300 in Belarus. After 1976 the annual number of reported cases throughout this area gradually fell to 2,000-3,000. Despite diagnostic improvements (immunofluorescence was introduced in the 1970s), a comparison of medical and veterinary data (Table 5.5) shows that animal rabies reports remained incomplete.

Changes in the species of rabid animals during the period are presented in Table 5.5. Increase in the livestock morbidity rate, with simultaneous reduction in dog morbidity rate, were considered as indicators of wildlife rabies prevalence until 1967, when wildlife rabies statistics began to be included in veterinary records. The crossover point of dog and cattle rabies morbidity rates occurred in 1957 in the USSR (46). On the basis of this indication, the change of epidemiological pattern occurred in 1957-1970 in the European part of Russia, in 1959-1965 in the Ukraine and in 1951-1960 in Belarus (Table 5.6; 71).
In the early period of wildlife rabies, spread in eastern Europe coincided with a sharp increase in the incidence of dog rabies. A dog rabies epizootic reached its maximum in 1951-1954 and was accompanied by a significant increase in human rabies and a rapid expansion of the rabies-affected area (25, 46, 57, 72). Within only a few years, canine rabies reached its northern limits. Human rabies following dog bites were reported from the Leningrad, Pskov, Yaroslavl, Ivanovo, Kastroma, Perm and Sverdlovsk provinces. In the 1950s, rabies appeared in the forest zone of Arkhangelsk province (25). The 1960s were comparatively rabies-free. Many northern areas of Russia became rabies-free at this time, but a further epizootic was observed in the mid-1970s due to the activity of rabies in wild canidae. By the 1970s fox rabies had spread to many parts of eastern Europe. At the beginning of the 1980s the northern border of fox rabies distribution was located at approximately 56°N (57). By the second half of the 1980s wildlife rabies had again entered Leningrad and Novgorod provinces from Estonia, reached and then crossed the border with Finland (42). After a long interval, fox rabies appeared in Moscow province and affected some areas near the Urals. The northern border of the rabies-affected area was 56-61°N, which approximately coincides with the southern border of Taiga forest zone and with the maximal dog rabies distribution in the middle of the 1950s. In 1965, Kantorovich reported increasing numbers of rabies cases in Belarus and the Baltic, proceeding to a general rabies increase in the European part of the USSR. The zone of Taiga forest with wide marshes generally remained rabies-free. Sporadic rabies cases among dogs and wolves were reported from this zone only during periods of high rabies prevalence. Further north, in tundra and forest-tundra zones from the Kolsk peninsular to the polar Urals, arctic rabies was distributed among polar foxes (24, 71). By the middle of 1990s animal rabies had increased again in many parts of eastern Europe (73)

Change of main rabies epidemiological pattern

A qualitative transformation of the rabies epizootic took place after the Second World War. Only individual rabid raccoon dogs were found in the Volga delta in 1942, but in the winter of 1945-1946 deaths in massive numbers were observed, as well as rabies among wolves and foxes. Isakov (23) emphasised that the raccoon dog was the most affected species. At the same time, an intensive fox rabies epizootic was described in the Crimean peninsula (44). In 1944-1946, a rabies epidemic among foxes, wolves and martens occurred in Kiev and Zhytomyr provinces of Ukraine near the borders with Belarus, where fox rabies occurred simultaneously (45, 55, 76). In 1947, individual rabid foxes were observed in Moscow and Tula provinces (14, 57, 58). A fox rabies outbreak was described in Voronezh province on both banks of the Don in 1945-1946 (14). Thus, during 1942-1947, rabies epizootics among foxes and raccoon dogs were simultaneously observed at different points distanced from one another by hundreds of kilometres (Fig. 5.4). In some of these places, for example in Moscow province and the Crimea, fox rabies soon disappeared.

It is considered that the European fox rabies epizootic started from two foci located in eastern Prussia and in the Volga delta (5, 57, 71) but not all of the facts support this view. Indeed, the fox rabies wave moved from west to east and southeast in Ukraine and Belarus (19, 25, 55, 71, 76). Already in 1951-1954
the fox rabies outbreak was observed extending from Penza province bordering the Volga to 700 km north of the delta (2). It is perhaps more logical to propose that rabies had reached this point from the Don (Voronezh province). In 1949, a fox rabies outbreak was described in the Asian part of the USSR in Kazakhstan (67), more than 1,000 km to the east of the Volga delta. Therefore, in the wide territory from eastern Prussia to the south of Kazakhstan, some independent points of wildlife rabies activity took place during the ten year period.

**Rabies virus vectors and reservoir species**

Before the 1960s, Russian publications on wildlife rabies were descriptive. Firstly, Kantorovich (25) summarised the data in a thesis. Overviews and other works on wildlife rabies were presented in Belarus (19, 32, 76), in the Ukraine (20, 48, 55, 65) and in the European part of Russia and the USSR (1, 8, 11, 39, 57, 66, 71, 73).

According to Kantorovich (25), the circulation of rabies virus in eastern Europe was via a single host vector. As in western Europe, the red fox is the main host species, although many other species may act as victims (Tables 5.6, 5.7 and 5.8). A feature of eastern European rabies is the significant role of other canids (wolf, raccoon dog, and corsac fox) which took part in rabies virus distribution. Almost everywhere two or three canid species are affected simultaneously, so virus circulation is probably maintained by host changes within the canid family. Perhaps the red fox alone provides rabies virus circulation in the steppe zone of the Ukraine, where the wolf and raccoon dog are today almost absent. The raccoon dog certainly occupies second position as vector and reservoir of the disease (11, 57, 65). Attacks by rabid wolves are reported more regularly from regions with high population densities of this predator. The problem of wolf bites remains to the present time in Belarus and many provinces of Russia and the Ukraine (Table 5.4). However, wolves have not been an independent reservoir of the disease in recent years.

**Table 5.6 – Animal rabies cases (%) in Russia, Ukraine and Belarus 1950-1985** (56, 57, 76)

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>Domestic</th>
<th>Wild</th>
<th>Wild animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dog</td>
<td>Cat</td>
<td>Fox</td>
</tr>
<tr>
<td>Russia</td>
<td>1954-1957</td>
<td>49.8</td>
<td>50.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1967-1979</td>
<td>4.5</td>
<td>1.0</td>
<td>91.5</td>
</tr>
<tr>
<td></td>
<td>1976-1985*</td>
<td></td>
<td>90.9*</td>
<td></td>
</tr>
<tr>
<td>Ukraine</td>
<td>1954-1957</td>
<td>56.8</td>
<td>43.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1967-1976</td>
<td>15.5</td>
<td>14.6</td>
<td>62.2</td>
</tr>
<tr>
<td></td>
<td>1976-1985</td>
<td></td>
<td>62.2*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1950-1977</td>
<td></td>
<td>88.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Belarus</td>
<td>1954-1957</td>
<td>34.7</td>
<td>65.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1967-1976</td>
<td>18.0</td>
<td>7.6</td>
<td>61.5</td>
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<tr>
<td></td>
<td>1976-1985</td>
<td></td>
<td>50.5*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1949-1963</td>
<td></td>
<td></td>
<td>68.5</td>
</tr>
</tbody>
</table>

*: All species; +: European Russia only, other figures refer to Russian Federation

Badgers (*Meles meles*), martens (*Martes martes, Martes foina*), and polecats (*Putorius putorius, Mustela eversmani*) are involved in epizootics in temperate latitudes, although not as reservoir species. In the European tundra, the main reservoir of rabies virus is the polar fox, and the roles of the red fox and wolf are significantly less important. In general, the list of wild animals with laboratory-confirmed rabies includes about 50 species (12, 57, 71). Dogs and cats remain important vectors of rabies to humans and livestock. Since 1964, lyssavirus isolations in the Ukraine have been made from three bat species: *Eptesicus serotinus, Vespertilio murinus* and *Nyctalus noctula* (49, 62). These isolates were classified as European bat lyssavirus Type 1 (EBLV-1) (29). Approximately 1,000 other bats from eastern Europe were tested, but no rabies viruses were isolated from them (34). However, two additional rabies-related viruses have been isolated more recently from bats in Russia. In 2002, Irkut virus was isolated from a greater tube-nosed bat (*Murina leucogaster*) in eastern Siberia. Later that year, WCBV was isolated from a bent-winged bat (*Miniopterus*
Historical Perspective of Rabies in Europe and the Mediterranean Basin

(36). The first human rabies cases following bites from unknown bat species were reported in the Ukraine in 1977 and southern Russia in 1985 (54, 63).

Table 5.7 – Animal rabies in the Russian Federation 1989-2001*

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th>Wildlife animals</th>
<th>All animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dogs</td>
<td>Cats</td>
<td>Cattle</td>
</tr>
<tr>
<td>1989</td>
<td>231</td>
<td>174</td>
<td>547</td>
</tr>
<tr>
<td>1990</td>
<td>396</td>
<td>440</td>
<td>1,283</td>
</tr>
<tr>
<td>1991</td>
<td>339</td>
<td>215</td>
<td>762</td>
</tr>
<tr>
<td>1992</td>
<td>166</td>
<td>52</td>
<td>379</td>
</tr>
<tr>
<td>1993</td>
<td>135</td>
<td>58</td>
<td>282</td>
</tr>
<tr>
<td>1994</td>
<td>103</td>
<td>48</td>
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<td>1995</td>
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<td>128</td>
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<td>1996</td>
<td>466</td>
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<td>293</td>
<td>143</td>
<td>260</td>
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<td>1998</td>
<td>473</td>
<td>285</td>
<td>522</td>
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<tr>
<td>1999</td>
<td>405</td>
<td>227</td>
<td>509</td>
</tr>
<tr>
<td>2000</td>
<td>227</td>
<td>181</td>
<td>290</td>
</tr>
<tr>
<td>2001</td>
<td>346</td>
<td>306</td>
<td>526</td>
</tr>
<tr>
<td>Total</td>
<td>3,731</td>
<td>2,394</td>
<td>6,740</td>
</tr>
</tbody>
</table>

Sources: Rabies Bulletin Europe (official rabies statistics)

Table 5.8 – Animal Rabies in Belarus 1993-2001

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th>Wildlife animals</th>
<th>All animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dogs</td>
<td>Cats</td>
<td>Cattle</td>
</tr>
<tr>
<td>1993</td>
<td>26</td>
<td>9</td>
<td>10</td>
</tr>
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<td>1997</td>
<td>13</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>1998</td>
<td>23</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>1999</td>
<td>14</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>2000</td>
<td>38</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>2001</td>
<td>63</td>
<td>46</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>215</td>
<td>152</td>
<td>129</td>
</tr>
</tbody>
</table>

Sources: Rabies Bulletin Europe (official rabies statistics)

* Third quarter only
** No data June-October
*** No data November-December
**** No data for January, May and June

Occasional rabies cases due to bites from the corsac fox, brown bear, polecat and suslik (gopher) (species unknown) have also been described (57). Recently, cases of human rabies of unknown origin have more frequently been reported (Table 5.4).

Molecular epidemiological data confirmed the exchange of rabies viruses between different canid species. Investigations using anti-nucleocapsid monoclonal antibodies (Mab-Ns) showed that strains with the same antigenic profile were isolated from wild and domestic animals within a defined area (6, 60). At least three areas with specific antigenic variants may be identified in the European part of the USSR.
1) Northwest of Russia, Baltic and probably west of Belarus. Strains from the Kolsk peninsula differ widely from Asian arctic strains.

2) The central part of the region near the junction of Russia, Belarus and Ukraine borders.

3) South of Russia and Northern Caucasus. The two variants predominant in the Asian part of Russia and Middle Asia are also widely distributed in other areas of eastern Europe, excluding the north. Antigenic variants limited to one canid or one mustelid species have not been found.

Despite the use of different methods, our conclusions coincide with new data for eastern Europe and the FSU by Bourhy et al. (9) and Kuzmin et al. (35). Thirty-eight rabies virus strains of human origin from the European part of the FSU were tested with Mab-Ns (7). The frequency of variants and their geographical distribution agreed with results from animal isolation studies. With this Mab-N panel, approximately 90% of human rabies virus isolates showed no variation. The strain from a patient bitten by a bat in Russia was of the EBLV-1 virus group (29, 63); only serotype 1 viruses have been isolated from humans who died from rabies of unknown origin.

Abundance of wild canids and rabies

A relationship between rabies epizootics and wild canid distribution was demonstrated in the European part of the FSU (66). Large-scale rabies geographical distribution accords with areas of higher canid abundance, such as areas with a high population density of two to four different species close to one another: in Belarus, woodlands of the Ukraine and the central and south-eastern provinces of Russia. Using smaller scale maps, the direct relationship between canid population density and rabies epizootics is less obvious. This is one reason for the contradictory opinions on this question in different publications (1, 13, 14, 65, 66). In general, the situation corresponds to observations in western Europe (5).

The long-term periods of rabies expansion in eastern Europe, as a rule, were in line with an increase in the wolf population (Fig. 5.2), even though today the principal host species is the red fox. Three to five year periodicity of fox abundance is well known in connection with rabies cycles, although there are variations in some regions (14, 71). The post-acclimatisation peak of raccoon dog numbers took place in the 1950s and 1960s. Later, the population density of this species was reduced in the main part of its secondary habitat. Raccoon dog population density almost everywhere is three to twenty times less than that of the red fox. Natural expansion of raccoon dog populations sometimes results in an unusual annual spread of 130-300 km (18, 40).

A number of campaigns aimed at reducing wolf populations have been conducted with State support. The post-Second World War wolf abundance was kept in check by hunting at the end of the 1950s. During the 1960s and 1970s the wolf population in eastern Europe was reduced, probably to its lowest level in history. The wolf disappeared from one-third of its previous habitat, especially within the steppe zone. However, by the middle of the 1970s a resurgence of the wolf population to two or three times its former size occurred in many regions of Russia, Belarus and the woodlands of the Ukraine (4). This resurgence was supressed more quickly than previously after 5-6 years. As a result of the disruption of the wolf population structure, wild domestic dogs and dog/wolf hybrids appeared and enhanced rabies virus circulation in some provinces (37). Attempts to regulate the population densities of foxes and raccoon dogs were local and generally had no influence on rabies distribution.

Animal vaccination

Mass vaccination of dogs began in the early 1950s. The first large-scale field trials were conducted at Kharkov, Dnepropetrovsk (Ukraine), and Moscow and were successful (20, 56, 57, 72, 73). Vaccination campaigns gradually increased to include every State. According to veterinary regulations, all dogs were to be vaccinated independent of the presence of rabies in the area, but in practice only part of the dog population was vaccinated. Exact information on dog numbers is absent. In 1976-1985, the ratio of dogs vaccinated per 100 people was more than 4.0 in the Ukraine and 2.7-3.9 in Belarus, Central Russia and North Caucasus (71). In Russia, most of the dogs were vaccinated in the towns, with not more than 20% vaccinated in rural settlements. All rabies experts affirm that the proportion of dogs currently vaccinated
must be significantly increased. In the 1970-1980s, rabies vaccination of cattle was widely used in areas affected by fox rabies. Between one to eight million cattle were vaccinated annually. For example, 1.6 million cattle were vaccinated in 1985 in Rostov province of Russia and, as a result, rabies morbidity was reduced by 8.5 times (71).

Oral rabies vaccination of wild carnivores has not yet been widely used. Limited field trials have been conducted in Belarus, the Kolsk peninsula, and in some other areas (15, 28, 58, 64). Programmes for oral vaccination have been prepared in Ukraine (64).

CONCLUSIONS

Eastern Europe remains a focus of wild canid biodiversity (six species) and rabies virus. In the early years many researchers remarked that fox rabies was more widely distributed in the steppe and forest steppe zones, but in later years the situation in the steppe parts of Ukraine and southwest of Russia improved. Rabies-free areas expanded here due to the monotonous agricultural landscapes – the epicentre had moved northwards. The most active rabies front is now at the junction of forest steppe and mixed forest zones (known as ‘Polesie’ or woodlands) of Ukraine, Belarus and central Russia. The prevalence of fox rabies extends to the Don and Volga basins and northern Caucasus, and the highest population density of the red fox of the steppe zone remains in foothills and broken ground. In general, the natural habitats of wildlife rabies in eastern Europe appear different from those described by Winkler (75).

Since the disintegration of the USSR, the rabies situation remains the same. Fox rabies still predominates in Russia, Ukraine, and in Belarus. However, according to official rabies statistics, the number of animal cases did increase in the middle of the 1990s (Tables 5.7 and 5.8). Increases in dog rabies are reflected in the increased incidence of human rabies (27). In recent years, dogs and cats were the source of infection for more than 50% of human victims in the European part of Russia (58) and in the Ukraine (64). It is very probable that conditions for the next rabies outbreak are gradually forming against a background of economic crisis. History, once again, will repeat. National rabies experts and international organisations (OIE, WHO) must intervene and quickly coordinate control strategies to halt the spread of rabies in animals and decrease the threat to public health.

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* in Russian
** in Russian with English abstract


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CHAPTER 6
RABIES IN POLAND, CZECH REPUBLIC
AND SLOVAK REPUBLIC

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Summary

Rabies has been known in Poland, Czechoslovakia and other central European States since ancient times and in many of them it is still present in endemic form. However, no information about wildlife rabies can be found in the historical records of Poland and Czechoslovakia from the period 1919-1939, although it was claimed that rabies in foxes and wolves was sporadically reported in the eastern parts of Slovakia and western Ukraine. At the beginning of the epizootic of fox rabies in Europe, it was reportedly localized in a focus south of Kalinograd on the Russo-Polish border during the Second World War and that in the 1950s it spread southwards and westwards, eventually to encompass most of western Europe. The data from Poland and the Czech and Slovak Republics indicate that the front line of the epizootic did not move uniformly and that the new outbreaks showed neither temporal nor spatial patterns.

Keywords: central Europe, epizootic, oral vaccination, rabies

INTRODUCTION

In this chapter, an historical record of the disease in Poland, the Czech Republic and the Slovak Republic is reported (Chapter 2, J. Blancou). From analysis of these data, the historical view of the origins of the western European epizootic is presented. Czechoslovakia was established as an independent country in 1918. In 1968 it was declared a Federation of the Czech and Slovak Republics under the name Czechoslovak Socialist Republic (Czechoslovakia). On 1 January 1993, Czechoslovakia was separated into the Czech and Slovak Republics and since that time rabies cases have been independently reported. This chapter gives a detailed overview of rabies past and present through these central European countries.

POLAND

Human rabies

One of the earliest reports of rabies in Poland concerns an event in 1766 when a rabid wolf near Warsaw bit 23 people, all of whom died of rabies (3). At the beginning of the 20th Century, rabies was reported only in domestic animals. Western areas of the country remained almost rabies-free, but the most frequent sources of infection for both humans and animals in the central and southern provinces were rabid dogs. Historical data from the period 1919-1938 show that 5,000 cases of rabies in animals were reported annually and that there were 622 human deaths from rabies. In one year alone (1922), 34 of 5,801 bitten people died of rabies. Between 1927-1929, 470 men and 292 women were given post-exposure treatment at the Pasteur Institute in Warsaw (19). In recent years human deaths from rabies have been reported only rarely, with one death in 1977, two in 1979 and one in each of the years 1980, 1983, 1984 and 1985.

Animal rabies

In the same year (1922), 34 of 5,801 bitten people died of rabies, administration of veterinary measures resulted in the destruction of 7,135 dogs ‘suspected’ of rabies and 4,500 stray dogs and cats. In the following years the numbers of suspect and stray dogs destroyed increased, but urban rabies was not eliminated until the beginning of the Second World War.

By the end of the Second World War, domestic animal rabies was again at very high levels, reaching a peak of 3,670 cases in 1948 (Table 6.1). It is noteworthy that until 1957, few wildlife rabies cases were reported, only 49 cases in 11 years, compared with 13,489 cases in domestic animals. Control of rabies became a
task of prime importance. Compulsory vaccination of dogs throughout Poland was introduced in 1949 and the number of canine and other domestic animal cases decreased from 3,749 in 1949, to 264 in 1951 and to 65 in 1956 (14). Throughout the late 1980s and until the oral vaccination of wildlife began to be effective, the number of dog and cat cases increased (Table 6.1; Fig. 6.1). Between 1989 and 1996 no fewer than 2,271 of these animals (947 dogs and 1,324 cats) died of rabies. This annual average of 284 cases in dogs and cats was despite the compulsory vaccination programmes.

Table 6.1 – Domestic and Wildlife Rabies in Poland 1946-2001

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic</th>
<th>Wild</th>
<th>Total</th>
<th>Year</th>
<th>Domestic</th>
<th>Wild</th>
<th>Total</th>
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<td>9</td>
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<td>1974</td>
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<tr>
<td>1947</td>
<td>2,999</td>
<td>8</td>
<td>3,007</td>
<td>1975</td>
<td>324</td>
<td>1,363</td>
<td>1,687</td>
</tr>
<tr>
<td>1948</td>
<td>3,670</td>
<td>5</td>
<td>3,675</td>
<td>1976</td>
<td>282</td>
<td>918</td>
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<tr>
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<td>1</td>
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<td>1977</td>
<td>322</td>
<td>973</td>
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</tr>
<tr>
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<td>1,035</td>
<td>5</td>
<td>1,040</td>
<td>1978</td>
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<td>915</td>
<td>1,168</td>
</tr>
<tr>
<td>1951</td>
<td>259</td>
<td>7</td>
<td>266</td>
<td>1979</td>
<td>210</td>
<td>853</td>
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<tr>
<td>1952</td>
<td>182</td>
<td>5</td>
<td>187</td>
<td>1980</td>
<td>215</td>
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<tr>
<td>1953</td>
<td>183</td>
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<td>190</td>
<td>1981</td>
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<td>1982</td>
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<td>1984</td>
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<td>1985</td>
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<td>175</td>
<td>1986</td>
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<td>147</td>
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<td>1989</td>
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<td>228</td>
<td>1992</td>
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<td>73</td>
<td>143</td>
<td>1994</td>
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<td>98</td>
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<td>308</td>
<td>1995</td>
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<td>1,973</td>
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<tr>
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<td>166</td>
<td>363</td>
<td>529</td>
<td>1996</td>
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<td>2,065</td>
<td>2,526</td>
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<td>2000</td>
<td>350</td>
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<td>1,123</td>
<td>2001</td>
<td>379</td>
<td>2,579</td>
<td>2,958</td>
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</tbody>
</table>

Total 24,632 41,609 66,241

Fig. 6.1a – Wild animals
Rabies in wildlife

As mentioned above, prior to the Second World War, although literary data indicate that there were a few cases of rabies in foxes and wolves, none of these cases were confirmed in the laboratory. The first laboratory confirmed cases of rabid foxes and badgers were published during 1941-1943 and these were found in the northwestern areas of the country (21) (Fig. 6.2). The number of laboratory diagnosed cases of rabid foxes and badgers from Bydgoszcz, Gdańsk and Olsztyn in the north of Poland slowly increased, (Fig. 6.2), but even by 1955 there were no cases of wildlife rabies in the neighbouring eastern provinces. On the other hand, in the years 1947-1948, a rabies epizootic in foxes was reported in the south of Poland. In the following years no waves of rabies were noticed and new outbreaks were isolated.

1941-1943 1946-1955 1957-1959

Foxes and badgers Foxes and badgers Foxes

Observation and reporting of fox rabies in Poland over the twenty years 1941-1960 suggest that the disease spread from the northwest and from the south towards the central and eastern parts of the country. The front line of the infection wave did not move regularly or continuously; new foci showed neither temporal nor spatial continuity. Movement was rather slow and in some areas of the central regions such as Lodz, wildlife rabies was not observed until October 1978. Sporadic cases in wildlife occurred in the period 1948-1955, reaching about one to seven cases per year, but wildlife rabies increased significantly from 1957 and the disease in foxes, badgers and raccoon dogs became a serious problem (14, 15).
Control policy

In early 1962 control measures which included the help of foresters and hunters were put into operation. In wildlife rabies outbreaks, infected and suspected zones were defined and in such areas hunting, shooting or trapping were not permitted. These measures were carried out on the presupposition that any interventions would increase migration and spread of the disease. On the contrary, hunting in the surrounding areas was supported (14). However, none of these measures were effective and the number of positive cases in wild animals continued to increase, from 142 in 1961, to 168 in 1962, 154 in 1963 and to 173 in 1964 (Table 6.1). The majority of cases were foxes but there were also 18 badgers, 11 roe deer, two raccoon dogs and one wolf. A significant increase in rabies was noticed, mainly in the 1970s when the overall incidence reached 1,200 – 1,500 cases per year. Attention was drawn to the fact that in some places the number of wildlife rabies outbreaks had increased, whereas in others it appeared stationary (20, 21).

Sylvatic foci are the sources of infection for domestic animals. Prophylactic vaccination of dogs, and occasionally cats, as well as the elimination of stray carnivores, remained the basic measures that prevented transmission of the disease from wildlife. Control of rabies by fox den-gassing was not authorised. From the mid-1980s the number of rabies cases dramatically increased and the next ten years or so saw the highest incidence ever recorded in Poland. During 1989-1994 there were 11,278 cases, of which 81.9% occurred in wildlife. Of all affected wild animals, 82.7% were foxes, followed by the raccoon dog with 8.7%. The peak of rabies cases was experienced in 1992, with 3,084 cases reported, 2,547 of which were in wildlife species (Table 6.1).

In 1992, the Polish Veterinary Administration decided to introduce oral vaccination. The first campaign was carried out in 1993 when an area of 39,916 km² along the German-Polish and Czech-Polish borders was covered by airplane bait delivery (28). In the following years the area was extended to the neighbouring east provinces. As a result, the rabies situation considerably improved. In 1997, the overall number of cases was almost half that of 1993 (Table 6.1), the year oral vaccination commenced. Rabies was eliminated from a large area adjacent to the German border in the western part of the country, but residual rabies foci are still irregularly scattered in the eastern half of the country (Fig. 6.3).

CZECHOSLOVAKIA

Human rabies

During 1919-1937, 132 inhabitants of Czechoslovakia died of rabies and nearly 25,000 were given post-exposure treatment at the Pasteur Institute in Prague. Hundreds of other people living in eastern Slovakia were treated at the Pasteur Institute in Kosice (26). In the 1920s, 86% of the 400-600 cases of rabies cases confirmed in the laboratory were dogs. Human rabies is now rarely reported.

Animal rabies

In 1890, rabies in dogs, cats and other animals were reported in 68 of the 128 districts of Bohemia and Moravia (7). Each year hundreds of cases were recorded, of which 90% were in dogs. The majority of cases in domestic carnivores and farm animals occurred in villages and small towns in the heart of the country. Outbreaks of rabies in border areas in the former Austro-Hungarian empire were rather sporadic.
but they indicate that rabies was present not only in Bohemia and Moravia but also in the territory of present-day Poland and Hungary. Unfortunately data concerning Slovakia from that time are not available, but we can suppose that the epidemiological situation was not very different.

Rabies diagnoses were originally made on the basis of clinical signs and were sometimes supported by autopsy of the carcasses. Laboratory examination of rabies was established in 1920 in the State Diagnostic and Serotherapy Veterinary Institute, in Ivanovice. The capacity of this laboratory was sufficient only for the examination of domestic animals and humans.

More precise documentation of rabies in the former Czechoslovakia comes from 1906-1910 and later from 1919-1939 (Table 6.2). No records are available from the years 1911-1919 (1). For the 22.5 years 1906-1939 when data were available, of the 7,497 cases recorded, 6,871 (91.7%) were in dogs and only 317 (4.2%) were in species other than dogs or cats. Although the data for individual animal species were very often incomplete, they prove convincingly that the highest incidence was in dogs. The disease had a typical urban character and domestic dogs were considered to be the main rabies vector throughout the country. Rabid dogs transmitted the disease by attacking other domestic animals, dogs and humans, not only in the territory of their origin but also within a radius of several kilometres. The veterinary measures at the time were focused mainly on the elimination of suspected and stray dogs or cats. According to old data, wildlife rabies was not then a problem and little diagnostic attention was devoted to this matter.

Table 6.2 – Domestic animal rabies in Czechoslovakia 1906-1939

<table>
<thead>
<tr>
<th>Year</th>
<th>Dog</th>
<th>Cat</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
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<td>346</td>
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<td>0</td>
<td>887</td>
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<td>550</td>
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<td>574</td>
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<td>365</td>
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* 1920 data half year only

From 1929, the number of rabies cases in domestic animals gradually decreased; from 608 (519 dogs, 47 cats, 32 cattle, 2 goats) in 1928, to 455 (401 dogs, 24 cats and 30 other domestic animals) in 1929 and to 33 cases in 1939 (Table 6.2, Fig. 6.4). The reduction was achieved by huge dog vaccination campaigns carried out in some parts of Slovakia and Bohemia and in Kosice during 1929-1931 (26). In spite of a slight increase in rabies in 1935-1937 (Table 6.2), the overall situation had been stabilised. No records of rabies between 1940 and 1947 remain because the institute that was carrying out rabies diagnoses was severely damaged during the war. After the war the occurrence of rabies cases increased and the disease spread into new areas.
domestic animals showed typical distribution. Most cases were diagnosed in winter, from January till April and the lowest incidence was July-September. Geographical occurrence of rabies in dogs was bound more to border areas of Bohemia and Moravia, reaching about 700m above sea level, and mountainous parts of Slovakia. Stray rabid dogs from hilly, endemic areas transmitted the disease into the lowlands (16).

**Rabies in wildlife**

For many years, wildlife animals were of little veterinary and public health service interest, although from time to time, mass mortality of foxes was noticed, for example, in 1919-1920. However, foxes were not examined in the laboratory and the aetiology remains unexplained. No information about rabies in wildlife can be found in the historical records from the period 1919-1939 although Ursiny and Stolzová-Sutoriusová (26), claim that rabies in foxes and wolves was sporadically recorded in the eastern parts of Slovakia and in western Ukraine. In 1929, a rabid wolf was killed in Povazska Bystrica district (Slovakia).

**CZECH REPUBLIC (post-1945)**

The rabies situation significantly changed after the Second World War. Populations of foxes dramatically increased, mainly in border hilly and forested areas. Towards the end of 1946 and at the beginning of 1947, mass mortality of foxes, suspected to be of rabies, was noticed. Laboratory examination was extended to include wildlife species. In 1947, two specialised diagnostic laboratories were established, the first in Liberec-Vratislavice to cover Bohemia and the second in Bratislava for Slovakia (16).

In March 1947, the first case of fox rabies in the Broumov district of Bohemia, neighbouring the Czech-Polish borders was diagnosed in the laboratory (17). Further cases followed in the same year. One was found in the Jesenik district, also near to the Polish border, 50 km east of the first focus. Another was recorded in the Jinrichuv Hradec district in south Bohemia, bordering Austria. Novicky (17) considered the foci were not connected because the distance between them was more than 150 km (Fig. 6.5). Cross-border transmission was also unlikely because at that time no rabies was reported in Austria. He concluded that rabies did not enter Czechoslovakia from neighbouring countries but was indigenous without having been diagnosed. In the following year (1948), a considerable increase in rabies incidence was reported and of a total of 143 cases, 106 (74%) of the 117 wildlife cases were in foxes (Table 6.3). Rabies in foxes and other wild animals was verified in many border Czech and Moravian districts.

![Fig. 6.5 – Distribution of rabies cases in foxes 1947-1948](image)

Although the incidence thereafter declined, wildlife rabies became endemic. In the 1950s, the importance of foxes in rabies epizootiology increased and they became the principal reservoir and vector of the disease. In January 1953, compulsory and free-of-charge vaccination was ordered throughout the State (17). The incidence in domestic animals consequently fell to 0-10 annually during 1954-1970 and sylvatic rabies predominated. Several hundreds of fox cases were reported annually (Fig. 6.6 [8, 11, 17, 24]).
Chapter 6

Historical Perspective of Rabies in Europe and the Mediterranean Basin

### Table 6.3 – Domestic and Wildlife Rabies in the Czech Republic 1947-2001

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**Fig. 6.6a – Wild animals**

**Fig. 6.6b – Domestic animals**

**Fig. 6.6 – Development of rabies in the Czech Republic 1947-1998**
Retrospective epizootiological analyses and surveys of results carried out in different periods (6, 10, 11, 12, 18) proved the dominant role of foxes and brought other important findings.

Rabies in domestic animals was diagnosed only in areas of fox rabies; other wildlife species (roe deer, badgers, martens) were victims rather than vectors. The incidence of fox rabies exhibited roughly four-year cycles and a seasonal distribution, characterised by peaks in March-April, troughs in summer and mild peaks in autumn. Since the 1950s, rabies in the Czech Republic has persisted in the typical sylvatic form with occasional transmission to domestic animals, but no direct transmission among domestic animals has been reported.

Continual research carried out during 1960-1974 proved that fox rabies had become endemic in the border areas of west and north Bohemia and north Moravia (11, 13, 18). This situation did not change until 1975. In 1976, rabies began to spread from the western borders towards the interior (12).

During 1977, the situation constantly deteriorated and the mountain barrier in border areas did not restrict the movement of foxes and the spread of rabies to new territories. Further spread was slowed but not stopped by the Vltava – the first cases were found near bridges and places where the river becomes frozen in winter. Neither the payment of a bounty for hunted foxes, introduced in 1969, nor gassing of fox dens, carried out during 1979-1984, permanently improved the situation.

In the 1980s, rabies reached its greatest geographical range. With the exception of several districts, the whole territory of the Czech Republic was affected. The maximum incidence was recorded in 1984, when 2,052 of 2,232 cases were in foxes (Table 6.3). Although the incidence declined slightly towards the end of the decade, not until oral vaccination of foxes was launched in a few districts adjacent to German borders in 1989 was there any significant improvement. In the course of the following years the vaccination area was extended and vaccination campaigns increased (Fig. 6.7), reaching about 60% of the country in 1992 (9) and covering the whole of the country by 1993. From then onwards a continual decline of rabies cases was reported, reaching in 1998 a 94% reduction in comparison with the initial year of 1989 (Table 6.3). The number of cases was reduced from 1,501 in 1989 to 85 cases in 1998. Much of the country has now been cleared of rabies; the geographical distribution of remaining foci is shown in Figure 6.8.
SLOVAK REPUBLIC

The expansion of wildlife rabies in the Slovak Republic was not as intensive as that in the Czech Republic. The first rabies case was reported in April 1947 in a district formerly called Sobrance and was followed as late as 1950 by another in the Presov district. During the next eleven years rabies in foxes and other wild animals was reported only sporadically (Table 6.4). This was thought to be due to the effective veterinary measures carried out in 1950-1955 that slowed the wave of rabies in foxes and wolves which had spread from deep Carpathian forests (24, 26). In addition to compulsory dog vaccination, stray dogs were destroyed and individual and mass hunting of wild beasts of prey were organised. Only one wildlife rabies case was reported in 1959, but from 1962 a considerable increase of rabies was noticed in both wildlife and domestic animals and the sylvatic form, with foxes as the principal vector, has persisted ever since (Table 6.4; Fig. 6.9 a & b).

Wolves played a special role in rabies epidemiology. Rabies in wolves was found quite rarely but the epidemiological consequences were usually dramatic. The first rabid wolf was noticed in east Slovakia (Stropkov) in 1951 and in the following years wolves participated in the spread of rabies in the Republic. Rabid wolves infected a great number of domestic and farm animals in 1958, 1959 and 1960. For example, a rabid wolf bit 51 cattle, 3 horses, 2 goats and many dogs. The majority of them had to be destroyed but 14 cattle and one goat became ill with rabies. One cow became ill after an incubation period of nine months. In 1961, another rabid wolf infected not only cattle, but also a man who died of rabies (26).

The growing importance of foxes in rabies epidemiology had been noticed in the Slovak Republic since the early 1960s. The role of foxes from the post-war period to present time has been described and analysed by many Czech and Slovak authors (12, 13, 18). Their conclusions confirmed the dominant position of foxes in the spread of the disease. The essential reduction of disproportionately high numbers of foxes was often suggested. To fulfil this objective, gassing of fox dens at the time of cub births was introduced (25). The first gassing campaign was carried out in the most affected districts of central
Slovakia in spring 1971 and further campaigns during the following two years covered the whole of Slovakia, but this control method was then abandoned as it was considered unethical and ineffective.

Table 6.4 – Domestic and Wildlife Rabies in the Slovak Republic 1947-2001

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<th>Year</th>
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<th>Total</th>
<th>Year</th>
<th>Domestic</th>
<th>Wild</th>
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The incidence of rabies in the following years varied, but with an upward trend. Significant increases were noted in the 1990s, with the highest figures of positive findings being 489 cases in 1993 and 564 in 1994. Foxes accounted for up to 80%, with domestic animals at 15-20% (23; Table 6.4).

The Slovak Republic joined the European programme of oral vaccination in 1992-1993 when the first few districts were vaccinated. In 1994, a three-year plan (1994-1996) for the oral vaccination of free-living foxes throughout Slovakia commenced (5, 23). In selected districts oral vaccination has continued, bringing positive results, although in 1998-1999 the incidence again increased (Table 6.4).

Rabies control of domestic animals is based on annual compulsory vaccination of dogs and voluntary vaccination of cats and farm animals (23). In 1998, 414 cases of rabies were reported, of which 16% were in domestic animals and 84% in wildlife species. Geographically, rabies foci were scattered almost throughout the country, with the highest concentration of cases near the southwestern area bordering Austria and Hungary.

A role for rodents in wildlife rabies epidemiology?

During the period 1969-1979, rabies strains with biological properties different from common street rabies virus were isolated from small wild rodents. The first Czech strains were isolated in 1969-1972 during the course of a WHO/FAO-coordinated research programme on wildlife rabies in Europe. Originally, on account of their less common hosts, these isolates were designated as ‘rabies-like’ viruses,
but later they were identified by several WHO reference laboratories as strains of rabies virus and their designation as 'murine variants of rabies virus' was recommended (2).

A total of 3,174 wild rodents of the genus *Muridae* and **Microtinae** (predominantly *Microtus arvalis*) were examined during the research period. The animals were trapped in five localities differing in type of epizootiological situation – fox rabies occurred in them either enzootically or epizootically, and had been absent for several years in one of the locations. In all, 71 rabies strains were isolated from brain, brown fat and salivary glands. Basic biological characteristics were determined in each isolate. The isolated strains differed in their rate of adaptation in albino mice and in intracerebral virulence. All isolates exhibited extraneural pathogenicity for common laboratory animals, dogs and foxes; showed distinct viscerotropism, stimulated formation of interferon and produced various unusual forms of non-lethal infection.

These findings and the fact that small rodents constitute a major source of fox diet supported the theory that species other than the fox, specifically small wild rodents, might also function as rabies virus reservoirs. ‘Murine’ rabies attracted a great deal of discussion over several years. The epidemiological and epizootiological importance of rodent strains was discussed primarily because of their low detectability and relatively low virus content in the tissues of their natural hosts (22), but no definite conclusion has been drawn in this regard. Rodent virus strains could be modified; for example, by mouse-to-mouse serial passaging in specific epidemiological situations and by high population densities.

Further investigation was devoted to this problem in 1986-1990. More than 10,000 trapped small terrestrial mammals (belonging to 16 species) and 1,969 rodents (12 species) which had injured humans, were examined for rabies to elucidate the possible role of these animals in rabies epidemiology. In none of the experiments was the occurrence of rabies virus proved. These murine rabies cases led to discussions of a possible role for rodents as natural rabies reservoir species (22) but this hypothesis was not confirmed by further investigation (4).

**CONCLUSIONS**

Historically, the origin of the European epizootic of fox rabies is reported to have been the focus of infection located south of Kaliningrad on the Russo-Polish border. The infection was presumed to have spread from this area southwards and westwards during the 1940s and should have reached the Czech and Slovak Republics and Germany in 1950 (27). Low numbers of wildlife rabies cases were reported in Poland until 1957 (none in 1956) (Table 6.1; Fig. 6.1). The first cases in the Czech and Slovak Republics were reported in 1947 and were followed by a huge increase in cases in the Czech Republic in 1948. In addition, on the evidence available at that time, Novicky (17) considered that the early foci found in the Czech Republic were not connected and did not equate with cross-border invasion. His opinion was that the disease in the Czech Republic was indigenous, without having been diagnosed. The data from Poland and the Czech and Slovak Republics indicate that the front line of the epizootic did not move uniformly and that the new outbreaks showed neither temporal nor spatial patterns. Fox rabies developed nearly at the same time in the above mentioned countries and thus, the historical reports concerning the origin of fox rabies in western Europe are open to further debate.

**References**

CHAPTER 7
RABIES IN GERMANY, DENMARK AND AUSTRIA

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Summary

Rabies has been reported in northern Europe since the Middle Ages. Reports have ranged from sporadic accounts recorded in historical documents to the well documented rabies epizootic in foxes that has spread westwards throughout Europe since the Second World War. However, it is only in the last three decades that the epidemiology of the rabies virus has been understood, and this understanding, combined with extensive surveillance and the development of effective oral vaccines, means that the disease is now being eliminated from much of Europe.

Keywords: epizootics, European surveillance system, fox rabies, oral vaccination, SADB19

PRE-PASTEUR

As we describe rabies in Central Europe throughout the centuries before Louis Pasteur, the reader should keep in mind the influence of the human situation on the course of this disease. If we arbitrarily take the year 1200 AD as a starting date, then we begin with a low human population density which increases over the centuries, but is constantly fluctuating due to the tremendous upheavals caused by war, disease, famine, etc. These changes, which encompassed practically all of Europe, also had a profound effect on the animal population, i.e. the rise of urbanisation caused an increase in the number of domesticated dogs and a decrease in the number of certain wild animal species, such as the wolf. All of these different factors meant that rabies in the early history of Germany, Austria and Denmark could not be classified simply as urban rabies or sylvatic rabies, as it was a mixture of the two types depending on the conditions present at any given time. Due to the many changes in the geographical areas of these three countries over the centuries, this chapter will be limited to the rabies situation which occurred within the present-day political borders.

References to disease outbreaks that could be construed to be rabies can be found in the earliest European literature. The reader is referred to the excellent articles by Steele and Fernandez (52, 53) in which a detailed and very informative chronological history of rabies in pre-Pasteur Europe is described. The period leading up to the Middle Ages is characterised by isolated reports of attacks by rabid dogs, wolves, badgers, foxes and bears. With the increase of human settlements in central Europe, the incidence of rabies began to take the form of epizootics where larger numbers of domesticated animals and humans were involved. As reported by Steele and Fernandez (53) a large outbreak occurred in 1271 in an area of central southern Germany where rabid wolves invaded towns and villages attacking animals and humans, resulting in at least 30 human fatalities. The centuries that followed were characterised by severe epizootics in wolves, foxes and an increasing ‘spillover’ into the dog population. The disease in wolves was especially feared, due to their ferocity and their tendency to roam over large areas, spreading the disease and resulting in numerous human victims. As a result of the reduction of the wolf population, the most prominent natural enemy of the fox, an ever increasing number of fox epizootics were observed in the seventeenth and eighteenth centuries. In parallel with this form of sylvatic rabies, increased urbanisation with an accompanying increase in the number of domestic dogs resulted in rabies epizootics among dogs in large cities, i.e. 1715 in Cologne, 1815-1816 in Copenhagen, 1837-1841 in Vienna, 1851 in Hamburg and 1852 in Berlin (39).
In the years 1803-1830 there were widespread fox epizootics in southern Germany and Switzerland. The Duke of Württemberg issued royal decrees in the years 1779, 1780, 1782 and 1792 that dealt with preventive measures for the control of rabies. These included the muzzling of dogs within cities, yearly inspections of all dogs, the destruction of old or sick animals and a nightly curfew for all dogs. The authorities were instructed to kill all stray dogs, to bury them deep in the ground and to avoid contact with their blood and saliva (23).

With the increase of urban rabies the first control measures, which consisted of containing all owned dogs and eliminating stray dogs, were put into effect in the large cities. Haubner (13) reported an epizootic of urban rabies in Hamburg. In October 1851, after a 23-year rabies-free period, the first case of dog rabies was observed, and by September 1852 more than 203 cases had been registered. When the number of cases in August 1852 reached 44, the authorities ordered all stray dogs to be captured and destroyed, more than fourteen thousand animals. This resulted in a drastic decrease of the disease and in January 1853 only four cases were registered. Due to a slackening of these control measures the number of cases increased again, which led to a more severe control programme and the complete elimination of the disease in 1856.

Delafond (9) published an official Handbook of Veterinary Safety Regulations that was based in part on a decree of a French royal commission dating back to 1784. The regulations stated that the authorities must be notified when rabies was found, vicious dogs must be contained and rabid dogs destroyed. Areas frequented by a rabid dog were to be disinfected by rinsing with hot water. One interesting aspect of the regulation stated that if a stray dog bit a human, the dog should not be killed, but put in quarantine, so that the bitten person could be reassured if the dog did not develop rabies. No mention is made of measures to be taken if the opposite was true. In his Textbook for Veterinary Safety Officers, Adam (1) proposed the establishment of cordon areas, the destruction of all dogs that had had contact with suspicious animals and a six-week quarantine for dogs. Haubner (13) demanded a general reduction in the number of domestic dogs, especially so-called ‘luxury dogs’, by legislating breeding restrictions and by levying very high taxes. All dogs had to wear a collar and those without were to be captured and destroyed within three days. All female stray dogs in heat were to be killed immediately. In larger cities, dogs had to be muzzled when outside the home.

In summary, we have seen that rabies in pre-Pasteur Europe developed from a disease prevalent in wild-living carnivores, the origin of which most likely dates back to the spread of the Roman Empire. With the increase of urbanisation over the centuries a gradual concentration of the disease is observed in those animal species which have best survived and adapted to the new situation, namely the fox and the domestic dog. Due to the increasing contact between man and dogs in large cities, the authorities were forced to implement control measures that, in the light of present-day knowledge, were for the most part sensible and effective. It should be remembered that there was no real knowledge of the aetiology of this disease and the general population regarded rabies with fear and superstition (Chapter 22, J.M. Swabe). This situation changed in the 19th Century with the outstanding studies of Zinke (58), Galtier (12), Roux (37, 38) and, of course, Louis Pasteur and his colleagues (30, 31, 32, 33).

1880-1945

Due to the tremendous advances in the scientific knowledge of rabies made in the latter part of the 19th Century, a new era in the surveillance and control of this disease began. The authorities now had well-founded information available regarding the method of transmission, the possibility of human post-exposure vaccination and, gradually, more tools for the precise diagnosis of rabies. In light of these advances, which also occurred in other animal diseases, legislation was initiated in Germany, Denmark and Austria, as elsewhere. This dealt with disease control and the establishment of a network of veterinary examination centres in which the occurrence of rabies could be determined and these statistics included in a national data collection.

In Germany, from 23 June 1880, the Reichsviehseuchengesetz (Imperial Animal Disease Law) regulated the movement of dogs and defined control measures to be taken, such as the quarantine of dogs, the elimination of stray and suspect dogs and, most importantly, the official registration of all rabies cases (15). In the years that followed, statistical evaluation showed that the disease had developed into a disease
that was principally present in domestic dogs. One of the characteristics was the rapid spread of the disease resulting from the long distances traveled by rabid dogs. Some cases were noted where dogs roamed more than 75 km within a few days, infecting many other dogs along the way (19). This created problems for control authorities, since the disease could leap within a short time from a known infected area to areas previously free of rabies. In the period from 1886 to 1925, 34,727 rabies cases were registered in Germany, with a yearly average of 868. The cases were 79.1% dogs, 15.1% cattle, 1.6% cats, 1.6% sheep, 1.2% pigs, 1.1% horses and 0.3% goats (39). No cases in wild animals were recorded. It is not known whether these statistics include the number of rabies cases in wild animals or whether they are simply a reflection of what was happening in urban areas. Other statistics dramatise the danger of this form of urban rabies for humans due to their close contact with domestic dogs. From 1919 to 1927, 87.3% of post-exposure rabies vaccinations of humans were administered after contact with dogs, 4.9% with cats, 5.0% with cattle and 2.9% with other animals (39). In the years 1915 to 1926, 180 human rabies cases were reported (40).

In the years leading up to the First World War, the application of the above-mentioned control measures led to a marked reduction of rabies cases in Germany, Austria and Denmark. In Germany, the number of cases decreased from more than one thousand per year to 393 in 1912 (39). Even without the help of present-day tools such as dog vaccination, it was possible to eliminate rabies from west and central Germany. However, due to the constant introduction of cases from the heavily infected neighbouring countries to the east, it was not possible to completely eliminate rabies from eastern Germany: a gradient of cases from east to west was established and there were sporadic outbreaks in border areas in southeast and southwest Germany (15). In this period up to the First World War the concept of control measures in the form of barriers or cordons was introduced, with the use of very strict dog control measures to prevent the spread of rabies into the much larger areas of central and western Germany. This barrier concept was to find application at a later date with the introduction of oral vaccination of wildlife in Europe.

In Denmark and Austria the situation was similar. Due to strict control measures and the relatively narrow border with Germany, Denmark was able to completely eradicate the disease and prevent its introduction in spite of pressure on their only border with the European continent. There were no cases of rabies reported in Denmark from 1889 to 1964 (28). In Austria, the period leading up to World War I was characterised by sporadic cases of dog rabies in the southeast section bordering Yugoslavia. Once again, using veterinary control measures, it was possible to completely eradicate the disease prior to 1914.

The chaos resulting from World War I brought about a new wave of rabies in Germany and Austria. The strict control measures that had led to a satisfactory containment of the disease were no longer applied. The displacement of humans and their domestic animals resulted in the spread of rabies into areas that had previously been free of the disease. The uninhibited increase in the number of stray dogs presented a perfect breeding ground for the disease. Therefore, it was no surprise that the average number of rabies cases in Germany increased during 1914-1918 to more than one thousand. The cases were no longer concentrated in eastern Germany, but occurred throughout the country. In the years immediately following World War I the incidence of rabies increased due to the breakdown of the bureaucratic system. In 1923, the number of cases reached 2,467 and increased to 2,699 in 1924 (39).

The re-establishment of veterinary control measures led to a drastic reduction in the number of cases, so that in 1927 only 691 were registered and between 1927 and 1932 the yearly average was 486, once again concentrated in eastern Germany. Published statistics from the period leading up to World War II are somewhat misleading, since the geographical areas covered included large portions of present-day Poland. For example, Eichwald and Pitzschke (10) reported that from 1923 to 1933, 10,123 rabies cases were registered, of which 78.8% were dogs, 13.3% cattle, 3.6% cats and 4.3% horses. These cases occurred almost exclusively in east Prussia, and the territory comprising the Federal Republic of Germany as it exists today was, by 1939, virtually rabies free.

One example of the human influence on the course of rabies epizootics can be found at this time. Before 1914 there were isolated cases of rabid wolves wandering into Germany from the Ardennes forest area of Belgium and Luxembourg. This potential source of infection ceased to exist following the Ardennes offensive in the First World War, during which the wolf population was completely eliminated (15).
With the beginning of World War II the number of reported rabies cases increased in eastern Germany. In order to control these outbreaks, the Ministry of the Interior issued a decree on 28 March 1941, the main points of which can be summarised as follows (15):

1. The establishment of restricted districts (Sperrbezirke) where rabies had been determined.
2. Within these restricted districts, dogs had to be contained at all times.
3. Stray dogs and all suspect animals had to be killed immediately.
4. Owners who allowed their dogs to roam free were to be fined.
5. Dogs taken out of the restricted districts had to have an official document attesting to their freedom from rabies.
6. Dogs that had bitten a human in non-restricted areas had to be locked-up for at least three months and the key deposited at the local police station.
7. If these measures were not successful, then all dogs three months of age and older had to wear a collar on which was noted the owners name and address and other pertinent information (tax number, police registration number, etc.).
8. All confirmed and suspected cases of rabies had to be registered with the veterinary authorities giving detailed information regarding location, human exposure, animal contact, etc.

By the rigid application of these control measures it was possible to contain dog rabies in east Prussia. However, as the war progressed, an increase in the incidence of wildlife rabies in foxes and badgers was noted (15). The retreat of the German occupation forces from Poland and the displacement of millions of people left a huge area that was almost entirely free of human habitation, thus creating ideal conditions for a spectacular increase in wildlife, especially in the fox population. The consequences of this wildlife explosion will be seen in the next section.

1945-1976

In 1947, rabies crossed the Odra (Oder) River from Poland into the former German Democratic Republic (GDR). Germany had been virtually rabies free for a long time. Starke et al. (50) recorded that the last significant outbreak, from 1915-1924, involved 9,773 dogs, 327 cats and 3,071 agricultural pasture animals. The new epizootic developed immediately and began to affect wild animals. According to Starke et al. (50), between 1947 and 1952, 1,099 dogs, 80 cats, 189 agricultural pasture animals and 134 wild animals were affected by rabies in the GDR.

Table 7.1 shows rabies data for domestic and wild animals in Germany in 12 post-war years (1947-1958), as recorded by Pitzschke (34). It can be seen that from 1952 onwards the number of cases of rabies in wild animals exceeds the number in domestic animals. However, it can be assumed that the earlier data were influenced by a lack of wildlife samples. The reasons could be disinterest in hunting following World War II and a deficit in knowledge regarding the vector function of wildlife in rabies dissemination. Out of the total number of cases of rabies that occurred over the 12 year period, 71.5% affected wild animals and 28.5% affected domestic animals. Over the years, the percentage of domestic animals involved varied between 15% and 25%, probably because of seasonal changes in the biology of the fox and because of the changing immune status of the domestic animals as a result of vaccination programmes.

Table 7.1 – Domestic animal and wildlife rabies in Germany 1947-1958 (34)

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th>Wild animals</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>1948</td>
<td>58</td>
<td>18</td>
<td>76</td>
</tr>
<tr>
<td>1949</td>
<td>114</td>
<td>9</td>
<td>123</td>
</tr>
<tr>
<td>1950</td>
<td>423</td>
<td>19</td>
<td>442</td>
</tr>
<tr>
<td>1951</td>
<td>860</td>
<td>612</td>
<td>1,472</td>
</tr>
<tr>
<td>1952</td>
<td>523</td>
<td>885</td>
<td>1,408</td>
</tr>
<tr>
<td>1953</td>
<td>291</td>
<td>645</td>
<td>936*</td>
</tr>
<tr>
<td>1954</td>
<td>571</td>
<td>1,387</td>
<td>1,958*</td>
</tr>
<tr>
<td>1955</td>
<td>657</td>
<td>2,181</td>
<td>2,838</td>
</tr>
<tr>
<td>1956</td>
<td>548</td>
<td>2,290</td>
<td>2,838</td>
</tr>
<tr>
<td>1957</td>
<td>999</td>
<td>3,836</td>
<td>4,835</td>
</tr>
<tr>
<td>1958</td>
<td>630</td>
<td>2,387</td>
<td>3,017</td>
</tr>
<tr>
<td>Total</td>
<td>5,683</td>
<td>14,270</td>
<td>19,953</td>
</tr>
</tbody>
</table>

*: Incomplete data
However, in spite of the prevalent wildlife rabies, the animal species predominantly responsible for human infection was the dog. Starke et al. (50) recorded that out of the 32 people who died of rabies in the GDR between 1950 and 1960, 23 were infected by dogs, three by cats, one by a bovine and five by foxes. The number of human post-exposure treatments rose from 72 in 1947 to more than 8,000 in 1960 (50).

In 1950, the disease broached the well-secured border between East and West Germany (Iron Curtain) and moved westward from the GDR into Schleswig-Holstein. The disease developed in three directions: to the north through Schleswig-Holstein toward the Danish border, westward into Lower Saxony and Nordrhein-Westfalen (crossing the Rhine river in 1960 for the first time and establishing itself on the left side of the river in 1965 [18]) and southward through Hesse and into Bavaria.

Independent of the above extension of the outbreak was a focus in the very eastern part of Bavaria that developed in 1951, most probably infected from Austria and/or the former Czechoslovakia. Interestingly, the focus in Bavaria disappeared in 1954, as did the focus in the adjacent area of Austria in the following year (18).

Pitzschke (34; 35) showed the progression of the disease by drawing maps with the annual distribution of cases in Germany from 1947 to 1962. At the end of this period, approximately three quarters of the country was infected, leaving a corridor in the west and a great deal of the federal states Baden-Württemberg and Bavaria in the south rabies-free. Another study of rabies data from 1953 to 1966 and from 1966 to 1974 produced maps for each of these periods in regard to the distribution of cases (18; 20). During the 1960s and the beginning of the 1970s rabies moved into nearly every part of Germany – including those mentioned above – to the left of the Rhine river in the west and Baden-Württemberg and Bavaria in the south. During this time rabies also crossed the border from Germany to Denmark (1964 and 1968), Belgium, the Grand Duchy of Luxembourg and Austria (all in 1966), Switzerland (1967), France (1968) and the Netherlands (1974) (48).

Denmark had been rabies-free from 1889 until 1964. Due to rigid control measures (see below) the disease, which had crossed into southern Jutland, spread no further than 10km over the border. In 1964 and 1965, 83 rabies cases were recorded before the outbreak ceased (63 foxes, four roe deer, one stone marten, seven cats, five cattle and three sheep). A second outbreak developed late in 1968, although the new focus had no connection with the area in which the 1964/1965 outbreak occurred. From December 1968 until the end of the outbreak in November 1970, 155 animals were diagnosed as rabid (123 foxes, six stone martens, two roe deer, five cats, one dog, 10 cattle, six sheep, one pig and one horse) (28). A further outbreak in Denmark between 1977 and 1982 involved 48 farm animals and 327 wild animals, 308 (82% of the total number of infected animals) were foxes (48).

Following the Second World War, Austria experienced three different rabies epizootics. From 1946 to 1948, Hecke (14) reported 625 rabies cases in domestic animals. They derived from an area bordering the former Yugoslavia and Hungary in the southeast of the country and thus had a connection to countries with an urban rabies cycle. This focus disappeared in 1951 due to vaccination efforts. In 1949, for the first time, a total of 329 cases were reported, 274 (83%) of which were in wild animals (222 foxes, 42 badgers, nine roe deer and one hare). The focus, however, was in the north – the Waldviertel and Mühlviertel – with infection most probably originating in the former Czechoslovakia. In 1950, 85% of the cases occurred in wild animals and in 1951 this figure rose to 93% (14). In 1951, the disease probably moved from the north of Austria to Bavaria, Germany. Interestingly, as mentioned above, both foci ceased, the one in Bavaria in 1954, the one in Austria in 1955. Pitzschke (34) reported that in Austria there was one case each in 1956 and 1957 and no cases in 1958.

Kauker (20) describes Austria as rabies-free from March 1959 until April 1966. On 25 April 1966, the Federal Province of Tyrol was infected from Germany in the district of Reutte. The Federal Province of Vorarlberg was also infected from Germany in November 1967 in the district of Bregenz. The disease established itself in these two federal states and by 1974 there had been between nine (1966) and more than 200 (1974) outbreaks (not cases) in newly infected communities. The disease expanded eastward in 1975 and 1976 and the number of rabies cases increased. During this time Austria was also infected from Hungary at her eastern border (21).
Over the years much thought has been given to the control of the disease in wildlife and the specific issues that this involves, e.g. the participation of certain animals in the disease, the wildlife reservoir, the spread of the disease to other areas or countries, seasonal changes in the intensity of outbreaks, etc. As some of these subjects are being covered in detail elsewhere in this volume, a short description only of the specific contributions of the three countries involved is given.

Soon after 1947 the distribution of animals was such that conditions became ideal for the spread of wildlife-mediated or, more specifically, fox-mediated rabies. The latter fact is important since all attempts to find another wildlife species that could independently maintain the disease had failed. As mentioned above, Pitzschke (34) reported that 19,953 animals were diagnosed rabid in the Federal and Democratic Republics of Germany between 1947 and 1958, 5,683 (28.5%) of these were domestic animals and 14,270 (71.5%) were wild animals. Schneider (45) noted that in the Federal Republic of Germany there were 74,950 animals diagnosed rabid between 1954 and 1976: 14,494 domestic animals (19.3%) and 60,456 wild animals (80.7%). Schneider and Müller (48) reported that there were a total of 51,987 rabid animals in the two German Republics between 1977 and 1983: 7,822 domestic animals (15%) and 44,165 wild animals (85%). The percentage of foxes involved was 57.6% (34), 66.6% (45) and 73.7% (48) respectively. Additionally, an unknown number of non-identified cases should also be taken into consideration. Von Braunschweig (cited by Schneider) estimates this unknown to be as high as at least 97% for the fox (45).

In Austria, 12,968 animals were registered rabid from 1977 to 1983: 739 (5.7%) in domestic animals and 12,229 (94.3%) in wildlife species. Of the latter, 10,299 (84.2%) were foxes (48). The species distribution of cases in Austria is summarised in Table 7.3.

In addition to the obvious dominance of fox rabies in the statistics there were other reasons for considering the fox to be the main vector. The number of cases in animals which could come in contact with the fox – pasture animals, stray cats and other wild animals – depends on the magnitude of the outbreak caused by the fox. Using three examples from southern Denmark and the German federal states of Baden-Württemberg and Schleswig-Holstein (for details, see below), Weinhold (56) demonstrated that measures for the control of foxes may reduce and even eliminate the disease. The reduction of rabies among foxes was shown to result in a reduced number of rabies cases among dogs and cats, which are the main source of infection in humans.

The fox was obviously an important rabies reservoir, but in Germany there were efforts to find other possible reservoir species amongst rodents and insectivores. Pitzschke and Gottschalk (36) investigated 23 bats, 425 hamsters, four moles and 202 muskrats with negative results. Within the framework of a European rabies research programme coordinated by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO), 1,048 wild rodents and insectivores in formerly infected areas of the federal state of Hesse were tested, also with negative results (11). The latter authors concluded that these animals are of no epidemiological importance for rabies.

However, contrary to the above results, Schneider and Schoop (43) were able to isolate eight virus strains from 635 apparently healthy animals of the rodent families Microtinae and Murinae in southern Germany, partly from areas that had been rabies-free for several years. These rodent rabies variants adapted to laboratory mice were able to infect foxes. Though these viruses may be latent in certain rodents, a WHO working group that analysed the results as part of a WHO/FAO research programme on wildlife rabies saw no evidence to link fox rabies with a reservoir in rodents (2).

One characteristic of fox-mediated rabies as opposed to urban rabies was a steady moving of the front line into previously non-infected areas – an important fact in regard to the course of the disease. Moegle et al. (26) investigated this phenomenon in the Südwestmemo-Hohenzollern region of the federal state of Baden-Württemberg in the south of Germany. Based on 2,822 cases of animal rabies recorded in the study area from 1963 to 1971, the new cases of rabies pushed the front line of rabies cases forward by a mean distance of 4.8 km beyond the front line of the preceding month. No difference was observed between areas of different fox population densities and different frequencies of rabies cases. One other result of the study was that no carnivore other than the fox played a significant role in the spread of the disease beyond the front line.
With the changeover from urban rabies to wildlife or fox-mediated rabies in central Europe, the measures for the control of rabies needed to be outlined anew. The logical approach to the problem was to control the wild vector animal, the fox. In the beginning, control could be affected by shooting, trapping, poisoning and gassing. That meant that hunters had to be involved to effectively reduce the fox populations.

The method which developed most effectively, based on studies in the federal state of Hesse in Germany, was the gassing of fox dens as suggested by Kersten and Zinn (22), in combination with the promotion of shooting and paying bounties.

Moegle et al. (25) analysed (from hunting statistics) in the federal state of Baden-Württemberg the number of foxes killed annually per km² as a measure of the relative density of the fox population. A comparison of areas of different topography or degree of fox control showed a distinct relationship between the relative population density of foxes and the incidence and trend of wildlife rabies. The authors recommended continuously checking the density of the fox population as a basis for decisions on control measures.

An example whereby the combination of gassing and shooting not only led to the reduction of the vector species but also eradicated the disease can be shown from Denmark. The country was infected three times via the federal state of Schleswig-Holstein in Germany; in 1964-1965, 1969-1970 and 1977-1982. Each time a protective belt of 60-80 km in depth in southern Jutland in Denmark along the German/Danish border significantly hampered the spread of the infection. Shooting for bounty within the belt and gassing with cyanogens were the methods used. Danish wildlife biologists, who co-operated in the fox reduction programme, estimated that shooting as the sole measure of control produced a 25% reduction, but shooting and gassing combined resulted in an 80% reduction in the fox population compared to the pre-campaign level (28). The animals involved in the three outbreaks were mentioned above.

Gassing was an effective method of reducing the number of foxes, but investigations were carried out in the federal states of Baden-Württemberg (24) and Hesse (55) because there was concern that it might also be affecting the badger population in Germany. Moegle and Knopp summarised their observations as follows:

1. According to hunting statistics the population of badgers (Meles meles) had fallen to 10% of the previous population level through rabies alone.
2. Gassing of fox dens alone had less effect in reducing the badger population than rabies itself.
3. Rabies and gassing activities together had reduced the badger population to around 10% and in some areas even lower. In areas where rabies had existed among badgers for a long time the reduced badger population stayed at around 10-13% of its original level and showed no further decrease despite continued gassing.
4. The badger affected with rabies was not particularly aggressive and was seldom involved in human exposure.
5. In the epidemiology of wildlife rabies the badger was more the victim of the disease than its active propagator. It played no special part in the dissemination of the disease. Rabies in badgers unaccompanied by the disease in foxes was not observed. The badger on its own could not support a rabies epidemic.

With gassing established as the most effective method for fox reduction there was an official federal government Order in 1970 stating that it had to be applied countrywide in the Federal Republic of Germany. However, for judicial reasons the Order was rescinded in 1974 (45) and gassing was prohibited. This is perhaps the reason for the all-time peak of 8,842 rabies cases in 1976 in the Federal Republic of Germany (45).

Along with the control of wildlife rabies the control of domestic animals had to be considered. Unfortunately, the two Germanys were for many years the only countries that did not vaccinate domestic animals. This decision was based on evidence that showed that vaccinated dogs coming in contact with
the street virus could become carriers and disseminators of this virus, and could, in the worst cases, transmit it to humans (7). The results were vehemently debated [see (42) for arguments in favour and (54) for those against]. In the Federal Republic of Germany official permission to vaccinate domestic animals on a voluntary basis was first established in 1969 (44).

1977-1999

Surveillance of rabies has a direct impact on the treatment of exposed persons and on the control of rabies in natural reservoirs of the disease. In 1977, a European surveillance system was established in Tübingen, Germany, due to an initiative of the World Health Organization. Data from European countries was provided by veterinary and medical authorities and, over the years, as national systems developed to a common acceptable standard, Europe-wide disease surveillance improved. These data are now presented as text, tables and maps and published quarterly in the Rabies Bulletin Europe with the inclusion of new cumulative epidemiological information as well as general articles on the disease (3).

The Federal Republic of Germany accumulated statistics from 1950 to 1981 that were studied to investigate regional differences in the occurrence of rabies. At the level of the Landkreis (an administrative unit with a mean area of 1,013 km²), four basic patterns of rabies incidence were identified. The distribution of these four epidemiological patterns was geographically localised to show how the influence of landscape is associated with the different patterns of occurrence and interpreted in terms of fox population density and contact rate. The results of such a surveillance study can be used to plan control measures (16). Kroczak et al., cited by Jackson et al. (17) reached similar conclusions when they studied the relationship between rabies occurrence and habitat in Austria.

In spite of developing optimal conditions for reducing the fox population as a control measure (see above), success in reducing or eradicating rabies, as seen for example in Denmark, was limited. Therefore, the time had come to consider alternative methods of disease control. Many scientists in North America and Europe had long envisioned the implementation of a revolutionary new approach to disease control in wildlife and, on the basis of intensive scientific studies, it was decided that European field trials for the oral vaccination of foxes against rabies would be initiated (57). The Swiss were the forerunners and they started the first large-scale field trial for the immunisation of foxes in October 1978 in the Canton of Valais (Chapter 24, P.-P. Pastoret et al.). They used chicken-head baits containing a modified live rabies virus (SAD Bern). German scientists observed the field trials and also contributed monoclonal antibodies to distinguish between the vaccine and wild-type virus. This was important for the intensive follow-up examinations that were necessary to prove the safety of this method (51).

In Germany the preconditions for a field trial were established in 1983 (46, 47). A new improved vaccine (SADB19) had been developed and, as in Switzerland, chicken heads were used as bait. In 1984, a decisive breakthrough was achieved with the development of a bait consisting of fat and fish meal that could be mass-produced by machine, the so-called Tübingen fox bait. Furthermore, field tests revealed a much higher seroconversion rate (protection) than was achieved using chicken heads. By 1987, 2.6 million Tübingen fox baits had been used in Germany (49).

In 1985, field trials using the German method were extended to northern Italy and in the following year trials began in Austria, Luxembourg and border areas of Belgium and France (49). The tremendous success of the oral vaccination of foxes in Germany and Austria can be seen in Tables 7.2 and 7.3 respectively.

In spite of the obvious success of this method there were also setbacks and criticisms. Setbacks occurred when, due to oral vaccination, the survival rate of the fox increased, which resulted in an increase in reproduction, but the new high fox populations were not sufficiently supplied with vaccine baits. Thus, residual foci developed and by not increasing the number of vaccine baits/km² accordingly, the disease could not be eliminated (41, 29). Criticism arose that the increased fox populations could favour the spread of other diseases such as echinococcosis or mange and that endangered prey animals of the fox could become extinct (29). The distribution of rabies cases in Germany, Austria and Denmark at the end of 1999 presented a very favourable picture due to the successful method of oral vaccination (6).
Table 7.2 – Rabies in Germany 1979-2001

<table>
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<tr>
<th>Year</th>
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<th>Wildlife animals</th>
<th>Total</th>
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Source: Rabies Bulletins Europe, issues 1/77 to 4/2001. Data have been taken from the original reports to the Rabies Bulletin Europe. They differ slightly in summary reports where corrections have been made for data sent late.

Within the time span described here (1977-1999), Denmark had a third invasion of rabies from Schleswig-Holstein, Germany, which lasted from 1977 to 1981 but, as in the two previous instances, it was stopped by using conventional control measures. From 1985 onwards, only bat rabies was reported in Denmark, mainly in Jutland. There were 10 bat rabies cases in 1999. In Germany in the same year there were 55 cases in terrestrial animals distributed throughout several states in the centre of the country: 37 foxes, seven other wild animals and 11 domestic animals. Furthermore, there were 15 bat rabies cases in the north of the country. In Austria, only five cases were reported: one fox close to the Hungarian border, two foxes and one roe deer near the border with the Czech Republic and one dog which had been imported from Turkey.

**Human rabies**

A total of 54 human rabies cases were recorded in Germany between 1950 and 1999. Thirty-four indigenous cases occurred within the first 10 years, but in the following 40 years there were only ten indigenous cases and a further 10 people were infected abroad (two in Greece in 1965, four in Turkey [one each in 1971, 1972, 1975 and 1976], one in Iran in 1975, one in Egypt in 1978, one in India in 1986 and one in Sri Lanka in 1996) (4, 5). Of the 42 indigenous rabies cases where the source of infection was described, 29 originated in a dog, four in a cat, one in a bovine and only eight in a fox. There was only one human case reported from Austria, it occurred in 1979 and the origin of the infection was a fox. There were no reports of human rabies from Denmark.
Table 7.3 – Rabies in Austria 1977-2001

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<th>Wild animals</th>
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Source: Rabies Bulletins Europe, issues 1/77 to 4/2001. Data have been taken from the original reports to the Rabies Bulletin Europe. They differ slightly in summary reports where corrections have been made for data sent late.

Bat rabies

The first diagnoses of rabid bats was in 1954 in Hamburg, Germany (27), and in Ansager, Jutland, Denmark in 1985 (8). Since then bat rabies has been regularly reported in these two countries but there have been no cases reported from Austria. In Denmark the cases were distributed throughout the country and in Germany they were mostly restricted to the northern coastal areas of the Baltic and the North Sea. In 1998, there were for the first time three sheep infected in Denmark with a bat rabies virus or European Bat Lyssavirus type 1 (EBLV 1) indicating that transmission from bats to terrestrial animals is possible (Chapter 17, A.A. King et al.).

CONCLUSIONS

After the Second World War there were three different types of rabies experienced in Austria, Denmark and Germany: urban rabies in Austria (only for a short time), the new wildlife rabies in all three countries, and bat rabies in Denmark and Germany.
A focus of urban rabies existed in 1946 in Austria along the state borders with Hungary and the former Yugoslavia. This focus was completely eradicated by vaccination of dogs in 1951. North of the river Danube a focus of wildlife rabies established itself in 1948 along the border with the former Czechoslovakia. By using only the reduction of vector species and dog vaccination, Austria became rabies-free in 1959 and remained so until 1966. At the end of 1999 the country was nearly rabies-free due to the application of a programme of oral vaccination of foxes which had been started in 1986.

Germany was infected in 1947 with wildlife rabies from Poland and over the years the disease was found in all areas of the country. No control methods to reduce the vector species were able to halt its spread. The most effective method was the gassing of fox dens in combination with increased hunting of foxes and the payment of bounties, but overall, the success of these methods was transient.

Oral vaccination of foxes, which began in 1983, has had a great impact. Improved vaccines and baits, together with a WHO coordinated programme of European co-operation for dealing with the infectious pressure of rabies in border areas has helped to speed up the progress of controlling the disease. However, at the end of 1999, there were still great efforts needed to cope with the high fox populations and to completely eradicate the disease. The drastic decrease of rabies cases in terrestrial animals and the growing public awareness of the disease combined with the development of excellent human rabies vaccines have dramatically reduced the number of human cases. Among the few cases remaining, more are imported than are indigenous. Since the 1980s bat rabies cases have been regularly registered in the north of Germany.

Denmark was invaded three times by wildlife rabies from Germany, in 1964-1965, 1968-1970 and 1977-1981. Each time the disease was successfully eradicated by reducing vector species numbers using fox den gassing and increased hunting. Since 1985, bat rabies cases have been regularly reported in the country. This represents a new epidemiological situation for which there are presently no control measures available.

References
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CHAPTER 8

RABIES IN ITALY, YUGOSLAVIA, CROATIA, BOSNIA, SLOVENIA, MACEDONIA, ALBANIA & GREECE

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Summary

There is a rich historical record of rabies from Italy, Greece and countries of the former Republic of Yugoslavia. Italy and Greece have succeeded in eradicating the disease, whereas countries such as Albania, Bosnia, Croatia and Slovenia continue to deal with rabies in wildlife due in part to the movement of infected foxes from the north. This chapter gives a detailed overview of rabies past and present in these southern European countries.

Keywords: dog rabies control, hemp vaccine, oral fox vaccination

ITALY

Epimarcus, Virgil, Horace and Ovid mentioned rabies in ancient times. Lukian, a Roman writer, believed that not only was the disease spread by biting dogs but that persons who became rabid could spread the disease by biting other persons, and therefore affect several people (68). The infectivity of the saliva of rabid dogs is described by Cardanus, a Roman writer. The Roman writers described the infectious material as a poison for which the Latin was ‘virus’. Celsus, a physician and naturalist, made rabies his particular study in the 1st Century AD. He was emphatic that the bites of all animals that contained virus were dangerous to man and to other animals. Indeed, Celsus and his contemporaries recognised that saliva alone contained the poisonous agent. In his description of wounds he says, ‘I have spoken concerning those wounds which are mostly inflicted by weapons, so it follows that I may speak concerning those which are caused by a bite, sometimes of a human, sometimes of an ape, often of a dog, and sometimes of wild animals or of a serpent. But every bite contains some venom’. Of the disease itself he writes in De Medicina ‘The Greeks call it hydrophobia, a most wretched disease, in which the sick person is tormented at the same time with thirst and the fear of water, and in which there is but little hope’ (68). The sagacious precautions recommended by Celsus not only show the disease was well understood but that it was more or less prevalent and taxed the medical skills of the time. It was an Italian savant, Girolamo Fracastoro (1478-1553), who described rabies as we know the disease today and recorded the true nature of rabies in his script ‘The Incurable Wound’, dated 1546. He described how humans are not only susceptible to rabies, but also that they invariably die once clinical symptoms occur. Unfortunately, this still holds true today, with very few exceptions (26). For a fuller account of rabies in ancient times (Chapter 1, J. Neville).

Early events in Italy

In 1763, rabies appeared in France, Italy, and Spain. Dogs were slaughtered by the hundreds by the authorities (68). In Crema, Italy, in 1804, a mad wolf descended from the mountains and bit 13 persons, nine of whom died of hydrophobia. Negri, who in 1903 discovered the bodies which bear his name, thought that he had discovered a micro-organism which could be included among protozoa (53). This conclusion was drawn since Negri was working in Golgi’s laboratory in Pavia, Italy, where studies on
malaria were being intensively pursued. The predilection site for Negri bodies was in the Ammon's horn or hippocampus, but they were also found in the spinal ganglia and the spinal cord of dogs in which rabies virus occurred naturally or experimentally, and in experimentally inoculated rabbits. In another study, Negri used their presence as a practical diagnostic test for rabid animals and laid the groundwork for the long-used test (74).

In 1904, Bartarelli showed that virus reached the salivary glands of rabid dogs via the peripheral nerves (74). In 1907, Fermi in a review of a large number of experiments, pointed out the difficulty of demonstrating rabies virus in the saliva (74). In 1908, Fermi indicated various defects in Pasteur's vaccination regime and he introduced a new method in which the vaccine was treated with carbolic acid (74). The uniformity of this vaccine and simplicity of preparation were its main advantages and as it was preserved it could be made available anywhere.

According to Fermi (61, 73) a recrudescence of rabies cases was recorded in Italy after the First World War and in 1928, 1,492 outbreaks of rabies in animals were reported. However, rabies had almost disappeared from Italy by 1940, but from 1944 the incidence rose to an alarming level, according to the figures provided by the High Commissariat for Hygiene and Public Health (17).

1945 to the present time

During the Second World War and in the following years, Italy experienced a serious increase in the number of outbreaks of rabies, a disease which previously had been limited to a few areas in the south of Italy and Sicily. The infection spread to the northern provinces where human cases occurred. In order to improve the situation, the central authorities reorganised and strengthened anti-rabies services, and their first objective was to reduce the great number of stray dogs (Table 8.1). Provisions relating to dog registration, dog ownership tax collection, the seizure of stray dogs and the segregation of biting dogs were strictly enforced. After 1950 veterinary police activities were supported by the application of an immunisation strategy.

In 1954, the ‘Regolamento di Polizia Veterinaria’ (Italian Veterinary Order) was approved by the Italian Parliament (9), providing the Veterinary Services with an official tool for the implementation of rabies control (Articles 83 to 92). Preventive anti-rabies vaccination of dogs was made compulsory and within four years 900,000 doses were administered. These prophylactic measures gave satisfactory results in all the northern and central provinces of the country and in Sardinia, these areas becoming free from the disease after only two or three annual vaccination campaigns. In the south, the situation also improved. Only in Sicily were the results less satisfactory, in spite of the active seizure of stray dogs. But it was precisely on this island that very little consideration was given to immunisation despite the presence of the disease.

Phenolised or carbol-glycerinated vaccines were used, because they were better tolerated than formalised vaccines. Illness due to the administration of vaccines was of very low incidence (not more than 0.1%). Health measures which were applied for rabies control reduced human losses to five or six annually, compared with a mean of 62 cases just after the war (Table 8.1). Urban rabies spread significantly in the years 1947-1950; then the Veterinary Services were reorganised, with the subsequent control of stray dogs and the first vaccination campaign with killed vaccines (live vaccines were introduced in 1962). The measures taken were reported to the OIE (1, 2). With a single exception, no rabies cases were reported in northern Italy from 1957 to 1967-1968.

An increase in cases was recorded in the municipality of Rome (central Italy) and southern Italy in the years 1963-1965 (28, 64). A total of 66 dogs were diagnosed rabid in the municipality of Rome in early 1963 and two human cases also occurred (28). Italy, but particularly the municipality of Rome, had a great number of stray dogs and the measures applied for rabies control were not fully effective at the time. In 1969-1970, it was decided to try to eliminate urban rabies from Italy by vaccinating the dog population with Flury HEP. About 2,500,000 doses were distributed free of charge for a total dog population estimated at 4,000,000, including unregistered animals. No cases of rabies have been reported in central Italy since 1970.
Table 8.1 – Human and animal rabies in Italy 1946-1975

<table>
<thead>
<tr>
<th>Year</th>
<th>Human rabies</th>
<th>Animal rabies</th>
<th>Domestic animal cases</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P.E.T Died</td>
<td>Vaccinated</td>
<td>Destroyed</td>
<td>Dogs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cats</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>1946</td>
<td>ND 46</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1947</td>
<td>17,648 87</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1948</td>
<td>16,725 83</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1949</td>
<td>15,102 53</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1950</td>
<td>23,243 41</td>
<td>147,950</td>
<td>166,039</td>
<td>1,141</td>
</tr>
<tr>
<td>1951</td>
<td>22,254 11</td>
<td>383,226</td>
<td>141,239</td>
<td>638</td>
</tr>
<tr>
<td>1952</td>
<td>20,150 7</td>
<td>209,029</td>
<td>122,689</td>
<td>307</td>
</tr>
<tr>
<td>1953</td>
<td>18,351 6</td>
<td>153,238</td>
<td>120,455</td>
<td>292</td>
</tr>
<tr>
<td>1954</td>
<td>16,916 8</td>
<td>111,467</td>
<td>122,058</td>
<td>203</td>
</tr>
<tr>
<td>1955</td>
<td>16,761 1</td>
<td>145,344</td>
<td>122,053</td>
<td>163</td>
</tr>
<tr>
<td>1956</td>
<td>16,299 1</td>
<td>100,750</td>
<td>109,189</td>
<td>227</td>
</tr>
<tr>
<td>1957</td>
<td>16,597 8</td>
<td>177,594</td>
<td>115,026</td>
<td>285</td>
</tr>
<tr>
<td>1958</td>
<td>17,575 6</td>
<td>163,145</td>
<td>106,690</td>
<td>252</td>
</tr>
<tr>
<td>1959</td>
<td>17,707 5</td>
<td>187,811</td>
<td>107,015</td>
<td>261</td>
</tr>
<tr>
<td>1960</td>
<td>18,511 2</td>
<td>149,607</td>
<td>96,294</td>
<td>213</td>
</tr>
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<td>1961</td>
<td>15,751 4</td>
<td>128,524</td>
<td>96,940</td>
<td>148</td>
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<td>19,507 1</td>
<td>73,628</td>
<td>92,645</td>
<td>149</td>
</tr>
<tr>
<td>1963</td>
<td>23,187 7</td>
<td>254,563</td>
<td>109,848</td>
<td>434</td>
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<tr>
<td>1964</td>
<td>25,823 6</td>
<td>406,630</td>
<td>106,714</td>
<td>686</td>
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<tr>
<td>1965</td>
<td>24,949 1</td>
<td>551,107</td>
<td>143,349</td>
<td>532</td>
</tr>
<tr>
<td>1966</td>
<td>23,295 4</td>
<td>553,516</td>
<td>102,426</td>
<td>185</td>
</tr>
<tr>
<td>1967</td>
<td>21,977 1</td>
<td>538,201</td>
<td>98,183</td>
<td>140</td>
</tr>
<tr>
<td>1968</td>
<td>20,925 2</td>
<td>531,240</td>
<td>103,742</td>
<td>142</td>
</tr>
<tr>
<td>1969</td>
<td>19,262 0</td>
<td>1,816,271</td>
<td>97,875</td>
<td>38</td>
</tr>
<tr>
<td>1970</td>
<td>18,781 1***</td>
<td>538,625</td>
<td>99,788</td>
<td>10</td>
</tr>
<tr>
<td>1971</td>
<td>20,051</td>
<td>582,120</td>
<td>92,614</td>
<td>10</td>
</tr>
<tr>
<td>1972</td>
<td>22,493</td>
<td>480,000</td>
<td>86,006</td>
<td>44</td>
</tr>
<tr>
<td>1973</td>
<td>23,776</td>
<td>350,000</td>
<td>93,594</td>
<td>2</td>
</tr>
<tr>
<td>1974</td>
<td>25,671</td>
<td>436,000</td>
<td>96,177</td>
<td>0</td>
</tr>
<tr>
<td>1975</td>
<td>28,857</td>
<td>570,000</td>
<td>58,111</td>
<td>0</td>
</tr>
</tbody>
</table>

**P.E.T:** post-exposure treatment; **ND** = no data
* : includes 22 wildlife cases from Messina, Sicily
** : includes 4 wildlife cases from Palermo, Sicily
*** : infected in India
**** : last case, March 1973

According to Goffredo (27), the last cases of rabies in Puglia (southern Italy) were diagnosed in three dogs bitten by a wolf in the province of Foggia. Rabies persisted in the provinces of Cosenza, Catanzaro and Reggio Calabria (Calabria region) of southern Italy, where 6, 6 and 57 cases respectively were reported in the period 1967-1973 (61, 16). Control measures were not enforced at the time because of political problems.

In Sicily, rabies was reported in red foxes in the years 1961-1963 (Table 8.1) in the province of Messina (69, 70, 72) and in 1968-1969 in the province of Palermo (71, 56). The disease also spread to cattle: in 1961, 226 died, while a further 54 and 8 died in 1962 and 1963, respectively. In 1968-1969, rabies was diagnosed in 77 cattle. The control measures enforced were based on the control of the fox population (mainly by poisoning) and on vaccination of cattle and dogs in the infected provinces. No cases of rabies have been reported from Sicily since 1971.
In Campania, reports from 1967 to 1971 involved dogs and cats mainly from urban areas. Three human cases were diagnosed in the province of Naples in 1967 (1) and 1968 (2, 16). In the provinces of Trento, Bolzano and Belluno one, 19 and 2 cases of sylvatic rabies respectively were reported during 1967-1968. Control measures including fox population reduction and dog vaccination were taken. By March 1973 the whole of Italy was free from both sylvatic and urban rabies. Reports on the rabies situation and control in Italy were presented at the OIE (1, 2, 63). Other reviews of the Italian situation were given in 1972 (10, 16). However, Italy has borders with Austria, Switzerland, France and Yugoslavia, countries in which sylvatic rabies was present. Despite the physical barrier to rabies represented by the Alps, measures were taken to monitor and limit the entrance and/or presence of the disease (15).

Sylvatic rabies in Italy: 1977-1995

Sylvatic rabies has been recorded in the alpine area of northern Italy from the Aosta to Trieste provinces. The first epizootic lasted from 1977 to 1986 (Table 8.2). Oral vaccination of foxes against rabies using SAD B19 vaccine (Table 8.3) began in 1984 and continued until 1987. The second epizootic lasted from 1988 to 1989, caused by an infection originating from Slovenia. Two vaccination campaigns were carried out in 1989 to extinguish this outbreak. The third epizootic started in 1991, again at the Italian/Slovenian border and lasted until December 1995. In 1993 and 1994, a new epidemic originating from Austria occurred in the province of Bolzano. From 1992 to 1999 vaccine-baits were distributed at the Italian/Slovenian border and from 1993 to 1995 in the Bolzano province.

Table 8.2 – Rabies in Italy 1977-present*

| Year | Domestic animals | | | | Wildlife animals | | | | Total |
|------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|      | Dog | Cat | Cattle | Other | Total | Fox | Badger | Other | Total |                  |
| 1977 | 0   |     |        |      | 82    |      |        |      |  5    |     12 |         99 |
| 1978 | 1   |     |        | 1    | 203   | 25   | 21     | 249  | 250   |          |
| 1979 | 1   | 1   |        | 1    | 61    | 10   | 7      | 78   | 79    |          |
| 1980 | 0   |     |        | 1    | 10    | 2    | 12     | 12   | 12    |          |
| 1981 | 2   | 2   | 4      |      | 320   | 23   | 20     | 363  | 367   |          |
| 1982 | 3   | 1   | 8      |      | 291   | 31   | 15     | 337  | 345   |          |
| 1983 | 3   | 2   | 9      |      | 404   | 22   | 13     | 439  | 448   |          |
| 1984 | 2   | 1   | 7      |      | 316   | 20   | 11     | 347  | 354   |          |
| 1985 | 2   | 1   | 4      |      | 101   | 11   | 3      | 115  | 119   |          |
| 1986 | 1   |     | 22     | 1    | 5     | 1    | 28     | 29   | 29    |          |
| 1987 | 0   |     |        |      | 0     |      |        |      | 0     |          |
| 1988 | 0   |     | 21     |      | 21    |      |        |      | 21    |          |
| 1989 | 1** |     | 50     | 4    | 54    |      |        |      | 54    |          |
| 1990 | 0   |     |        |      | 0     |      |        |      | 0     |          |
| 1991 | 0   |     | 4      |      | 4     |      |        |      | 4     |          |
| 1992 | 1   | 19   | 1      | 2    | 22    |      |        |      | 23    |          |
| 1993 | 1   | 1    | 67     | 7    | 80    |      |        |      | 82    |          |
| 1994 | 0   | 31   | 2      | 36   | 36    |      |        |      | 36    |          |
| 1995 | 1   |     | 8      | 2    | 10    |      |        |      | 11    |          |
| 1996 | 0   |     |        |      | 0     |      |        |      | 0     |          |
| Totals| 14 | 5 | 4 | 39 | 2,010 | 169 | 115 | 2,294 | 2,333 |          |

* : surveillance is continuous but no case has been reported since 1995

**: dog imported from Ivory Coast, not included in totals

The landscape of the sylvatic rabies infected area in Italy was composed almost entirely of typical alpine valley and consisted of approximately thirty valleys 10-60 km long and 5-15 km wide, to give an area of 50-1,500 km². In these valleys there are many natural barriers to the spread of sylvatic rabies, which maintain the fox population density under 0.3 fox km⁻² at about 1,500 m. Above this altitude high mountains prevent fox movement. The high alpine passes are seldom reached and crossed by the fox during the autumn migration period, and rivers and tarmac roads are rarely crossed. Furthermore, villagers
keep foxes away. Thus, sylvatic rabies was spread by foxes only along a narrow strip on both sides of the valley, advancing at a rate of approximately 40 km per year.

Table 8.3 – Effect of oral vaccination with SAD B19 in Italy 1984-2004

<table>
<thead>
<tr>
<th>Year</th>
<th>Provinces</th>
<th>Municipalities</th>
<th>Area (km²)</th>
<th>Baits</th>
<th>No. wildlife cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1984</td>
<td>1</td>
<td>45</td>
<td>700</td>
<td>7,500</td>
<td>316</td>
</tr>
<tr>
<td>1985</td>
<td>1</td>
<td>45</td>
<td>700</td>
<td>7,500</td>
<td>101</td>
</tr>
<tr>
<td>1986</td>
<td>3</td>
<td>165</td>
<td>3,228</td>
<td>9,955</td>
<td>22</td>
</tr>
<tr>
<td>1987</td>
<td>1</td>
<td>73</td>
<td>764</td>
<td>36,600</td>
<td></td>
</tr>
<tr>
<td>1988</td>
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<td></td>
<td>21</td>
</tr>
<tr>
<td>1989</td>
<td>3</td>
<td>61</td>
<td>3,365</td>
<td>25,000</td>
<td>50</td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1991</td>
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<td>4</td>
</tr>
<tr>
<td>1992</td>
<td>3</td>
<td>64</td>
<td>1,000</td>
<td>34,508</td>
<td>19</td>
</tr>
<tr>
<td>1993</td>
<td>4</td>
<td>81</td>
<td>2,075</td>
<td>46,360</td>
<td>67</td>
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<td>1994</td>
<td>4</td>
<td>90</td>
<td>3,596</td>
<td>46,360</td>
<td>31</td>
</tr>
<tr>
<td>1995</td>
<td>4</td>
<td>79</td>
<td>2,906</td>
<td>35,000</td>
<td>8</td>
</tr>
<tr>
<td>1996</td>
<td>3</td>
<td>67</td>
<td>1,618</td>
<td>25,000</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>3</td>
<td>67</td>
<td>1,618</td>
<td>25,000</td>
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<td>2000</td>
<td>3</td>
<td>67</td>
<td>1,618</td>
<td>25,000</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>3</td>
<td>67</td>
<td>1618</td>
<td>25,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>67</td>
<td>1618</td>
<td>25,000</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>483,783</td>
<td>639</td>
<td>78</td>
<td>717</td>
<td></td>
</tr>
</tbody>
</table>

*: last rabies case in Trieste Province in December 1995

As mentioned above, oral fox vaccination campaigns using SAD B19 vaccine baits started in 1984. Similar campaigns were performed up to spring 2000 and further campaigns along the border with Slovenia were covered by oral vaccination in 2003 and 2004. Since 1977 wildlife has accounted for 98.3% of total rabies cases and among wildlife, foxes amounted to 87.4%, mustelids 9.6% and herbivores 3%.

Together with oral vaccination of foxes, a wildlife surveillance programme and an intensive reduction in fox density have been implemented. Dogs and domestic herbivores at pasture are compulsorily vaccinated against rabies in areas at risk. Stray dogs are captured and garbage-dumps are controlled to reduce food availability to wild animals and stray dogs (50). For further accounts of the epidemiology of sylvatic rabies in Italy see (62, 51, 32, 31). In December 1995, the last case of rabies was reported in a fox in Trieste (northeastern Italy) and Italy is now a rabies-free country. The surveillance programme is still in force and oral vaccination of foxes against rabies is still performed according to WHO and EU recommendations at the border with Slovenia, but since January 2000 dog vaccination has not been compulsory.

Bat rabies

More than 500 bats captured in three Italian regions, Emilia-Romagna, Marche and Lazio, were negative for rabies (49). Following reports of rabies in European bats, a survey of the indigenous insectivorous bat population was carried out (52) with the participation of the Istituti Zooprofilattici Sperimentali and Istituto Superiore di Sanità as well as the collaboration of bat biologists and naturalists. None of 153 bats found dead or moribund was rabies positive. Of 46 bats examined in Sicily from 1991 to 1996, none was positive (18).
Chapter 8

Imported dog rabies

In recent years three cases of dog rabies were imported, from the former Republic of Yugoslavia (1984, Rome), from the Ivory Coast (1989, Milan) and from the Lake Balaton region of Hungary (1992, Brescia). These findings have contributed to the strengthening of controls on dogs and cats traveling abroad with tourists and hunters, in particular from Eastern Europe, Africa and Asia.

Human rabies

Indigenous rabies cases were reported in man from 1946 to 1968 (Table 8.1) (15). Since then three imported cases were recorded, two from India in 1970 and 1977 (43) and one from Nepal in 1996 (14). Human vaccination using HDCV is recommended for some categories at risk.

FEDERAL REPUBLIC of YUGOSLAVIA, CROATIA, BOSNIA & HERZEGOVINA AND SLOVENIA

Federal Republic of Yugoslavia

The central part of the Balkan Peninsula, which nowadays comprises the Federal Republic of Yugoslavia, has been a politically unstable region for centuries, over which numerous tribes, nations and empires have struggled for domination. In such circumstances, documents and other records of life and culture of its inhabitants were often lost or destroyed. Throughout the Middle Ages, two great empires Austria and Turkey fought over Yugoslav lands. According to Austrian military archives, dog rabies was surely present in the territory around the Sava and Danube Rivers. Whilst in Austria, authorities tried to control disease outbreaks including rabies, in the Turkish part of the region Turks protected stray animals by leaving organic waste as a source of animal food in the streets and even intentionally feeding them. These customs led to the establishment of numerous populations of stray dogs and to the emergence and maintenance of urban rabies.

When Serbia became an autonomous state within the Ottoman Empire at the beginning of the 19th Century, the rabies problem was a priority for its public health authorities. According to Divljanovic (19), in 1834 the first rabies control measure was the introduction of a high tax on pet dogs, but not on livestock-guard dogs, in order to discourage keeping dogs solely as pets. Five years later ‘Lessons about rabies’, the first comprehensive scientifically based rabies review was issued by the Sanitary Department of the Ministry of Internal Affairs (about 1,000 booklets in total), and sent to all subordinate state authorities. These instructions, though marked by a relative ignorance of the subject (reflecting the paucity of scientific knowledge at that time), rejected many misconceptions (especially concerning treatment of manifest rabies patients) as useless or even dangerous. As the single most important procedure after a bite injury it was recommended that the wound be cauterised. In 1858, in ‘Public orders against animal rabies’ it was recommended that the numbers of each animal species susceptible to rabies, especially wolves, should be reduced, rabid or rabies-suspected animals should be killed and animals which have had contact with the former should be confined and watched for four weeks. Measures for safe disposal of infected carcasses and disinfection were also included.

In 1880, the Municipality Court in Belgrade ordered that dogs must not be left wandering freely and they should be muzzled. Furthermore, a special hygienic service was ordered to capture stray dogs and drive them to quarantine for 48 hours. If the owner did not ask for the dog in the meantime, the dog was destroyed. One of the most important public measures against rabies, ‘The law of protection from livestock contagious diseases in general and of measures for suppression of these diseases’ was issued in 1881. In relation to rabies, the law specified control measures which included restraint, supervision and/or destruction of suspect animals and particularly supervision of suspect animals which had bitten other animals or humans.
Two years later, regular records of domestic animal rabies cases in Serbia were established and maintained until 1914 (Table 8.4). Cases were diagnosed on clinical appearance and macroscopic pathology. At the same time, although there were no data specifically concerning wild animals, based on the data on animal species which had injured persons given post-exposure treatment (PET) in Nis 1901-1904, one can see that sylvatic rabies was not a significant public health problem. Partly because dog rabies control measures were not strictly applied, urban rabies in Serbia in the 19th Century was accompanied by many human cases.

Table 8.4 – Animal rabies cases in the Kingdom of Serbia 1883-1914

<table>
<thead>
<tr>
<th>Year</th>
<th>Dogs</th>
<th>Cats</th>
<th>Cattle</th>
<th>Sheep</th>
<th>Pigs</th>
<th>Horses</th>
<th>Total</th>
</tr>
</thead>
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<td>1883</td>
<td>12</td>
<td>18</td>
<td>3</td>
<td>33</td>
<td></td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>1884</td>
<td>27</td>
<td>29</td>
<td></td>
<td>56</td>
<td></td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>1885</td>
<td></td>
<td>7</td>
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<td></td>
<td>7</td>
</tr>
<tr>
<td>1886</td>
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<td></td>
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<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>1887</td>
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<td>6</td>
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<td>3</td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>1888</td>
<td>1</td>
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Following the introduction of Pasteur’s PET method, several other Pasteur Institutes were established. In 1890, King Milan approved the foundation of the first Pasteur Institute in Serbia, sited at Nis in 1900, the second largest city in the country and located in its southeastern part. Human antirabies treatment and variolation were the only two activities in the Institute during the first years. In Nis, patients were treated by the Hogyes dilution method, which was equally effective as the original Pasteur drying method (4). During 1901-1910, of 3,825 persons given PET 34 died, a failure rate of 0.89% (75). Between 1901 and 1904, of 1,132 treatments, dogs were responsible for 1,014 (89.6%), cats for 52 (4.6%), other domestic animals for 49 (4.3%), wolves for nine (0.8%) and other animals for eight (0.7%). During 1911-1915 the number of people treated increased annually and from 1901 to 1915, 8,649 persons were treated (54).
During the First World War, the Pasteur Institute in Nis was destroyed and important archives were lost. Shortly after the War, Serbia and Montenegro were included in the ‘Kingdom of Serbs, Croats and Slovenes’ (the name of which was changed, in 1929, to the ‘Kingdom of Yugoslavia’). A comprehensive analysis of the rabies situation at that time (5) revealed that police authorities in charge of animal rabies control did nothing to implement control measures (unsatisfactory in themselves) prescribed by the existing laws; in city streets, packs of dogs wandered freely. As a consequence, the number of injured persons increased sharply. For example, in Nis alone in 1921, 2,022 were treated (33). Also in 1921, 1,837 were treated in the Zagreb Institute and 1,083 treated in its department in Velika Gorica (33); data from the Pasteur Institute in Novi Sad, which began its activity by the end of the same year, are unavailable.

Immediately after the First World War, the Pasteur Institute in Nis was reconstructed under the guidance of the new director, Dr Gerasimos Alivisatos from Greece. In 1919 and 1920, the street rabies virus which prevailed apparently acquired greater virulence and Alivisatos decided to try to improve Hogyes method by using ether for attenuation (3). He devised this improved method of attenuation in order to inject a greater amount of the vaccine at the beginning of treatment. Before the application of his method in humans, he performed several PET experiments in sheep. For testing the innocuity of the vaccine, sheep were given 44 g of the vaccine in the abdomen over 66 days and were then observed for more than 18 months. No signs of illness were noticed. The ‘Alivisatos ether method’ as it was called, was applied in humans using 10 g in total of killed virus-containing nervous tissue, usually administered over 13-15 days. He described a group of 315 patients with most severe injuries of which all remained healthy up to one year after treatment, while 11 of 287 treated by the Hogyes or mixed method died of rabies at or within 15 days after treatment. At the same time, no CNS damage was noted in over 1,100 patients. This method was soon accepted in all Yugoslav Pasteur Institutes and also in Pasteur Institutes in Athens, Vienna, Sofia, Madrid and Buenos Aires.

Introduction of Alivisatos’ method was particularly important bearing in mind that, according to Ivanic (34, 35), the number of persons given PET in the Kingdom during 1921-1925 was the highest in Europe, an annual average of over 5,500 cases. Of this number, those treated in Nis comprised about one-third. In the Vojvodina region the number treated per 100,000 population rose from 610 in 1921 to 1,170 in 1925, in Central Serbia, from 414 in 1924 to 558 in 1925, and in Montenegro, from none in 1921 to 157 in 1925.

While 27,906 persons were given PET in the Kingdom during 1921-1925, there were 93 registered human rabies cases unsuccessfully treated. Of these, 38 were from Central Serbia and 13 from Vojvodina. There was a periodicity in human rabies case incidence in that in 1919 there were five cases, in 1920 there was a first peak of 22 cases which fell to nine cases in 1922, a second peak of 27 cases in 1924, and second fall to five cases in 1925. We might suppose that this periodicity reflected the periodicity of animal rabies, the data of which are lacking; just as, according to several notes of physicians involved in antirabies treatment (including Alivisatos himself), animal rabies control measures was completely lacking at that time. Eventually, in 1925 a limited campaign for the elimination of stray animals was initiated and in 1926, 637 dogs and 11 cats were killed.

During 1919-1928 the Pasteur Institute in Nis treated 12,856 people, with 43 (0.33%) treatment failures (47). Because of the great increase in the number of patients given PET immediately after the First World War, the second Pasteur Institute in Serbia was founded in 1921 at Novi Sad, in its northern province, Vojvodina, where the highest rabies incidence was recorded. The first director of the Institute was Dr Adolph Hempt, a former Austrian military medical doctor born in Novi Sad in 1874.

From the beginning, the new Institute attracted patients not only from Vojvodina, but also from the northern Central Serbia, eastern Croatia and northern Bosnia, so that the number of patients was enormous. At first Hempt used the original Hogyes method, but in 1922 he was introduced to the Alivisatos ether method and soon the latter became the only method used in Novi Sad. Thus, 234 persons were treated with one (0.42%) treatment failure. Because the rabies epizootic expanded and the street virus in the region became more virulent, for severe injuries Hempt shortened the injection course to only five days, a method he called the ‘rapid ether method’ or ‘Serbian method’. In this way, until April 1933, 6,368 persons were treated with five (0.08%) failures and eight (0.13%) neurological complications (54). By the end of 1927, Hempt succeeded in the preparation of a vaccine containing phenol as a preservative and which could be safely kept up to one year and transported over long distances. This vaccine became
famous as the ‘ether-phenol vaccine’ or simply ‘Hempt vaccine’ (29). From then, there was no need for a decentralised system of PET and several Pasteur Institutes were closed, while the Institute in Novi Sad manufactured rabies vaccine for the whole country (48).

Data about animal rabies at that time were scarce and irregular, but it was evident that dog rabies remained the most difficult problem. Vukovic (80) stated that rabies cases in 1931 comprised 376 dogs, 19 cats, 33 cattle, 15 pigs and 10 horses, whereas in 1932 the figures were 619 dogs, 36 cats, 45 cattle, 27 pigs, 12 horses and four goats. Rabies-infected municipalities increased from 285 in 1931 to 447 in 1932.

As has been noted above, dog rabies control began in the mid-1920s. Apart from disposal of stray dogs and cats, many veterinarians called for the vaccination of animals against rabies. From 1926 to 1933, the main vaccination strategy was post-exposure vaccination performed with two doses of a killed ether-phenol vaccine combined with a third dose of the so-called Gonsalves lipovaccine. Thereafter, this schedule was changed to three doses of ether-phenol vaccine injected on three consecutive days. By 1935, of 2,910 domestic animals given PET by this method, the registered mortality rate was 0.68%, whereas of 190 immunised dogs not one died (29).

During and after the Second World War, the incidence of dog rabies remained high and dogs represented more than 50% of all animal rabies cases. In the former Yugoslavia during 1946-1957, 5,489 (56%) of 9,785 animal cases were in dogs. However, there were also 372 wildlife cases, 281 in foxes and 91 in wolves. In the same period the human death toll was 338 (Table 8.5). The chaotic war period favoured a population increase in stray dogs and also of wildlife such as wolves and foxes. It was estimated that in the whole of former Yugoslavia in 1946-1957, there were 1,600,000 dogs (260,000 in Vojvodina, 750,000 in Central Serbia and Kosovo and 31,000 in Montenegro), while the number of wolves was around 6,000. In the same period, annual dog population destruction was about 5.5%. In addition, more than 3,000 wolves and 40,000 foxes were killed annually. The most efficient methods were poisoning of wolves with strychnine or cyanide baits, and organised fox hunts (37). From the early 1950s in Vojvodina, fox rabies seems to have become a significant problem.

According to Dobrenov (21), the first organised campaign against dog rabies in Vojvodina after the Second World War took place in 1947, whereby the main measures were registration and vaccination (with Hempt vaccine) of dogs and elimination of strays. That year, 152,000 dogs were vaccinated, but because of a lack of public interest and fears about dog vaccine safety, far fewer dogs were vaccinated. Since the epizootic was still out of control, the Veterinary Service warned authorities and proposed more comprehensive measures, including a tax on dog ownership, the preventive vaccination of cattle kept outdoors, and payments for dead foxes, wolves and stray dogs. From 1954, a steady decline in dog rabies was noted (Table 8.5). Before 1952 there had been no official evidence of rabies cases in foxes and other wild animals. However, according to personal experience of the authors and their communications from the field, in the period 1946 – 1952, rabies was present in wild animals, especially in foxes. According to these observations, and also taking into account two officially registered epizootics in foxes in 1952-1953 and in 1962-1963, it was concluded that foxes were the main rabies vectors throughout the whole period.

Vojvodina was free of dog rabies by 1958, but in 1962 fox rabies re-emerged and from then onwards was the only registered epizootiological form (Table 8.6). In Central Serbia early dog rabies control measures were not as successful and there were 12-47 dog cases annually during 1958-1963, but from 1965 there were no further cases and for several years the region was rabies-free. However, because control measures were not regular and comprehensive, sporadic dog rabies cases occurred in the 1970s in Central Serbia and Kosovo, accompanied by several human cases (8).

Elimination of dog rabies was achieved while using Hempt pre-exposure vaccination. The first annual organised campaign was in 1947. In 1981, Hempt vaccine was replaced with a modern live Flury HEP vaccine (36). At the beginning of 2000, the latest advance was the use of an inactivated adjuvanted vaccine prepared in BHK cell culture (D. Lalosevic, Novi Sad, 2000, personal communication) in a field trial in dogs and cats.
### Table 8.5 – Rabies in the former Yugoslavia (FR Yugoslavia, Croatia, Bosnia, Slovenia and Macedonia) 1946-1991*

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* Totals: 6,523 665 2,193 2,177 11,558 106 13,560 13,666 414

* : 1937 included for comparison only/ ** : complete data not available/ *** : data from Slovenia and Croatia not included
In the meantime, in 1977 fox rabies invaded from the neighbouring territories of Hungary and Romania and advanced slowly southwards. The Sava and Danube may have been barriers to its spread, but there was also a relatively low fox population density in southern areas. Fox rabies in Central Serbia was first noted only in 1986 (two cases in the northeastern part near the Danube), then it spread further southwards, so that in 1998 the epizootic reached Kosovo. Rabies in Montenegro was noted in 1959 (three dogs), 1962 (13 cattle, nine sheep, two horses and two dogs), 1963 (one dog) and then 1978 (four cattle). Throughout the 1990s sporadic cases were registered in livestock and foxes (8).

**Table 8.6 – Rabies in Vojvodina 1946-1963**

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<th>Humans</th>
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<td><strong>18</strong></td>
<td><strong>178</strong></td>
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The first organised action against sylvatic rabies was performed during the second fox rabies epizootic in Vojvodina in 1962 (21). Veterinary authorities in cooperation with the hunters’ association organised the shooting of foxes; auxiliary measures were the vaccination of livestock in the field and reaffirmed dog rabies control. This second epizootic eventually subsided, just as the first one in foxes in 1952-1953 had done. Later, the same measures were performed less enthusiastically and this may be why the epizootic dating from 1977 (Table 8.7) has not been eliminated. In the late 1980s and in the 1990s, there were no attempts at fox population reduction. Instead, at the beginning of 1999 fox oral immunisation with Lyssvulpen vaccine was initiated (D. Lalosevic, Novi Sad, 2000, personal communication).

In 1955, apart from routine detection of rabies virus in terrestrial mammals, mostly connected with human injuries or apparent abnormal behaviour of the animal, an active, albeit limited surveillance of rabies cases in insectivorous bats was initiated by Nikolic (8). That year, an agent serologically linked to rabies virus was isolated from three *Nyctalus noctula* Schreb. bats. The isolate was extensively passaged through mice and rabbits, and its pathogenicity and corresponding histopathological lesions determined. In 1956, there were four additional groups of bats (from Cortanovci, Petrovaradin and Novi Sad) examined by mouse inoculation test (MIT) for the presence of rabies virus, but all were negative. In parallel, shrews and wild mice were examined but 20 shrews captured in the vicinity of Novi Sad where the infected bats had been found were rabies negative. Samples from wild mice were also rabies-negative, but in two (of 60) mice, a pathogenic agent subsequently identified as LCM virus was isolated. There were no data on bat specimens until recently, when around 50 bats submitted to the Pasteur Institute in Novi Sad were negative by both FAT and MIT. Further surveillance is planned (Chapter 17, A.A. King et al.).

Rabies diagnosis in animals in the 1950s was performed by examination for Negri bodies and by inoculation of mice and rabbits. Rabbit inoculation was particularly important for detecting Aujeszky’s disease, which often resembled rabies clinically. Direct immunofluorescence was first introduced in 1968.
as a routine practice within the laboratory of the Pasteur Institute in Novi Sad (M. Petrovic, Novi Sad, 2000, personal communication). MIT has remained the diagnostic method, and virus isolation in N2a cell culture has occasionally been used as a trial procedure. For the last two decades, two other laboratories have also been engaged with routine rabies diagnosis by FAT.

Table 8.7 – Rabies in Vojvodina 1964-1988

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*: includes 18 deer, 1 badger, 1 wild boar and 3 wild cats

from after the Second World War until the end of the 1970s, human antirabies PET in Serbia and Montenegro consisted of Hempt vaccine injected on six consecutive days. The vaccine was prepared in the Pasteur Institute in Novi Sad and distributed to about 200 antirabies stations. During 1946-1957 in Central Serbia 83,466 were treated, with 49 (0.06%) treatment failures, in Vojvodina treatment failures were 11 (0.08%) of 14,544, in Kosovo 13 (0.45%) of 2,861 and in Montenegro 11 (0.81%) of 1,345. In addition, deaths in untreated patients were 75 in Central Serbia, 20 in Vojvodina, five in Kosovo and two in Montenegro (8).

Despite the relatively effective PET, while urban rabies was still present the number of human cases was closely related to the number of animal cases recorded (Table 8.5). From the beginning of the 1980s, imported cell culture vaccines replaced the Hempt vaccine. Equine antirabies gamma globulin (ERIG) was prepared for routine use in 1970 (Institute Torlak) and later used in parallel with imported HRIG. From 1991, locally prepared HRIG has been available, so the use of ERIG was abandoned. The last human rabies cases were recorded in Montenegro (1962), Vojvodina (1964), Central Serbia (1976) and Kosovo (1980). Despite the obvious success in elimination of human rabies, further work on public education, strict PET procedure and continuous animal rabies control strategy is warranted. Since 1992, animal rabies cases in Yugoslavia have been increasing (Table 8.8).
Croatia

From the archives of Austrian border troops gathered from local Slavic inhabitants, it is evident that rabies in man and animals in the territory which now belongs to Croatia was present in the 19th Century as a significant public health problem. This was also a difficult financial problem for the military authorities, who were providing funds for treatment of troops who contracted rabies, and therefore were very interested in the implementation of public rabies control measures (54).

The first to gain the glory of being a rabies ‘cure’ in those days was Josip Lalic, a teacher, inventor and medical practitioner. In 1837, Lalic gained official permission from the supreme military authorities in Vienna to practise his rabies cure. Not long afterwards he published details of his 35 years’ experience of the emergence of rabies, its signs and his therapies (42). He was well aware that saliva was responsible for transmission of ‘the toxin’. The proper medicine for an apparently rabid person was the cutting of the veins of the root of the tongue followed by intensive treatment with the root of the herb *Gentiana cruciata*.

For wound detoxification, he prescribed flushing of the wound with rosemary brandy.

According to Hogyes (30), in the period 1890-1898 from the territory of Croatia and Slovenia there were 519 persons treated at the Pasteur Institute in Budapest. In 1918, Croatian lands became a part of the newly founded Kingdom of Serbs, Croats and Slovenes. The dog rabies epizootic had spread extensively and as a result the new Ministry of People’s Health founded a Pasteur Institute in Zagreb (along with its local Department in Velika Gorica) (5). Initially and until 1925, live vaccine was applied by the Hogyes dilution method. During the period 1921-1925, PET was widely used, in Croatia at 50.2, 61.7, 45.1, 44.4 and 26.4 cases per 100,000 population and in Dalmatia at 8.5, 12.6, 24.8, 16.7 and 7.0 per 100,000 population respectively. In this period, 37 rabies cases in persons treated in Zagreb (36 bitten by dogs, one by a wolf) were recorded. The Hogyes dilution method of vaccination was replaced by the application of the Alivisatos ether vaccine during 1925-1928. From 1929 to May 1979, Hempt vaccine was used (76).

In 1934, the first campaign of preventive dog vaccination was performed (38). However, since the campaign was not comprehensive enough, it did not result in significant suppression of the dog rabies epizootic. During the Second World War the stray dog population, as well as the number of wolves and foxes, increased, stimulating spread of the epizootic and consequently more frequent human rabies cases. In wildlife, 36 rabid foxes and 11 rabid wolves were diagnosed from 1946 to 1950.

Immediately after the Second World War the Veterinary Service initiated a broad strategy of dog vaccination along with the extermination of stray dogs. The percentage of vaccinated dogs rose from 0.1% in 1932-1937, through 20% in 1946-1951 to 66% in 1952 and afterwards. As a consequence, the number of animal cases in Croatia fell from 243 in 1937 to only eight in 1958 (38, 39). From 1958 to 1964 the annual figure fluctuated between seven and 25, 90% of which were recorded in Banija, Kordun and

### Table 8.8 – Animal rabies in Yugoslavia 1992-2001

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<td>37</td>
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<tr>
<td>Totals</td>
<td>76</td>
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<td>28</td>
<td>24</td>
<td>304</td>
<td>839</td>
<td>13</td>
</tr>
</tbody>
</table>

*Source: Rabies Bulletins Europe, 1992-2001*
northern Lika, a region adjacent to the northwestern part of Bosnia. This region, together with Bosanska Krajina in Bosnia, harboured the enzootic for decades, not only in dogs but also in wildlife.

Upon introduction of systematic dog vaccination, the number of dogs vaccinated yearly in Croatia reached 140,000 in 1958, then fluctuated between 130,000 and 190,000 during the next decade. While other regions of Croatia had become virtually free of dog rabies by 1959, the region of Banija, Kordun and northern Lika remained a persistent rabies focus. In 1962, a field trial with a new Flury LEP vaccine of local origin was initiated, which, along with the continuation of existing control measures, resulted in a reduction of rabies cases to zero in the region and in the whole of Croatia in 1967. It was claimed that this success could have only been achieved by live Flury LEP vaccine, since systematic and regular administration of Hempt vaccine here did not result in the complete elimination of dog rabies, as was the case in other parts of Yugoslavia (38).

For the next ten years Croatia remained rabies-free until the fox rabies epizootic came from the north in 1977. Thereafter, the number of rabid foxes steadily rose, from four in 1977 to the first peak of 485 in 1985 (8), afterwards acquiring a characteristic cyclical pattern. Oral vaccination of foxes began only in the 1990s (12), and so far has not resulted in the elimination of fox rabies (Table 8.9).

Table 8.9 – Animal rabies in Croatia 1992-2001

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
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<th>Total cases</th>
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<td>8</td>
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<td>14</td>
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</table>


While dog rabies prevailed, occasional human rabies cases occurred in spite of massive PET with Hempt vaccine. In the period 1941-1950, there were 68 human rabies cases. Until 1948, when obligatory immunisation of dogs was introduced, there were 4-17 human cases each year, but in 1949 only one case and none in 1950. The rate of Hempt vaccine failure in Zagreb was calculated at 1:548 (0.18%) (76). In 1952, there was one case, then another in 1961 and the last human case was recorded in 1964 (8), despite the large epizootic of fox rabies which broke out in the 1970s.

HDCV replaced the old nervous tissue vaccine for human PET in 1977. At that time, no HRIG was easily available for human PET in Zagreb, but fortunately the Institute of Immunology in Zagreb had already been producing human leucocyte interferon (HL-IFN), which was shown to have a beneficial effect in rabies post-exposure animal trials. Under the guidance of Dr Ivan Vodopija it was decided to use HL-IFN instead of HRIG in cases of severe exposure (76). Despite successful treatment with HL-IFN, Vodopija and his co-workers felt it was necessary to also use HRIG. However, in cooperation with the Institute of Immunology in Zagreb, in 1982 a successful trial using HRIG alone led to the registration and routine production of domestic HRIG (76). This was followed by the development of an abbreviated PET schedule, called the ‘2-1-1 scheme’, ‘Vodopija’s scheme’ or ‘Zagreb scheme’ (77, 78, 79). The advantages of this schedule over the classical Essen schedule were enhanced early antibody response, reduced number of visits to the doctor and reduced total number of vaccine doses in the course of treatment. The schedule received recommendation by the WHO.
Bosnia and Herzegovina

In the 15th Century Bosnia and Herzegovina (BiH) came under Turkish rule which lasted until 1878, when Austria assumed control. During the four centuries under the Turks, most inhabitants became Islamic and acquired customs which were, among other things, favourable to the maintenance of dog-mediated rabies. After administration passed to Austria, one of the first to become familiar with the rabies situation and problems of its control in BiH was Dr Adolph Hempt, who was at that time practising there as a municipal physician. He noted that human rabies cases frequently occurred because many people refused for religious reasons to travel abroad for antirabies treatment. Although Hempt's appeal to the Bosnian government to found a Pasteur Institute in Sarajevo was welcomed, it was refused by the supreme authorities in Vienna (54).

After the First World War BiH was incorporated into the new ‘Kingdom of Serbs, Croats and Slovenes’. The rabies situation at that time was particularly disturbing and several Pasteur Institutes in the country were founded, one of them being the Institute in Sarajevo in 1922 (48). The number of people treated against rabies per 100,000 inhabitants in BiH rose from 21.7 in 1921 to 42.7 in 1923. From 1921 to 1925 there were 10 human rabies cases despite treatment in Sarajevo, nine of whom were bitten by dogs and one by a wolf (35). From 1928 a decentralised system of human PET with the Hempt vaccine was introduced. At the same time animal rabies control measures were not fully implemented (80). It was not until after the end of the Second World War that dog rabies control changed substantially.

According to Kodrnja (37), rabies in BiH was prevalent for many years because as well as the presence of dog-mediated rabies, wildlife rabies also appeared. During 1946-1957 more than half of the wolf rabies cases and more than a third of rabid foxes in the entire former Republic of Yugoslavia were registered in BiH. The dog population in BiH was estimated to be 200,000, of which 40%-50% were vaccinated and about 10% destroyed annually from 1948. The number of animal rabies cases fell from 304 in 1954 to 32 in 1957 (37). From 1945 to 1966 there had been 2,168 rabid dogs, cats and other domestic animals, but no cases were registered during 1967-1970. From 1946 to 1959 there were 77 rabid foxes and 29 rabid wolves (39) and the last wildlife rabies case was a fox in 1959. In the early 1960s, 3,000-6,000 cats, 200-300 wolves and 9,000-13,000 foxes were killed annually (39).

In 1971, a new dog rabies outbreak emerged in northeastern BiH, where rabies had been absent from 1964 (65). Of 135 animal brains examined, 45 from the northeastern region and two from the northwestern region were positive. Dogs accounted for 76% of the cases, with the remainder in cats, cattle, pigs and sheep. There had been a significant increase in the number of stray dogs in northeastern BiH as a result of the loosening of dog population control measures. In response, the Veterinary Service reinforced dog vaccination and other control activities and the epizootic was eliminated. Sylvatic rabies spread from the north to BiH in 1982. That year, rabies was diagnosed in 13 foxes, two cattle and one wild cat. The next year the epizootic spread to central and eastern regions and 92 rabies cases, of which 68 were foxes, were reported (20).

The last indigenous human rabies case before 1991 was in 1974 (8), although in 1989, a boy became rabid after being scratched by a dog whilst visiting his father in Algeria. He was not given PET (44). Since 1991 there have been no official data on rabies (12), but recently there have been reports of human rabies following the skinning of rabid foxes (see below).

Slovenia

Before the First World War, Slovenian territories had been under Austrian rule for centuries. Although precise data are lacking, one might suppose that the rabies situation in Slovenia throughout past centuries was similar to that in neighbouring Croatia and other Austrian provinces. After Pasteur, patients from Slovenia were treated in Budapest (30). After the First World War, during 1921-1925 the number of patients per 100,000 inhabitants of Slovenia who underwent PET slowly but steadily decreased, from 18.3 in 1921 to 14.6 in 1925, one of the lowest rates in Yugoslav territories at that time (35). At first, the closest Pasteur Institute was that in Zagreb, but in 1925 an anti-rabies ward in Celje was established as the first
institution in Slovenia in charge of PET (48). It was estimated that 100-200 people were treated in Celje each year (55).

The urban rabies epizootic in the former Yugoslavia expanded during and after the Second World War and comprehensive dog vaccination campaigns began in 1947. In Slovenia, from the beginning up to 97% of dogs were vaccinated each year, which yielded the highest rate of elimination of dog-mediated rabies. Thus, in 1946 and 1947 there were 133 and 126 rabies cases respectively, in 1948 this figure fell to 26, then to eight cases in 1949, while in 1952 and 1953 no rabies case was recorded. During 1952-1969 just one additional rabies case, in a dog, was recorded in 1954. Between 1946 and 1969 the only human case was in 1950 (37, 39).

Unfortunately, the rabies-free status of Slovenia changed in 1973, when fox-mediated rabies spread from Hungary to two border municipalities, with 11 fox rabies cases registered. No case in any other species was noted that year (59). This focus in northeastern Slovenia did not spread further, and the number of cases increased little. In fact, in 1975 there was a decrease to only one rabid fox, but in the following years the number slowly increased to 32 in 1978. At the beginning of 1979 however, a separate wave of sylvatic rabies crossed the northwestern territory of the country from neighbouring Austria (60). By 1981, almost the whole Slovenian territory was affected (20) and the first peak (1,766 cases) of a cyclical pattern was recorded. Other epizootic peaks were in 1988 (805 cases) and in 1995 (1,084 cases), but from 1995 the rabies incidence consistently decreased such that in 1999 there were only six cases (13); although there was a marked increase to 114 cases in 2000. Despite persistent sylvatic rabies in Slovenia, no human cases were registered.

After the 1979 introduction of sylvatic rabies from Austria, veterinary authorities together with the hunters’ association undertook regular and long-term oral immunisation of foxes. The first campaign was in 1988 and a clear decrease in rabies incidence was noted at the end of 1989 in the border territories with Austria and Italy where oral vaccination was applied (11). However, this was not a long-term result, since the neighbouring territories from the east and south were heavily infected and the vaccination areas were not large enough. Recently, as indicated above, fox immunisation over large areas seems to have been quite successful (Table 8.10). Slovenia has been free of human rabies since 1950.

Table 8.10 – Animal rabies in Slovenia 1992-2001

<table>
<thead>
<tr>
<th>Year</th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
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<td>Cat</td>
<td>Cattle</td>
<td>Other</td>
<td>Total</td>
<td>Fox</td>
<td>Others</td>
<td>Total</td>
<td>Fox</td>
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<td>110</td>
<td>114</td>
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<td>194</td>
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<td>3,208</td>
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MACEDONIA (FYROM)

Before the First World War and until the Second World War rabies represented a difficult problem in Macedonia. The Republic became free from Turkish rule only in 1912 and in 1918 it became a part of the newly founded Kingdom of the Serbs, Croats and Slovanes. Dog rabies was expanding and up to 1,500 persons from the region were given PET annually (46). Until 1928, when decentralisation of PET was introduced, patients received treatment at the Pasteur Institute in Nis, where the diagnosis of rabies-suspected animals by inoculation of rabbits was also performed. Later, PET with Hempt inactivated ether-
phenol vaccine was applied in local health institutions. No official data of rabies cases and treated persons were preserved.

The chaotic situation during the Second World War brought about an enormous expansion of domestic stray and wild animals, with an accompanying increase in rabies incidence. The Veterinary Service of the People’s Republic of Macedonia (founded in 1945) decided to initiate a broad and systematic programme to control dog rabies and eventually eliminate the disease. In 1949, the Ministry of Agriculture issued orders to limit the number of dogs that could be kept and to eliminate excessive numbers, with considerable success (7). While in 1948 only 3,350 dogs were killed, 22,446 dogs (about 25% of the dog population) were killed in 1949. The carcasses were mostly taken by leather-goods manufacturers. At the same time (1949) the first extensive campaign of dog vaccination (with Hempt vaccine) took place and 29,063 dogs were vaccinated. In the following years, vaccination and elimination campaigns were regular and were followed by a significant decline in the incidence of rabies. In addition to the dog rabies control programmes, the Veterinary Service cooperated with hunter and forestry organisations to eliminate dangerous wild animals. Thus, from 1949 several hundred wolves and 4,000-8,000 foxes were killed annually. During the 1950s, rabies was virtually eliminated in central and eastern parts of the Republic, while sporadic cases occurred near the borders with Greece and Albania.

However, a local outbreak of dog rabies occurred in 1958 in the municipality of Bitola on the border with Greece, when the disease spread from the south through the lowland of Pelagonija (24). The outbreak came under control in the years to follow but the focus in Pelagonija was not eliminated. In 1971, rabies spread from this focus to Kicevo municipality in the western part of Macedonia and the epizootic reached its peak in areas near the Albanian border in 1971 (25). Complete rabies elimination in the Republic was achieved in 1977 and since then the country has remained rabies-free (7).

Despite the difficult situation with urban rabies after the Second World War, human cases were relatively rare – not more than three cases annually, except in 1971 during the epizootic in the western part of the Republic when five people died of rabies. For the most part these people were not given PET. Up to the 1980s, PET was performed with Hempt vaccine, which was eventually replaced with HDCV. An overview of the rabies situation in humans during the 50 years 1954-1994 shows low morbidity and mortality in selected years, amounting to a total of 29 cases, with no cases in the periods 1959-1970 and 1977-1994 (7).

ALBANIA

Albania has been rabies-free since 1976. Kusi suggested that freedom from rabies may be because its northern and northeastern borders (with Yugoslavia) are of mountainous terrain and its other two border countries (Macedonia and Greece) have been rabies-free for a long time (40). The last reported human cases (in 1976) were in Kaçinar, a community of the Mirdita district, following the bites of a rabid German shepherd dog or a wolf, (the species was not accurately determined). Ten of the 14 severely bitten people died of rabies. Mandatory rabies vaccination in confined areas for domestic animals and the culling of wild carnivores suspected of being rabid were carried out for rabies control (41).

Following dramatic political, economic and social changes in 1990, Albania faced an uncontrolled influx of pet dogs from countries such as Turkey and Bulgaria where dog rabies was present. A diagnostic system was installed, combined with the establishment of an effective surveillance system. In 1997, a large scale rabies survey of important vector species commenced, but of 140 animals examined during 1997 and 1998, including 66 foxes and 26 dogs, none was rabies-positive (40).

GREECE

Various sources prove that rabies was known among Greeks since the 10th Century BC (Chapter 1, J. Neville). Such references are included in the poem of the Iliad by Homer, in the works of Democritus (5th Century BC), Euripides (406 BC), Aristoteles (322 BC), as well as lesser known physicians and writers up to the 1st Century of our era.
In more recent times rabies is referred to on the Ionian island of Zante as being among the most important hazards for the public. Therefore, in 1816, the governor of the islands, in a proclamation, ordered that ‘firstly, all dogs should have a collar defining the name of the owner. Dogs without collars will be killed on the spot, and secondly, in order to prevent dog rabies or ‘hydrophoby’ affecting these animals, being thirsty because of summer, all grocers, retailers and butchers should place outside their shops, pots with clean water. Transgressors will be severely punished’ (22).

In a memorandum of 1933 the Hellenic Veterinary Medical Society states that ‘rabies is endemic in almost the whole country with hundreds of animals dying and thousands of human beings treated following exposure to rabid animals, with some of them dying’. The Government was accused that ‘although our country is among the first where rabies is spreading, it was never seriously dealt with’. The same Society recommended to the Government that the Royal Decree No. 7/2 of 1914 ‘should be finally put into action’. The Decree includes ‘general regulations and measures against communicable diseases of domestic and farm animals’ according to which ‘rabies is included among transmissible animal diseases and the diseased animals should be killed’ (6).

Human rabies

The first ‘Human Rabies Public Station’ was established in Athens in 1914. According to Law No. 384 of 1923, its scope included ‘the production of an-rabies vaccine, the implementation of post-exposure treatment in humans, the diagnosis of and research on the disease’. All services ‘are delivered free-of-charge to public servants and the poor’. Similar anti-rabies public stations were established during the 1930s, in district city centres of major epidemiological importance (22).

The first date that could be identified records the year 1930, when 2,893 persons received PET. Of these, 87% were due to dog bites. During the Second World War and the following years, rabies cases among animals increased. Between the years 1949 and 1951 in the island of Zante (48.59 km²) numbering at that time 41,000 inhabitants and 2,850 registered dogs, 29 animal cases were recorded, 13 persons received PET and five of the latter died (58, 57).

Animal rabies

The first vaccination trials ever made in dogs in Greece were performed in 1949 on the island of Zante using an imported vaccine. Dog vaccination campaigns followed over the next years covering the whole country, except for islands known to be free of rabies. During the 1950s and part of the 1960s, animal rabies (mainly among dogs) spread throughout almost all the Greek mainland, while it sporadically occurred in some islands. In 1950, the highest number of human deaths (42) was recorded (57), while in 1954 the highest incidence (1,135 cases) of rabies amongst animals was reported (23). Table 8.11 summarises the prevalence of human and animal rabies, human PET and dog vaccination in Greece since 1950.

<table>
<thead>
<tr>
<th>Years</th>
<th>Human rabies</th>
<th>Animal rabies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PETs</td>
<td>Deaths</td>
</tr>
<tr>
<td>1950-1960</td>
<td>129,825</td>
<td>91</td>
</tr>
<tr>
<td>1961-1970</td>
<td>80,928</td>
<td>2*</td>
</tr>
<tr>
<td>1971-1980</td>
<td>45,700</td>
<td></td>
</tr>
<tr>
<td>1981-1987</td>
<td>20-25,000</td>
<td></td>
</tr>
<tr>
<td>1988-1999</td>
<td>20-25,000</td>
<td></td>
</tr>
</tbody>
</table>

*: last human case 1970
**: last animal case (dog) 1987

Compulsory, free-of-charge vaccination campaigns implemented by the Veterinary Services, as well as public awareness, could be considered as the most important parameters that contributed to the gradual elimination of the disease from Greece. As rabies cases were reduced to zero for a number of years,
compulsory vaccination was gradually suspended. Vaccination is still performed every year, particularly among shepherd and hunting dogs, along the borders with Albania, Macedonia, Bulgaria and Turkey, to a depth of up to 30 km. In addition, voluntary vaccination by the authorities or by NGOs is always encouraged (66, 67, 45).

Wildlife rabies

During the thirty years of major rabies prevalence (1950-1980), wildlife rabies was at very low levels; during 1950-1974 only ten cases in foxes were recorded. Since then, no positive case has been identified among hundreds of different species tested every year (66, 67, 45).

RABIES IN THE BALKAN

The area covered by this overview includes countries of the Central and Western Balkans (excluding Bulgaria and Romania). All of them have been affected by canine and/or wildlife rabies since the antiquity.

In 1900, in Serbia, it was constituted the first Pasteur Institute in the Balkans. Serbia has made important contributions (the Alivisatos and Hempt vaccines between the two World Wars, then shortly after the Second World War isolation of the bat rabies strain by Nikolic), mostly linked to the Pasteur Institute in Novi Sad.

A Pasteur Institute has existed in Croatia since its independence from Austria-Hungary, and is more recently known for the activities of the Zagreb group of investigators. Slovenia introduced modern cell culture rabies vaccines for human use as well as campaigns of fox oral immunisation.

Bosnia, the hinterland of the Balkan peninsula, with its rugged mountains and dense forests providing sanctuary for wolves – the natural reservoir for rabies virus throughout recorded history. The formation of a Pasteur Institute in Sarajevo in 1921 should be noted, as well as the activity of Dr Hempt prior to his posting in Novi Sad.

Macedonia and Albania almost certainly have been endemic for canine rabies since antiquity, but the destruction of archives in Nis during the First World War destroyed available records. In Albania, there was a Central Public Health Institute in Tirana during the government of Enver Hoxha. The province of ethnic Albanians in Serbia, Kosovo, now under NATO protection, has on record numerous attacks on people by rabid dogs, wolves and bears. The shortest recorded incubation period of rabies in humans of only four days following a bear-bite was extensively documented and published by Dr Baljosevic from Pristina in 1975. Dr Baljosevic kept detailed records of the rabies situation in Kosovo where rabies was a real threat until the advent of modern vaccines in the 1980s. Since then there have been no human cases.

Greece, with predominantly dog rabies (a legacy of long Turkish rule) had important treatment centres in Thessaloniki and Athens, but the treatment methods and vaccines used were those developed in Nis and Novi Sad. These were endorsed by international rabies experts of the time (e.g. the First International Congress on Rabies in Paris, 1927). Greece contributed to rabies knowledge through Dr Alivisatos.

Pre-Pasteur era

The earliest document in which we find a mention of rabies in the countries reviewed in this chapter was by Frederico Grisogono, a physician from Zadar, Dalmatia, published in Venice in 1528. The treatise, ‘De Modo Prognosticandi et Curandi Febres’, is a typical Renaissance medical work and the chapter on rabies includes: ‘In case of bite of a rabid dog the process takes several months because the poison is hidden in the blood for three, four, or even longer than five months, until the heart gets infected as well. When the heart becomes afflicted, there follow abrupt changes and adverse reactions – the patient starts losing his mind, is afraid of water and bites with a poisonous and contagious bite which is a consequence of the bite of a rabid dog.’ The ‘poison theory’ was the prevailing Renaissance view of the cause of rabies disease, though invented much earlier.
Several centuries followed without preserved written records, or perhaps not yet unearthed, until as late as 1823. The document that we possess from that year, however, seems to be very important. It was printed in the northern Croatian town of Osijek, on the Turkish border (Serbia was then a Turkish province) on low quality paper, but in a surprisingly large format, resembling a public announcement. Only one copy has survived, but it is clear from its style and form that it was a widely circulated pronouncement, clearly indicating a major concern of Austrian Imperial physicians about the threat of dog rabies to the population on the border. The chapter on dog rabies, about 70 lines long, describes its manifestations, detailing all the necessary measures of precaution, the rules for handling the corpse of an animal, and instructions for the cleansing and surgical treatment of the bite-wound that would undergo few changes if compared with present-day WHO guidelines. A drawing of a rabid dog with paralytic rabies is given.

The next step in following the evolution of man’s desperate attempt to grapple with the hideous nature of the rabies disease is ‘The Book on Rabies’ published in 1844 by Josip Lalic, a Croatian school teacher, also known in his time as inventor and self-appointed healer of rabies- and snake-bite victims. Lalic represents a breakaway from the mass of superstition that ruled the popular notions of rabies at the time, repeats correct procedures for wound cleansing and surgical treatment but also, in tune with the medical views of the period, expounds the ‘worm theory’ (Chapter 1, J. Neville). Precise instruction is given to conduct a surgical resection under the tongue, and extract the ‘worm’.

From Pasteur to 1945

News of the breakthrough achieved by Pasteur in 1885 spread fast in this region, though technology was much slower to follow. A major obstacle was the fact that Pasteur’s vaccine had to be prepared on site, was not transportable, nor stabilised for any period of shelf-life. Until the end of the Austro-Hungarian Empire, patients from Croatia, Slovenia and Bosnia travelled to Budapest and Vienna to receive treatment. This journey, which many completed on foot became unnecessary only in 1918 when, upon the collapse of the Empire, Croatia formed its own Pasteur Institute in Zagreb, including vaccine production and hospital facilities.

In fact, production of rabies vaccine at the Pasteur Institute in Zagreb started as a result of a theft. The ‘thief’ was Dr Ludevit Gutschy, a Zagreb-born Czech who worked on the preparation of vaccines at the Pasteur Institute in Vienna. In the chaos following the breakup of the Empire, he stole two bottles of infected rabbit spinal cord preparations and took them to Zagreb. He readily produced a workable Pasteur-type vaccine and began treatments. Having a sound sense for profit, he placed posters on train stations and similar locations throughout Croatia. The initiative was, of course, government-controlled and the Zagreb Pasteur Institute, under Gutschy’s command, was absolutely legal.

Serbia fared somewhat better in that it gained independence much earlier (The Berlin conference of 1878 formally ended five centuries of Turkish rule) and formed its first Pasteur Institute in 1900. This was not in the capital Belgrade but in the southern town of Nis, on the Bulgarian border. By the end of that year the Institute started its own vaccine production and treated nearly 5,000 people from 1901 until 1911. Meticulous records were kept, but they were almost all destroyed, along with the laboratory and production equipment, in the mayhem of the First World War.

Serbian rulers tried to enforce a number of very strict but rational measures, such as the law on dog ownership put into force in 1888. Apparently, merely making a law was not enough, forcing King Milos, shortly before 1900, to issue another royal decree ordering the elimination of all dogs in the country, except shepherd dogs. The exception granted was a most reasonable one, as the larger part of Serbian economy at the time was based on cattle herds and sheep flocks.

A key role in establishing a network of hygienic institutes throughout the country (including four independent Pasteur Institutes) in the 1920s was played by the then Deputy Minister of Public Health and Social Works, Dr Andrija Stampar. Stampar met Dr Adolph Hempt in the immediate aftermath of the First World War in a remote Bosnian village of Lukavac, 50 km from Sarajevo, treating patients bitten by Bosnian wolves. Originating from the German ethnic community in Belgium, Hempt demonstrated a brilliant scientific mind. Stampar’s immediate order was to send Hempt to Novi Sad, a town north of
Belgrade, to start the work on improving the existing rabies vaccines of the time – Hempt succeeded in 1925.

Hempt’s inactivated ether-phenol vaccine (see above) was a big step forward from the Pasteur-type vaccines, including Fermi’s, Semple’s, Hogyes’s, Alivisatos’s and other crude nerve-tissue preparations used at that time. His was the first stabilised vaccine, packed in ampoules, which meant that it was transportable and had a shelf-life of one year. Although still based on nerve tissue, the method of inactivation was better and produced fewer side-effects. Fatal complications of vaccination occurred in one in 25,000 vaccinees. Moreover, Hempt shortened the vaccination regimen to six doses, administered daily, with one booster given a month later.

The ability to produce stabilised and transportable rabies vaccines led to a decision, in 1928, to close down all Pasteur Institutes in Yugoslavia apart from the one in Novi Sad, which retained the sole licence for production and distribution throughout the country. A large part, produced under Hempt’s supervision, was exported.

1945 to the present time

Hempt’s successor as the head of the Novi Sad Institute was Dr Milan Nikolic, another scholar with enormous knowledge of natural science and skilled in research. It was he who in 1955 identified a bat rabies strain in insectivorous bats in Yugoslavia, one of the first confirmations of this form of rabies in Europe (Chapter 17, A.A. King et al.).

As the glory of Novi Sad faded, the Institute of Immunology in Zagreb came to the forefront of Yugoslav immunology, particularly with its original research into interferon therapy. The interferon story was given a boost in 1978 when Pierre Sureau reported on a corneal transplant from a rabid donor. The recipient was saved by combination of HDCV, HRIG and interferon. The Zagreb group of investigators used interferon, along with HDCV and HRIG a year later on a group of patients sustaining genuine rabies bite-exposure (category A patients, according to the WHO schedule).

Hundreds of similar treatments were performed in Zagreb until the present time, all on patients in the highest category of rabies risk. All survived, but the role of interferon in rabies post-exposure treatment was never conclusively proven.

In the mid-1980s, research in Zagreb with Dr Baklaic, Dr Ljubicic and Dr Svjetlicic, and the benefit of serological analyses and intellectual input from Dr Pierre Sureau of the Pasteur Institute in Paris, also left some tangible contributions to the rabies field. These are: (1) early clinical studies with the second generation of cell culture rabies vaccines, in particular the five-vaccine comparative trial of 1985, which demonstrated the immunogenicity of four new vaccines – PCEC, PDEV, FBKC and PVRV against the reference HDCV. This eased the way for their registration and worldwide use; and (2) experimentation with abbreviated regimens of vaccine application. The latter work resulted in the now official ‘Zagreb 2-1-1 schedule’ of post-exposure rabies treatment.

No human death from rabies has been associated with the application of the 2-1-1 schedule. It was officially endorsed by the WHO in 1992, and used in some of the world’s most dangerous areas for rabies infection. As pioneers of short schedules, we have been convinced, in theory as well as through exhaustive serologic investigations (more than a thousand sera were tested for rabies antibody levels), that the immune system has optimal ways of assimilating and responding to vaccine antigen where both the antigen load, means of application and timing are important. Many scientific observations remain unpublished, but the wisdom received from experienced colleagues in the rabies field can be summarised as: a patient bitten really badly, or reporting late, or immunologically weak, should receive a split dose in two sites, or two full doses bilaterally, followed by a third on day seven. Even in the absence of serum – though it should never be omitted – the vaccine itself, given as described, should suffice to save the patient, and it does.

The Federal Republic of Yugoslavia has not had a case of human rabies since 1980. Neither has Croatia, although there were two imported cases in 1993, both of whom died in the Clinic for Infectious Diseases
Chapter 8

in Zagreb. One was a boy licked, not bitten by a stray dog in Algiers in whom clinical symptoms were already apparent upon admission. The other case, a hunter and Skinner of foxes, came from Bosnia. Skinning a fox to preserve the fur is an extremely delicate process (the fur, to have value, must not be damaged or torn) which can only be done with bare hands. We calculated that approximately 5% of Skinners sustain injuries on the hands in the process. This manner of obtaining fox furs has been documented only in the Balkans but is particularly dangerous in Bosnia, infested as it is with wildlife rabies.

This leads us to reflect for a moment again on Dr Hempt and his Bosnian episode in 1919. The rugged mountains and dense forests of Bosnia indeed offer sanctuary to a large population of wolves that provide a reservoir of rabies virus even today. The records of the period 1927-1951 show that 863 rabies treatments followed wolf-bites in the region, with several deaths occurring among them. The risk of rabies infection following wolf bites is among the highest of all animal species.

The Pasteur Institute in Novi Sad led by Dr Nikolic managed to continue vaccine production during the war. The nationwide production of rabies vaccine, this time in Yugoslavia, was again centralised in Novi Sad in 1948. Nikolic introduced some improvements of his own and his name to the Hempt vaccine, which, until the mid-1950s still counted among the best in the world.

In June 1979, Dr Stan Smerdel, on a visit from the United States of America, gave an informative lecture at the Hospital for Infectious Diseases in Zagreb about the newly registered HDCV. The vaccine used in Yugoslavia at that time was the sheep-brain vaccine produced at the Pasteur Institute in Novi Sad. The treatment course of the nerve tissue vaccine took six 5 ml injections, given into the abdominal muscles. The information shared by Dr Smerdel might have passed us by as a marginal matter had there not been the case of a female patient, a young woman six months into pregnancy with grade A indications for immediate post-exposure rabies treatment. The woman was vaccinated with HDCV the next day, completed a regular course of HDCV and later gave birth to a healthy child. Within five years Novi Sad itself converted to HDCV.

CONCLUSIONS

During World War II and in the following years, Italy experienced a serious increase in the number of outbreaks of rabies, a disease which previously was limited to a few areas in the south of Italy and Sicily. Urban rabies had an important diffusion in the years 1947-1950, with consistent human losses; then the Veterinary Services were reorganized, with the consequent control of stray dogs and first vaccination campaign with killed vaccines. With a single exception, no rabies cases were reported in northern Italy from 1957 to 1967-68. An increase of rabies cases was recorded in central Italy in the years 1963-1965 and persisted in the provinces of southern Italy in the period 1967-1973. By March 1973 the whole of Italy was free from both urban and sylvatic rabies. However, Italy was surrounded by countries in which sylvatic rabies was a relevant problem. In particular, the infection was present in regions of Austria, Switzerland, France and former Yugoslavia. But despite the physical barrier to rabies spread represented by the Alps, measures were applied to monitor the entrance and/or presence of rabies, to limit the possibility of entrance of the infection and to limit the possibility of spread of the infection. Together with oral vaccination, a surveillance programme on wildlife and an intense reduction of fox density was started in 1977. Dogs and domestic herbivores at pasture have been compulsorily vaccinated against rabies in areas at risk. Stray dogs are captured and rubbish-dumps are controlled to reduce food availability. Italy was recognized rabies-free in 1997, rabies surveillance is still active and oral fox vaccination practiced at some border.

All of the Balkan nations have been affected by both canine and sylvatic rabies, however the control of dog rabies remained the principal issue. It was not until after the end of the Second World War that canine rabies was reduced substantially, which lessened the impact on public health. Concurrently, between the late 1920s until the 1980s, widespread human PET in the Balkans was undertaken using the Hempt vaccine; eventually being replaced with HDCV.
References


CHAPTER 9
RABIES IN HUNGARY, ROMANIA, MOLDOVA AND BULGARIA

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Summary

Rabies has been a constant problem in central Europe since the Middle Ages, with numerous reports of attacks by rabid dogs and wild carnivores including foxes, wolves and lynx. An important milestone in the control of rabies in Hungary was the introduction a Pasteur-type vaccine by Dr Endre Hogyes in the late 1880s. This was superseded in the 20th Century with the development of vaccines using ether-phenol treatment of infectious material by Dr Adolf Hempt, which resulted in a more stable vaccine preparation. This enabled wider availability and more rapid access to vaccination following attacks by rabid animals. This is followed by brief reviews of the current state of rabies control in Romania, Moldova and Bulgaria.

Keywords: Hempt vaccine, Hogyes, human vaccination

RABIES IN HUNGARY

The past

A considerable number of communications, regulations and directions proves that, as in many other European countries, rabies caused a significant problem in Hungary from the Middle Ages. Instructions for the 'cure' for a bite from a furious rabid animal included the use of salt water or urine to rinse the wound and then the multiple incising of the wound which was then covered with a 'pus'-inducing material such as ground insect powder (1). In parallel, the government ordered the collection and killing of stray dogs, the quarantine of suspicious animals, and the deep burial of carrion.

Data for the years 1712 and 1722 show that extremely high numbers of rabid dogs were observed. The regulations probably were not too successful, as from year to year more and more appeared. In 1813, a new regulation prescribed the immediate reporting of each animal rabies case to the country physicians (medical officers), who were obliged to collect the data and report on them yearly, including their experiences and medical observations of the human rabies cases. During this period, the declared main aim was to prevent the disease by inhibiting the entry into the wound of disease-containing saliva (11). In 1837, the chief medical officer of Hont county, J. Horváth complained that ‘When the rabid dog-originated rabies is broken out in a human, upon till now there is not any safe, effective medicine’.

A more important monograph by Lenhossék in 1837, which appeared in the middle of the 19th Century, gave a detailed review of the pathology, prophylaxis and effects of rabies, including the side effects of the medicines used to cure rabies. Data on ‘secret medicaments’ are also available from applications for registration of the medicines. Another publication reported a dog-bite case involving 30 men and two women who were treated by a number of experienced doctors, with unknown results. A Governmental regulation from 1836 declares that – taking into consideration the present findings – the most important species in connection with rabies infection are foxes, wolves, lynx and badgers, in the meantime mentioning the importance of collecting stray dogs (2). The chief official of the town of Pest in 1842 ordered the collection and killing of stray dogs to prevent human rabies, declaring this an important procedure for public health. A new era began at the end of the 19th Century when, mostly on the basis of the work of the excellent Hungarian scientist Endre Hogyes, an extended study was made on rabies.
From 1885 to 1942

Hogyes had close contact with Pasteur's laboratory in Paris and was well informed on their research. Thus, in 1885 he started research in his laboratory, which was supported by the Hungarian Academy of Science (4). The main purposes of his study were firstly to prepare a stable, fixed infective material, secondly to prepare a protective vaccine from it and finally to study its effect to determine if it was capable of giving protection against rabies infection and of preventing the disease after infection. He studied the relationship between the age of the animals used for the passage of the infective material and the appearance of the disease after infection. He also recognised the relationship between dose and effect of the infective material. This led him to introduce the so-called 'dilution' method instead of the 'drying' method of Pasteur, using the same infective spinal cord material in a more diluted suspension for the initial vaccination and later increasingly concentrated suspensions. When sufficient animal experiments proved the efficacy of his method to produce an effective material for vaccination to prevent rabies, pre-exposure immunisation was introduced for dogs.

In this period (the end of the 1880s) there were about 500-600 human cases from the bites of rabid dogs, but human vaccination was not generally introduced, mainly because of insufficient data about the effect of post-exposure vaccination. At the same time, some human cases were vaccinated after suspected exposure to rabies. Hogyes (5) reported 647 such cases in 1893 and he proposed the establishment of a definitive Pasteur Institute in Hungary, as from 1890 already there had been a so-called Pasteur Institute at the University in Budapest. In the years 1890-1896, 6,041 persons were treated at the Institute. These numbers show that at this time patient numbers were at about the same level as that of the Pasteur Institute in Paris. The effectiveness of vaccination is proved by the fact that death among vaccinated persons was between 0.57% and 1.54% (5).

At that time, from 15 April 1890 (opening of the Pasteur Institute at the Budapest University) until 1903 (opening of the definitive Pasteur Institute in Budapest), Hungary consisted of 63 counties, most of them infected with rabies. The worst infected area was Transylvania (nowadays Romania) and the least infected the northern part (nowadays Slovakia). From the officially published data of 1903, 2,040 rabid animals were notified (1,596 dogs, 158 cats, 26 horses, 135 cattle, 12 sheep and 113 pigs). In addition, 2,558 human-rabies infection suspected cases were treated at the Pasteur Institute in Budapest and 17 of them developed rabies (6).

Detailed evaluations of data, taking into consideration the time of infection, the timing of vaccination, the part of the body bitten and the length of the incubation period were published annually. The data were also analysed for age, gender and occupation (12), comparing the data of the Budapest Institute which used the so-called 'dilution' method of Hogyes and that of the Paris Institute, which used the 'drying' method of Pasteur. In Paris, of 28,474 vaccinated persons, 121 (0.42%) died, while in Budapest of 21,339 vaccinated persons 62 (0.29%) died.

A summary of the first 25 years of the Budapest Pasteur Institute was published in 1915 (13). During that period 86,937 persons visited the Institute, of which 19,148 were discharged when it became obvious that the contact was not a rabies-suspected case. Of 66,252 persons fully vaccinated, 507 (0.76%) died of rabies. However, a number of them died within 14 days after vaccination was completed, so the vaccination efficacy was re-calculated as 199 (0.30%) deaths in 65,944 vaccinated persons. In this period, using the 'dilution' method, the vaccine material was prepared from the spinal cords of infected rabbits showing signs of rabies. Dilutions of 1:2000, 1:1000, 1:500, 1:200 and 1:100 were prepared in physiological saline. Starting with the 1:2000 dilution, daily vaccinations were performed for at least 10 days and the most seriously injured (multiple, face) were vaccinated for 28 days. With regard to adverse effects, Dr Székely declared that, on the basis of their 25 years of observations, there was nothing to mention, neither on sterility (as the procedure was carried out under rigorous controls) nor on other adverse events, as they found no cases with serious complications. Revaccination in the case of a second exposure was proposed, in response to an observation that one person who had been vaccinated against rabies, had died of rabies after he had suffered another suspected rabies bite but had not been re-vaccinated because he had been treated one and a half years earlier.
The next summary of the Hungarian rabies situation was again by Székely (14). During the years 1915-
1925, of 58,946 fully vaccinated persons, 189 (0.32%) died, but the real efficacy of vaccination could be
calculated from 58,786 vaccinated persons, of whom 29 (0.05%) died. About 6.4% of those treated were
bitten by category A (confirmed rabid) animals, 22.2% by category B (suspect rabid) animals and 71.2% by
category C (unknown, stray or wild) animals. Taking the collective data from the period 1890-1925
(36 years), there were 124,730 suspected cases, 89.6% of which were bitten by dogs, 6.6% by cats and
1.8% by cattle. The gender proportions were 35.27% female and 64.72% male, while age group 0-15
accounted for 47% and others 53%. Interesting data were published about the incubation period, as 17%
of those infected became ill after 11-30 days, 49% after 31-60 days and 34% after 61 days or more (up to
more than 100 days!).

In the late 1920s new methods were devised for dog immunisation using only one dose and thus in the
second half of the 1930s the mass vaccination of dogs was introduced. Together with a compulsory dog
register and the capture of stray dogs, Hungary was the first country in the world to obtain very good
results with respect to the control of dog rabies.

**From 1942 to 1967**

During the early 1940s a new vaccine using ether-phenol treatment of infected rabbit or sheep brain
material was developed. This type of inactivated vaccine made possible the decentralisation of vaccine
production, as the vaccine could be posted without any loss of activity or other damage. Thus, by Home
Office Decree 1091/1941, the Pasteur Hospital was closed and the Pasteur Institute was incorporated into
the National Institute of Public Health. The vaccine was produced until 1945 at the Újvidék (nowadays,
Novi Sad) department of the Institute.

In the first year (1942) of this new era, 1,540 persons were treated, following contact with 1,313 dogs,
175 cats and 33 ruminants. Healthy animals had caused injuries in 696 of these cases and thus vaccination
was carried out unnecessarily – a disadvantage of decentralisation. There were no reports of significant
(i.e. paralytic) events in connection with the vaccine use, 99 febrile reactions only were notified. After the
end of the Second World War, at the beginning of December 1945, vaccine production was restarted. In
this year, there were no notifications of human rabies or serious vaccination complications and only two
rabid animals were found in laboratory tests. Of the 448 persons vaccinated, 258 had had contact only
with healthy, observable animals.

The period 1945-1950 was characterised by a slight increase in the number of persons treated, concurrent
with an increase in the number of rabid animals (Table 9.1). Seven human rabies cases had not been
vaccinated, while four cases were vaccinated but the detailed case reports are not available. The last slight
modification of the Hempt-type vaccine production method of the Hogyes-strain vaccine was made in
1949 and this vaccine was then used until the end of 1988, when a tissue culture originated (TCO) purified
and concentrated vaccine was introduced for humans (Fig. 9.1).

![Number of cases vs Year](chart.png)

**Fig. 9.1 – Some characteristic data on rabies (Hungary, 1984-1998)**
In 1950, the national control system against domestic rabies was restored after the period of post-war disorder. Between 1950-1966, only sporadic cases of animal rabies appeared in the country and one human (unvaccinated) case resulting from a dog bite was registered. Another human rabies case, this time following exposure to a rabid fox, was recorded in 1967.

**Table 9.1 – Human deaths from rabies in Hungary, 1945-1950**

<table>
<thead>
<tr>
<th>Year</th>
<th>Category of biting animal</th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
<th>Total</th>
<th>Rabid animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>1945</td>
<td>17</td>
<td>10</td>
<td>163</td>
<td>190</td>
<td>–</td>
</tr>
<tr>
<td>1946</td>
<td>54</td>
<td>65</td>
<td>407</td>
<td>526</td>
<td>2</td>
</tr>
<tr>
<td>1947</td>
<td>213</td>
<td>566</td>
<td>931</td>
<td>1,710</td>
<td>–</td>
</tr>
<tr>
<td>1948</td>
<td>233</td>
<td>186</td>
<td>919</td>
<td>1,338</td>
<td>1</td>
</tr>
<tr>
<td>1949</td>
<td>233</td>
<td>41</td>
<td>825</td>
<td>1,099</td>
<td>1</td>
</tr>
<tr>
<td>1950</td>
<td>17</td>
<td>27</td>
<td>597</td>
<td>641</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>767</td>
<td>895</td>
<td>3,842</td>
<td>5,204</td>
<td>4</td>
</tr>
</tbody>
</table>

*: data not recorded

**From 1968 to 2000**

The only human rabies cases to be reported in Hungary since 1967 included one case imported from Nigeria in 1978, two cases in 1985 (fox and cat origin), one case (cat origin) in 1991 and two cases in 1994, both of which were infected by the same cat. In the period 1974-1988, the annual number of persons treated varied between 2,000 and 3,000. However, after the introduction of the human diploid cell vaccine (HDCV) in 1988, there was a considerable increase in the number of persons treated. It has proven impossible to stem this increased demand for anti-rabies vaccination since, although human rabies cases have been extremely rare, public awareness and fear of the disease are at a high level. Moreover, the two human rabies cases originating from one cat in 1994 promoted great media publicity and, as the vaccine is free of charge to the patient, any financial disincentive is removed. Thus a large number of the treatments are not in accordance with the WHO recommended criteria for post-exposure prevention. In Hungary, post-exposure treatment does not include the use of rabies immunoglobulin, except in the treatment of immunocompromised patients.

None of the six indigenously infected persons who died of rabies since 1967 had been vaccinated (7). However, brain tissue from two of the cats was negative for rabies antigen both in the immunofluorescence test and in the mouse inoculation tests carried out in two experienced diagnostic laboratories. The human brain samples were also negative in immunofluorescence tests, but positive in the mouse inoculation tests (8). The viruses were all of serotype 1 (H. Bourhy, Paris, 1996, personal communication). Because of these results, a comparison of immunofluorescence test negative and mouse inoculation test positive results was made. An analysis of more than 8,000 animal test results showed that in 0.4%-1.1% of the immunofluorescence negative tests, the mouse inoculation test proved positive for rabies. Recommendations for the cessation of treatment in cases of negative laboratory test results were reconsidered.

**Species involved in human rabies exposure**

Over the past 25 years, the number of post-exposure treatments due to dog bites has remained relatively constant (41%-46% of all treatments), whereas those given in response to injuries from cats have almost doubled (18.6% to 35.5%). However, during the same period the percentage of treatments following exposure to foxes has fallen from 31.1% to 10.2% of all treatments, despite the continued relatively high number of fox rabies cases (Table 9.2).
Table 9.2 – Animal rabies in Hungary, 1979-2001

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th>Wildlife animals</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dog</td>
<td>Cat</td>
<td>Cattle</td>
</tr>
<tr>
<td>1979</td>
<td>24</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>1980</td>
<td>13</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>1981</td>
<td>23</td>
<td>41</td>
<td>8</td>
</tr>
<tr>
<td>1982</td>
<td>23</td>
<td>54</td>
<td>20</td>
</tr>
<tr>
<td>1983</td>
<td>23</td>
<td>50</td>
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<td>87</td>
<td>38</td>
</tr>
<tr>
<td>1991</td>
<td>52</td>
<td>89</td>
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</tr>
<tr>
<td>1992</td>
<td>47</td>
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<td>1993</td>
<td>85</td>
<td>116</td>
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</tr>
<tr>
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<td>57</td>
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<td>1995</td>
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<td>41</td>
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<tr>
<td>2000</td>
<td>24</td>
<td>61</td>
<td>25</td>
</tr>
<tr>
<td>2001</td>
<td>14</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>Totals</td>
<td>869</td>
<td>1,652</td>
<td>681</td>
</tr>
</tbody>
</table>


Wildlife rabies

During the period 1954-1965, fox rabies cases were reported only sporadically, and indeed during this period dog and cat rabies cases outnumbered fox cases by 127 to 113. From 1966 however, fox rabies cases increased rapidly, from 17 in 1966 to 212 in 1967 and 772 in 1968. By 1974 rabies was epizootic among foxes throughout the country, with an average of 1,151 laboratory-diagnosed cases reported annually (9). In 1974, domestic animals accounted for only 5% of the total number of rabies cases, but this gradually increased and has remained at approximately 20% of the total ever since. An oral fox vaccination program commenced at the beginning of the 1990s, but as the vaccination area was only a 20-25 km broad zone along the Austro-Hungarian border it had no real effect on the number of rabid animals. Step-by-step the program was extended to the whole Trans-Danubian part of the country and thus the number of rabid animals began to decrease. Through these incremental steps the western half of the country has been cleared of the disease. As in other European countries, the decline in animal rabies cases has only slowly been followed by a fall in the demand for human post-exposure treatment. In September 1999, a rabid bat was diagnosed in Budapest; thus bat rabies also appeared as a potential human danger.

ROMANIA, MOLDOVA AND BULGARIA

Romania

According to Bisseru (3), in Romania dogs and cats are the vectors of rabies, with dogs, foxes and wolves as the reservoir species.
Historical Perspective of Rabies in Europe and the Mediterranean Basin

Human rabies

In Romania before 1944, rabies was a serious problem and the average human death toll from the disease was 255, 59% of whom had no anti-rabies treatment since treatment was only available in three centers (Bucharest, Cluj and Jassy) and travel involved expense. Between 1951 and 1955, 69 persons were bitten by rabid wolves and all the patients died although treatment with anti-rabies vaccine was given. Between 1956 and 1966, a further 44 persons were bitten by rabid wolves; some of the injuries were very deep and severe and combined serum and vaccine therapy was instituted. Nevertheless, during 1951-1961 there was a marked decrease in human mortality from rabies with the use of sheep brain Fermi vaccine in association with serum therapy being thought to be largely responsible. Booster doses of vaccine were given in all cases of severe bites (3).

Animal rabies

In 1965, rabies in animals was observed mostly in mountainous and forested areas where wolves were an important component. In 1966, it was found that street virus had infiltrated progressively among foxes during the previous years.

Attempts to control the disease were continued by the Ministry of Health, firstly from 1944-1955 by increasing anti-rabies treatment centers to 86, secondly from 1956 to 1960 by continual and energetic publicity campaigns conducted by press, radio and film, and thirdly from 1961-1965 by reducing the number of unregistered dogs and stray animals, and dog mass vaccination campaigns. These control measures were made permanent through legislation in 1966.

These measures decreased the morbidity and mortality rates of injuries, and the number of rabies cases declined from 1,300 in 1950 to 161 in 1961 (3). In 1958, the number of dog vaccinations rose from 192,000 in 1950 to 1,305,791. In the 86 centers anti-rabies treatment was given only to persons definitely at risk and thus savings in treatment costs were made (3). Nevertheless, the fox rabies epidemic that swept through Europe after the Second World War also encompassed Romania. Details of the animal death toll between 1980-2001 are shown (Table 9.3).

Table 9.3 – Animal rabies in Romania, 1980-2001

| Year | Domestic animals | | | | | | Wildlife animals | | | | Total |
|------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|      | Dog          | Cat          | Cattle          | Other          | Total          | Fox          | Badger          | Other          | Total          | Fox          | Badger          | Other          | Total          | Fox          | Badger          | Other          | Total          | Fox          | Badger          | Other          | Total          |
|      | 1980         | 11           | 10             | 14             | 7              | 42           | 39             | 3              | 3              | 45           | 87             |      |      |      |      |      |      |      |      |      |      |      |
|      | 1981         | 10           | 7              | 44             | 27             | 88           | 36             | 1              | 3              | 40           | 128            |      |      |      |      |      |      |      |      |      |      |      |
|      | 1982         | 8            | 9              | 17             | 15             | 49           | 35             | 5              | 2              | 42           | 91             |      |      |      |      |      |      |      |      |      |      |      |
|      | 1983         | 4            | 14             | 12             | 4              | 34           | 19             | 1              | 5              | 25           | 59             |      |      |      |      |      |      |      |      |      |      |      |
|      | 1984         | 5            | 16             | 9              | 73             | 103          | 30             | 3              | 4              | 37           | 140            |      |      |      |      |      |      |      |      |      |      |      |
|      | 1985         | 6            | 11             | 14             | 20             | 51           | 21             | 1              | 1              | 23           | 140            |      |      |      |      |      |      |      |      |      |      |      |
|      | 1986         | 6            | 7              | 12             | 7              | 32           | 34             | 3              | 3              | 37           | 69             |      |      |      |      |      |      |      |      |      |      |      |
|      | 1987         | 5            | 6              | 6              | 7              | 24           | 21             | 1              | 2              | 22           | 46             |      |      |      |      |      |      |      |      |      |      |      |
|      | 1988         | 4            | 6              | 9              | 1              | 20           | 16             | 1              | 1              | 18           | 38             |      |      |      |      |      |      |      |      |      |      |      |
|      | 1989         | 1            | 4              | 5              | 7              | 17           | 3              | 3              | 6              | 23           | 49             |      |      |      |      |      |      |      |      |      |      |      |
|      | 1990         | 7            | 12             | 12             | 2              | 33           | 13             | 1              | 2              | 16           | 49             |      |      |      |      |      |      |      |      |      |      |      |
|      | 1991         | 7            | 11             | 7              | 12             | 37           | 13             | 4              | 17             | 54           |      |      |      |      |      |      |      |      |      |      |      |
|      | 1992         | 12           | 6              | 5              | 8              | 31           | 18             | 3              | 21             | 52           |      |      |      |      |      |      |      |      |      |      |      |
|      | 1993         | 10           | 12             | 10             | 6              | 38           | 32             | 1              | 6              | 39           | 77             |      |      |      |      |      |      |      |      |      |      |      |
|      | 1994         | 6            | 6              | 4              | 3              | 19           | 13             | 1              | 13             | 32           |      |      |      |      |      |      |      |      |      |      |      |
|      | 1995         | 5            | 6              | 5              | 16             | 12           | 1              | 1              | 14             | 30           |      |      |      |      |      |      |      |      |      |      |      |
|      | 1996         | 10           | 6              | 9              | 3              | 28           | 13             | 1              | 14             | 42           |      |      |      |      |      |      |      |      |      |      |      |
|      | 1997         | 7            | 4              | 4              | 3              | 18           | 13             | 1              | 2              | 16           | 34             |      |      |      |      |      |      |      |      |      |      |      |
|      | 1998         | 3            | 9              | 5              | 18             | 35           | 13             | 2              | 15             | 50           |      |      |      |      |      |      |      |      |      |      |      |
|      | 1999         | 5            | 8              | 4              | 8              | 25           | 17             | 3              | 20             | 45           |      |      |      |      |      |      |      |      |      |      |      |
|      | 2000         | 20           | 12             | 5              | 7              | 44           | 50             | 3              | 55             | 97           |      |      |      |      |      |      |      |      |      |      |      |
|      | 2001         | 30           | 23             | 17             | 23             | 93           | 282            | 1              | 10             | 295          | 386            |      |      |      |      |      |      |      |      |      |      |      |
| Totals| 182          | 205           | 224            | 266            | 877           | 743           | 23             | 60             | 826          | 1,703        |      |      |      |      |      |      |      |      |      |      |      |

Moldova

Moldova was part of Romania but was annexed by the Soviet Union in 1940. It became an independent State of some 33,700 km² in 1991 and the rabies situation began to be reported in 1993 (Table 9.4).

Table 9.4 – Animal rabies in Moldova, 1993-2001

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th>Wildlife animals</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dog</td>
<td>Cat</td>
<td>Cattle</td>
</tr>
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<td>1993</td>
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<td>1</td>
<td>1</td>
</tr>
<tr>
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<td></td>
<td></td>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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<td>7</td>
<td>10</td>
</tr>
<tr>
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<td>3</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Totals</td>
<td>26</td>
<td>19</td>
<td>31</td>
</tr>
</tbody>
</table>

* : incomplete data
** : no data for April-August


Bulgaria

According to Bisselu (3), dogs and cats were the rabies vectors. Between 1927 and 1966, 44 patients with rabies were admitted to the Infectious Diseases Hospital in Bulgaria (10). In one case, an incubation period of 25 months was established and according to the authors, in two others the history suggested incubation periods of 18 and 20 months. In the final 12 years, there was only one case in each of the years 1957, 1958 and 1964, and in 1958 thirteen dogs and two bovines were reported rabid.

Animal rabies

There is some discrepancy in the published figures for Bulgaria. Valtchovski (15) gave figures covering the period 1984-1994 in which, for example, fox rabies cases averaged 21 annually (Table 9.5), but no rabies cases in any animal species were reported to Rabies Bulletin Europe (at Tübingen) between the years 1979-1991 (Table 9.6). In the overlap years (1992-1994) only 37 cases were reported to Tübingen, whereas Valtchovski records 73 cases.

Table 9.5 – Animal rabies in Bulgaria, 1984-1994 (15)

<table>
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<tr>
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<th>Domestic animals</th>
<th>Wildlife animals</th>
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</tr>
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<td>5</td>
<td>16</td>
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<tr>
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Table 9.6 – Animal rabies in Bulgaria, 1979-2001 (7)

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<td>Fox</td>
<td>Other</td>
<td>Other</td>
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</tr>
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<tr>
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<td></td>
<td>22**</td>
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<td>2001</td>
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<td></td>
<td>62**</td>
<td>62</td>
<td></td>
<td>62</td>
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</tr>
<tr>
<td>Totals</td>
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<td>7</td>
<td>8</td>
<td>26</td>
<td>10</td>
<td>161</td>
<td>171</td>
<td>197</td>
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</tr>
</tbody>
</table>

* : incomplete figures  
** : species unspecified  
*** : No cases reported to Rabies bulletin Europe

CONCLUSIONS

Canine and sylvatic rabies has been a recurrent problem in central Europe with numerous reports of attacks by rabid dogs and wild carnivores including foxes, wolves and lynx. The use of human PET in the treatment of rabies due to dog bites has remained relatively constant. In contrast, the number of treatments following exposure to foxes had declined despite the high number of fox rabies cases. In the late 1880s, Dr Endre Hogyes, with the development a Pasteur type vaccine, aided the treatment of human rabies. The Hogyes vaccine was superseded with a more stable vaccine preparation prepared from ether-phenol treatment of infectious material by Dr Adolf Hempt. These vaccines enabled wider availability and more rapid access to PET in central European countries following attacks by rabid animals.

References


CHAPTER 10
RABIES IN FRANCE, THE NETHERLANDS, BELGIUM, LUXEMBOURG AND SWITZERLAND

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(6) Institute of Pathology, University of Bern, P.O. Box 62, 3010 Bern, Switzerland

Summary

In the majority of European countries, throughout the 1900s, the dog was the main reservoir, vector and victim of rabies. Human cases were reported as a result of infection from dogs and other domestic animals. The application of strict sanitary measures allowed the elimination of canine rabies in these countries by the middle of the 20th Century. Sylvatic fox rabies spread to Belgium and Luxembourg in 1966, Switzerland in 1967, France in 1968, and The Netherlands in 1974. In all these countries, the different measures aimed at fox population decimation failed to stop the progression of the rabies wave, whereas oral vaccination of foxes by means of vaccine bait was shown to be the only efficient tool to control the disease. As a result of successful oral vaccination programmes, these countries have been reported officially free of terrestrial rabies: The Netherlands in 1991, Switzerland in 1999, France in 2000, Belgium and Luxembourg in 2001. However, cases of bat rabies have been, or are still, reported in most of these countries.

Keywords: Belgium, dog, fox, France, Luxembourg, rabies, Switzerland, The Netherlands

FRANCE

The history of rabies in France has been summarised by Blancou (Chapter 2, J. Blancou). From this it is clear that, at the end of the 19th Century, there was an ‘explosion’ of canine rabies in France and other European countries. Canine rabies continued to predominate well into the 20th Century and, although the annual number of cases declined from a peak of over 4,000 following the First World War, it was not until the early 1950s that case numbers fell to double figures. France became rabies-free in 1960, but in 1968 was invaded by a wildlife rabies epizootic that was finally eliminated 35 years later.

Human rabies

The contribution by Pasteur and his colleagues, in France, to our knowledge of human rabies and its treatment is legendary. His beliefs that each case of rabies arose from another, that there was a link between a bite and infection, that saliva played a role in infection, that the infectious agent was consistently present in the central nervous system of animals dying of the disease and, of course, his successful treatment of patients at risk, are all testaments to his insight.

In 1886, prior to widespread rabies vaccination of humans, 125 indigenously acquired human rabies deaths occurred in France. During the following years, thanks to the application of control measures for dogs and post-exposure treatment (PET) of dog bite victims, human rabies cases decreased progressively
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until, in 1910, no indigenous human rabies deaths occurred. This success was repeated during the following years but, in 1915, human rabies reappeared resulting in a total of 21 deaths between then and 1921 when it was eradicated again. No cases were recorded in 1922 and 1923, but in 1924 there was one other human case, the last from natural infection in France (25). However, the last human rabies case acquired in the country was in 1979, following transplantation of a cornea from a woman whose cause of death had not then been determined. The recipient of the transplant died of rabies. Laboratory tests on tissues of the donor led to the conclusion that she had died of rabies, probably acquired in Egypt (40).

Animal rabies

Dog rabies

Since Pasteur, the history of dog rabies in France can be divided into two periods:

1) from 1919 until 1960 and
2) from 1960 to present time (Table 10.1).

The former period was associated with a steady reduction in cases, the latter with local eradication of the disease and control of sporadic importation.

1) 1919 to 1960

During this period there was a slow but steady control of the disease by the application of sanitary measures which included a dog registration, pre-exposure vaccination and/or the destruction of strays. The number of rabies cases in animals, which had reached 4,541 in 1919, was almost halved in two years. In 1925, the first year with no human case, the number of rabies cases in animals, while still very high at 1578 (20), continued on a downward trend, although the disease only became close to elimination during the 1950s. Interestingly, unlike the First World War, the Second World War was not marked by an increase of the disease but by its maintenance at a low level.

A detailed examination of the situation that prevailed after the period 1936-1937 shows that the number of dog rabies cases fell and that rabies epidemiology followed one of two patterns: either several cases in dogs were recorded but did not provoke local epizootics, or, the social context, including the relative efficacy of veterinary policy, usually prevented dog-to-dog transmission. Rabies cases were either the last ones of centuries-old local epizootics, or were imported from still infected neighbouring countries and overseas colonies. In a few, but spectacular, situations isolated (and very probably imported) cases provoked a local massive outbreak, which was eliminated by severe and widespread application of control measures. Such outbreaks occurred at least three times:

– in the French Pyrénées (1937-1940),
– in Corsica (1943-1946)

a) Département of Pyrénées Orientales, 1937-1940

Before 1937 suspicious cases of dog bites on humans had been recorded but for many of them laboratory diagnoses, when performed, did not confirm the presence of rabies. However, undoubtedly a rabies episode did occur here during 1937-1940. Its origin was attributed to the Spanish Civil War with the accompanying mass immigration of Spanish civilians and members of the Spanish republican army. Rabies with unequivocal clinical symptoms was observed in dogs, horses, cattle and pigs. In 1937 and 1938, 80% of suspected cases were confirmed by laboratory diagnosis. During the two following years this percentage decreased to 40%, and, thanks to the application of sanitary measures, the dog rabies epizootic was eradicated in 1940 (13).

b) Corsica, 1943-1946

No rabies cases had been observed in Corsica since 1932 but in April 1944, following the landing of allied troops coming from North Africa, rabies cases appeared in dogs. The disease was not observed after October but suddenly reappeared in two distant places in April 1945. From dogs, the disease
rapidly spread to other domestic animals such as cats, cattle, donkeys, horses, goats and pigs (which had been released into the bush). Strikingly, foxes were found dead in great numbers, many were observed sick and aggressive in daytime and often entered sheep pens. Laboratory examination of cattle and donkey brains proved that rabies was responsible for these symptoms. The species responsible for human infection clearly indicated the pattern of a dog rabies enzootic: dogs (64%), cats (13%), goats (12%), donkeys (11%), horses (8%), cattle (2%), pigs (1%), but there were only three fox cases (189). The limited records from this period indicate that dogs were ‘restricted’ – and vaccinated. Fox culling was encouraged, with bounties paid in money and cartridges. The disease disappeared from Corsica in 1946.

### Table 10.1 – Terrestrial animal rabies in France 1979-2000

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th>Wildlife animals</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dog</td>
<td>Cat</td>
<td>Cattle</td>
</tr>
<tr>
<td>1979</td>
<td>49</td>
<td>39</td>
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</tr>
<tr>
<td>1980</td>
<td>47</td>
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<tr>
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<td>45*</td>
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</tr>
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<tr>
<td>Total</td>
<td>694</td>
<td>1,256</td>
<td>2,153</td>
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</tbody>
</table>

* imported dog

**Source:** Rabies Bulletins Europe

### c) Pyrénées and neighbouring areas, 1956-1958

In 1950, dog rabies appeared to be absent, with the exception of sporadic cases in dogs imported from the still infected neighbouring countries of Italy, Germany and Spain, and from overseas colonies, mainly North Africa. The Algerian independence war, with the increase of Mediterranean crossings, explains several rabies cases in dogs in 1955-1957, but not all of the sporadic importation of rabid dogs provoked long lasting rabies outbreaks. However, in April 1956, a stray dog captured in the small city of Ossun, close to the Spanish border (Hautes Pyrénées) was confirmed to have rabies by laboratory examination. This case was followed by a rapid spread of the disease towards other Départements of the same region, notably Landes, Basses-Pyrénées and Gers. Whereas during the years 1950-1955, ten sporadic rabies outbreaks had been suspected, in the area of the Ossun, between 1957, 170 rabies
foci were officially recorded (however, only 72 cases were confirmed by laboratory diagnoses). Among the species involved in the epizootics, the dog was foremost. No wild species were involved as confirmed by laboratory examination of foxes and badgers. Prophylactic measures were more rigorously undertaken in nine (not all contiguous) Départements of the southwest of France, covering a total area of more than 54,500 km². In addition, all unleashed dogs were culled (5). As a result, the last rabies case of the epizootics was recorded in July 1958 and the most severe measure (the immediate killing of unleashed dogs) was abrogated in March 1960 (30).

2) 1960 to present time

All dog rabies infections introduced into the country during this period have been rapidly controlled and eliminated. After July 1958 there were no rabies episodes until 1968, when fox rabies invaded France. The geographical position of France, being at a crossroads of coasts and terrestrial frontiers, has lead to the entry of at least 20 rabid dogs or cats since 1960. At least four of these infections generated a chain of transmission to several others dogs and cats. Interestingly, two of these serial outbreaks took place in the Pyrénées region, as had been the case in 1937-1940 and in 1950-1958. But this time, both epizootics were rapidly eradicated (lasting two and four months respectively) and affected only eight dogs and seven cats. Fifteen of the 20 imported, infected animals had identifiable owners who declared that they had acquired them when visiting infected countries or had brought them from; North Africa (seven), sub-Saharan Africa (three) and the Middle or Far-East (five). Among the five other animals were one stray dog found in a nomadic camp and one cat found near Orly airport (1).

Wildlife rabies

Wildlife rabies invaded France in March 1968 when a fox entered the village of Montenarch in Moselle near the Franco-German border. After it had bitten a dog belonging to a farmer it was beaten to death. The examination of its brain at the Pasteur Institute, Paris showed it had been rabid (4). Two more rabid foxes were killed in the Thionville area of the Moselle in June 1968. These incidents started the fox rabies epizootic in France. Prior to this incident there had been no indigenous rabies cases since 1959 and indeed, of 198 animals examined for rabies at the Pasteur Institute the previous year (1967), only one (a dog imported from Togo) was rabid. By the end of 1968 the disease was confirmed in a further 58 foxes.

The disease progressed along valleys and, although rivers and canals delayed its advance, in many instances the crossing of bridges and small rivers was clearly observed. From 1968 to 1974, the disease inexorably progressed at a mean speed of 30-40 km per year. The contaminated area and the number of animal rabies cases increased accordingly. Limitation of the potential vector population was the only sound (and available) method of control, but as elsewhere the implementation of this policy was unable to halt the spread of the disease. In contrast, prevention of disease by rabies vaccination of domestic animals met with resounding success and cattle rabies, which had increased along with fox rabies, dramatically decreased in 1972 as a result.

As in other European countries, the areas infected experience, for several years, enzootic cycles with low and high incidence alternation, but in 1975 the front wave slowed and eventually came to a stop. In 1981, after a four-year period of calm, old foci were re-activated and, until 1986, the front pulsed, advancing at some points and receding at others. At this time, France moved towards wildlife oral vaccination (Fig. 10.1). Limited areas were treated, in extension to the vaccination plans of Belgium and Luxembourg in the north, and to the Swiss plan in the south. Close to Belgium and Luxembourg, the vaccinated areas were too small and therefore were rapidly re-infected from other non-vaccinated or poorly vaccinated areas (the vaccination campaign of spring 1988 was cancelled in Belgium due to lack of funds). In 1990, the strategy was to concentrate the effort at the rabies front in response to a new and sudden extension of the disease. Rabies cases had reached record numbers (Tables 10.1 and 10.2) and large rivers (Seine, Loire, Allier) had been crossed at several points.

Backed by the unaffected half of the country, a continuous immunological barrier was established from the English Channel to the Swiss border (Fig. 10.1).
This 50 km-wide strip was created in autumn 1990 and was successful in halting the advance of the disease (Fig. 10.2). With the durable clearing of large areas now possible, vaccination was extended to the north and the east, towards the borders with Belgium, Luxembourg and Germany. Since 1990 the number of rabies cases for the whole of France decreased by 30%-80% annually. More specifically, the latter value was obtained in 1993 after vaccination was extended to cover the whole contaminated area (which in the 1992, spring and autumn campaigns reached a total of 192,418 km²). It was shown that rabies incidence could be diminished by more than 90% (42) after a first vaccination campaign was carried out with potent vaccines using an appropriate strategy of bait dropping (26). After one year with close surveillance, if no rabies case in the treated areas occurred, vaccination could be stopped provided surveillance was maintained. Rising expectation that rabies could be eliminated motivated the public and local veterinary services to submit more samples to the laboratory for diagnosis.

The following field protocols were shown to improve the efficiency of oral vaccination campaigns: supplementary vaccination at den entrances (42), increase of bait density (11), double bait distribution at 15 or 30 days interval (11), vaccination during summer period (27).

From 1968 to 2000, 19 imported dog or cat rabies cases have been documented. In 1999, an additional case was recorded in an imported tropical fruit bat, Rousettus aegyptiacus, which was infected with a strain of Lagos bait virus (genotype 2).
Historical Perspective of Rabies in Europe and the Mediterranean Basin

### Table 10.2 – Terrestrial animal rabies in The Netherlands 1979-2000

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<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th></th>
<th>Wildlife animals</th>
<th></th>
<th>Total</th>
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</thead>
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</tr>
<tr>
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<td>8</td>
<td>13</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

* Dog imported from India

Source: Rabies Bulletins Europe
For cases in bats: Chapter 17, A.A. King et al.

In 1996, only 17 fox rabies cases were recorded; all were less than 27 km from the border with Belgium. Since then, fox rabies in France has been dependant upon the situation in Belgium and Germany, but no terrestrial animal rabies cases have been reported since December 1998. An immunity barrier was maintained at the Belgium border until the year 2000 and at the German border until.

**THE NETHERLANDS**

Descriptions of rabies in humans and animals date from many centuries ago. However, in The Netherlands, no adequate survey of rabies epizootics or the resulting number of casualties, in man or animal, existed until the 20th Century. From 1822 it is known that rabies was normally present, although it remains uncertain whether this was exclusively dog rabies. In a newspaper article of 1843 one human casualty was reported following a rabid dog bite. In the same article, attention was given to treatment of such wounds both for humans and agricultural domestic animals. From 1873 until 1912 a quarantine building was in use, at the Veterinary University in Utrecht, for animals suspected of being infected with malleus or with rabies.

The high frequency of rabies in dogs, cattle and humans in The Netherlands led, in 1875, to national legislation to control rabies in cats and dogs. These rules may have led to the complete eradication of the disease in 1923. Apart from a single case, it was not until 1974 that wildlife rabies (re)occurred. Therefore, three distinct historical periods of rabies occurrence can be distinguished: until 1923, 1923-1974 and after 1974.

**Human rabies**

Complete figures of the incidence of rabies up to 1923 are not available, but rabies in man was a regular phenomenon especially during the 19th Century. Treatment of patients in the first place concerned bite wounds. Cauterisation and the application of acids and mixtures of herbs were in common use until the results of Pasteur’s work became available in 1885 and vaccination was possible. However, it is not clear if or how often Pasteur’s vaccine was applied. In 1887, Högyes (Netherlands) developed a live vaccine with the virulence reduced by dilution. Later, Högyes vaccine was combined with a glycerine treatment according to Phillips (Netherlands). This Högyes-Phillips live attenuated vaccine was used until the early 1960s. From the early 1960s until 1978, UV-treated tissue culture (new-born rabbits) vaccine was mainly used. After 1978 a dog kidney cell vaccine (DKCV) was (and still is) used, as is the human diploid cell vaccine (HDCV). Preventive vaccination of humans is applied on a very small scale.

In an incident in 1962-1963, five people died of rabies (see animal rabies below). As a result, 548 people, all contacts with rabid or rabies-suspect animals, were given post-exposure vaccination. In 1996, a 49-year-
old Moroccan man, who was bitten on the face by a rabid dog whilst on vacation in Morocco, was hospitalised and died of rabies 11 days later. Thus, only six persons have died of rabies in The Netherlands since 1923; five indigenous and one imported case.

Animal rabies

From the above we can assume that dogs were the main carriers of rabies until its eradication in 1923, since up to that time rabies was found regularly in dogs, cats and agricultural domestic animals. As fox rabies spread westward through Germany from Poland in 1947, it was expected that The Netherlands would also become infected. The Veterinary Inspection Service of the Ministry of Health, Welfare and Sport began research in 1954 on dead and shot foxes in a 10 km wide strip along the former West Germany border. All foxes found dead or killed were handed to the police, who recorded relevant details for the whole country. Carcases were sent to the Central Veterinary Institute via the Veterinary Service of the Ministry of Agriculture, Nature Management and Fisheries where they were tested for rabies. In order to promote this submission the Ministry, until January 1994, paid a FL.15 bounty for each fox. In addition, a Ministry Decision of 1954 prohibited the import and transit of dogs, unless the animals were vaccinated at least 30 days and no more than 1 year before transport. In 1967, this Decision was expanded to the outer borders of the Benelux countries.

In 1962-1963 rabies was found in four dogs, two cats and one goat; the result of infection from a small rabid dog held in an animal pound. Remarkably, human rabies was diagnosed prior to knowledge of the animal cases. During those years, five people died of rabies (see above). The origin of the small dog’s infection was never determined but it might have been the result of contact with an imported rabid cat from Nigeria. In response to this outbreak police measures were implemented and, from the end of 1962 until the spring of 1963, obligatory cat and dog vaccination was adopted. This resulted in 70%-80% of the national dog population being vaccinated during that time. Rabies was again found in 1965, 1972 and 1979. These cases were three dogs illegally imported from Sri Lanka, Afghanistan and India, respectively. Thanks to early discovery, the disease did not spread.

In 1967, because of the serious threat of the introduction of wildlife rabies from Germany and Belgium into the area of South Limburg, all dogs (30,000) were vaccinated. Furthermore, the drive to exterminate foxes and the shooting of stray dogs and stray cats was intensified. The numbers of foxes were reduced by hunting and digging-out fox dens but gassing was never used.

On 28 August 1974, a rabid fox was found in the province of Groningen. In 1975, several further cases occurred in the same area and also in the provinces of Drente and Overijssel, bordering West Germany. In 1976-1977, the province of Limburg was confronted with rabies. Between 28 August 1974 and 17 June 1977, 42 cases of rabid foxes, seven badgers, two stone martens and one sheep were found throughout the country, mostly in Southern Limburg, but from July 1977 until February 1983 no other cases were found.

On 4 March 1983 fox rabies was again diagnosed in the province of Groningen. Another two rabid foxes were found in the same area that same year and, during the last three months of 1983, 12 fox rabies cases were diagnosed in Southern Limburg. In 1984, 65 cases (38 foxes, nine badgers, one deer, ten sheep and seven cattle) occurred in Southern Limburg (Table 10.2). The sheep and cattle originated from seven farms and in each case contact with rabid foxes had occurred. Another 12 foxes, one badger and three sheep were found rabies positive in the same area in 1985, and another fox was found positive in 1986. In 1988, a third wildlife outbreak took place and included six foxes, a stone marten, a cow and a cat.

During the first six months of 1984 an experiment was performed over a 450 km² area in order to determine if oral vaccination of at least 50% of the fox population in that area was possible. The area had a high wild boar population, which could compete with foxes for baits (one day-old chicks). During the experiment, the bait contained no vaccine, only tetracycline as an indicator. In the spring of 1985, it was shown that, despite the wild boar competition, 60% of the foxes investigated had consumed the bait.

The occurrence of rabies in 1988 led to an oral vaccination programme covering an area of 260 km² in the extreme south of Limburg. In this area, SADB19 vaccine was distributed by hand, twice yearly, at 15 baits
per km². The last of six vaccinations took place in the fall of 1991. Investigations showed that a sufficiently high immunity was present in 55% of the examined foxes and that 57% of foxes had consumed the vaccine-containing bait. There are strong indications that the rabies cases in Southern Limburg came from Belgium and the cases in Groningen probably originated from Germany. The disease always occurred in young foxes found at a short distance from the borders. In January 1995, rabies was diagnosed in one of two gray fox recently imported from the USA, but further examination of other animals in the area showed no rabies. All terrestrial animal rabies cases reported in The Netherlands are summarised in Table 10.2.

In 1987 rabies was found for the first time in a bat (Eptesicus serotinus, A.A. King et al., Chapter 17) and, since then, the disease in bats has been regularly reported, especially in the northern part of the country. In addition, in July 1997, a lyssavirus (EBLV1a) was detected by Immunofluorescence Test (IFT) in brain material from Rousette bats exported from a Dutch zoo into Denmark. Clinical signs related to rabies had never been seen in the (850) colony of bats in the Dutch zoo, but nevertheless the whole colony was destroyed, except for 50 bats destined for experimental purposes. Of 274 tested bats, 49 showed a weak positive IFT result.

BELGIUM

The incidence of rabies in Belgium, up to and including the 19th Century, is poorly documented. Nevertheless, some data are available in the ‘Traité de la rage’ published by Babes (2). For example, during 1856-1860 Belgium recorded from two to six human rabies deaths annually, and from 1889 to 1900 inclusive, 1697 animal cases were recorded. The creation, in 1900, of a rabies centre in the Pasteur Institute of Brabant permitted a systematic follow-up of the evolution of urban dog rabies, but unfortunately, the centre was closed in 1930 (17). During 1905-1930, 2,709 animals were submitted for rabies diagnosis, of which 905 (33.4%) were positive. Canine rabies predominated and of the positive cases 821 (90.7%) were in dogs, 34 in cats, 48 in cattle and two in pigs. The last animal rabies case for 36 years was recorded in 1930.

Human rabies

During the period 1905-1922, 2,249 persons were given PET, but of these only 1,129 cases followed exposure to the 535 animals in which rabies was confirmed. The contact animals were 493 (92.2%) dogs, 29 (5.4%) cats and 13 (2.4%) cattle. Amongst the 1129 exposed people, 303 were seriously bitten and in spite of prolonged PET eight of them died, the last being in 1922. This represents a rate of 3% treatment failure with the Pasteur’s vaccine (rabbit spinal cord, desiccated and stored in glycerine) that was used in Belgium from 1902 until 1959. There have been no indigenously acquired human rabies cases since 1922 and, of four imported cases, three were from Zaire (in 1973, 1988 and 1990) and one from Rwanda in 1981.

PET again became necessary following the re-introduction of rabies into Belgium in 1966. In the 34 years to the end of the century 11,247 persons were treated, an annual average of 331 but with a peak of 1,279 in 1989. Concomitant with the decline in animal rabies cases, over the past nine years the average annual need for treatment has declined to 166 cases.

Animal rabies

As mentioned above, historically the incidence of rabies in Belgium has been poorly documented, but undoubtedly the dog was the chief vector and victim before the disease died out in 1930. However, in 1961 a dog incubating rabies was imported from the former Belgian Congo and three months after its arrival it developed clinical rabies. Three bitten persons were successfully treated.

Sylvatic fox-vector rabies invaded Belgium in 1966. The first rabid animal was detected on the 25 June in the ‘commune’ of Manderfeld, close to the German border (17). The epizootic moved to the west and south of the country and reached the valleys of the Meuse and Sambre rivers, which appeared to constitute a natural barrier to the spread of the disease. The evolution of the epizootic was characterised by a succession of peaks that, until 1982, had a mean periodicity of four years. However after the severe
outbreak in 1982, the expected lull did not occur, and during the following seven years the annual numbers of rabies cases remained abnormally high (Table 10.3), with a peak of 841 cases in 1989.

Table 10.3 – Terrestrial animal rabies in Belgium 1966-2000

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<tr>
<th>Year</th>
<th>Domestic animals</th>
<th>Wildlife animals</th>
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<tr>
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Most (61%) animal rabies cases were in the red fox (*Vulpes vulpes*). Other wildlife victim species included badgers (*Meles meles*), roe deer (*Capreolus capreolus*) and stone marten (*Martes foina*). Amongst domestic animals, ruminants and cats were the main victims (cattle 23%, sheep 6%, cats 4.5%) and these species were responsible for most of the human contacts and the need for PET. As in other European countries, several methods for fox population reduction were applied. Fox dens were gassed from 1967 until 1981 (except in 1973 and 1976) and bounties were paid for fox culling from 1967 until 1989. But these control measures were only temporarily effective and did not prevent the spread of the disease.
In 1986 and 1987, Belgium participated in an international field trial of oral vaccination of foxes using the SAD_{B}19 attenuated strain of rabies virus (33). The project, which also involving the Grand Duchy of Luxembourg, France and Germany, consisted of creating an immune belt around the Grand Duchy, whose entire territory was covered by vaccination. The Belgian vaccination area covered 2,100 km² in a heavily infected region in the south of the country, along the border with the Grand Duchy. In October 1987, a restricted field trial was carried out over a 2.7 km² military zone in which foxes were vaccinated with V-RG, the recombinant vaccinia virus expressing rabies glycoprotein (32). Two larger scale field trials using the latter vaccine were conducted from 1988 until 1990 (10, 31).

The Belgian national programme of rabies elimination by fox vaccination began in autumn 1989. Five vaccination campaigns, covering the entire infected area (10,000 km²), were carried out from autumn 1989 until autumn 1991. The first two campaigns (in autumn 1989 and spring 1990) were conducted using both attenuated rabies virus strain (SAD_{B}19) and V-RG as vaccines. From autumn 1990, V-RG was used exclusively. The campaigns drastically reduced the rabies incidence and achieved the elimination of the disease from 80% of the initial infected area (8).

New strategies for bait dispersal were planned for 1992, 1993 and 1994 to address the geographical evolution of rabies in Belgium and in adjacent regions of neighbouring countries. Successive restricted campaigns were conducted along political borders only. These campaigns caused a further decrease in disease incidence and no rabid foxes were detected in 1993, despite improved epidemiological surveillance (8). In 1994, rabies was again confirmed in 41 foxes and 18 domestic animals from a region close to the French border. These cases demonstrated that an area previously freed from rabies had been re-infected. Unfortunately, three campaigns carried out in 1994 and 1995 were not able to prevent the initial outbreak from spreading, and in 1995 213 rabid animals were detected in a 3,000 km² area in southern Belgium.

In 1996, strategies for fox vaccination were modified to control the rabies re-infection focus in the presence of a high density fox population. Two aerial vaccination campaigns were carried out during the cold season. The baiting density was increased to 17 baits per km² and an additional campaign of cub vaccination was performed by manually distributing 10-20 baits per breeding den. With these modifications and good cross-border co-operation, the re-infection focus was controlled and, over the four years 1996-1999, the number of rabies cases fell to 44, eight, one and one respectively (Table 10.3). The last case of fox rabies was recorded in April 1998 and the last rabies case was diagnosed in a cow in July 1999 in an area close to the Grand Duchy of Luxembourg (9). The eradication of rabies has led to other beneficial effects. The reduced rabies incidence in animals (mainly cattle) has led to a fall in the number of humans requiring PET (12) and the elimination of rabies in wildlife has improved survival of threatened wild species such as the Eurasian badger (3).

THE GRAND-DUCHY OF LUXEMBOURG

Urban rabies pre-1912

From 1830 until 1878, the following animal rabies cases were reported: 66 dogs, 19 cattle, eight sheep, seven pigs and one wolf. On the 7 October 1872, the rabid wolf attacked and bit two humans, two dogs, three sheep, four cattle and one pig. On the next day, after having attacked a woman, it was killed. Two of the bitten humans died from rabies, on the 2 November and on the 8 December respectively. The last cases of urban rabies (three dogs) were recorded in 1912.


Sylvatic rabies invaded the Grand-Duchy of Luxembourg in October 1966. The first recorded case was in a fox killed in the north east of the country 12 km from the capital. Conventional control measures were rapidly set up. Fox population reduction was attempted by gassing (1966-1969) and culling with the payment of bounties. Compulsory vaccination of dogs, prohibition of free-roaming domestic carnivores and new restriction regulations for carnivore imports and exports were implemented. In spite of these measures the disease spread and persisted (except for the two year period 1971-1972) throughout the 2,586 km² country (46). Rabies epizootic peaks followed in 1967, 1982, 1986 and 1989 (with two peaks of
lower magnitude in 1975 and 1978). Between 1966 and 1999, 1,684 animal rabies cases were reported, of which most (57%) were foxes. Among other wildlife victims were roe deer, badgers and stone martens. Among domestic animals, cattle, sheep and cats were the main victims. Due to mandatory dog vaccination, only six rabid dogs have been reported since 1966 (Table 10.4).

Table 10.4 – Rabies in Luxembourg 1966-2000

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic animals</th>
<th>Wildlife animals</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Dog</td>
<td>Cat</td>
<td>Cattle</td>
</tr>
<tr>
<td>------</td>
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<td>--------</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
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</tr>
<tr>
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<td>0</td>
<td>13</td>
<td>55</td>
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<tr>
<td>1968</td>
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<td>2000</td>
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<td>0</td>
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<tr>
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<td>410</td>
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</table>

Regulations allowing rabies vaccination in wildlife were introduced in January 1985. However, due to the small size of its territory, the Grand-Duchy did not start independent vaccination campaigns, since more than 60% of its territory lies within 10 km of national borders and re-infection from non-vaccinated neighbouring countries was likely.

Belgium (1986), France (1986) and Germany (1987) agreed to conduct simultaneous fox vaccination campaigns in order to create an 18,000 km² immune belt around Luxembourg (15). In this international field trial, three vaccination campaigns were carried out in September 1986, May 1987 and September 1987. The Grand-Duchy followed the German strategy of manual distribution of ‘Tübingen’ baits
containing SAD_{b99} attenuated vaccine at a mean density of 15 vaccine-baits per km². Good results were obtained after these three experimental operations, so the vaccination programme was continued (7, 35). Since 1988 biannual campaigns have been carried out in April-May and September, except in 1994 when only one campaign was performed, in September. In these campaigns SAD_{b99} vaccine was used exclusively until 1991, when it was replaced by V-RG vaccine. In 1990 manual distribution was replaced by helicopter-drop.

Since the beginning of the vaccination programme, ‘full’ campaigns covering the 2,586 km² of the country were performed. Nevertheless, due to a temporarily good epidemiological situation, two restricted campaigns were conducted in May 1988 (200 km²) and May 1989 (400 km²). On several occasions the Grand-Duchy was a victim of residual rabies foci (or re-infection foci) spreading from the province of Luxembourg in Belgium or from the ‘Saarland’ German lander. Nevertheless, as in Belgium, sylvatic rabies now seems to have been eliminated, the last positive case being a pony in January 1999 in the north of the country. During 1966-2000, no indigenous or imported human rabies case was reported.

SWITZERLAND AND LIECHTENSTEIN

Little is known about the distribution and frequency of rabies in Switzerland in earlier times but Köchlin (24), mainly citing official reports, gives an account of the disease at the beginning of the 19th Century. According to this source, rabies was present among foxes in the canton of Vaud in 1803-1804, although there were some doubts about the nature of the disease. From 1819 onwards fox rabies was widespread in Eastern Switzerland with the incidence fluctuating from year to year in the cantons of Zürich, Thurgau, St. Gallen, Schwyz, Zug, Luzern, Glarus and Grisons. While foxes were the main victims, cases in other wildlife species and in dogs, cats, and cattle were frequently observed. At least two human deaths were recorded: in Glarus in 1825 and in Grisons in 1834. Steck et al. (37) examined summaries of earlier reports similar to those used by Köchlin and found it likely that rabies had disappeared from Eastern Switzerland around 1840. Schaller (34) described an incident in the canton of Fribourg in 1855, where a dog bit 13 people, three of whom died within one to four months with symptoms of rabies. In 1869, in the Orbe, canton of Vaud, a dog bit a young man and several animals. Although the man survived, six of the animals died from rabies within five to six weeks. These reports suggest that rabies persisted in the second half of the 19th Century, at least in the western part of Switzerland. Steck et al. (37) found evidence for isolated cases as well as minor outbreaks among dogs in old reports of the Federal Office of Veterinary Public Health. The same sources revealed a maximum of 130 rabies cases in domestic animals in 1895 and of 35 cases in 1925. Steck and his colleagues speculated that the improved diagnostic accuracy offered by histopathology (Negri bodies) after 1903 may be one of the reasons why the number of reports of rabies cases decreased after the turn of the century. Indeed, their analysis found no evidence for rabies cases after 1928, possibly with the exception of an incident in southern Switzerland, in the canton of Ticino, where a man and five dogs supposedly died of rabies in 1949 after contact with dogs from Italy. Switzerland then remained free of rabies until 1967, when the first case of a new rabies epidemic was recorded in Merishausen, canton of Schaffhausen, near the border to Baden-Württemberg, Germany.

Human rabies

Apart from the cases mentioned above, which date back to periods when diagnosis was based on clinical symptoms alone, Switzerland has experienced only three human rabies deaths, all of them in 1977, when the fox rabies epizootic was at its peak. The first case was a 36-year old man who had been bitten by an unidentified cat in August 1976. He did not receive PET and died 165 days later (18). The second case was a 57-year old veterinarian who had received four doses of a duck embryo vaccine after having treated a cow that later died of rabies. He did not receive booster doses after the oral examination (without gloves) of another rabid cow in August 1976, nor was his antibody titre checked. Early in February 1977 he began to develop prodromal symptoms and was admitted to the intensive care unit of a hospital where he died five weeks later, 219 days after the oral examination of the second rabid cow (16). In the last case, a 33-year old biologist and dog breeder had been bitten by one of his dogs, which had supposedly been vaccinated with Flury LEP four months earlier. The dog died shortly after the biting incident and was not necropsied. The biologist succumbed to rabies a maximum of 68 days after having been bitten (36).
In the quarterly reports of the Swiss Rabies Centre (41) 479 bite exposures by proven rabid animals were recorded, 77.9% by cats, 2.6% by dogs, 1.3% by other domestic animals, 11.3% by foxes, 9.4% by stone martens, 1.9% by badgers, and 1.7% by other wildlife species. However, these reports only list cases for which the person submitting an animal for examination specified an exposure, therefore their real number is certainly under reported. Persons receiving post-exposure treatment were not officially recorded until the early 1990s however, and Zanoni et al. (47) estimate their number to be around 25,000 for the period of 1967-1996.

Animal rabies

The history of rabies in Switzerland and the Principality of Liechtenstein before and after the onset of oral vaccination campaigns has been described in detail (22, 28, 39). These descriptions have been supplemented by an animated visualisation that shows the dynamics of the process and which can be downloaded from the website http://www.cx.unibe.ch/ivv/ of the Swiss Rabies Centre (29).

After the fox rabies epidemic which had swept through Central Europe, reached Switzerland in 1967, the disease rapidly crossed the Rhine and spread in a semicircular manner over eastern Switzerland. The rivers Aare and Limmat stopped the westward advance of the disease in winter 1968-1969. The efficiency of these barriers was probably increased by the intense control measures (gassing fox dens and shooting foxes at the den) imposed on the fox population on both sides of the rivers. Similar control measures were applied up to the 1970s in other cantons, but they usually did not succeed in preventing outbreaks, although they may have led, together with rabies itself, to a faster decline of the local fox population and thus to shorter rabies episodes (44, 45). Rabies then advanced in a south-eastward direction between the lakes of Constanze and Zürich towards the Rhine valley, and finally Liechtenstein and the canton of Grisons, where it arrived in 1971. The complex topography of this particular area allowed the disease to persist for many years (Chapter 20, U. Müller et al.).

From 1971 onwards, in a backward movement, rabies spread westward north of Lake Zurich through a previously affected area, as well as south of the lake towards central Switzerland. In the winter of 1974-1975, the rivers Aare and Limmat were crossed without delay and the disease spread over large parts of the Swiss Plateau and the Jura. In the meantime, in France, rabies had reached the Swiss border in the Jura, where the two waves merged in 1976. Shortly thereafter the disease reached Lake Geneva in the western part of Switzerland. While the disease had developed independently from neighbouring countries up to that point, its course would, from then on, always be linked with the epidemiological events abroad, mainly in France (28). In the following years, rabies reached several mountain valleys that, until then, had been spared, but after 1981 there were no new infected areas.

The year 1978 not only marked the epidemic’s largest spatial extension (28), but also was the year of the first campaign to orally immunise foxes against rabies. In summer 1978, a wave-front moved upwards from Lake Geneva into the Rhone valley, which previously had not been reached by the disease. On 17 October 1978, 4,050 chicken head baits containing SAD Bern vaccine were distributed over an area of 336 km² in the path of the disease. The disease did not cross the vaccination zone, in which later, up to 60% of foxes showed tetracycline marks in their bones as a proof of bait uptake (38). Bait applications were repeated twice a year during the following years. From 1981 onwards, vaccination zones were extended, first to other mountain valleys and then to the Swiss Plateau. The concept for the elimination of rabies in Switzerland relied on geographical features such as rivers, lakes and high mountain areas that had been shown to impede the advance of the epidemic in previous years (23, 43).

Based on these features, Switzerland was divided into epidemiological compartments and potential points of rabies entrance were identified. The strategy for vaccinations consisted in treating infected compartments as a whole until they were free of rabies, or to perform vaccination campaigns to protect the entrances to rabies-free but threatened compartments. The consistent application of the concept freed the Alpine valleys, including Liechtenstein, along with most of the Swiss Plateau from the disease by the end of 1986, and also finally eliminated a small focus in the lower Rhone valley near Lake Geneva. The only remaining area of concern was the Jura between Basle in the North and Geneva in the West, where rabies was still endemic. From autumn 1988 onwards, the whole area on the Swiss side of the 335 km long common
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border with France was included within the vaccination campaigns. These efforts, and a total of 1.33 million baits distributed since 1978, finally reduced the number of rabies cases to 25 in 1990 (Table 10.5). All these cases were limited to that particular border area.

Early in 1991 a new outbreak occurred in the Jura next to the border with France and the number of cases increased steadily over the next years to reach a new maximum of 225 in 1994 (47). In spring 1991, Switzerland gave up its SADBern vaccine-containing chicken head baits in favour of an artificial bait produced by Virbac, which contained the avirulent SAG-1, and later the SAG-2 vaccine virus strain. Retrospectively, there are some indications that the new bait-vaccine system was less efficient, at least initially, than the chicken heads had been (6, 47). However, fox mortality figures (animals killed by hunters or found dead) had increased four-fold during 1984-1995 and bait uptake by foxes, as judged from tetracycline marks, was similar in 1984 (64%) and in 1995 (71%). This meant that the absolute density of non-vaccinated foxes had considerably increased, and may have surpassed the critical value necessary for maintaining a chain of infection (6). As rabies was still prevalent right across the border late in 1990, and France had only just begun to vaccinate this particular area, it seems likely that the new epidemic originated there. Once the disease became re-established in the high-density fox populations of the Swiss Jura in 1991, it was able to persist until 1996. In 1995, faced with the increasing number of rabies cases, the Swiss Rabies Centre changed its vaccination strategy. It increased the bait density from 15 per km² to 25 per km² to compensate for higher fox densities, it performed two vaccination campaigns within one month in any new vaccination area and, to increase the percentage of young foxes that would be immunised before leaving their parents’ territory, it distributed baits specifically at fox dens in an additional campaign in early summer (6). In late 1996, less than two years after the implementation of these measures, the last endemic rabies case was recorded. From 1991 to 1998, when the last vaccination campaign took place, another 1.44 million baits had been distributed to reach this goal. Finally, in spring 1999, Switzerland was officially declared rabies-free and was the first country to reach that status as a consequence of the oral immunisation of foxes against rabies.

Of the 17,109 rabies cases recorded between 1967 and 1996 (Table 10.5), 73.3% occurred in foxes, 4.7% in badgers, 4.3% in roe deer, 0.4% in other wildlife species, 4.6% in cattle, 4.3% in sheep, 0.6% in dogs and 0.9% in other domestic animals. There were only two cases of lyssavirus in bats recorded, one in September 1992 in ‘Schwarzsee’, community of Plaffeien, canton of Fribourg, the other in July 1993 in Versoix, canton of Geneva. In both instances the animals were identified as Daubenton’s bat (Myotis daubentonii, Chapter 17, A.A. King et al.). Surveillance for lyssavirus in bats had been at a very low level from 1967 to 1985, with only 38 animals examined. After the events in Denmark and the death from rabies of a Swiss bat researcher in Finland in 1985, an increasing number of animals were received, and between 1986 and 1996 more than 600 bats from at least 17 species were examined and found negative (21, 41).

CONCLUSION

In most European countries, canine rabies has been successfully controlled and eliminated thanks to strict sanitary and prophylactic measures, and the application of post exposure treatments of contaminated humans. Switzerland was the first country to initiate rabies vaccine field trials for wildlife and to eliminate the disease thanks to aerial oral vaccination programmes. The different successful experiences of these programmes in various geographical and ecological conditions have proved that the oral vaccination method is a powerful means for fighting fox rabies in Europe so long as a suitable long term strategy is present and adequate surveillance and laboratory techniques are available.

References


CHAPTER 11
RABIES IN THE IBERIAN PENINSULAR

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Summary

Rabies has been reported in the Iberian Peninsula since the 12th Century and it is possible that the disease was recognised in Roman times. This review provides an outline of the attempts to control rabies over the centuries in both Spain and Portugal including early references from the middle of the 19th Century to the thorough washing of bite wounds with soap in an attempt to prevent disease. This advice would not be out of place to this day. The authors also report the successful elimination of terrestrial rabies from the Iberian peninsular during the 20th Century and the subsequent discovery of rabies in bats.

Keywords: bat rabies, control, Portugal, rabies, Spain

SPAIN

Introduction

In the second book of the Hunting Agreement the writing of which was ordered by King Alfonso XI (1312-1350), both paralytic and furious forms of rabies are described, with the latter being considered as the more dangerous. The Royal Assembly of Health publication of 23 November 1786 adopted measures to avoid transmission of rabies by controlling the movement of dogs and cats, with sanctions against their owners. In the same publication is the Order ‘to kill immediately any dog found on the streets without its owner’. Owned dogs were supposed to wear a collar of iron, brass, leather or other compound and their owners were required not to let them wander (8). In 1793, the Order was ratified for Royal Agreement by King Carlos IV (9).

In the first half of the 19th Century, at the beginning of the War of Independence, animal control measures were not well enforced due to the unstable political and social situation, giving rise to a significant increase in the number of aggressive and sick animals. This led to a request by Queen Isabel II for the Council of Health to promulgate the Real Orden (Royal Order) of 17 July 1863, in which instructions were given to prevent the disease and to ‘cure’ people or contaminated animals (10). The urgent need for measures against the so-called ‘hydrophobia’ was well recognised.

Aspects of the nature of rabies were publicised:

‘very seldom is it found spontaneously, or of unknown and mysterious causes, there is no way of avoiding or ignoring such cases. Generally, rabies is communicated from one animal to another, and also to humans. For this reason it is necessary to prevent an increase in the number of animals, which could compromise the health of the people, and to adopt measures to avoid disease from bite inoculation. Rabies is seen mainly in dogs, wolves, foxes and cats but they transfer it via their bite to horses, donkeys and mules, cows, sheep, goats, pigs and even birds, besides frequently transmitting it to man. Also, you must know that the saliva of rabid dogs maintains its potency for up to 24 hours after the dogs’ death and it seems, if we are to believe certain examples, that infection has been obtained from dried saliva. Rabies, in animals as in man, has a long period of incubation; therefore it may be 10 to 100 days from the inoculation of the virus, until the illness shows. Sometimes it has been
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extended to 170-200 days, and there are mentioned cases of incubation periods that have lasted for years'.

In Portugal, Carmona Rodrigues, in his work ‘Rabies’ mentions that the disease was already known to the invaders of the Iberian Peninsula, namely, the Romans. They left us with beliefs and traditions that in some regions of Portugal remain to this day. These beliefs are supported by the ancient popular definition of rabies: ‘it is a disease that God sends, which is in the air and attacks the dogs it can. Once it is prevented in the dog it goes to Man because it has to stitch to some living being’.

In 1788 minister Pina Manique, during the reign of Dom Maria I, declared by Royal Decree that all stray dogs found without a collar or a muzzle must be destroyed. In 1862, during the reign of Dom Luis I, Intendents of Animal Health, which were district veterinary health authorities responsible for the fight against animal diseases transmissible to man (zoonoses), were formed. Later in the same reign, in 1868, a Consultative Committee for Animal Health, at which the Intendents of Animal Health were present, was also formed. In 1889, still in the reign of Dom Luis I, the General Regulation of Animal Health was promulgated, which in its Chapter XVIII defined the rules of a health policy for rabies control. Only dogs with a collar showing the name and address of the owner were allowed to circulate in public streets; all others were considered to be free-living dogs. All free-living and stray dogs were captured and destroyed.

In the case of rabies, the infected dog and any other dog that it had bitten was immediately destroyed. An edict was passed whereby, if an infected dog had been observed on the streets, other dogs were not permitted to enter the streets for a period of six weeks unless they were muzzled and on a leash. In 1892, during the reign of Dom Carlos I, the Instituto Bacteriologico, later named Câmara Pestana, was founded and became an important Institution for the protection of Portuguese citizens against rabies.

Human rabies

After describing the clinical characteristics of the process in cattle, sheep, goats and pigs, and with special reference to dogs, relating them to of the characteristics in people, the Real Orden of 1863 describes ‘measures of preservation that one has to follow in each case where the bite has been from a supposed rabid animal’, indicating the ‘necessity of compression of the wound in all directions with the aim to take out the blood and saliva that could have penetrated, the application of a tie above the wound, the cleansing of it with bleach, with soapy water, with lime water, with salt or any astringent liquid, with pure water, or with urine’. Also indicated is ‘deep cauterisation with burning metal’ and advice to ‘quickly obtain the aid of a doctor, surgeon or veterinarian, avoiding black magic and fortune-tellers’, which were used and popular at the time.

The Real Orden was succinct in its advice for action, mentioning giving help to people who had been bitten by rabid or suspect rabid animals, emphasising the urgent need of treatment and reinforcing the dangers of delay and false trust placed in certain superstitious and empirical methods. It pointed to the need to detail information of each biting incident, to include the name, age and status of the bitten person, the rabid animal species, the time of the event, the part of the body bitten, the help that was given to the patient, who gave it, the time it was given and the result.

Shepherds and keepers of cattle, hunters and owners of dogs were required to give the Authorities a precise account of those animals which were infectious and those which had been bitten, and the animals and persons that had been bitten by them. It recommended that the production of spontaneous rabies should not be helped by persecuting and mistreating the dogs. Finally, there was a requirement to ‘Transfer to the Deputy Doctor of the Party a copy of the information to which Chapter 4 (of the Order) refers, and give all information about people and animals bitten by rabid animals’ (10).

In the first two decades of the 20th Century, the annual human death toll from rabies averaged 45 persons (2). In 1919, an outbreak of human rabies with many deaths (Table 11.1), occurred in the province of Murcia and the whole region was declared an ‘epidemic state’. In 1922 a rabies focus in Madrid became a significant health problem, and within a few months 200 people were given anti-rabies treatment. An Order was passed for the collection of all stray dogs, but this gave rise to a campaign organised by the press against ‘cruelty to the poor dogs’. However, the Order was applied with excellent results, since the
number of dogs showing aggressive behaviour decreased and with it came a reduction in the number of human treatments (15).

The Civil War (1936-1939) marked a period of relaxation and alteration of health control measures, leading to a higher annual incidence of human cases (Table 11.1). For the first post-war years (1940-1943) there are no data on human rabies cases, but the resumption of epizootic control measures by extending vaccination coverage gave rise to a drastic reduction in human and animal mortality from the disease. The Second World War had little effect on public health conditions.

### Table 11.1 – Human rabies cases and post-exposure treatments in Spain 1901-1999

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<th>Humans treated</th>
<th>Year</th>
<th>Human cases</th>
<th>Humans treated</th>
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NA = North Africa  ND = No data

The substantial legislation was relaxed when the disease came under control and the public was no longer in a state of panic. Human rabies cases continued to occur, but from 1945 onwards post-exposure treatment was regularly used and the death toll began to fall. Although the occasional case was reported after 1959, with the exception of a single case in 1975, the last indigenously acquired case occurred in 1965 (Table 11.1).
Animal rabies

The Royal Order of 1863 also set down the measures against rabies in animals which were to be adopted by Local Authorities. These included the capture and destruction of animals in the population which appeared to be rabid and the destruction of animals which had been bitten by an infected animal. Dogs without a well-made muzzle were not allowed to walk unattended. This was one of the most important precautions and owners who did not comply were to be punished. Stray dogs were to be poisoned by strychnine in their food. This had to be given with care and directly to the dogs, to avoid their suffering and to avoid humans becoming poisoned.

The Order also contained directions regarding health regulations. The streets were to be maintained in a good state of cleanliness, dead animals were to be removed, and waste food or other matter that could serve as food for dogs was not to litter the streets nor to act as encouragement for them to fight over it. In the countryside, ‘unburied horse carcasses that could serve as food for dogs and give them rabies’ were to be removed. Also, shepherds, keepers and any other keeper of animals in the country were required to promptly inform the Authorities of the presence of wolves or rabid foxes, and of any dogs or cattle which had been bitten by these animals. The regulations were to be reinforced by repeatedly publishing edicts which require faithful execution of all of the depositions mentioned in the Order and any others that were deemed appropriate to adopt.

At the beginning of the 20th Century rabies appears in the legislation of the time as the Law of 18 December 1914, in the provisional Regulation of 4 June 1915 and the Royal Ordinance of 15 May 1917, in which the Regulation is approved to prevent the transmission of human rabies, but without dictating specific measures to combat it (7, 11). On 1 June 1927 a Royal Command, ratified on 16 June 1928, established the obligations of the City Councils to organise the collection of stray or abandoned dogs:

‘More severe measures will be adopted by civil governors and inspectors of public health in order to achieve the precepts of the Epizootic Regulations for rabies, and they will put into practice as many measures as are needed in order to attract the cooperation of the citizens to resolve such a serious problem. It is not possible to vaccinate the dogs, nor for the Institutes to facilitate preventive vaccine against this disease, if the authorisation request to the Mayor’s office does not ensure that the animal would remain subject to health surveillance for forty days, and that the concealment of this illness and any transgressions would be punished in accordance with the regulatory sanctions’ (12).

During the 1940s the first national statistics on rabies appeared. On 12 May 1947 the Ministry of Agriculture issued a General Order establishing the measures to be taken against rabies and a second Order on 28 January 1948 established the norms for animal vaccination and control. During the 1950s the first mass dog vaccination campaigns took place.

Control policy

Prior to 1952, data on the rabies situation in Spain are scanty. In the decade 1911-1920, 5,052 cases of animal rabies were reported, with a further 6,850 cases during 1941-1950, figures that express with clarity the importance of this zoonotic disease in Spain in the first half of the century. In 1952, more than 600,000 dogs were vaccinated and in successive years this number was increased with compulsory annual vaccination campaigns, eventually to cover the whole of Spain (4); (Table 11.2).

Under the Order of 17 May 1952, the Ministry made the registration and vaccination of dogs the obligatory responsibility of the owners. A dog census, the collection of unregistered stray dogs and the impounding (at the owner’s expense) of registered but suspect rabid dogs became the responsibility of City Councils. The Order established that, after June 15 of that year, ‘all dogs which have not been registered and vaccinated will be considered as strays and therefore liable to capture and destruction’. It provided that in rabies infected areas vaccination should be by two injections given within one week, with one injection given in other areas.
Table 11.2 – Dogs vaccinated and animal rabies cases in Spain 1944-1999

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</table>

Note: No terrestrial animal rabies cases have been reported from mainland Spain since 1979. Other cases cited in this Table (100 dogs, 11 cats and 1 horse were from Ceuta and Melilla, North Africa.

* Bat cases: The 12 bat cases were from Huelva (5), Granada (2), Valencia (1), Sevilla (3) and Murcia (1)

In all provinces where there has been a focus of rabies there will be constituted an Anti-Rabies Commission, presided over by the Civil Governor and integrated by the Provincial Head of Health, the Head of the Provincial Services of cattle raising, the Head of Local Administration, the Provincial Inspector of Veterinary Health and other Authorities. The functions of this Commission will be the following:
a) to carry out the anti-rabies measures, derived from the regulations and agreements that in each case are adopted for the Provincial Councils of Health

b) to oversee the carrying out of measures on behalf of the government, municipal and health authorities

c) to regulate the supplies of anti-rabies vaccine with sufficient potency to assure the effective vaccination of domestic dogs

d) to ensure that the Municipalities have established dog registration procedures

e) if necessary, to reduce to 24 hours the period in which impounded non-suspect dogs may be claimed by their owners, to be followed by their destruction if unclaimed.

Also, it is proposed that the heads of captured wild carnivores should be sent to the Provincial Institutes of Health for examination for rabies (3).

The Epizootics Law of 20 December 1952 (4) established the general regulations of the anti-rabies programme and, in the Order of 20 June 1953, related powers were given to the Commission. In 1955, the Anti-rabies Central Commission was created and with the publication of the Order of 4 February 1955 the Regulation of Epizootics, an important advance incorporating specific measures leading to the prevention, control and eradication of rabies was approved. This Order established that dogs must wear a collar and disk with the name and address of the owner, that uncollared dogs may be collected by the municipal services, and that dogs and cats for export must have a vaccination certificate (5).

The strict application of article 347 of the Order was decisive in the success obtained in the control of rabies and in the prevention of its transmission to man, indicating that:

‘An official declaration of rabies requires the adoption of the following measures:

a) The vaccination of all dogs in the municipality affected, if during the preceding year there had not been a national or provincial campaign. This operation will be completed by means of the administration of two injections within one week, a measure that will apply to the dogs of municipalities bordering the focus. In cases where dogs have been vaccinated within the year, vaccination will be boosted with one injection.

b) All dogs in the infected zone will be confined to the home of their owner unless they are muzzled and are wearing a collar with identification disk.

c) Cats will be contained.

d) Dogs on public roads not wearing a muzzle, collar and disk will be captured and impounded by the authorities. If they are not claimed within 24 hours they will be destroyed; if they are claimed by their owners, they will undergo veterinary observation for fourteen days on premises set aside for such purpose or, if these are inadequate, at the home of the owner.

e) Any rabid animal, of any species, will be destroyed without right to compensation. Dogs and cats attacked and bitten by a rabid animal, even when they show no signs of rabies, will also be destroyed immediately without right to compensation. Pigs bitten by a rabid animal could be subjected to treatment, on the condition that they remain isolated and quarantined for three months. The fat of those not destroyed can be used industrially. Herbivores bitten by a rabid animal will be impounded for three months, unless the owner prefers to subject them to anti-rabies treatment, in which case they may be discharged one month after treatment. When working bovines are bitten by a rabid animal, they may continue working, provided they wear a muzzle.

f) When a dog suspected of being rapid has bitten one or more persons, it will be impounded on local authority premises or, if these are inadequate, at the home of its owner, and will be subject to health surveillance by the veterinary inspector for 14 days; expenses incurred will be paid by the owner (4).
From 1952 the number of people and animals infected with rabies slowly declined until in 1966 the disease was declared eradicated – no new human or animal cases were reported from the whole of Spain (5); (Table 11.1).

In 1975, a further epidemic was declared in the province of Malaga, in the south of Spain. The index case could have been a rabid dog from North Africa. The outbreak continued until 1978 and one person died. The victim was bitten by her own dog and, although she began anti-rabies treatment, it was discontinued after the fifth vaccine dose. The dog had been destroyed and buried without laboratory diagnosis. During the epidemic, which lasted two years, 81 animal cases were diagnosed, of which 51 were dogs and 30 were cats (Table 11.2). By 1977 the situation, referred to as the Focus of Málaga, was controlled, only one case (a dog) was reported, but a new focus for the zone appeared when two rabid foxes were found only 12 km from the first focus. This led to the supposition that the foci were related. The discovery started a new alert and for the first time sylvatic rabies was suspected. Nevertheless the focus was under control by 1979 and despite exhaustive surveillance, no new cases of terrestrial animal rabies have been recorded since 1979 (6).

By the Order of 5 December 1974, rules were drawn up whereby municipalities with a population in excess of 5,000 should have a service to capture stray dogs, whereas those of fewer than 5,000 should be serviced by specialist units at the call of the provincial administration. The Order of 14 June 1976 paid particular attention to the relationship between man and animals, particularly dogs and cats, and defined the health measures required to avoid spread of the disease from animals to man, including a dog census, the confinement of suspect animals to the home, the collection and destruction of strays, the observation of biting dogs, and the vaccination of cats (13, 14).

Animal rabies in Portugal

In 1921, Umeno and Doi prepared a live vaccine for animals from a phenolised attenuated rabies strain (Fermi method) and this was tested by Eichorn and Lyons in 1922. In 1923, Agueda Ferreira and Sá Viana Rebelo produced a Umeno and Doi-type rabies live virus vaccine from 20% nervous tissue of rabbit origin and 1% glycerol-formol (1).

In order to eradicate rabies, in 1925 through National Decree 11242 it became compulsory to vaccinate against rabies all dogs greater than four months of age. Dogs were classified according to their use as guard, hunting or companion dogs. Vaccination was the responsibility of the municipalities and all dogs within the municipality were compulsorily registered, the issue of a licence being dependent on proof of vaccination. In addition, the importation of dogs was forbidden unless they had been vaccinated for at least one year before importation. New rules (National Decree 11242) were defined for the capture of free-living and stray dogs. A further Decree (18725) issued in 1930 strengthened the existing rules by introducing an annual dog tax, making the owners responsible for the muzzling of dogs when on the street and by defining the rules by which free-living and stray dogs could be captured and destroyed.

In 1938, the importation of animals from rabies-infected countries was forbidden (Decree 28467) and in 1939 the General Directorate of Veterinary Services was made responsible for the supervision of compulsory vaccination campaigns throughout the country (Decree 29441).

In 1953, health policy measures to avoid, limit or eradicate animal diseases (Decree 39209) were defined and in 1955 the roles of municipal veterinarians were defined and reformulated such that they became health authorities for the municipality, cooperating with the Animal Health Intendents in all matters relating to animal health (No. 15 of article 153 of National Decree 40335). Subintendents of animal health, which assisted the Animal Health Intendents (Veterinary Health authorities for the municipality and the district) to improve co-ordination of the General Directorate of Animal Health Services (Decree 48755), were created in 1970 and in 1976. A health educational campaign was carried out in order to promote rabies vaccination of dogs. This contributed to a progressive increase in the number of dogs vaccinated in rabies vaccination campaigns, but the winding down of this campaign from 1979 immediately contributed to a reduction in the number of vaccinated animals.
In 1977 the General Directorate of Veterinary Services was created in order to promote and control the actions of public health authorities against zoonotic diseases. The Directorate was strengthened in 1979 by the addition of a Commission responsible for the epidemiological surveillance and control of rabies (18, 19). On 2 August 1985 National Decree 317/85 was published. This Decree collected, reformulated and adopted legislation published through previous decades and restated the rules of rabies prophylactic and health policy measures. This now constitutes the on-going National Programme of Epidemiological Control and Surveillance of Animal Rabies. We are currently working on new legislation which will reform the 1985 National Decree. We intend to implement the medical prophylactic measures against rabies and reinforce its epidemi-surveillance and health policy. It is intended to extend the National Programme of Epidemiological Control and Surveillance of Animal Rabies to other zoonotic diseases such as echinococcosis/hydatidosis, leishmaniosis and leptospirosis.

Rabies in animals was present in Portugal in the early 1920s, early 1930s and again in the 1950s but, apart from four cases in 1960 (two dogs and two cats in the municipalities of Mértola and Alcoutim), the last animal rabies case was in 1956 (Table 11.3).

Table 11.3 – Rabies evolution in Portugal 1925-1998

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<th>Year</th>
<th>Animal cases</th>
<th>Humans treated</th>
<th>Animals vaccinated</th>
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*: minimum number vaccinated  
**: approximate number vaccinated

Rabies in bats

In 1987, two sick bats, one in Valencia (Mediterranean Region) and one in Granada (Andalucía), which had bitten members of the public were found to be positive for rabies (Table 11.2). This new alarm led the Spanish Health Administration to issue advice to the public on the procedures to be taken in the case of contact with sick bats as recommended by international health authorities. The alert lasted only a short time, but there remained some concerns about the cases and in 1989 a survey of bats within a defined
territory found five positive cases in a colony of *Eptesicus serotinus* bats in the county of Huelva, in the autonomous community of Andalucía (Chapter 17, A.A. King et al.).

In response to this new situation, the General Directorate of Public Health of the Ministry of Health and Consumer Affairs promoted a multidisciplinary study of the impact of the rabies virus on the bat population and on the interaction with the human population that was developed. From 1990 to 1997, the Faculty of Biology of the University of Barcelona, in collaboration with the above Ministry, the Faculty of Medicine of the University of Valencia, the Veterinary Faculty of the University of Zaragoza and the Institut Pasteur, Paris took part in the study. During 1990-1993, neural tissue and sera from 849 bats of 20 species from different geographical areas were examined, but none was positive for rabies. However, in a second phase undertaken during 1994-1997 in which 778 samples from 13 species were analysed, 31 were serologically positive, with antibody titres of 1/90 to 1/311 in *Myotis myotis* and *Miniopterus schreibersii* species (17).

In 1994, another positive bat which had attacked a person in Granada was found. The original two cases (in Valencia and Granada) were classified as Lyssavirus serotype 4 Duvenhage virus, but later molecular studies of all three isolates classified them as European Bat Lyssavirus (EBLV-1). From evidence provided by the serological studies and virus isolations it was concluded that bat rabies in Spain is limited to the Mediterranean coast (16). In 1999, four further cases in *E. serotinus* bats were reported.

**CONCLUSIONS**

Since 1966 Spain has been free of terrestrial animal rabies, with the exception of the imported outbreak in Málaga in 1975 which lasted until 1978. However, the geographical position of Spain, with its proximity to North Africa and continuous commercial traffic, fishing activities and migration between the two continents, coupled with cases in Ceuta and Melilla (North Africa) require a constant state of alert, obliging us to maintain measures and systems of control to prevent entry of any ‘vector’, as occurred in Málaga in 1975. In addition, in the 1970s Spain was threatened by the advance of the European fox rabies epizootic that spread from Poland and extended to central France. Spread to Spain via the Pyrenees seemed inevitable, but the threat has abated, thanks to the efficacy of fox oral vaccination programmes in France (Chapter 10, M.F. Aubert et al.).

This double threat of rabies from the north and the south has meant that, in spite of having eradicated the disease, preventive measures have remained in place throughout Spain, including annual compulsory dog and cat vaccination campaigns. The lessening of the threat of European fox rabies has led some autonomous communities to lower their guard. Since 1993 in the Basque Region, although a dog census, the impounding of aggressive dogs and stray dog control have continued, dog vaccination is now on a voluntary basis only. Also, in the autonomous community of Galicia, where urban and sylvatic rabies were declared eradicated in 1962, since 1994 a policy of voluntary dog vaccination has been adopted, there being no evidence for the need of compulsory vaccination.

Portugal has not reported a case of indigenous animal rabies since 1956.

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prevenir la transmisión al hombre de las enfermedades epizooticas. Gaceta de Madrid.

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se dictan medidas para evitar la transmisión de la rabia, controlar, proteger perros y gatos y se
establecen medidas sancionadoras contra sus dueños.

9. Real Junta de Sanidad (1793) Real Acuerdo de 13 de Septiembre de 1793. ‘Control de los llamados
perros de ayuda o de presa’

10. Real Orden (1863). Gaceta de Madrid. Real Orden de 17 de julio de 1863, por la que se daban
pormenorizadas instrucciones para prevenir esta enfermedad y ‘curen’ a las personas o animales
contagiados, reconociendo la necesidad urgente de medidas contra la llamada ‘Hidrofobia’.

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CHAPTER 12
RABIES IN TURKEY, CYPRUS, SYRIA AND LEBANON

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Summary

Turkey forms a critical land link between the countries of Europe and those of the Middle East. The following chapter provides a brief history of the use of vaccines in Turkey, it then documents administrative and practical steps taken to reduce the disease burden of rabies within the country. This is followed by an overview of the current rabies epidemiological situation in both Turkey and a number of its neighbours.

Keywords: canine rabies, dog control, rabies diagnosis, Semple vaccine

TURKEY

Introduction

Turkey occupies a unique geographical and cultural position at the cross-roads between Europe and Asia. The country is bordered by the Black Sea to the north, the Mediterranean Sea to the south, and the Aegean Sea to the west. It shares land borders with Greece and Bulgaria to the northwest, Georgia, Armenia and Azerbaijan to the northeast, Iran to the east and Iraq and Syria to the southeast. The geography and climate of Turkey varies greatly, providing suitable habitat for both domestic animals and for wildlife, which thrives in the mountainous and forested areas. In addition, rapid urbanisation has led to an increase in the dog population. Within the Turkish administrative system there are 80 provinces, each having a Provincial Agriculture Directorate responsible for agricultural issues and a Provincial Health Directorate, which is responsible for human health issues excluding those concerning hospitals and Human Health Centres.

Human rabies

Historical developments

Rabies has been present in Turkey for many centuries. The first detailed description of the disease was written in the 15th Century and correctly suggested that infection was spread by bites of animals such as the fox, dog, cat and jackal. Advice was also provided for rabies treatment, some of which bordered on psychic suggestion, whilst the remainder involved the use different medicinal compounds.

Pasteur’s studies on rabies and his vaccination methods for humans were closely followed by all countries in the Ottoman Empire. After the first successful human treatment in 1885, Sultan Abdulhamid II sent Dr Zoeros (who had been trying to treat the disease with curare), Lieutenant Colonel Huseyn Remzi (a teacher of zoology) and veterinary teacher Lieutenant Colonel Huseyn Husnu to Paris, in order to gain experience that would later allow them to produce the vaccine in Turkey. The committee arrived in Paris in June 1886, carrying Sultan Abdulhamid II’s imperial monogram (to be given to Pasteur) and a gift of 10,000 Francs to be given for studies at the Institute. The committee stayed in Paris for six months, studying the preparation and application of the rabies vaccine and taking special theoretical and practical
Dr Zoeros, who had been commissioned to produce the rabies vaccine by the Sultan, successfully produced a vaccine using two immunised rabbits and material and equipment brought from Paris. As he also conducted bacteriological diagnosis in his laboratory, it was called the Rabies and Bacteriology Surgery. When a new laboratory of bacteriology, called the Imperial Bacteriology Institution, was established in 1893, the original Rabies and Bacteriology Surgery continued as the Rabies Institution. The second member of the original Paris committee (Lieutenant Colonel Huseyin Remzi) published a book that he called 'The Rabies and its Treatment'.

Because of the late notification of suspected rabies cases and the consequent delay in vaccinations, many deaths from the disease continued to occur and Dr Zoeros’ vaccine trials were not considered successful. For this reason he was dismissed and the Rabies Institution, for a time, worked under the Imperial Bacteriology Institution. At this time, Dr P. Remlinger, from France, was invited to work at the institute. During his eight year study he published many scientific papers and made the Rabies Institution a respected scientific establishment. Dr Hayim Naum succeeded Remlinger and, during his administration, the Rabies Institution became internationally famous when he proved that chickens could be infected by the disease and become vectors. Dr Zekai Tunçman, who managed the Institution after Dr Naum, developed the laboratory and introduced the innovations of the day. During his 30 years of administration he enriched the rabies literature with his many publications. One of his notable achievements was the discovery of rabies virus in an insectivorous bat.

By 1983 The Rabies Institution had occupied seven different sites and had been run by ten different directors. Vaccines were produced by Pasteur’s method until 1934. This method was then replaced by the Pasteur-Calmette method until and by the Phillips-Hogyes method until. After 1943, Marie used serum and vaccine together, whereas previously they had been used separately.

Other rabies institutes were opened in Selanik (Thessaloniki, Greece) in 1905 and in Sivas (Turkey) in 1917. Rabies hospital laboratories were founded in Sam (Damascus, Syria) in 1925, and further hospital laboratories and branches dealing with rabies within Turkish hospitals were established in Diyarbakir (1925), in Konya (1927) and in Elazig (1954). In 1929, in Izmir (Turkey), the Harbour Custom Bacteriology Laboratory, which included rabies diagnosis and vaccine production, was opened. All of these laboratories could produce and supply vaccine to their own organisations.

From 1933 Semple rabies vaccine, which had been produced in Refik Saydam Hüzûsfâha Institute in Ankara, was sent to hospitals and rabies stations. This gave way to a decentralisation system. The Semple vaccine was at first prepared by Dr M. H. Sagun at the Hûzûsfâha Institute and then the process was transferred to Dr A. Gilesz. Vaccine production in the Institute started in July 1932 and vaccines began to be sent to hospitals and rabies stations by March 1933. The vaccine contained 2% sheep brain in 1932-1934, 3% in 1935 and, from 1945, 5% sheep brain was prepared. In 1937, sheep immune serum production was started. Later, donkey immune serum was also produced.

The inactivated vaccine produced by the Semple method was successfully used throughout Turkey. At first there were only 25 rabies stations, but by the end of 1953 the number had increased to 127 sites within various hospitals and health centres. At the beginning of the 1970s the number of stations reached 500. According to a directive of 1982, the use of Semple vaccine was put into practise until 1996. In 1987, the Refik Saydam Hygiene Center ceased Semple vaccine production. Between 1987 and 1996 either Semple vaccine or imported cell culture vaccine was used in suspected cases, but from 1996 only imported cell culture vaccine was used for both pre- and postexposure treatment (PET). Vaccine and sera are now imported from EU countries, especially from Germany and France, and today vaccination units are present in all health centres and hospitals in Turkey.

Human rabies epidemiology

Records of rabies treatment in Turkey have been kept since 1887 (Tables 12.1 and 12.2). They show that, at the rabies treatment station from 1887 until 1899, Dr Zoeros treated at least 2354 cases, 45 (1.91%) of whom died of rabies. In Remlinger’s time, 6808 patients applied for treatment and 99 (1.45%) died of rabies. During Naum’s time, 95 of 6,691 (1.42%) of patients died of rabies.
### Table 12.1 – Human rabies cases in Turkey, 1887-1972 (12) and 1973-1987 (1)

<table>
<thead>
<tr>
<th>Year Treated</th>
<th>Deaths</th>
<th>Year Treated</th>
<th>Deaths</th>
<th>Year Treated</th>
<th>Deaths</th>
<th>Year Treated</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1887</td>
<td>NA</td>
<td>1916</td>
<td>1,780</td>
<td>7</td>
<td></td>
<td>1945</td>
<td>1,739</td>
</tr>
<tr>
<td>1888</td>
<td>39</td>
<td>1917</td>
<td>1,619</td>
<td>17</td>
<td></td>
<td>1946</td>
<td>2,105</td>
</tr>
<tr>
<td>1889</td>
<td>NA</td>
<td>1918</td>
<td>1,030</td>
<td>19</td>
<td></td>
<td>1947</td>
<td>3,068</td>
</tr>
<tr>
<td>1890</td>
<td>37</td>
<td>1919</td>
<td>514</td>
<td>2</td>
<td></td>
<td>1948</td>
<td>2,967</td>
</tr>
<tr>
<td>1891</td>
<td>77</td>
<td>1920</td>
<td>351</td>
<td>2</td>
<td></td>
<td>1949</td>
<td>3,011</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1892</td>
<td>112</td>
<td>1921</td>
<td>344</td>
<td>3</td>
<td></td>
<td>1950</td>
<td>3,549</td>
</tr>
<tr>
<td>1893</td>
<td>223</td>
<td>1922</td>
<td>899</td>
<td>2</td>
<td></td>
<td>1951</td>
<td>3,590</td>
</tr>
<tr>
<td>1894</td>
<td>252</td>
<td>1923</td>
<td>1,035</td>
<td>19</td>
<td></td>
<td>1952</td>
<td>3,885</td>
</tr>
<tr>
<td>1895</td>
<td>254</td>
<td>1924</td>
<td>1,360</td>
<td>24</td>
<td></td>
<td>1953</td>
<td>4,903</td>
</tr>
<tr>
<td>1896</td>
<td>329</td>
<td>1925</td>
<td>1,339</td>
<td>17</td>
<td></td>
<td>1954</td>
<td>3,851</td>
</tr>
<tr>
<td>1897</td>
<td>266</td>
<td>1926</td>
<td>1,358</td>
<td>7</td>
<td></td>
<td>1955</td>
<td>3,826</td>
</tr>
<tr>
<td>1898</td>
<td>339</td>
<td>1927</td>
<td>1,442</td>
<td>8</td>
<td></td>
<td>1956</td>
<td>4,465</td>
</tr>
<tr>
<td>1899</td>
<td>426</td>
<td>1928</td>
<td>1,314</td>
<td>3</td>
<td></td>
<td>1957</td>
<td>4,423</td>
</tr>
<tr>
<td>1900</td>
<td>578</td>
<td>1929</td>
<td>1,154</td>
<td>4</td>
<td></td>
<td>1958</td>
<td>4,243</td>
</tr>
<tr>
<td>1901</td>
<td>569</td>
<td>1930</td>
<td>1,160</td>
<td>7</td>
<td></td>
<td>1959</td>
<td>4,643</td>
</tr>
<tr>
<td>1902</td>
<td>622</td>
<td>1931</td>
<td>1,262</td>
<td>1</td>
<td></td>
<td>1960</td>
<td>5,379</td>
</tr>
<tr>
<td>1903</td>
<td>734</td>
<td>1932</td>
<td>2,018</td>
<td>9</td>
<td></td>
<td>1961</td>
<td>6,088</td>
</tr>
<tr>
<td>1904</td>
<td>1,075</td>
<td>1933</td>
<td>1,753</td>
<td>17</td>
<td></td>
<td>1962</td>
<td>5,634</td>
</tr>
<tr>
<td>1905</td>
<td>892</td>
<td>1934</td>
<td>1,819</td>
<td>8</td>
<td></td>
<td>1963</td>
<td>5,701</td>
</tr>
<tr>
<td>1906</td>
<td>874</td>
<td>1935</td>
<td>2,391</td>
<td>10</td>
<td></td>
<td>1964</td>
<td>5,984</td>
</tr>
<tr>
<td>1907</td>
<td>982</td>
<td>1936</td>
<td>2,113</td>
<td>7</td>
<td></td>
<td>1965</td>
<td>6,288</td>
</tr>
<tr>
<td>1908</td>
<td>978</td>
<td>1937</td>
<td>1,764</td>
<td>3</td>
<td></td>
<td>1966</td>
<td>7,595</td>
</tr>
<tr>
<td>1909</td>
<td>771</td>
<td>1938</td>
<td>1,269</td>
<td>0</td>
<td></td>
<td>1967</td>
<td>7,020</td>
</tr>
<tr>
<td>1910</td>
<td>736</td>
<td>1939</td>
<td>1,316</td>
<td>0</td>
<td></td>
<td>1968</td>
<td>8,159</td>
</tr>
<tr>
<td>1911</td>
<td>730</td>
<td>1940</td>
<td>1,302</td>
<td>1</td>
<td></td>
<td>1969</td>
<td>10,116</td>
</tr>
<tr>
<td>1912</td>
<td>923</td>
<td>1941</td>
<td>2,029</td>
<td>1</td>
<td></td>
<td>1970</td>
<td>11,401</td>
</tr>
<tr>
<td>1913</td>
<td>732</td>
<td>1942</td>
<td>2,464</td>
<td>2</td>
<td></td>
<td>1971</td>
<td>8,797</td>
</tr>
<tr>
<td>1914</td>
<td>1,131</td>
<td>1943</td>
<td>2,112</td>
<td>2</td>
<td></td>
<td>1972</td>
<td>8,695</td>
</tr>
<tr>
<td>1915</td>
<td>1,636</td>
<td>1944</td>
<td>1,552</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(NA=\) information not available

Records for the 16-year period 1932 to 1948 (8) allow a significant comparison of two treatment methods. At the Ankara Rabies Foundation and its dependent laboratories, Semple vaccine was used for 55,219 patients, 70 (0.13%) of whom died of rabies. Two of 11 of these cases were paralysed, which may be an indication that some of the treatments were started too late. At the Istanbul Centre Dr Tunçman used a modified Hogyes-Phillip vaccine and the death rate was 0.39%. Both foundations reported that most of the cases (70%) were as a result of dog bites.

In a broader study (10, 11), during 1932-1959, of 122,446 persons treated at the Istanbul Rabies Foundation, 426 (0.35%) died of rabies. At the Ankara Refik Saydam Hýfzýsýhha Institutes the post-treatment death rate was 0.36% during the years 1949-1959. However, this had been reduced to 0.1% during the years 1970-1975. At Ankara, during this latter period, complications due to the vaccine were at 0.001%. In an analysis of 120 human rabies cases during 1949-1969, dogs were responsible for 106 (88%), wolves seven (5.8%), jackals three (2.5%), cats two (1.6%) and two cases were the results of bites by other animals.
Table 12.2 – Semple rabies vaccination at Refik Saydam Hayzysyha Institute, Ankara, 1949-1969 (5)

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients given post-exposure treatment</th>
<th>Healthy after observation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine only</td>
<td>Vaccine + serum</td>
</tr>
<tr>
<td>1949-1959</td>
<td>169,680</td>
<td>266</td>
</tr>
<tr>
<td>1960-1964</td>
<td>121,819</td>
<td>1,022</td>
</tr>
<tr>
<td>1965-1969</td>
<td>116,224</td>
<td>702</td>
</tr>
<tr>
<td>Total</td>
<td>407,723</td>
<td>1,990</td>
</tr>
</tbody>
</table>

The number of post exposure treatments given in Turkey continues to rise. During 1949-1969, excluding those vaccinated at the Istanbul Rabies Foundation, 518,827 persons were given treatment. In this period dog bites were the most frequent cause of treatment (60%), but a significant number of vaccinations were given following rat bites. However, none of 444 rat brains examined were positive. Of the 518,827 vaccinees, 14.7% had had contact with infected farm animals and/or had unsuspectingly eaten their meat. In addition, 7% were vaccinated following contact with an infected person. The data shows that wolves and jackals form the rabies reservoir in the wild, but it is also clear that the number of dog-mediated cases in Turkey poses a serious problem. Most cases of human rabies were seen among the villagers and those who could not reach a doctor.

In Istanbul there are now eight vaccination stations, including the treatment station in Cemberlitas. Between 1980 and 1984 these stations vaccinated 75,544 people, an annual average of 15,109. Recent data indicates that between 1988 and 1996 rabies cases were generally observed in big cities, especially Istanbul.

The number of rabies treatments fell significantly in the latter years (Table 12.1). In 1997, human rabies cases increased in southeast Anatolia. Today, the highest number of rabies cases occurs in south-eastern cities such as Adiyaman, Siirt, Kilis and Urfa, but overall there are fewer rabies cases in the country.

In recent years the production of Semple vaccine has declined and has been replaced by human diploid cell vaccine (HDCV). The doses of these vaccines and of anti-rabies serum administered since 1988 are shown in Table 12.3. Human cases usually originated through the transmission of rabies from dogs. Of the 59 human deaths from rabies since 1988 (Table 12.3), 50 (84.7%) were of dog origin, three (5%) of wolf origin, one (1.7%) of fox and one (1.7%) of donkey origin; the origin of four cases (6.8%) was unrecorded.

Table 12.3 – Human rabies in Turkey, 1988-1998 (January to June only) (1)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number bitten</th>
<th>Number treated with Semple</th>
<th>Number treated with HDCV</th>
<th>Serum</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>89,685</td>
<td>42,675</td>
<td>39,193</td>
<td>1,820</td>
<td>6</td>
</tr>
<tr>
<td>1989</td>
<td>84,795</td>
<td>35,658</td>
<td>22,864</td>
<td>1,847</td>
<td>10</td>
</tr>
<tr>
<td>1990</td>
<td>91,291</td>
<td>55,529</td>
<td>33,371</td>
<td>1,735</td>
<td>7</td>
</tr>
<tr>
<td>1991</td>
<td>90,049</td>
<td>58,168</td>
<td>31,757</td>
<td>1,553</td>
<td>9</td>
</tr>
<tr>
<td>1992</td>
<td>89,399</td>
<td>54,441</td>
<td>33,691</td>
<td>1,476</td>
<td>5</td>
</tr>
<tr>
<td>1993</td>
<td>97,354</td>
<td>51,789</td>
<td>44,070</td>
<td>1,268</td>
<td>4</td>
</tr>
<tr>
<td>1994</td>
<td>107,766</td>
<td>64,002</td>
<td>40,821</td>
<td>1,212</td>
<td>1</td>
</tr>
<tr>
<td>1995</td>
<td>116,226</td>
<td>58,124</td>
<td>45,915</td>
<td>1,341</td>
<td>1</td>
</tr>
<tr>
<td>1996</td>
<td>99,641</td>
<td>11,789</td>
<td>85,705</td>
<td>1,116</td>
<td>1</td>
</tr>
<tr>
<td>1997</td>
<td>80,630</td>
<td>0</td>
<td>83,695</td>
<td>859</td>
<td>5</td>
</tr>
<tr>
<td>1998</td>
<td>86,276</td>
<td>0</td>
<td>39,190</td>
<td>781</td>
<td>3</td>
</tr>
<tr>
<td>1999*</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
</tr>
</tbody>
</table>

160 Historical Perspective of Rabies in Europe and the Mediterranean Basin
**Animal rabies**

**Historical developments**

Turks have lived with animals throughout time. Sheep and horses have always been of great interest and their breeding has been of great importance. Turkish people even name years after animals: rat year, ox year, tiger year, rabbit year, fish year, snake year, horse year, sheep year, monkey year, chicken year, dog year and pig year. These twelve animals each represent a year of a 12 year cycle. Sometimes months are also given animal names.

The best examples of studies on animal health can be found in old veterinary documents called 'Baytarname'. Some of these documents were written in Turkish and others were translated from Arabic and Latin languages. Both types can be found as far back as the 16th Century. The first example of a veterinary publication is a book by Cami who says much about horses and speaks of the god’s good sight for breeding horses. He writes about diseases such as Coryza contagious equi and malleus, rhinitis, warts, tumours on eyes and face, epidermophytose, hurts in eyes, bleeding of nose, icter, leeches in mouth, laryngitis, pharyngitis, tetanus, pains, coughs, diarrhoea, problems of urinary system, lymphangitis, scabies, rabies and fight wounds. However, advice given about some of these diseases is useless!

The most important early veterinary study, a book called ‘Gazaname ve Baytarname’ (the battlefield and animal health), was written in 1565 by Ali bin Omer. The first part of this book is devoted to battle stories, however, the second part deals with animal health. His best success is with his explanation of malleus, but he also studied rabies and states that the disease was seen in the fox, dog and wolf and also was contagious through biting humans and animals. He detailed the symptoms of the disease and gave ways of diagnosing this and several other diseases through examination. His studies of malleus and rabies were better than those made by his European contemporaries.

The first teaching of veterinary subjects in Turkey was by Godlewsky who was invited from Prussia in 1842. His work highlighted the army’s need for veterinarians. Dr Ahmet Efendi, Dean of the Veterinary School, later continued the teaching. In 1849, Dubroca, a French Military veterinarian, was invited to Turkey. Sultan Abdülmecid had sent him to London to study veterinary education. Later, civilians were allowed to be educated at the Military Veterinary School and in 1889 a civil Veterinary School was established. The first students graduated in 1893, but initially there was no tuition in bacteriology at the School. The School became a veterinary academy in 1894 and Lieutenant Colonel Mehmet Ali Bey, the founder of the civilian Veterinary Faculty in Turkey, was appointed Director. In 1933, the Veterinary Faculty in Istanbul was moved to Ankara to become the Agriculture Faculty. This became part of Ankara University in 1946. Today, there are 14 Veterinary Faculties in universities throughout Turkey.

The 1880s saw the establishment of a Veterinary Services Inspectorate Department in the Ministry of Thrace, Agriculture and Prosperity. This department was then affiliated with the Ministry of Agriculture and Forestry. This Ministry founded a new regulatory organisation in the form of an Agriculture Science Committee. The committee comprised five branches. Each branch chief had the title of Supervisor General of the Science Committee and together they formed the Veterinary Service General Directorate. In 1883, in order to establish the methods and principles of infectious diseases control, extensive (in five sections and 22 parts) animal health sanitary legislation was passed by the Ottoman Empire Administration. Late in 1913, further temporary sanitary legislation was passed. This in turn was followed, in 1914, by Animal Health Sanitary Legislation consisting of 45 parts. However, these regulations neither met the requirements of the country, nor included principles for the control of important animal diseases, and thus disease control programmes were ineffective.

At the foundation of the Turkish Republic in the 1920s, the animal population of approximately 23 million had low productivity. Wars, exodus, famine and enzootic disease had caused great economic loss during the preceding period, the last period of the Ottoman Empire. However, in 1928, with the establishment of the Animal Health Sanitary Legislation Act 1234, the first steps were taken in the control of animals and their movements. In 1937, with the Law of Service and Organization of the Ministry of Agriculture, the Veterinary Services General Directorate (consisting of 13 branches) was reorganised and
principles for the control of 33 microbial and parasitic, contagious and transmissible diseases (including rabies) were determined. Disease control was further improved at this time by the establishment of some research institutes and vaccine production facilities. In 1985, Act 1234 was abolished and Act 3285 was adopted in its place.

Early in 1901, the Veterinary Bacteriology branch was separated from Imperial Bacteriology Institutions and moved to the Veterinary Faculty at Sultanahmet (Blue Mosque) in Istanbul. Its main role was to produce vaccine and antiserum against Rinderpest. In 1909, it was decided to move the Institute to the Anatolian side of Istanbul for greater safety of the facility and the environment, but although the building in Pendik was started in 1910, it was not finished until 1914 because of the First World War. The Institute was initially named the Pendik Veterinary Bacteriology and Serology Institute, but from 1930 to 1994 its name was changed several times. In 1994 it was renamed the Veterinary Control and Research Institute, although the main activities did not change. These activities are research, production of vaccines and biologicals, diagnosis, training and publishing.

In addition to the Pendik laboratory, there are now seven regional Veterinary Control and Research Institutes (VCRI) – the Etlik VCRI established in 1921, Bornova VCRI (1933), Elazığ and Samsun VCRI’s (1948), Konya VCRI (1950), Adana VCRI (1964) and Erzurum VCRI (1967). Each institute is located in a different region. The regional VCRI’s carry out research, production and diagnostic services including rabies diagnosis for the Director of Agriculture Provinces (field Veterinarians) that are under the Institute’s responsibility. The Etlik VCRI is a national reference laboratory for rabies. The first rabies observations and histological diagnoses were made here in 1929.

The Pendik Institute was reorganised in 1930 and a research laboratory, two bacteriology laboratories, food control and zootechnical laboratories were established. Rabies diagnosis was carried out in the first bacteriology laboratory along with many other tasks, including the production of mallein, tuberculin, BCG vaccine and the diagnosis of malleus, tuberculosis and piroplasmosis. In 1938, a new bacteriology laboratory was established. This laboratory carried out rabies diagnosis using Lens and Gerlach histological methods and Rabbit Inoculation. Between 1931 and 1942, 1381 animals were kept under observation and 209 suspect brains examined, of which 77 (37%) were rabies positive.

In 1946, the observation of suspect cases was devolved to the Municipality Veterinary Services. At about this time there were further technological advancements at Pendik. Phenol-inactivated goat or sheep brain Semple vaccine was produced, Seller’s staining method was introduced for diagnosis and mice were used for animal inoculation tests. In 1962, live attenuated lyophilised Kelev strain virus was imported from Israel and used for vaccine production from 1968 (Table 12.4).

Diagnosis by the Fluorescent Antibody Test (FAT) was started at the Etlik VCRI in 1966. Today, 600-1,000 specimens sent from the various provinces are examined there annually. The techniques used for diagnoses at Etlik and other VCRI’s include rapid microscopic examination for Negri-bodies, FAT and the Mouse Inoculation Test (MIT). The Rapid Fluorescent Focus Inhibition Test (RFFIT) and Rabies Tissue Culture Infection Test (RTCIT) are used exclusively at Etlik and then only as a research tool. Anti-rabies conjugate and control positive and negative mouse brain suspensions for use in the FAT are also produced here. These products are distributed for use in all Turkish rabies diagnostic laboratories. In Etlik, the freeze-dried live virus Kelev vaccine is produced in embryonated eggs. Only cats and dogs are vaccinated with this vaccine, which gives a guaranteed immunity of one year. The figures for annual production and imported vaccine are shown in Table 12.4. The fall in vaccine production is a result of the decreasing demand due to low rabies incidence and cheap locally available rabies vaccine. Kelev Rabies Vaccine is now hardly used.

Animal rabies epidemiology

The Ministry of Agriculture and Rural Affairs is responsible for programmes and plans aimed at combating animal diseases. Also it must structure and co-ordinate all duties assigned to the General Directorate of Production and Control as described under law number 3285 on animal health. According to this law, rabies is a notifiable disease.
Turkey is the only European country with dog-mediated rabies. Cases of wildlife rabies have been confirmed but whether they represent transmission from dogs or are indicative of an independent reservoir in wildlife remains unclear. During 1980-1999, 66.4% of all rabies cases were reported in dogs and only 1.6% in wildlife (Table 12.5). Nowadays, rabies is becoming increasingly an urban problem. Towards the end of the 1970s, mass human migration from rural areas to cities like Istanbul, Ankara, İzmir, Bursa and İzmit started and this trend continues to this day. As a result, an increase in the urban dog population has been observed in these cities and, in some cases, this increase has coincided with an increase in rabies cases.

Table 12.4 – Annual production of rabies vaccine and imported vaccine for animal health, 1959-1999

<table>
<thead>
<tr>
<th>Year</th>
<th>Sample</th>
<th>Kelev</th>
<th>Year</th>
<th>Sample</th>
<th>Kelev</th>
<th>Imported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1959</td>
<td>26,000</td>
<td></td>
<td>1980</td>
<td>38,700</td>
<td>71,000</td>
<td></td>
</tr>
<tr>
<td>1960</td>
<td>27,475</td>
<td></td>
<td>1981</td>
<td>32,100</td>
<td>68,585</td>
<td></td>
</tr>
<tr>
<td>1961</td>
<td>31,500</td>
<td></td>
<td>1982</td>
<td>26,700</td>
<td>93,500</td>
<td></td>
</tr>
<tr>
<td>1962</td>
<td>41,850</td>
<td></td>
<td>1983</td>
<td>28,825</td>
<td>262,834</td>
<td></td>
</tr>
<tr>
<td>1963</td>
<td>48,750</td>
<td></td>
<td>1984</td>
<td>20,190</td>
<td>205,820</td>
<td></td>
</tr>
<tr>
<td>1964</td>
<td>50,380</td>
<td></td>
<td>1985</td>
<td>23,548</td>
<td>263,744</td>
<td></td>
</tr>
<tr>
<td>1965</td>
<td>30,807</td>
<td></td>
<td>1986</td>
<td>16,535</td>
<td>359,721</td>
<td></td>
</tr>
<tr>
<td>1966</td>
<td>37,135</td>
<td></td>
<td>1987</td>
<td>15,767</td>
<td>412,425</td>
<td></td>
</tr>
<tr>
<td>1967</td>
<td>34,685</td>
<td>2,600</td>
<td>1988</td>
<td>18,700</td>
<td>350,102</td>
<td>575,000</td>
</tr>
<tr>
<td>1968</td>
<td>43,927</td>
<td></td>
<td>1989</td>
<td>21,300</td>
<td>362,170</td>
<td></td>
</tr>
<tr>
<td>1969</td>
<td>33,060</td>
<td>12,276</td>
<td>1990</td>
<td>7,795</td>
<td>337,962</td>
<td>593,000</td>
</tr>
<tr>
<td>1970</td>
<td>31,230</td>
<td>17,850</td>
<td>1991</td>
<td>7,570</td>
<td>396,490</td>
<td>7,000</td>
</tr>
<tr>
<td>1971</td>
<td>32,707</td>
<td>26,445</td>
<td>1992</td>
<td>8,293</td>
<td>368,448</td>
<td>867,000</td>
</tr>
<tr>
<td>1972</td>
<td>35,925</td>
<td>42,852</td>
<td>1993</td>
<td>7,368</td>
<td>215,264</td>
<td>344,000</td>
</tr>
<tr>
<td>1973</td>
<td>35,150</td>
<td>41,107</td>
<td>1994</td>
<td>5,495</td>
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<tr>
<td>1974</td>
<td>35,291</td>
<td>40,450</td>
<td>1995</td>
<td>4,425</td>
<td>166,529</td>
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<tr>
<td>1975</td>
<td>37,914</td>
<td>40,753</td>
<td>1996</td>
<td>4,130</td>
<td>185,835</td>
<td>138,000</td>
</tr>
<tr>
<td>1976</td>
<td>30,695</td>
<td>45,997</td>
<td>1997</td>
<td>4,540</td>
<td>166,350</td>
<td>412,000</td>
</tr>
<tr>
<td>1977</td>
<td>40,250</td>
<td>55,695</td>
<td>1998</td>
<td>2,415</td>
<td>123,678</td>
<td>317,000</td>
</tr>
<tr>
<td>1978</td>
<td>43,325</td>
<td>74,000</td>
<td>1999</td>
<td>3,585</td>
<td>181,250</td>
<td>114,000</td>
</tr>
<tr>
<td>1979</td>
<td>39,550</td>
<td>73,800</td>
<td></td>
<td></td>
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</tbody>
</table>

In the last decade or so the rabies incidence has significantly decreased throughout the whole country and, between 1980 and 2000, the number of rabies cases dropped from 2,088 to 297 (Table 12.5). This decrease was observed not only in dogs but also in all domestic animals. In 1980, 1,289 dog cases were recorded, whereas this number dropped to 252 in 2000. Rabies cases in cattle (after dogs, the most common rabies victim) dropped in this period from 482 to 26. This decrease is a result of the implementation of control measures (e.g. vaccination campaigns).

Turkey is divided into seven major geographical regions: Marmara, Aegean, Mediterranean, Central Anatolia, Black Sea, East Anatolia and Southeast Anatolia. Presently, the highest rabies incidence is observed in the Province of Istanbul (Marmara region). In contrast to other areas, the number of rabies cases increased here in 1995 and 1996 (Table 12.6). Other provinces in the Marmara region with large urban centres, Bursa and Sakarya, showed a steady decrease in the rabies incidence. In İzmir (the third largest city in Turkey) in the neighbouring Aegean region, the number of rabies cases also fell sharply between 1988 and 1996 from 137 to only two cases, but unfortunately in 1997 rabies cases increased in the Aegean and Southeast Anatolia regions.
Table 12.5 – Animal rabies in Turkey, 1980-2001 (2)

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic Animals</th>
<th>Wildlife animals</th>
<th>Annual total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dog</td>
<td>Cat</td>
<td>Cattle</td>
</tr>
<tr>
<td>1980</td>
<td>1,289</td>
<td>142</td>
<td>482</td>
</tr>
<tr>
<td>1981</td>
<td>1,422</td>
<td>130</td>
<td>547</td>
</tr>
<tr>
<td>1982</td>
<td>1,342</td>
<td>104</td>
<td>554</td>
</tr>
<tr>
<td>1983</td>
<td>1,204</td>
<td>160</td>
<td>392</td>
</tr>
<tr>
<td>1984</td>
<td>890</td>
<td>120</td>
<td>335</td>
</tr>
<tr>
<td>1985</td>
<td>852</td>
<td>93</td>
<td>226</td>
</tr>
<tr>
<td>1986</td>
<td>848</td>
<td>90</td>
<td>212</td>
</tr>
<tr>
<td>1987</td>
<td>695</td>
<td>84</td>
<td>155</td>
</tr>
<tr>
<td>1988</td>
<td>546</td>
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<tr>
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<td>439</td>
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<td>80</td>
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<tr>
<td>1990</td>
<td>431</td>
<td>36</td>
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<tr>
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<td>315</td>
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<tr>
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<td>239</td>
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<td>45</td>
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<tr>
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<td>3</td>
<td>19</td>
</tr>
<tr>
<td>1996</td>
<td>103</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>1997</td>
<td>117</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>1998</td>
<td>104</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>1999</td>
<td>181</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>2000</td>
<td>252</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>2001</td>
<td>127</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>Totals</td>
<td>11,885</td>
<td>1,082</td>
<td>3,479</td>
</tr>
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</table>

Table 12.6 – Rabies incidence in the different regions of Turkey 1988-1999

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mamara</td>
<td>184</td>
<td>226</td>
<td>229</td>
<td>156</td>
<td>100</td>
<td>79</td>
<td>84</td>
<td>159</td>
<td>117</td>
<td>55</td>
<td>52</td>
<td>122</td>
<td>1,563</td>
</tr>
<tr>
<td>Aegean</td>
<td>137</td>
<td>71</td>
<td>79</td>
<td>70</td>
<td>71</td>
<td>43</td>
<td>28</td>
<td>6</td>
<td>2</td>
<td>43</td>
<td>42</td>
<td>50</td>
<td>642</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>62</td>
<td>41</td>
<td>39</td>
<td>59</td>
<td>44</td>
<td>30</td>
<td>13</td>
<td>3</td>
<td>1</td>
<td>9</td>
<td>19</td>
<td>5</td>
<td>325</td>
</tr>
<tr>
<td>Central Anatolia</td>
<td>59</td>
<td>50</td>
<td>79</td>
<td>46</td>
<td>20</td>
<td>21</td>
<td>0</td>
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<td>1</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>294</td>
</tr>
<tr>
<td>Black Sea</td>
<td>201</td>
<td>130</td>
<td>86</td>
<td>34</td>
<td>21</td>
<td>67</td>
<td>21</td>
<td>0</td>
<td>2</td>
<td>11</td>
<td>9</td>
<td>11</td>
<td>593</td>
</tr>
<tr>
<td>East Anatolia</td>
<td>17</td>
<td>19</td>
<td>19</td>
<td>17</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>94</td>
</tr>
<tr>
<td>SE Anatolia</td>
<td>50</td>
<td>47</td>
<td>52</td>
<td>45</td>
<td>60</td>
<td>41</td>
<td>14</td>
<td>0</td>
<td>2</td>
<td>20</td>
<td>9</td>
<td>8</td>
<td>348</td>
</tr>
<tr>
<td>Totals</td>
<td>710</td>
<td>584</td>
<td>583</td>
<td>427</td>
<td>320</td>
<td>287</td>
<td>170</td>
<td>168</td>
<td>125</td>
<td>142</td>
<td>137</td>
<td>206</td>
<td>3,859</td>
</tr>
</tbody>
</table>

Control programmes

Control of stray dogs

Turkey is faced with an increasing number of stray dogs, especially in urban areas. The elimination of these strays is the responsibility of the municipalities. However, removal programmes meet increasing opposition from the public due to greater animal welfare awareness. As a result, more facilities for dog rehousing have been established and several neutering programmes have been initiated.
Chapter 12

Historical Perspective of Rabies in Europe and the Mediterranean Basin

Vaccination

There is voluntary parenteral vaccination for rabies in animals. The first vaccination programme in Turkey took place in 1946 (when Semple vaccine was first produced here using phenol as inactivating agent). Nowadays, besides the locally produced Kelev rabies vaccine, many imported inactivated vaccines are available. The number of outbreaks and vaccination results are shown in Table 12.7.

Table 12.7 – Animal rabies vaccination in Turkey 1977-1999

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of outbreaks</th>
<th>Number of animals vaccinated</th>
<th>Year</th>
<th>Number of outbreaks</th>
<th>Number of animals vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>1,205</td>
<td>Not available</td>
<td>1988</td>
<td>710</td>
<td>209,200</td>
</tr>
<tr>
<td>1978</td>
<td>1,482</td>
<td>Not available</td>
<td>1989</td>
<td>584</td>
<td>233,400</td>
</tr>
<tr>
<td>1979</td>
<td>1,595</td>
<td>80,340</td>
<td>1990</td>
<td>583</td>
<td>361,334</td>
</tr>
<tr>
<td>1980</td>
<td>2,088</td>
<td>82,690</td>
<td>1991</td>
<td>427</td>
<td>303,431</td>
</tr>
<tr>
<td>1981</td>
<td>2,260</td>
<td>105,691</td>
<td>1992</td>
<td>320</td>
<td>298,973</td>
</tr>
<tr>
<td>1982</td>
<td>2,172</td>
<td>108,000</td>
<td>1993</td>
<td>287</td>
<td>219,848</td>
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<tr>
<td>1983</td>
<td>1,932</td>
<td>172,400</td>
<td>1994</td>
<td>170</td>
<td>189,670</td>
</tr>
<tr>
<td>1984</td>
<td>1,460</td>
<td>177,200</td>
<td>1995</td>
<td>168</td>
<td>184,071</td>
</tr>
<tr>
<td>1985</td>
<td>1,284</td>
<td>169,900</td>
<td>1996</td>
<td>125</td>
<td>160,008</td>
</tr>
<tr>
<td>1986</td>
<td>1,266</td>
<td>215,500</td>
<td>1997</td>
<td>142</td>
<td>147,215</td>
</tr>
<tr>
<td>1987</td>
<td>1,005</td>
<td>344,600</td>
<td>1998</td>
<td>133</td>
<td>109,215</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1999</td>
<td>206</td>
<td>161,589</td>
</tr>
</tbody>
</table>

Public information and training programmes

Quarantine measures are implemented in areas where a rabies case has been diagnosed and the movement of animals (pets and livestock) to and from the region is banned for six months. If applicable, suspected animals may not be killed for consumption, or dairy products of these animals consumed. As a corollary to these measures, public information is disseminated by television, radio and other communication means, particularly through schools.

Plans for the future

Eradication of rabies from Turkey is possible in the near future. However, due to the increasing dog population, future control schemes should focus on ‘responsible dog ownership’ programmes. Meanwhile, intensified vaccination campaigns should be carried out in areas where rabies is still present. In addition to the control programmes, the Veterinary Services are implementing dog population and oral vaccination studies in both cities and rural areas. These activities are supported by special units at the Regional Veterinary Control and Research Institutes and by Provincial Control Laboratories.

The feasibility of oral rabies vaccination of dogs under Turkish field condition was investigated by a joint technical Co-operation Project of GDPC and the World Health Organisation (WHO) Collaborating Centre for Rabies Surveillance and Research at Tübingen, Germany. We used the live-attenuated virus strain SADB19, a vaccine that has been in used in many European countries since 1983. The studies in Turkey were both laboratory and field based.

The laboratory trials were carried out at the Etlik VCRI in Ankara. Here, efficacy and innocuity of the vaccine was tested on the target population: free-roaming dogs and cats. In addition, tests on the most common local rodent species were conducted to investigate the behaviour of the vaccine virus in these species. Studies were also carried out to estimate the minimum vaccine titre necessary for an effective immunisation.
Field studies focused on bait formulation and acceptability, bait delivery systems and dog ecology (assessment of the dog population). Comparison of the different baits tested showed that the so-called ‘Köfte’ bait (minced meat with bread) was more readily accepted than any other bait, including the widely used chicken-head bait. Two bait delivery systems have been examined so far: baits fed directly to free-roaming dogs and baits deposited at selected sites.

The objectives of the dog population studies were to estimate dog density, the structure of the dog population (sex ratio, age structure, turn over), the percentage of owned and unowned dogs and how many dogs could be vaccinated (accessibility). The techniques used in the study were capture and marking and recording. The study distinguished between rural, semi-rural and sub-urban areas and was carried out near the Tekirdağ.

Preliminary results showed that there were approximately 460 dogs per km², that their average age was 3.1 years and that approximately 25% of the dogs were juveniles. The human:dog ratio was 3.8:1 in rural areas, 5.5:1 in semi-rural areas and, surprisingly, more than 100:1 in urban areas. In rural areas, more than 80% of the dogs were free roaming, whereas in semi-rural areas the figure was 60%, and in cities the figure was only 10%. In areas of high dog density, groups of up to 30 dogs were noted, especially when female dogs were on heat. Fights that broke out could cover 5-50 metres. The accessibility of dogs for all three areas (city, suburban and rural) was approximately 60%.

Acknowledgements

I wish to thank all who helped to collect the information and data, especially Drs Ad Vos, Orhan Aylan and Selma Lyisan for critical review and suggestions.

CYPRUS

According to the existing data in Veterinary Department archives, rabies has never been diagnosed in man or animals in Cyprus except for two cases in quarantined dogs in the 1930s.

Measures for prevention and control

Rabies is a notifiable disease. All imported dogs and cats need import permits (official veterinary certification that they are healthy and that they have been vaccinated against rabies). Upon arrival, a booster vaccination, with an inactivated rabies vaccine, is given to all dogs and cats, which are then kept for six months under close veterinary supervision at an approved place provided by their owners. Only after this period are they allowed free movement. Imported dogs and cats are blood-sampled and ELISA tested for the presence of rabies antibodies. Any imported dog or cat that presents a disease risk is placed in quarantine. If it dies, post-mortem and brain histopathological examination is carried out to determine if the cause of death was rabies.

Brain samples from carcasses of stray dogs and foxes are also examined as part of our annual surveillance programmes. In addition, dogs caught by the United Nations Forces in, or near, the United Nations Protected Area are taken to the Veterinary Services for euthanasia or for laboratory examination. Examination for rabies includes histopathology,Seller’s stain for the detection of Negri bodies, FAT, mouse inoculation and the ELISA test for antibody detection.

SYRIA

Historical documentation of rabies in Syria is relatively sparse (Chapter 2, J. Blancou) but today it is one of the enzootic diseases present in the country. According to Biseru (6), rabies is present in the Latakia mountains from where it tends to spread to adjacent areas, with jackal, fox and wolf as reservoir species. In domestic animals, dogs form the reservoir species but transmission also occurs to a lesser extent in cats and other animals.
Human rabies

Diagnosis of rabies in humans is based primarily on neurological symptoms and a history of being bitten by a rabid animal or an unknown animal suspected of being rabid. Cell culture (Merial) vaccine is used for post-exposure treatment, sometimes with the addition of immunoglobulin. Treatment is given free-of-charge to the patient and the number of treatments given each year is 6,000-7,000 (Table 12.8).

Animal rabies

Animals known to have bitten humans are kept under strict control and observation for at least ten days. In the case of dead animals, the heads are sent to the Central Veterinary Laboratory for diagnosis.

Control

A national programme for rabies control has been applied since 1984 and depends upon three principles:

1. eradication of stray dogs (by shooting or poisoning)
2. vaccination of owned dogs
3. PET for humans.

Complete eradication of stray dogs is impossible because of open borders with other countries. With continuous movement of stray dogs, a culling policy, along with the vaccination of owned dogs, is the only way to minimise the risk of human rabies. Table 12.9 shows the number of stray dogs shot or poisoned, together with those owned dogs vaccinated, since 1994.

**Table 12.8 – Human rabies in Syria 1994-1999**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patients</th>
<th>Alone</th>
<th>Serum</th>
<th>Number of died</th>
</tr>
</thead>
<tbody>
<tr>
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<td>5,819</td>
<td>4,099</td>
<td>1,720</td>
<td>13</td>
</tr>
<tr>
<td>1995</td>
<td>6,613</td>
<td>5,170</td>
<td>1,443</td>
<td>9</td>
</tr>
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<td>1996</td>
<td>7,357</td>
<td>6,076</td>
<td>1,244</td>
<td>4</td>
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<td>1997</td>
<td>6,550</td>
<td>5,418</td>
<td>1,251</td>
<td>9</td>
</tr>
<tr>
<td>1998</td>
<td>7,865</td>
<td>5,878</td>
<td>1,987</td>
<td>3</td>
</tr>
<tr>
<td>1999</td>
<td>5,766</td>
<td>3,028</td>
<td>1,445</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 12.9 – Control of dog rabies in Syria 1994-1999**

<table>
<thead>
<tr>
<th>Year</th>
<th>Dogs Poisoned</th>
<th>Shot</th>
<th>Destroyed total</th>
<th>Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>3,271</td>
<td>8,906</td>
<td>12,177</td>
<td>2,247</td>
</tr>
<tr>
<td>1995</td>
<td>4,288</td>
<td>9,664</td>
<td>13,952</td>
<td>1,790</td>
</tr>
<tr>
<td>1996</td>
<td>4,062</td>
<td>3,522</td>
<td>7,584</td>
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</tr>
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<td>2,388</td>
<td>4,535</td>
<td>6,923</td>
<td>760</td>
</tr>
<tr>
<td>1998</td>
<td>3,522</td>
<td>4,889</td>
<td>8,411</td>
<td>1,105</td>
</tr>
<tr>
<td>1999</td>
<td>3,224</td>
<td>4,391</td>
<td>7,615</td>
<td>368</td>
</tr>
<tr>
<td>Totals</td>
<td>20,755</td>
<td>35,907</td>
<td>56,662</td>
<td>7,584</td>
</tr>
</tbody>
</table>

LEBANON

Lebanon is a mountainous country with a surface area of 10,452 km² and has borders with Syria to the east and north and Israel to the south, with a western shore on the Mediterranean. Administratively Lebanon is divided into five provinces (mohafazats) including Beirut. Except for Beirut, each Province is subdivided into several Qadas and further into Municipalities. The human population is approximately three million, almost half of whom live in the capital city Beirut and its environs. From the most recent census, the animal populations were approximately 77,000 cattle, 250,000 sheep, 450,000 goats, 40,000 pigs, 1,400 horses and 200 donkeys. Rough estimates indicate the existence of about 10,000 dogs and 5,000 cats. Information concerning the owned segment of the dog population in the country refers to approximately 8,000 dogs, but this needs to be further studied. Stray dogs live in the same area as the human population. Their survival and reproduction success depends on adequate whelping sites and human food waste. The recent seventeen years of armed conflict has resulted in considerable damage to
the infrastructure and economy of the country, as well as to significant migration and internal population movement. Current demographic data of the human and animal populations are scarce.

Concern about rabies has been growing during recent years. The disease has become a public health hazard that threatens people and livestock in both rural and urban areas especially in the Bekaa and Northern provinces. Since 1991, eight cases of human rabies have been reported to the Epidemiological Surveillance Unit of the Lebanese Ministry of Health. Between 1991 and 1996, three other cases were admitted to the American University of Beirut Medical Centre. All cases were diagnosed on clinical grounds only. During this period, 2,487 doses of rabies vaccine were given as postexposure treatment. Ten of the 11 cases occurred in farming areas close to the border with neighbouring countries (Bekaa, six, North, two and South, two). These are areas where wild animals such as foxes, hyaenas and jackals, which may or may not be local rabies reservoir species, are found. All of the human cases, however, resulted from dog bites, including a single case from Beirut. Incubation periods ranged from 11 days to two months, with the shortest being in a patient bitten on the head. Since in all cases death occurred from a few hours to a few days after presentation, it is clear that presentation for treatment was too late and that none of these deaths can be attributed to a failure of PET.

Table 12.10 shows, for Lebanon, during the period 1996 to 1999, the number of humans bitten, the number of post exposure treatments given and the species of animal responsible for the bite. Apart from dogs, cats and rats, other biting species included monkeys, donkeys and foxes. It can be demonstrated from the Table 12.10 that not all bitten patients were given PET. In response to the growing concern about rabies in Lebanon a national multisectoral, multidisciplinary control programme is being considered.

Table 12. 10 – Humans given PET in Lebanon 1996-1999

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine only</th>
<th>Serum only</th>
<th>Vaccine + serum</th>
<th>Total</th>
<th>Biting animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dog</td>
<td>Cat</td>
<td>Rat</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>1996</td>
<td>184</td>
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<td>29</td>
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<tr>
<td>1997</td>
<td>211</td>
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<td>236</td>
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<tr>
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<td>250</td>
<td>10</td>
<td>15</td>
<td>11</td>
<td>286</td>
</tr>
<tr>
<td>1999</td>
<td>313</td>
<td>7</td>
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<td>3</td>
<td>335</td>
</tr>
<tr>
<td>Totals</td>
<td>958</td>
<td>23</td>
<td>66</td>
<td>35</td>
<td>1,082</td>
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</tbody>
</table>

CONCLUSION

Turkey still reports dog-mediated rabies, although several cases of wildlife rabies have been confirmed. In the past, human vaccination in hospitals and rabies stations throughout Turkey relied upon the use of nerve tissue vaccines (Semple). In 1987 however, production of nerve tissue vaccines was discontinued. Between 1987 and 1996, either Semple vaccine or imported cell culture vaccine was used in suspected rabies cases, but from 1996 to the present time, only imported cell culture vaccine was used in pre- and post-exposure treatment (PET). Currently, both vaccine and sera are imported, especially from Germany and France, and vaccination units are now present in all health centres and hospitals throughout the country.

In Cyprus, rabies has never been diagnosed in man or animals except for two cases in quarantined dogs in the 1930s.

In contrast, in Syria and in the Lebanon, rabies is a serious enzootic disease. Rabies is transmitted principally by stray dogs or cats and rarely by other domestic animals with possible spread to wildlife species including jackals, rats, foxes, monkeys and wolves. Patients bitten by 'suspect' animals are not always treated with appropriate PET. In response to the growing concern about rabies in countries of the Mediterranean basin, a multi-national control programme is under consideration in the region.
References and statistical sources


CHAPTER 13
RABIES IN ISRAEL AND JORDAN

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Summary

A recent epidemiological survey of rabies in Israel indicated that the viral isolates analysed were related geographically, but not according to host species. Five different variants, distributed among four different geographical regions were identified. The mechanisms of rabies transmission from rabies-endemic areas to previously free regions is dependant on the susceptible animal species in the region. Different animal species, especially wildlife (jackals), domestic livestock and companion animals (dogs), are known to support rabies in the Middle East. This chapter describes the prevalence of rabies in animals and the measures being undertaken to control animal rabies and reduce the burden on public health. The proven policies used to effectively control rabies in Israel and Jordan could be extended to include Egypt, Israel, Jordan, Lebanon, Syria and the Palestinian Authority for the elimination of rabies throughout the region.

Keywords: Middle East, oral vaccination, rabies

ISRAEL

Introduction

Shoshan (50, 51) has summarised our historical knowledge on rabies in the Middle East in ancient times. He concludes that in Biblical times, Hebrews recognised that animal bites were a form of divine punishment as indicated in the scriptures ‘I will also send the wild beasts among you, which shall rob you of your children and destroy your cattle, and make you few in number’ (Leviticus 26:22), and ‘I will also send the teeth of beasts upon thee with the poison of serpents of the dust’ (Deuteronomy 32:24). The descriptions of the clinical signs are found in the Babylonian and Jerusalem Talmuds, wherein a rabid dog was recognised by five characteristic signs:

– open mouth with drooling saliva
– foul-smelling ears
– tail tucked between its legs
– wandering from side to side of the road
– attempting to bark but no sound emerging.

One of the first recorded cases of human rabies was that of Garmi, the servant of Rabbi Yehuda (4th Century, Tiberias), who was bitten by a rabid dog that was biting and killing other people. Even though he was treated with the diaphragm of the rabid dog, he died. Transmission of rabies by domestic animals was also recorded in the Jerusalem Talmud: ‘It occurs in the Land of Israel that ewes, cows and donkeys bite and the victim dies after a period of time’.

It was realised that, although in general a shepherd should be able to fend off a single wolf, in the time of a rabies epidemic a shepherd cannot be held responsible for the loss of sheep. ‘In times when there are wolf packs raging, even a single wolf is too dangerous for a shepherd to ward off’. Bartinura, a 15th Century Italian commentator explained, ‘When bad animals are rampant, even a single animal will attack a man’. The jackal was also recognised as a vector of rabies – ‘their bite is as the bite of a jackal and their sting like the sting of the scorpion’.
Already in these times there were public ordinances to prevent exposure to rabies. ‘A person may not keep a dog unless it is chained’ or, ‘If you see a rabid dog, hide from it as there is no known cure’, and ‘A mad dog should be killed anywhere it is found even on the Sabbath’.

Evidence of attempts to prevent and cure the disease can also be found in the ancient manuscripts. Rab Matyah ben Charash (Rome, 3rd Century) permitted feeding the diaphragm of a rabid dog. In Egypt (12th Century) there was a high incidence of rabid dogs. The Sultan commissioned the Rambam to write a popular treatise on procedures for the treatment of various animal bites. He placed the responsibility for rabid dogs on their owners and recommended aggressive measures against those who failed to properly restrain rabid dogs.

The following example can be found in The Medical Writings of Moses Maimonides ‘Rambam’ (45), ‘Physicians have asserted that the signs of a mad dog are numerous and all are correct. There is, therefore, no need to mention them in length in this treatise because man’s nature is to instinctively flee from a mad dog. Even a healthy dog flees from a mad dog. The mad dog is always seen walking alone; his path is crooked, he leans against the wall and does not bark. There is no doubt that people everywhere try to kill him as soon as they recognise his condition. But it sometimes happens that he bites before being recognised or sometimes a person is bitten in the dark by a dog without knowing whether or not it was a mad dog. Everything that is mentioned in the literature to cure the patient of the bite of a mad dog is only efficacious if used therapeutically prior to the onset of hydrophobia. If the therapy is applied after the patient develops a fear of water ‘I have never seen anyone survive’. A person bitten by a mad dog does not always suffer greater pain than the pain of the bite of any other dog. Rather, the serious symptoms which indicate rabies do not begin to appear in most cases until eight days have passed. Sometimes they do not appear until a much later time. Therefore, anyone bitten by a mad dog or by a dog whose condition is not known should adhere to the general rules, that is to say the ligature, the incision, the sucking, the copious blood-letting from the affected site by means of cupping vessels, the vomiting and imbibing of theriac’.

Human rabies

The disease undoubtedly did not disappear over the subsequent centuries, but as books, writings and recorded history of this area are very sparse up to the 20th Century, no mention of rabies can be found. The traveller and naturalist, P.G. Baldensperger in his article, ‘The Immovable East’ (11) describes the traditional treatment of rabies among Palestinian Arabs at the beginning of the 20th Century: ‘Hydrophobia (sa’ar) is supposed to be the spirit of a demon passing through the mad dog to the bitten person; consequently it is treated with verses from the Koran, which must be pronounced by a special sheikh who is an expert in the business. A sheikh in Lydd, who received such patients, put them in an isolated room and in secret performed sundry exercises unknown to the world. If the patient excretes young dogs (demons) about the size of hornets, there is nothing to be done, and seven months later the patient dies with all the horrors of hydrophobia, but if the demon-phenomenon does not appear, he is saved. The tree-lupine (salamone) is taken in decoction. Two of our servants were bitten by a mad jackal; one, a Feilah, was bitten on the naked skin and died within seven weeks, raging and foaming, in the room where he was shut up; the other, a Madany, was bitten through the pantaloons, and was wholly cured; although one was a Moslem and the other a Protestant Arab, both refused to be treated by our medical doctor, but went to the sheikh with the above result’.

During the Ottoman Empire, Palestinians who were bitten by dogs were sent to Istanbul or Cairo to receive antirabies treatment (16). A Pasteur Institute was established in Jerusalem in 1913 under the supervision of Dr Arie Beham (alias Leo Behm or Boehm) who was born near Kovno (Lithuania) in 1877, studied medicine in Kharkow, then served in the Russian army during the war with Japan. On his way back he travelled to Palestine and was appalled by the dire sanitary conditions. In 1906, he decided to build a Pasteur Institute, particularly devoted to the fight against rabies and smallpox, but also to serological diagnosis (38). He was the first and apparently the only Director of this Institute and gave to the disease its modern Hebrew name, kalevet (Dog’s ailment) (16). The Institute’s rabies department reported that between 1914 and 1920, 1,414 people were bitten (925 by dogs, 197 by foxes, 188 by cats, six by wolves and 98 by other animals) and 198 people received post-exposure treatment using Pasteur’s
original dried cord method. The first rabies diagnostic facility was established and on microscopic examination, 26 cases were found positive for rabies (38).

On the establishment of railway communications between Palestine and Egypt in 1918, the British Army decided that all military personnel affected should be sent to the Anti-Rabic Institute in Cairo. Loss of life was ascribed to lack of proper local facilities for treatment and ineffective treatment in Cairo because patients arrived too late. This unsatisfactory state of affairs continued until it became increasingly apparent to both military and civil authorities that if numbers of lives were not to be sacrificed every year it was necessary to provide adequate treatment in Palestine itself.

Early in 1923 the Palestinian Department of Health gave serious attention to cases of rabies exposure. There was no doubt that rabid dogs and jackals were biting ever-increasing numbers of people throughout Palestine. The result was a commitment given by the Laboratory Section of the Government of Palestine’s Department of Health to supply quality anti-rabies vaccine of proven reliability, to fulfill all army and civilian requirements. However, additional considerations highlighted the need for this undertaking. Not least was the fact that all expenses associated with poor patients presenting themselves for treatment at the private institute in Jerusalem had to be defrayed by the Government at considerable cost; whereas as well, having to send all exposed soldiers to Egypt involved the military in much inconvenience and expenditure. It will be appreciated, therefore, that the Department’s decision was based strictly on utilitarian and economic grounds. After careful analysis of current rabies post-exposure treatment, and with the accumulated evidence of twelve years experience, G. Stuart and K.S. Krikorian decided to uphold the recommendation first proposed by Fermi on the value of carbolised vaccine treatment. They were aided by Colonel Hamerton, who had earlier faced a serious problem of rabies in Iraq and used his experience to help with the situation in Palestine. He provided great encouragement to Stuart and Krikorian and it was with every hope of a similar success in Palestine that the two doctors established the Central Anti-Rabic Institute in Jerusalem in May 1923.

In order that the ‘greatest good for the greatest number’ of inhabitants likely to be at risk might be served, ten subsidiary treatment centres supplied with vaccine prepared at the Central Institute, were opened on the same day (21, 53, 54, 55, 56, 57, 58, 59, 60). Once it was possible to receive treatment in Jerusalem, the mortality rate from rabies in Palestine dropped dramatically and for more than 50 years the Semple type rabies vaccine was used, first in Palestine and, after 1948, in the State of Israel.

Although there was sufficient evidence of the immunogenicity of the vaccine, the rate of paralytic accidents was comparatively high in Israel, at one in 800 treatments. In order to lessen this risk, the purified duck embryo vaccine (PDEV), with fewer associated minor anaphylactic reactions was introduced in the 1970s and nearly 50% of patients, especially children, were treated with this vaccine (19). In the 1980s, the PDEV vaccine was replaced by a highly antigenic human diploid cell vaccine (HDCV), which was known to be safe and effective in eliciting protective antibodies.

The rabies immunoglobulin used in Israel is of human origin, is costly and is available only through regional health officers (12, 20). In the past two decades, almost 400 people have received full anti-rabies treatment each year. This is 5% of the total number of persons who present themselves for examination after being bitten or scratched by animals, mostly dogs, cats and cows, but sometimes by foxes and jackals. In the last quarter of 1996, the first fatal human case for 26 years occurred and two additional cases were reported in 1997 (14). Consultations and treatment for possible rabies exposure increased two-fold. The Ministry of Health reported that 4,400 of the 5,000 people who received post-exposure treatment in 1997 had been exposed to dogs and cats. The cost of rabies control activities and post-exposure treatment presents a great financial burden to the State of Israel (39).

The Pasteur Institute and the Central Laboratory of the Department of Health of the Government of Palestine began to keep records on the frequency of the disease in the 1920s and 1930s (2, 53). These data were analysed by Goor, who documented 2,207 cases of rabies between 1930 and 1947 (annual average of 122) as follows: dogs accounted for 67%, cats 12.1%, jackals 10.2%, horses and donkeys 5%, oxen 3.3% and others 1.7%, and between 1923 and 1946 at least 75 people died from the disease (24).
Animal rabies

Soon after the establishment of the State of Israel in 1948, the Kimron Veterinary Institute (KVI) assumed responsibility for rabies diagnosis in animals and, subsequently, also for the confirmation of fatal human cases (43; Tables 13.1 and 13.2). Brains of small animals were submitted to the Institute in two portions: one half in 10% formalin, and the other half in 50% glycerol saline. In the case of large animals, pieces of Ammon's horn, cerebellum, cerebrum and pons are submitted. From 1949 to 1951, rabies diagnosis was carried out by histological examination for Negri bodies, using Heidenhain's iron-haematoxylin and Mallory's connective tissue stains and by the mouse inoculation test (28). In 1951, Sellers' impression method (47) was introduced and the technique followed was that recommended by the World Health Organization (WHO) (61, 62). Histological examination of brain sections was performed concomitantly. The formerly mentioned histological techniques were too time consuming for routine diagnostic work and so a new method which consisted of utilising Sellers’ stain for histological sections was adopted (42). Other histological methods were also tried at one time or another, but once Sellers’ rapid impression method had been fully mastered, they become no longer necessary.

Table 13.1 – Animal and human rabies in Israel 1948-1970

<table>
<thead>
<tr>
<th>Year</th>
<th>Dog</th>
<th>Cat</th>
<th>Cattle</th>
<th>Sheep/goat/pig</th>
<th>Equine</th>
<th>Camel</th>
<th>Jackal</th>
<th>Fox</th>
<th>Other</th>
<th>Total</th>
<th>Human</th>
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<td>75</td>
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<td>107</td>
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<td>1,612</td>
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</tbody>
</table>

Mouse inoculation tests are carried as recommended by the WHO (4). Fluorescent antibody staining described by Goldwasser and Kissling (23) was introduced into the KVI in 1959. Preliminary data were published by Goldwasser and Kimron (22) and Kemron and Goldwasser (31). Results of one year’s comparative study of Sellers’ staining and fluorescent antibody technique were reported (32) and the technique was adopted for routine rabies diagnosis.

From 1996 the polymerase chain reaction technique on the saliva of rabies-suspected patients was introduced in Israel (14) and from 1999 as an additional alternative diagnostic tool for decomposed animal
samples. Today an immunohistochemical technique is used to identify rabies antigen in formalin fixed tissues. A separate rabies diagnostic laboratory was formed, in 1999, in which rabies virus isolation cell culture will replace the mouse inoculation test, while the rapid fluorescent focus inhibition test is used for rabies antibody detection in humans and animals.

### Table 13.2 – Animal and human rabies in Israel 1971-1999

<table>
<thead>
<tr>
<th>Year</th>
<th>Dog</th>
<th>Cat</th>
<th>Cattle</th>
<th>Sheep/goat/pig</th>
<th>Equine</th>
<th>Camel</th>
<th>Jackal</th>
<th>Fox</th>
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<td>32</td>
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<td>45</td>
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An epidemiological survey based on nucleotide sequence analysis of 328 bp from the C terminus of N coding region and the non-coding region between the nucleoprotein and the phosphoprotein (NS gene) was performed on 226 rabies virus isolates, from different areas of Israel, collected during 1993-1998.

 Phylogenetic analysis of the virus isolates showed that they are related geographically, but not according to host species. Five variants, related groups distributed among four geographical regions, were identified. In each region, rabies virus was isolated from more than one animal species. A comparison of sequence analysis of rabies virus samples revealed a 2-nucleotide change that distinguished the Middle East variants from the rest (15).
Wildlife rabies

Epidemiological trends in wildlife have been described up to 1980 (10, 33, 43, 44). In 1949-1961, dogs and cattle were the most commonly affected domestic animals and the jackal and mongoose among wild animals (43). In 1971, foxes replaced jackals as the most commonly affected wild animal (44). Between 1980 and 1994, the number of fox cases reached 45.8% of the total rabies-positive cases, while dog cases were 28.6% (33). In a recent review of the role of the fox as a vector, Shimshon y showed that the epidemiology of rabies and its trends in Israel have changed over the past 70 years (49).

A retrospective analysis of rabies diagnosis that deals with the period of 1948 through 1997, according to case distribution by animal species, geography, and monthly and seasonal variations has been published (64). A total of 2,243 rabies cases was diagnosed between 1948 and 1997. The highest number of cases was registered in the first decade (1948-1957). Dogs were the most commonly affected animals and this held true until the third decade (1967-1977), a situation that continues in neighbouring Jordan (1). The implementation of the Rabies Ordinance, mass poisoning of jackals throughout the country, and compulsory vaccination of dogs initiated in 1957 resulted in a 62% decrease in the number of cases during the subsequent ten years. The Rabies Ordinance (3) legislates for the compulsory vaccination of animals, elimination of stray dogs and cats and quarantine of suspected rabid animals.

From the mid 1970s a major transition from urban dog rabies to sylvatic fox rabies occurred and the total number of positive fox cases increased significantly (33). In 1991, a high percentage (73.5%) of dog rabies in Israel was reported. This figure was probably due to the first Gulf War in January 1991, when numerous residents of the metropolitan Tel Aviv area evacuated their homes, resulting in an increase in the stray dog population and a resurgence of urban rabies (49). Intensive control measures were then implemented (25, 27), the number of vaccinated, removed and quarantined animals increased and urban rabies was successfully eliminated within two years.

Between 1976 and 1997, foxes accounted for 46% of rabies cases whereas jackals accounted for only 4%. The increase in fox rabies is probably the result of human intervention. In the late 1950s, the jackal population had been decimated by countrywide poisoning and the fox population increased. This has been suggested as the reason for the re-emergence of the fox as the reservoir and vector of rabies in Israel. However, it is possible that the apparent absence of rabies in foxes between 1949 and 1970 was a result of misidentification of the fox as a jackal.

The distribution of rabies among wild species, including the mongoose (Herpestes ichneumon ichneumon), badger (Meles meles canescens), wolf (Canis lupus), striped hyena (Hyaena hyaena) and stone marten (Martes fina syriaca) is presented in Table 13.3. Rabies was first diagnosed in the marbled polecat, Vormela peregusna syriaca in 1999. Rabid bats have never been caught in Israel but in two limited surveys in 1993 and 1996 a total of 40 fruit bats, Rousetus aegypticus, was examined for rabies with negative results (40).

Urbanisation and agricultural development have resulted in an increase in untreated garbage dumps, which are a food source for wild canids, resulting in an increase in their population density as a result of the enhanced carrying capacity of their habitats. This animal overload is a major factor in the incidence of rabies in Israel.

<table>
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<tr>
<th>Species</th>
<th>Number</th>
<th>% of total cases</th>
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<td>478</td>
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<tr>
<td>Wolf</td>
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<tr>
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<td>0.9</td>
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<tr>
<td>Marten</td>
<td>2</td>
<td>0.3</td>
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<td>23.0</td>
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<td>Polecat</td>
<td>1</td>
<td>0.2</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>663</strong></td>
<td><strong>100</strong></td>
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</table>
The close contact between the habitats of humans, foxes and jackals is a major factor in transmission of the disease to domestic animals.

Cattle are the major domesticated species of economic importance affected by rabies. In Israel rabies transmission often involves a carnivore-bovine link. Voluntary immunisation of cattle against rabies started in 1970; in 1997 the number of vaccinated animals reached 72,000, which is 25% of the Israeli cattle population.

Rabies now occurred in almost all parts of the country with an apparent clustering in the north. In the decade 1988-1997, rabies had predominated in the southern part of the country (64). For the past 20 years, the densely populated and urbanised coastal areas have been almost rabies free, with the exception of 1991-1992 (49, 64). Monthly or seasonal patterns were not apparent when the data of 50 years were analysed for all animal species, nor when the data were grouped into ten-year intervals. When farm animals and fox/jackal cases were analysed separately, a pattern emerged where fox and jackal numbers rose gradually from April to peak in October, followed by a decline and then a minor peak in February. Farm animals followed the same pattern with each peak occurring two months after the fox/jackal peaks. Dogs comprised 50% of animals diagnosed as rabid over the 50-year period, although most of the rabid dogs were identified before 1958 and were mainly urban. From the mid 1970s, sylvatic rabies supervened, and rabid foxes accounted for 49% of all diagnosed cases between 1988 and 1997, establishing the fox as the principal current reservoir of rabies virus in Israel (64).

Rabies control

Despite the implementation of rabies control measures such as compulsory dog vaccination, elimination of stray dogs and cats and quarantine of suspected rabid animals, the prevalence of rabies in domestic animals has remained stable over the past 30 years. The Israeli rabies control programme is comprehensive compared with those of its neighbours. In the West Bank and Gaza there is no active dog vaccination programme; the only control measure is stray dog removal conducted in response to the complaints of residents (10). Three cases of human rabies in 1996 and 1997 have highlighted the risk of virus transmission if contact occurs between people and unvaccinated domestic or wild animals (64).

Original research on rabies in the State of Israel began with Komarov’s work (34, 35, 36, 37) and was continued by other investigators (12, 13, 17, 18, 26, 29, 30, 46, 48, 62). Komarov started in the early 1950s when he isolated the Kelev strain from a rabid dog. The strain was initially pathogenic for mice and rabbits. After four intracerebral passages in mice it was passaged in chick embryos. After the 21st egg passage, the virus, when injected intracerebrally, no longer produced Negri bodies in mice. At the 26th passage, the pathogenicity of the virus for mice, hamsters and rabbits became much reduced. An attenuated strain was developed for use in prophylactic rabies vaccination (35).

Rabies economics

The economic aspects of rabies and related control activities were evaluated in 1988 (52). The total nationwide expenditure for 1988 was estimated at $5,225,000, of which 84% was the cost of control activities carried out by municipal Veterinary Services. The cost of rabies diagnosis by the Veterinary Services and Animal Health was estimated at $273,000. Livestock vaccination costs were approximately $190,000 and an additional $11,000 were attributed to losses from the quarantine of suspected farms. The annual cost of post-exposure treatment of humans, carried out by the Ministry of Health was $316,000 in 1988 and this figure rose to $3,428,000 in 1997.

JORDAN

Introduction

The Hashemite Kingdom of Jordan covers an area of 89,550 km². It is bordered by Syria to the north, Saudi Arabia to the south, Iraq and Saudi Arabia to the east, Palestine and Israel to the west. Western
Jordan has essentially a Mediterranean climate with a hot, dry summer, a cool, wet winter and two short transitional seasons. However, about 75% of the country can be described as having a desert climate with less than 200 mm of rainfall annually. Jordan can be divided into three main geographic and climatic areas: the Jordan Valley, the Mountain Heights Plateau and the eastern desert, or Ba’dia region.

The occurrence of rabies has been known in Jordan for a very long time. Many people are aware of the dangers of this zoonotic disease, although it is not a major threat to human life. The surveillance of rabies is part of the general surveillance system for communicable diseases. The information is provided by local health authorities, by epidemiologists conducting investigations of human rabies cases and by laboratory personnel in the Vaccine Institute and the Veterinary Services. Data are collected in the Disease Prevention Department at the Ministry of Health and in the Veterinary Department at the Ministry of Agriculture. Exchange of information takes place between different administrative sectors and levels responsible for rabies control. Each report of a suspected case of rabies in animals is registered at the district veterinary office. In the case of human contact with a suspected animal, the medical officer is informed.

Suspect animals that expose humans or animals are confined and observed for 10 days and inspected by a state veterinarian. If no clinical signs are seen, the animal is either vaccinated or destroyed. All animals showing clinical signs for rabies are killed. All stray animals are considered potentially rabid if they cannot be captured or examined for rabies. Heads of suspected animals packed on ice are submitted to the Jordan Vaccine Institute where the brains are removed under aseptic conditions. The fluorescent antibody test (FAT) is presently used only at the Ministry of Health Jordan Vaccine Institute, Amman. Diagnoses of animals were carried out at the Animal Health Institute soon after its establishment in 1968 until 1980. Seller’s impression method and mouse inoculation tests were used, but these techniques were too time consuming for routine diagnostic work and a new method which consisted of using Seller’s stain for histological section was implemented.

**Human rabies**

The purpose of rabies control is to reduce infection in human and animal populations, although data show that human rabies is a rather rare occurrence in Jordan. During a period of 39 years, only 30 cases of rabies in man were recorded. Most of the cases occurred in the northern parts of Jordan. Dogs, cattle, foxes, jackals, sheep, goats, cats, equines and others were the source of infection for man and animals. During 1992-1998 only six human deaths from rabies (three in 1992, one in 1993, one in 1994, and one in 1996) were reported, diagnosed on clinical grounds. Dogs were the source of exposure in four cases and a fox and an hyaena were implicated in the other two. The number of humans bitten by animals reported during that period was 967, 969, 1,246, 2,364, 1,223, 1,368, and 1,407, respectively (8). Asaad (9) stated that the incidence of rabies in man is two per 10,000 inhabitants in Jordan.

The Ministry of Health is responsible for providing human rabies vaccine (Human Diploid Cell Vaccine, HDCV) and immunoglobulin free of charge for post-exposure treatment. The role of the private sector in application of post-exposure treatment is limited, since only Jordan University Hospital has vaccine for post-exposure treatment. During 1992-1996 dog bites were responsible for 72%-85% of human post-exposure treatments. The overall cost of the treatment (vaccine and serum) varied from year to year and according to the numbers bitten. From 1990 to 1997 a total of $2.3 million was spent on the cost of treatment only. The average annual cost of treatment for the past five years was $425,000.

All human bites by highly suspect or proven rabid animals are recorded as exposure cases. Human rabies cases with clinical signs and verification through identification of intracytoplasmic virus or positive results of fluorescent antibody technique are reported as rabies cases.

**Animal rabies**

Only a few verified cases of rabies in animals have been recorded. Before 1980, diagnosis of rabies was made at the Ministry of Agriculture’s Animal Health Institute, Amman, by the use of Seller’s staining of brain smears. Verification of the diagnosis was by mouse inoculation test. There were some doubts about
the accuracy of the diagnoses. Dogs were the major cause of rabies and post-exposure treatment. Since 1981, diagnosis of rabies has been carried out by modern methods such as immunofluorescence and serological tests at the Jordan Vaccine Institute in Amman. A more effective disease reporting system was introduced in 1971. Between 1971-1981, 3,115 persons were bitten by animals and of these animals, 2,880 (92.5%) were dogs (63).

The 135 confirmed animal rabies cases in Jordan in the years 1990-1998 were 9, 7, 24, 18, 23, 15, 19, 10, and 10, respectively. The affected animals were 55 dogs (40.7%) followed by 43 cattle (31.9%), 12 foxes (8.9%), five sheep (3.7%), four camels (3%), four donkeys (3%), three cats (2.2%), two goats (1.5%), two wolves (1.5%), two badgers (1.5%), one monkey (0.7%), one squirrel (0.7%) and one jackal (0.7%). During 1982-1995, 74 (45.1%) of 164 confirmed animal rabies cases were diagnosed in stray dogs, followed by 32 cattle (19.5%), 14 pet dogs (8.53%), 13 foxes (7.92%), eight donkeys (4.87%), four sheep and goats (3.65%), five wolves (3.04%), four camels (2.43%), two stray cats (1.21%), two pet cats (1.21%), two badgers (1.21%), one monkey (0.60%), and one hyaena (0.60%) (1).

The geographical distribution of confirmed animal rabies cases during 1982 -1992 was 54 (32.91%) of 164 reported were in Irbid, 35 (21.34%) in Amman, 27 (16.46%) in Mafrak, 18 (10.97%) in Madaba, nine (5.48%) in Zarka, seven (4.27%) in Ma’an, six (3.66%) in Jordan Valley, four (2.45%) in Tafileh, three (1.83%) in Balka and one (0.61%) in Aqaba.

In the period 1992-1998 when six human cases were reported, 129 cases of animal rabies were diagnosed (119 laboratory confirmed and 10 on clinical grounds only). Again, the most frequently reported species of the laboratory-confirmed cases was the dog (47 cases, 39.5%). Laboratory diagnosis was performed in the Vaccine Institute, Amman, using the FAT.

Animal rabies control

The present control measures against rabies are inadequate. Animals bitten by confirmed rabid animals are destroyed and animals suspected of rabies are placed in quarantine if a station is available. The annual report (5) shows that 478 of 500 dogs (95.6%) had bitten other animals, whereas figures for the following year show that 433 of 554 dogs (78.2%) had done so (6).

To date, vaccination of animals on a compulsory basis is done only in cities, towns and villages. Animals are usually identified after vaccination by a tag, registered and given a certificate. The vaccine is sometimes provided free of charge. In 1994, 549 animals were vaccinated following the vaccination of 620 animals in 1993.

If rabies is diagnosed either in man or in animals, the number of stray dogs and cats in the area is reduced by shooting or by strychnine poisoning. In 1996, 3,981 stray and owned dogs out of 4,093 animals were killed and 1,436 of 2,019 dogs were vaccinated against rabies (7).

With regard to rabies, there are no restrictions on animal importation since the movement of stray dogs and wild animals from neighboring countries into Jordan cannot be controlled.

All unvaccinated domestic animals with clinical signs of rabies which are the origin of a human or domestic animal exposure are killed immediately. An unvaccinated agricultural animal having contact with a rabid animal is either destroyed or quarantined for 6 months; milk for human consumption is discarded unless it is boiled; other animals in contact with exposed domestic animals are vaccinated.

The problem of stray dogs

Precise dog population numbers are not known, but in 1994 it was estimated to be 24,000. Only a minor proportion (less than 5%) of the dogs are owned; the majority can be considered as stray animals.
Due to the religious customs of many people in Jordan, dogs are not allowed to come into close contact to man as they are in Europe or America. Companion animals are not very common in the cities. All Bedouins keep dogs for guarding their flocks and in rare cases dogs are used for hunting.

Mass poisoning of dogs throughout the country, which is practised almost every year, has resulted in the killing of thousands of stray animals. The number of stray dogs killed either by poisoning or shooting for 1991-1994 was 3,296, 4,811, 3,113, and 4,060 respectively.

CONCLUSIONS

The re-appearance of human rabies cases in Israel prompted the Ministries of Health and Agriculture and the National Reserve Authority to reconsider rabies as a priority zoonosis. Active and intensive surveillance is currently being undertaken and budgets have been allocated for research on rabies prevention, especially in wildlife.

Sylvatic rabies is a serious zoonotic problem in many countries of the world, including particular countries in the Middle East. Oral vaccination trials of foxes and jackals are continuing in Israel (41). A successful national disease control programme requires several basic coordinated and scientifically based operative steps. These include the collection, mapping and processing of epidemiological data with rapid dissemination among veterinarians, public health officials, National Parks Authorities personnel, and the general public.

In Israel, control of rabies requires concerted efforts in three areas. Firstly, it is necessary to increase the vaccination coverage of dogs to over 70%, to introduce obligatory cat vaccination and to establish a national register with electronic identification; secondly, to implement an oral vaccination programme for wildlife, which would include monitoring fox and jackal populations; and thirdly, to extend the comprehensive rabies control program throughout the region to include Egypt, Israel, Jordan, Lebanon, Syria and the Palestinian Authority.

Acknowledgments

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References


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CHAPTER 14
RABIES IN NORTH AFRICA AND MALTA

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Summary

This chapter describes the history of rabies and its prevention in the North African countries of Algeria, Egypt, Libya, the island of Malta, Tunisia and Morocco. Limited records, predating the 18th Century, suggest the presence of rabies, albeit rarely, throughout North Africa. However, European immigration, accompanied by the introduction of numerous dogs, profoundly changed the situation. The establishment of Rabies Institutes (including Pasteur Institutes), reflected the increasing problem canine rabies posed in the individual countries and allowed for more accurate data to be obtained. Significant efforts have been made to control the disease in animals by vaccination e.g. under National Rabies Control Programmes (NRCP) or by the culling of stray dogs. However, the control programmes have been hindered or have failed as a result of poor surveillance networks, decentralisation of Veterinary Services, limited funding, underestimating dog populations and a lack of public cooperation.

Keywords: canine rabies, North Africa

ALGERIA

Some historical events related to the history of rabies in Algeria before the 20th Century have been reported earlier (Chapter 2, J. Blancou). Most of the historical information available was carefully recorded by George Fleming, and there are several points of interest regarding the origin of rabies in Algeria (15). The first point had been made clear by Dr Roucher, who was decidedly of the opinion that rabies was not imported into Algeria by the French ‘colonists’, but was indigenous and known at a time prior to 1830 and he stated in 1860 that ‘Algeria is the country for which rabies ..... has a special predilection’. The second point is that the Arabs knew the disease perfectly well. It was observed that the name they gave to rabies and to rabid individuals (mkloub, or ‘changed into a dog’) was proof of this, for it was derived from kelb, dog and mkelb, the mad dog.

Human and animal deaths were also recorded during this period. Among a total of twelve people to have died of rabies in the most distant parts of Algeria during 1844 to 1855, one French soldier died in 1845 and one Arab chief in 1846. From 1857 to 1862, four Europeans in a population of less than 4,000 died at the hospital in Muscara. In 1863, in the city of Algiers and in its suburbs, the Veterinary-Surgeon Decroix recorded 24 cases: 5 humans, 2 cats and 17 dogs.

Human rabies

At the turn of the 20th Century human rabies was common in Algeria. In 1933 alone, 2,512 post-exposure treatments (PETs) were administered. Surprisingly, the percentage of these PETs was ten times higher in Europeans than in the indigenous population, and the percentage of rabies cases three times higher in the
Europeans. According to Curasson, this was due to the fact that the dogs were considered as ‘unclean’ by the Arabs, and usually not welcome inside their villages (13).

The situation became quite different after Algerian independence in 1962. A review of the available data on human rabies in Algeria (8) is summarised in Table 14.1. Dogs were responsible for the largest number of human bites, accounting for 13,723 of 16,389 bites registered from 1970 to 1975 (9).

Table 14.1 – Human rabies post-exposure treatment (PET) in Algeria (6)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments at the Pasteur Institute in Algiers*</td>
<td>1,798</td>
<td>4,063</td>
<td>6,994</td>
<td>4,894</td>
</tr>
<tr>
<td>Estimated number of treatments throughout Algeria</td>
<td>10,287</td>
<td>20,245</td>
<td>37,714</td>
<td>35,843</td>
</tr>
</tbody>
</table>

*: In 1996, the number of treatments reported to the World Health Organization was 7,770

The post-exposure vaccine for humans was prepared from horse brain until 1983, when that was replaced by suckling mice brain vaccine inactivated with β-propiolactone. In 2000, 4,355 persons received this post-exposure treatment, and 922 received an additional therapy with anti-rabies serum (3). The number of human deaths totalled 81 from 1970 to 1975, 371 from 1976 to 1980 and 49 from 1981 to 1984 (8). Twenty two human deaths were reported for the year 1996, and 16 for the year 2000 (2, 3). In 2000, nine of these 16 deaths followed an exposure to dog bites, three to wild carnivore bites, one to a cat bite and three were of unknown origin (3).

Animal rabies

In dogs

In 1933, dogs were responsible for approximately 88% of human exposures (1,185 of 1,347 animal contacts). After the Algerian war of independence (1954-1962), which introduced several cases of rabies into France due to the movements of French troops (Chapter 10, M.F. Aubert et al.), the situation did not really improve. Fifteen years later, a review of the epidemiological situation of rabies in Algeria was presented (7) which can be summarised as follows:

- the disease is widespread in the country, with a high prevalence in the ‘Willayate’ of Algiers, El-Asnam, Tizi-Ouzou, Médéa and Séïf
- the main reservoir of the rabies virus is the dog
- a large number (around 40%) of the post-exposure treatments are related to stray dog bites.

The highest numbers of rabies cases in dogs are reported in May, and the lowest in August. Most of the cases occur in the Willayate of Algiers (more than 100 cases per year), Tizi-Ouzou, El-Asnam and Medea which are situated in the North-Centre of the country (9). In 2000, 348 cases of canine rabies were reported to the Office International des Epizooties (OIE) (4).

As in most of the countries of the Mediterranean Basin, the control of canine rabies is extremely difficult. A significant number of owned dogs are immunised: 87,405 in 1996, as reported to the World Health Organization (WHO) (2) and 76,166 in 2000 as reported to the OIE (4). Nevertheless, these numbers are far below the figures that would be necessary to halt the disease in dogs, the total number of which is probably around four million. Some efforts are also made to control the dog population by stray dog elimination: 10,968 stray dogs were destroyed in 2000 (4).

In other species

Among the species responsible for human exposures in the year 1933, cats were the most common (117 cases) but several herbivores were also involved including twelve donkeys, ten cattle and five horses. Wildlife rabies, at this time, was widespread throughout Algeria and ten monkeys, four jackals and three other wild carnivores were also recorded in the list of biting animals (13).
The numbers of animal rabies cases for selected years in the 1970s and 1980s are shown in Table 14.2. In 1996, the number of animal rabies cases in Algeria, as reported to the WHO, reached 1,129 (826 clinical cases and 303 confirmed in the laboratory) (32). In 2000, the figures reported to the OIE included 68 cases in equines, 60 in small ruminants and 37 in cats (4). There are no attempts to control wildlife rabies, which does not seem to be the reservoir of the disease in Algeria.

Table 14.2 – Animal rabies cases in Algeria in selected years of the 1970s and 1980s

<table>
<thead>
<tr>
<th>Years</th>
<th>1972</th>
<th>1975</th>
<th>1980</th>
<th>1985*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs</td>
<td>98</td>
<td>104</td>
<td>302</td>
<td>163</td>
</tr>
<tr>
<td>Cats</td>
<td>15</td>
<td>12</td>
<td>73</td>
<td>22</td>
</tr>
<tr>
<td>Cattle</td>
<td>10</td>
<td>11</td>
<td>34</td>
<td>43</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>4</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Wildlife</td>
<td>2</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>127</td>
<td>133</td>
<td>425</td>
<td>256*</td>
</tr>
</tbody>
</table>

* : figures for the nine first months only

EGYPT

Although the presence of the disease before the 18th Century cannot be disputed (Chapter 2, J. Blancou), it seems that it disappeared periodically, or became very rare, during that century. The epidemics started again in the middle of the century and Dr Prunel reported four definite cases of hydrophobia in Alexandria: in 1850, 1855, 1856 and 1857. Also in 1857, three other cases were reported by Burguières-Bey at Cairo (15). At the end of the 19th Century, according to Pruney and Piot-Bey, the disease became common in Alexandria and Cairo (13).

Human rabies

There are few reliable records of the figures for human deaths in Egypt at the beginning of the 20th Century. A few human cases were reported in 1904, 1905, 1911 and 1924. In 1925, more cases in humans followed a serious epizootic among animals (see below). At that time a ‘Rabies Institute’ was created in Egypt for PETs and rabies diagnosis. Diagnoses were performed by examination of the suspect brains for Negri bodies and/or by rabbit inoculation: 13 tested positive in 1932 (13). Subsequently the situation worsened, probably due to the growth of the human population and the relaxation of control measures after 1936. The number of human deaths officially reported during the last decades of the 20th Century did not differ significantly. Figures for the 1980s included 39 in 1980, 13 in 1981, 19 in 1982, 41 in 1983 and 41 in 1984. At the end of the 1990s the average number of human deaths reported to the WHO was around 30 to 40 every year and 35 were reported for the year 2000 (3).

Until the 1990s PETs were based on 20 subcutaneous injections of 5 ml of a suckling-goat brain vaccine: 60,000 doses of this vaccine were produced in the Rabies Unit of the General Organisation for vaccines and sera, Agouza, Cairo. A new vaccine, produced in cell culture, was subsequently introduced. Currently, PETs consist of the injection of vaccines produced in embryonated eggs (1,050,000 doses produced in 2000) or in tissue culture (1,000 doses imported in 2000) (4). During the year 2000, the origin of exposure to rabies in humans was mostly dog bites [114,414]. But other species also played an important role: cats (as the origin of 640 post-exposure treatments), ruminants [32] horses and donkeys [1,200], rodents [685] and mongooses [40] (3).

Animal rabies

Dogs

It seems that canine rabies was rampant in the country in the early 1900s. According to de Vregille (1917), two peaks of canine rabies are usually observed in Egypt and Sudan, in March (dog breeding season) and July (hot weather). In 1925, numerous outbreaks were reported in dogs in the two provinces of Darfour and Kordofan, and a huge number of them were killed. Nevertheless, the disease remained unabated in the Egyptian countryside: 340,211 dogs were destroyed in 1929 and 318,055 the following year, in addition to a large number of animals in urban areas (13). In 2000, the number of rabid dogs remained stable, the disease being reported in most parts of the country (4). The canine population in Egypt was
estimated in 1986 to exceed three million stray dogs and half a million owned dogs (16). These figures are probably far below the reality.

The control of canine rabies in Egypt is extremely difficult. Elimination of stray dogs and cats is achieved by direct capture (lassoo) and euthanasia, or by poisoning and shooting. During 1985 a total of 94,689 stray dogs were killed (16) and, during 2000, 316,069 were destroyed according to the annual report received by the OIE (4). Unfortunately, the population of stray dogs has remained stable over the years, due to new births in this population and/or the arrival of unwanted owned puppies.

A small number of owned dogs are immunised: 5,865 in 2000, as reported to the WHO (3). This number is obviously far below the figures that would be necessary to halt the disease in a population of 500,000 owned dogs. The vaccine used for many years to immunise dogs was the Low-egg-passage (LEP) of the Flury strain (23), which has now been replaced by a tissue culture vaccine (3).

Other animals

If dogs account for the majority of human exposures, other species, including wild animals, also play a role in Egypt. In 1917, 4,944 of 5,393 bite victims were of dog origin, 268 of cat and 181 of jackal origin. During the canine rabies wave which raged in 1925, numerous cattle, horses, donkeys and camels were bitten and succumbed to the disease (13). In the year 2000, more than 72,000 cats were destroyed to reduce the risk of transmission of the virus and human exposure and the disease was reported in many wild species, accounting for 1,482 PETs (3).

LIBYA

There have been no cases of animal or human rabies reported from this country for many decades (4).

MALTA

George Fleming was informed in 1847 by his friend Deputy-controller Rogers that rabies had appeared in Malta, supposedly for the first time. It was very serious in its consequences, as several people bitten by dogs and cats perished (15).

Human rabies

No indigenous human rabies cases have been reported for many years in Malta. However, a very small number of rabies vaccine doses for human use are imported every year (82 in 2000) (3).

Animal rabies

No rabies cases in animals have been reported recently in Malta and very few animals are vaccinated, although 100 tissue culture rabies vaccine doses for animals were administered in 2000 (3).

TUNISIA

Rabies has long been endemic to Tunisia and its incidence continues to be high. The dog, as both reservoir and principal vector of the disease, is the major link in the transmission cycle. Costs in terms of human treatment and lives, and economic losses of domesticated animals are also high. The Tunisian battle against rabies began even before the founding of the Pasteur Institute in Tunis in 1893 with the ‘treatment’ of persons bitten by infected or suspect animals (11). Treatment protocols have improved consistently over the years and are now buttressed by measures that aim to reduce and eventually eliminate the disease; however, despite unflagging efforts by the authorities, Tunisia continues to register human and animal rabies cases.

Rabies in Tunisia may be studied in two chronological periods. Prior to 1982, control consisted primarily of PET for persons bitten by a suspected animal but since 1982 PET has been augmented by active rabies
control (principally mass immunisation of dogs, elimination of stray dogs, epidemiological surveillance and health education).

**Rabies in Tunisia prior to 1982**

**Human rabies**

During the first years of French colonial power, foreigners living in Tunisia went to Europe for treatment whenever they were bitten by a suspect animal, whereas very few Tunisians did. In most cases the latter had recourse to home-grown remedies, sometimes combined with traditional rites (11). During 1891-1893, of 23 Tunisians who had been bitten by rabid or suspect dogs and who refused to go to the Pasteur Institute in Paris for treatment, six died of rabies. Between 1886 and 1893, a total of 140 patients were sent to Paris and approximately the same number of Italian nationals went to Sicily. In 1894, the Tunisian government decided to set up an anti-rabies unit linked to the bacteriological laboratory of the Regency of Tunis, created in 1893. The unit began its operations in 1894. Of the 827 individuals treated there during 1894-1901, only 323 were Tunisians (11). The number of consultations grew steadily: 62 in 1894, 1,166 in 1924, 1,872 in 1936, 4,333 in 1959, 4,477 in 1970 and 18,938 in 1981.

Treatment dispensed by the anti-rabies unit, which became the Pasteur Institute of Tunis in 1900 (the third in the world after Paris in 1888 and Saigon in 1895) followed Pasteur’s immunisation protocol (11). The standard treatment lasted 18 days, during which the patient received 16 inoculations. For particularly severe bites or bites over 10 days old, an intensive 23 day treatment was applied (20 inoculations and 3 days of rest). From 1943, Fermi’s phenol-inactivated vaccine with the Tangier vaccine strain was used and, from 1972, lamb instead of sheep brain and ß-propiolactone inactivation were used. From 1977, the Tangier strain was replaced with PV11 which brought permanent improvement to the vaccine quality.

Prior to 1960, the only rabies statistics were those derived from the number of persons given PET after exposure to a rabid or suspect animal, since laboratory diagnostic tests on humans and animals were rarely performed. The steadily growing number of patients receiving treatment was the only means used to estimate the overall rabies status in the country. The number of animal rabies cases grew steadily from 3 to 216 during 1952-1961. Laboratory tests for rabies (mouse inoculation, Seller’s staining and histology) were available by the 1950s and the fluorescent antibody test (FAT) was introduced in 1979.

During 1952-1971, there was a gradual increase in the number of persons requiring PET, but from 1972, as a consequence of decentralisation, rabies treatment was dispensed in district capitals and the increase became substantial (18). During 1973-1977 in one district alone, the number of patients tripled (18), possibly due to growing public awareness of the health hazard that rabies presented. Most treated patients were young (0-15 years) males needing treatment during the hot season of June-August.

**Table 14.3 – Rabies in Tunisia from 1976 to 1999, by six year periods**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs vaccinated</td>
<td>0</td>
<td>159,943</td>
<td>189,276</td>
<td>411,216</td>
</tr>
<tr>
<td>Dogs eliminated</td>
<td>0</td>
<td>30,000***</td>
<td>225,551</td>
<td>34,598</td>
</tr>
<tr>
<td>Animal rabies cases</td>
<td>211</td>
<td>91</td>
<td>265</td>
<td>138</td>
</tr>
<tr>
<td>Canine rabies cases</td>
<td>178</td>
<td>66</td>
<td>176</td>
<td>78</td>
</tr>
<tr>
<td>Percentage of canine cases**</td>
<td>84</td>
<td>73</td>
<td>66</td>
<td>57</td>
</tr>
<tr>
<td>Persons receiving PET</td>
<td>11,644</td>
<td>18,582</td>
<td>26,667</td>
<td>38,969</td>
</tr>
<tr>
<td>Human rabies cases</td>
<td>12-13</td>
<td>4-5</td>
<td>8-9</td>
<td>3-4</td>
</tr>
</tbody>
</table>

*: annual means

**: among all animal rabies cases

***: estimated number

Human rabies evolved along much the same lines as in animals. Between 1960 and 1981, the annual average number of human rabies cases was 15 and were mostly those who either did not receive PET, or
received inadequate treatment. The number of human rabies cases increased significantly between 1966 and 1975 (annual average of 22 cases) but fell during 1976-1981 to an annual average of 13 cases (Table 14.3).

Animal rabies

By calling rabies ‘kleb’, a word etymologically related to ‘kelb’, the word for dog, Arabs tacitly acknowledge the importance of dogs in its transmission cycle. The link between rabies and dogs has been confirmed by statistics of the Pasteur Institute in Tunis. Data for 1961-1970 show that up to 86% of bites, 86% of vaccine treatments and at least 91% of human rabies cases originated from dogs. During 1961-1980, dogs were responsible for 84% of medical consultations for rabies, followed by cats (8%) and herbivores (6%). Cats usually contract rabies as the result of an encounter with a rabid dog. Data from the Pasteur Institute, Tunis, for 1961-1980 shows that cats were responsible for only 8.1% of medical consultations for rabies while domestic herbivores (bovine, equine, ovine, caprine and camellidae) were responsible for 6.2% of persons receiving PET (11).

Tests conducted in 1960 did not detect the virus in 90 bats, ten jackals and two foxes. No virus was found in 1,900 sewer rats (1,841 captured and 71 found dead) in Tunis. Three cases of rabies in rodents (two in 1988 and one in 1992) have since been reported. During 1961-1987, only 5 of 129 wild animals that had bitten humans were positive for rabies. It therefore remains to be proven that non-domestic animal species constitute a rabies reservoir.

Rabies control in animals

Five decrees relative to rabies control were promulgated prior to 1982. The last of these, in 1966, amended and completed those of 1931, 1925 (inspired by Charles Nicolle), 1916, and 1885. These decrees contained draconian measures but were publicly acceptable. From 1931 to the end of 1941, 3,981 dogs received primary vaccination, 1,472 were boosted, 64 were vaccinated post-exposure and 105 herbivores were also given post-exposure vaccine. The 1952 decree of the Ministries of Public Health and Agriculture authorised the Pasteur Institute in Tunis to produce the Plantureux formalin-inactivated anti-rabies vaccine for use on animals. However, some of the measures provided for by the above decrees were never fully implemented and thus, except for those few dogs that received vaccination at their owner’s request, animal rabies evolved without control at the national level.

Rabies in Tunisia since 1982

A six-year national rabies control programme (NRCP) began in 1982. Its objective was the elimination of canine rabies and the risk of infection for other animals and humans (5). Operations started in a pilot zone and were extended to the rest of the country. A maintenance phase was planned for 1988 onwards and at this time a stringent surveillance network was established, with decentralised laboratories for the diagnosis of animal rabies, and a medical and preventive health care programme focusing on potential outbreak sites.

Human Rabies

There were 75 cases of human rabies in the six years prior to the NRCP (Table 14.3) but during the six years of the NRCP, the number of cases did not exceed 29 (6). Regression of human rabies occurred during the programme (10 cases in 1982 to one in 1987 and none in 1985). During the six years following the NRCP, the annual average was eight to nine cases, but during 1994-1999 only 21 cases were diagnosed, with the maximum (7) in 1996. One further case was diagnosed in 1998 and another in 1999. For the entire period 1982-1999, the annual average was five to six cases of human rabies, significantly lower than the mean for 1960-1981 (14 to 15 cases). Unfortunately, human rabies statistics for the first nine months of 2000 are not encouraging, with two cases in humans and 215 cases in animals, of which 143 were in dogs (Mejri, personal communication).

During the NRCP, 111,494 persons received PET, i.e. an annual average of 18,582. This shows a slight increase over the 88,804 (14,801 average) registered during the six years prior to the NRCP (Table 14.3).
In the six years after the NRCP (1988-1993), 160,007 persons received PET (annual average 26,668) and during 1994-1999, 233,816 persons were treated (annual average 38,969) (Table 14.3). Thus, the number of persons treated increased considerably during 1982-1999. This may be explained by growing public awareness, by the greater number of rabies treatment centres (which increased from 170 in 1986 to 236 throughout the country in 1989), and by the fact that the Tunisian population has practically doubled during the past 30 years. Regional committees to monitor rabies control were set up in 1992 and certainly improved the effectiveness of the measures.

The vaccine used after 1977 was PV11 in lamb brain, inactivated with β-propiolactone and lyophilised (6). However, a high incidence (2.5%) of neurological complications was observed. Therefore, the virology department of the Pasteur Institute (Tunis) produced a cell culture vaccine appropriate for human use (RABICELL®) and since 1996 it has gradually supplanted the use of lamb brain vaccine.

Animal Rabies

During the NRCP years (1982-1987), a total of 959,658 dogs were given either primary vaccination or a booster (6). Vaccination campaigns took place during April to June and on average 160,000 dogs were vaccinated annually (Table 14.3). During 1988-1993, 1,135,656 dogs were vaccinated, i.e. an annual average of 190,000 dogs and during 1994-1999 2,467,201 dogs, i.e. an annual average of 410,000. But the annual average for the entire period of active rabies control (1982-1999) was little more than 250,000 dogs, far short of the NRCP target of 75% of the dog population. Throughout the NRCP, an average of 30,000 dogs were eliminated annually and during 1988-1999, 530,000 stray dogs were eliminated.

During the NRCP period there was a significant decrease in the rabies incidence in animals – in 1982, 181 of 232 cases were in dogs, whereas in 1986 dogs caused 36 of 51 cases (6). Throughout the period the annual average number was 66 dogs of 91 cases. From 1985 however, the number of cases of animal rabies stabilised, particularly for dogs. Although in 1988 the incidence of animal rabies was the same as during the NRCP years, during subsequent years it grew steadily, from 40 cases (33 dogs) in 1988, to 581 cases (356 dogs) in 1992 (the highest level ever). This upsurge might have been due to an epidemic of foot and mouth disease in 1989 and brucellosis in 1990 that defocused efforts, cut budgets earmarked for rabies control and limited the availability of dog vaccination teams. Further elements included the decentralisation of veterinary services, organisational and financial difficulties, as well as inadequate quality of the vaccine protocol.

Faced with this alarming situation, the authorities set up an interdepartmental anti-rabies commission with representatives from the Ministries of Agriculture, Internal Affairs and Public Health. This commission was entrusted with several tasks: the organisation of mass canine vaccination campaigns to be conducted annually instead of biannually; the introduction of a faster information system and more accurate estimations of the canine population based on the results of research in Tunisia. Thanks to these measures the proportion of persons receiving PET among those who had been bitten increased and the vaccination coverage in dogs improved. The incidence of animal rabies was lowered to 192 cases in 1993 (113 dogs), a trend that continued until 1995, with 79 cases of animal rabies, (63 dogs). Since then, the incidence has again increased, reaching 175 cases (104 dogs) in 1999, and 214 cases (142 dogs) to September 2000.

Detailed studies of the ecology and biology of canine populations were conducted during 1986-1990 in different regions of the country in accordance with WHO guidelines on canine rabies control (20, 19, 31). They provided information on parameters that are important to the planning of vaccination campaigns for various habitat types (Table 14.4). Dog population density varies enormously according to the type of habitat (rural, semi-rural and urban) and the inhabitants’ cultural and socio-economic status. The average number of dogs per household is much higher in rural (1.3-2.2) than in semi-urban (0.3-0.8) and urban areas (0.1-0.3). The average age of owned dogs varies between 1.8 and 3.3 years. These are very low values in comparison to those noted for Europe (Switzerland) or the United States of America (USA), where the average age is approximately 4.5 years. Only 12% of Tunisian dogs are over five years old, while 21% are less than one year old. The latter value is important in assessment of vaccination campaigns, since they would not be included. Dog population annual turnover is high. For owned dogs it is 23% in rural areas, 30% in semi-urban areas and 40% in urban areas. Thus, over half the dog population is replaced, generally by unvaccinated juvenile dogs, every two years. Most dogs in Tunisia do have an owner, but ownerless
dogs represent 5%-15% of the total dog population. However, the level of dog supervision varies enormously between habitat types: 58%-65% in rural areas, 43%-50% in semi-urban areas and 35% in urban areas. In one rural area, 75% of the dogs were never tethered.

Table 14.4 – Characteristics of the dog population in Tunisia

<table>
<thead>
<tr>
<th></th>
<th>Rural</th>
<th>Semi-urban</th>
<th>Rural density (all dogs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Density (owned dogs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogs km⁻²</td>
<td>7.28</td>
<td>842-1,140</td>
<td>738</td>
</tr>
<tr>
<td>Habitants per dog</td>
<td>3.5</td>
<td>9-16</td>
<td>46</td>
</tr>
<tr>
<td><strong>Density (ownerless dogs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogs km⁻²</td>
<td>1</td>
<td>70-162</td>
<td>52</td>
</tr>
<tr>
<td>Habitants per dog</td>
<td>50</td>
<td>61-189</td>
<td>655</td>
</tr>
<tr>
<td><strong>Age structure (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 3 months</td>
<td>6.0-17.8</td>
<td>9.4-20.2</td>
<td>12.9-18.8</td>
</tr>
<tr>
<td>3 to 12 months</td>
<td>11.8-14.0</td>
<td>15.6-17.5</td>
<td>14.1-23.2</td>
</tr>
<tr>
<td>More than 12 months</td>
<td>70.4-79.4</td>
<td>64.2-73.1</td>
<td>58.0-73.0</td>
</tr>
<tr>
<td>Mean age</td>
<td>2.7-2.8</td>
<td>2.4-3.3</td>
<td>1.8-2.7</td>
</tr>
<tr>
<td><strong>Confinement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free-roaming owned dogs (%)</td>
<td>58.4-65.1</td>
<td>43.5-50.2</td>
<td>35.4</td>
</tr>
<tr>
<td>Free-roaming dogs km⁻²</td>
<td>8.8-28.7</td>
<td>387.6-442.4</td>
<td>242.9</td>
</tr>
<tr>
<td>Annual turnover (%)</td>
<td>36</td>
<td>27-37</td>
<td>27-37</td>
</tr>
<tr>
<td>Accessible to parenteral vaccination (%)</td>
<td>66.0</td>
<td>71.3</td>
<td>67.1</td>
</tr>
</tbody>
</table>

Rabies control in dogs

Immunisation of the canine population is a major element of any campaign to combat animal rabies. Its positive impact was demonstrated during the NRCP years and after a new outbreak of rabies in 1992.

Studies conducted to evaluate the accessibility of dogs to parenteral vaccination showed that in a rural environment, approximately 85% of three-month and older owned dogs were accessible and in urban and semi-urban areas this rate reached 90%. Dogs accessible to parenteral vaccination represented 65-70% of the overall canine population. Other studies conducted during the mass vaccination of dogs showed vaccination coverage of 87%-91% in densely settled areas and of 65%-72% in rural areas (farms and isolated douars).

Ben Youssef and colleagues tagged vaccinated dogs prior to a dog population census. They showed that vaccination coverage was low, hardly exceeding 50% in areas where people were insufficiently informed and vaccination centres relatively distant. In the converse situation, coverage reached 83%. Reasons for low vaccination coverage included absence or lack of cooperation of dog owners, owned-dog aggressiveness and a high proportion of ownerless dogs. Studies confirmed the importance of annual vaccination, benefits of vaccinating very young puppies and that most dogs respond to vaccine, even though in Tunisia they are frequently infected by parasites, undernourished, produce lower antibody titres and respond less well than laboratory dogs or for example dogs living in France.

Ownerless dogs and owned dogs that cannot be approached easily for parenteral vaccination can be orally vaccinated. Preliminary studies in Tunisia compared the effectiveness of various types of vaccine-baits and bait delivery systems (distribution to owners, door-to-door to dogs, wildlife immunisation model). Chicken-head baits proved the most effective. Distributing baits to dog owners in local distribution centres made it possible to reach 95% of dogs, including dogs which could not be approached, and dogs which had an owner but roamed free; although this method depended heavily on owner cooperation. A drawback was that people might inadvertently have come into contact with the virus. A bait uptake rate of about 60% was observed when baits were presented to owned dogs by the vaccination team (door-to-door). Finally, bait distribution according to the wildlife immunisation method reached 42% including free-roaming owned and ownerless dogs. However, this method is expensive. Studies of different vaccines
that can be used orally for dogs have been conducted in Tunisia and have shown that they are effective and innocuous.

Rabies control measures must be evaluated and rabies incidence assessed, and the establishment of an epidemiological surveillance network is crucial. However, Tunisian epidemiological surveillance has not been sufficiently developed and the decentralised rabies diagnosis system has many gaps. If there is no local diagnostic centre, rabid or suspect animal samples are sent for diagnosis only in cases involving human exposure. Rabies monitoring could be improved by means of the straw sampling method and a greater number of decentralised diagnostic centres. As long as there is no epidemiological surveillance network, the incidence of Tunisian animal rabies will continue to be underestimated.

MOROCCO

Historical overview

‘If one is to believe popular tradition and prescriptions by the ‘toubibs’ (medical doctors) and charlatans, rabies, or saar (rabies in Arabic) has always existed in Morocco, albeit occurring only very rarely. Also, despite the large number of Kabyle dogs (populating the mountains), whose movements have in no way been restricted, only a few sporadic cases of rabies were reported before the beginning of the 20th Century. European immigration, however, and French and Spanish immigration in particular, was accompanied by the introduction of numerous dogs into the country, which profoundly changed the situation.‘

It is in these terms that Remlinger and Bailly (1933) described the situation of rabies in Morocco (26). In fact, reports of animal rabies increased dramatically at the beginning of the 20th Century. While in 1920 there were 21 cases of rabies, 233 cases were reported in 1931. A tenfold increase within just a few years! As a consequence of the terrible dog rabies epizootics that ravaged Western Europe throughout the 19th Century, health legislation was rigorously administered. Moreover, in 1885 Louis Pasteur developed the first anti-rabies vaccine for humans. Anti-rabies vaccines (attenuated by the use of phenol, formic acid or ether) were produced at the same time for preventive veterinary use. However, in the early 20th Century, some time passed before the effectiveness of these vaccines was recognised, while the effectiveness of analogous vaccines for human use after Pasteur was never challenged.

The fight against rabies in Morocco was initiated in 1911 when the Pasteur Institute of Tangier was founded, under P. Remlinger MD. He had distinguished himself in the field by demonstrating, with Riffat-Bey in Constantinople, that it was possible to filter the rabies virus (24). From 1913 to 1965 the work in Tangier of Remlinger and his co-worker, the veterinary doctor J. Bailly, focused on virology, epidemiology, clinical medicine, and the prophylactic treatment of rabies (25, 27, 28). The Pasteur Institute of Tangier grew into an international centre for the research, diagnosis and production of anti-rabies vaccines, both for veterinary and human use (29, 30). In the meantime, in order to meet the needs of Morocco with regard to vaccines and anti-rabies treatment, the Pasteur Institute in Casablanca was created (under the French Protectorate) and in 1967, the two Institutes were joined to form the Pasteur Institute of Morocco.

Prior to 1932, there were seven anti-rabies treatment centres, one each at Rabat, Larache, Ceuta, Melilla and Villa Sanjurjo and two in Tangier. In 1951, another centre was created at Oujda and a further one at Marrakesh in 1956. Subsequently, numerous regional treatment centres sprang up, facilitating access for the rural population. In 1932, it was decided to create the Veterinary Diagnostics and Research Laboratory in Casablanca, under the Ministry of Agriculture, where the majority of diagnostic experiments on animal rabies were carried out until the early 1980s. The 1980s saw the decentralisation of experimental diagnostics of animal rabies, when the Ministry of Agriculture decided to establish regional laboratories at Tangier, Fez, Oujda, Marrakesh, Agadir and Rabat. The Rabat laboratory was established in 1984 but ceased its activity in rabies diagnostics in 1995.
Human rabies

Incidence

The most seriously affected regions are located in the south and north: Souss Massa-Draa, Marrakesh, Tensift, El Haouz, Taza, Al Hoceima, Taounate, etc., with 112 human cases since 1986. These regions represent a significant rural population. During 1932-1963, the rabies-related deaths of 162 individuals were reported, 49% of whom were children aged 8-15 years and the majority bitten by dogs (21, 22). From 1951 to 1963, five cases of human rabies following jackal bites were recorded. During 1965-1970 the number of human cases averaged 24 annually and during 1973-1988, 465 persons died of rabies, an annual average of 36 cases.

In the 11 years since 1989, the 236 human cases represent an annual average of 21 cases. This reduction overlapped with a period of serious drought, which led to a significant rural exodus and changing urban boundaries. In 92% of all human rabies cases reported between 1993 and 1995, the victims received no PET. Among the reported cases, 68%-80% were of rural origin and 77%-88% were infected by dogs. In 48% of these cases the dog’s owner was known. Of the victims, 68% were male, mostly 5-14 years old, or elderly men.

Vaccines for human use

At the Casablanca Pasteur Institute the classical Pasteur method of desiccated and glycerinated spinal cords was exclusively used between 1932 and 1939. In the course of 1939, vaccination by phenol-inactivated vaccines prepared on rabbit brain was applied for the first time in 215 individuals. This method was again adopted from 1943 onwards, but used Fermi-Kasauli’s modified technique. The vaccination protocol foresaw a daily series of 15, 21 or 25 injections, depending on the seriousness and location of the bite(s). Doses varied from 5-10ml, averaging 7ml, with children receiving half this dose. Until the end of the 1950s, the phenol inactivated dog-brain vaccine produced at the Pasteur Institute of Tangier from 1937 onwards was also used in Morocco. Like the vaccine for veterinary use, this vaccine was used in humans after its safety had been established in guinea pigs. Immune globulin was first used in Morocco in 1955. Hyper-immunised horse serum titred in rabbits was successfully used from 1955 to 1959, after which time preference was given to the purified, concentrated serum from Institut Pasteur, Paris.

A vaccine produced in human diploid cells, with six injections, was used from the late 1970s onwards. Since 1989, rabies PET centres have used Vero cell vaccines produced by ‘Vaccins Pasteur’, with four or five post-exposure injections, depending on whether or not the biting animal was known or available for observation. Treatment is free of charge, costs are borne by local communities and immune globulin is given in cases of serious exposure.

Post-exposure prophylaxis

The first vaccinations took place in 1911 when the Pasteur Institute of Tangier was founded and from 1932 to 1952, 24,204 patients were treated. A statistical study of biting animals between 1952 and 1963 showed that dogs were responsible for 85% of the bites, followed by cats, equines, and rats. The number of reported rat bites increased from 52 (0.43%) between 1932 and 1944, to 102 (0.8%) between 1945 and 1953, and to 502 (2.29%) between 1953 and 1963. From 1977 to 1994, the number of PETs remained almost unchanged despite the decentralisation of anti-rabies centres and an annual average of 11,000-12,000 persons were treated. Currently, there are some 50 centres, as against a mere seven in 1932. However, the majority of treated patients are from urban environments, which means that there is still a lack of treatment centres in rural areas. Of all treated individuals 68% are male, aged 15 and older. Biting animals are essentially dogs (76%), of which only 40% are owned, as well as cats (5%-10%), and rats (5%-20%). It is important to emphasise that not a single case of human rabies was due to a rat bite.
Animal rabies

The evolution of animal rabies

The epidemiological situation has not changed since the beginning of the 20th Century (Table 14.5). In fact, for 1920-1931, in cattle stations at Sfrou, Berkane, Rabat, Salé, Marrakesh, Oujda, Agadir, Machraa Belksiri, Fez, Taza and Meknes, 1,234 cases of animal rabies were recorded by Remlinger and Bailly in 1932. Of these, 1,043 (84.5%) were dogs. Domestic herbivores, mostly bovines but also equines, and porcines were their chief victims. Possible infection of bovines by rabid jackals, foxes, hyenas, wild boars and monkeys was signalled in certain provinces. Jackals, which are less timid and more resourceful than foxes, were more likely to attack herds.

Table 14.5 – Summary of reported cases of rabies in Morocco, 1920-1999

<table>
<thead>
<tr>
<th>Years</th>
<th>Domestic carnivores</th>
<th>Domestic herbivores</th>
<th>Wildlife species</th>
<th>All animal cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1920-1931</td>
<td>1,055*</td>
<td>117*</td>
<td>65*</td>
<td>1,237</td>
</tr>
<tr>
<td>1932-1942</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>1943-1950</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>1,866</td>
</tr>
<tr>
<td>1951-1960</td>
<td>2,191**</td>
<td>316**</td>
<td>5</td>
<td>4,270</td>
</tr>
<tr>
<td>1961-1970</td>
<td>2,789</td>
<td>622</td>
<td>10</td>
<td>4,825***</td>
</tr>
<tr>
<td>1971-1980</td>
<td>2,419</td>
<td>883</td>
<td>12</td>
<td>4,821/5,811****</td>
</tr>
<tr>
<td>1981-1990</td>
<td>476</td>
<td>493</td>
<td>10</td>
<td>4,204</td>
</tr>
<tr>
<td>1991-1999</td>
<td>350******</td>
<td>353******</td>
<td>7******</td>
<td>3,384</td>
</tr>
</tbody>
</table>

N.D. : no data
* : not laboratory confirmed
** : no data for 1959
*** : no data for 1970
**** : divergent data in source documents
***** : no data for 1998 and 1999

From 1943 to 1999, 24,058 animal rabies cases were reported, an annual average of 422, ranging from 112 in 1947 to 805 in 1978, although there is some discrepancy in reporting for that year. Only 40 of the 24,058 cases were in wildlife species, including 12 jackal and five fox cases, indicating that wildlife species play only a minor role in rabies in Morocco. Up to 1980 there was a steady decrease in reports of rabies in carnivores and in 1980, 1986, 1990 and 1991, herbivore rabies cases exceeded those in carnivores. At first sight this is a paradox, but the situation was probably due to an under-reporting of cases of dog rabies in rural areas, where herbivores, bovines in particular, live in close proximity to dogs, as well as equines, asses and, small ruminants. Observed seasonal variations are closely linked to the reproductive cycle of dogs. Animal rabies occurs twice as often in May as in October, increasing again in December. These peaks follow the autumnal and spring periods of sexual activity in female dogs.

Diagnosis

Experimental diagnoses of animal rabies were first carried out at the Pasteur Institute of Tangier until 1953, as well as, from 1932 onwards, at the Pasteur Institute of Casablanca and at the Laboratoire d’Analyses et de Recherches Vétérinaires of Casablanca. From 1951 to 1958, Chevrier (12) noted 2,181 positive samples. His approach was essentially histopathological, searching for Negri bodies. Reports of rabies virus isolation in Tangier in 1952 were made by Remlinger et al. (29) and in Casablanca by Chevrier (12) and by Noury (22). More recently, the majority of animal rabies cases are confirmed by laboratory tests (Table 14.5). In the six diagnostic laboratories, trained and experienced veterinary staff perform immunofluorescence tests (FAT) to detect rabies antigens. Occasionally the rapid rabies enzyme immuno-
diagnosis (RREID) test and inoculation of suckling mice are used, but at high cost. Histopathology and examination for Negri bodies have largely been abandoned (14). Studies of apparently healthy dogs carried out in 1985 and 1986 in three heavily infected regions (Casablanca, Rabat and Kenitra) confirm the seriousness of the epidemiological situation. The pathogenicity of canine rabies virus isolated in Morocco is high (1 LD\textsubscript{50} dog\textsuperscript{10^{-0.9}} = 0.3LD\textsubscript{50}/IC mouse). Typing by monoclonal antibodies from canine rabies strains reveals a virus of serotype 1 (14).

**Dogs as the principal reservoir and vector**

Animal rabies is endemic throughout the country but 80\% of cases occur in rural areas, as in Algeria and in Tunisia. Dogs play a major role as reservoir and vector of the disease, due to the existence of a significant number of inadequately vaccinated dogs in rural and peri-urban areas. Consequently, incidence rates of canine rabies are not only high in provinces with an important rural population such as Agadir, Taroudant, Taounate, Kenitra, Sidi Kacem, Settat, and Beni-Mellal, but also in rural communities on the periphery of large built-up areas, such as Oujda, Rabat, Casablanca, and Fez. Unvaccinated free-roaming dogs are responsible for the persistence of the disease, for the spread to domestic herbivores and the origin of more than 70\% of human rabies cases.

The most recent human population census in Morocco (in 1994) counted 28 million inhabitants, 50\% of whom live in rural areas (1). Assuming a ratio of five inhabitants per dog, the canine population in rural areas probably reaches 2.8 million. Socio-ecological studies have shown that the majority of these dogs do have an owner, that their numbers are quite stable and that they are accessible to vaccination campaigns.

**Rabies in wild animals**

Throughout the 20th Century, sporadic cases of rabies have been reported involving jackals, foxes, monkeys, panthers, wolves, wild boars and anthropophilic rodents. Since the 1980s, rabies in jackals, foxes, and wild boars has occurred every year in the eastern and southern regions of the country. Between 1932 and 1963, five human deaths following bites by rabid jackals were reported; during the same period bites by 706 rats, 60 monkeys, 15 rabbits, six panthers, four foxes, and two hyenas were also cited (22). During 1971-1983 rabies was isolated in six rats by the Laboratoire d'Analyses et de Recherches Vétérinaires and the Pasteur Institute of Casablanca and in 1973-1986, 11 cases of rabies, of which nine were laboratory confirmed, were reported in rats and mice that had bitten humans. However, many more recent and extensive studies have failed to detect the virus in rodents and Chabaud, quoted by Hamdoun (17), found no rabies virus in chiroptera in the Rif, the Middle and the High Atlas where bats are living in great numbers (17).

**Rabies control**

**Regulation**

The prevention of rabies based on health and medical methods goes back to the beginning of the 20th Century and is derived from a number of Orders by the Vizir, the first of which was laid down in 1914. Sanitary regulations are now based on the notification of rabies cases, the immediate culling of carnivores following contact with rabid animals, the obligation to keep dogs on a leash and for all dogs to wear a collar with an inscription stating its owner’s name and address. Preventive vaccination of owned dogs older than three months was made compulsory only in 1986. However, these regulations proved effective only in urban areas since culling of stray dogs and surveillance of dogs by their owners was only applicable to dogs within the urban perimeter. As a consequence of the harmonisation of health and medical control measures, which were made virtually obligatory for dogs after 1953, the city of Tangier was free from animal rabies by 1955. Although rural dogs were the principal reservoir and vector of the virus, rural stray dogs were only culled if they had been declared rabid. This changed from 1986 onwards, when the National Rabies Control Programme (PNLR) was in place, and campaigns for the culling of stray dogs were also organised in rural areas.
Vaccines for veterinary use

In Morocco, the first rabies vaccine for veterinary use, prepared on rabbit brain and inactivated by ether, was developed by Remlinger at the Pasteur Institute of Tangier and used from 1925 onward (25). However, high production costs led Remlinger and Bailly in 1928 to substitute rabbit with dog brain. In 1936, ether was replaced by phenol-inactivation. The vaccination protocol was modelled on that for the former ether inactivated vaccine. Injections were always subcutaneous; doses were identical, 40ml for dogs and 10ml for cats, with one primary vaccination and annual boosters. This phenol inactivated dog brain vaccine was used until the late 1950s. From the end of the Second World War until the 1970s, the vaccine produced by the Pasteur Institute of Casablanca on sheep brain was a Fermi vaccine, according to the method of Fermi-Kasauli. From the late 1970s until the inception of the PNLR in 1986, vaccines for animal use in Morocco were β-propiolactone inactivated cell cultures, with primary vaccination (two injections) and annual boosters. Since 1986, adjuvanted cell culture vaccines, with primary vaccination (one injection) and biannual boosters, have been applied. An adjuvanted cell culture vaccine was approved in 1999.

The National Rabies Control Programme

From 1925 to 1953, 86,047 animals were vaccinated, 84,242 (98%) of which were dogs. According to Chevrier (12) the number of dogs vaccinated annually varied between 7,000 and 15,000. Vaccinations were, however, chiefly applied in urban areas. Between 1942-1963, 200,000 dogs were vaccinated in provinces other than Tangier.

In 1982 a PNLR was established in collaboration with the Mediterranean Zoonosis Control Programme of the WHO (10). The PNLR had two objectives: to reduce then eliminate canine rabies within seven years (1986-1992) and to keep the country free from rabies after programme completion. The programme was to run in five chronological stages corresponding to five geographical areas. The canine population was estimated at 1.5 million, of which 30% was stray dogs. The plan envisaged the elimination of 450,000 dogs, 300,000 of them in rural areas, and the vaccination of 900,000 owned dogs older than three months using an adjuvanted cell culture vaccine. Costs of DH47 million were estimated, comprising DH27 million for health prevention and DH20 million for medical prevention; funding was essentially from national resources. However, the PNLR must be considered a failure since 184 cases were reported in 1996, as against 228 in 1985 and the number of human cases was little changed (Table 14.6).

Table 14.6 – Dog rabies control and human rabies deaths in Morocco, 1986-1998

<table>
<thead>
<tr>
<th>Year</th>
<th>Dogs vaccinated</th>
<th>Dogs culled</th>
<th>Dogs rabid</th>
<th>Human deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>N.D.</td>
<td>35,000</td>
<td>232</td>
<td>21</td>
</tr>
<tr>
<td>1987</td>
<td>14,717</td>
<td>32,139</td>
<td>194</td>
<td>28</td>
</tr>
<tr>
<td>1988</td>
<td>150,000</td>
<td>73,570</td>
<td>334</td>
<td>27</td>
</tr>
<tr>
<td>1989</td>
<td>200,000</td>
<td>258,254</td>
<td>192</td>
<td>17</td>
</tr>
<tr>
<td>1990</td>
<td>25,000</td>
<td>77,768</td>
<td>115</td>
<td>16</td>
</tr>
<tr>
<td>1991</td>
<td>N.D.</td>
<td>50,661</td>
<td>157</td>
<td>18</td>
</tr>
<tr>
<td>1992</td>
<td>N.D.</td>
<td>79,433</td>
<td>211</td>
<td>20</td>
</tr>
<tr>
<td>1993</td>
<td>250,000</td>
<td>65,986</td>
<td>167</td>
<td>24</td>
</tr>
<tr>
<td>1994</td>
<td>300,000</td>
<td>62,579</td>
<td>150</td>
<td>23</td>
</tr>
<tr>
<td>1995</td>
<td>264,739</td>
<td>74,425</td>
<td>167</td>
<td>29</td>
</tr>
<tr>
<td>1996</td>
<td>0</td>
<td>92,356</td>
<td>184</td>
<td>18</td>
</tr>
<tr>
<td>1997</td>
<td>0</td>
<td>59,562</td>
<td>188</td>
<td>21</td>
</tr>
<tr>
<td>1998</td>
<td>21,729</td>
<td>55,224</td>
<td>227</td>
<td>20</td>
</tr>
<tr>
<td>Totals</td>
<td>1,016,957</td>
<td>2,518</td>
<td>282</td>
<td></td>
</tr>
</tbody>
</table>

N.D. : no data

In essence, the considerable prophylactic effort did not lead to the expected results because one or two preparatory stages of paramount importance for such a programme were neglected.

The importance of the socio-ecological aspects of canine populations was underrated, leading to the underestimation, in rural areas, of dog populations requiring vaccination, and to an excessive number of dogs culled. This error was all the more regrettable since studies in various regions showed that in rural areas an important proportion of the dog population was actually owned and that it would have been preferable to vaccinate these dogs rather than to kill them. Rural inhabitants were inadequately informed and educated with regard to the objectives and modalities of the PNLR, hence their lack of interest in the programme.
CONCLUSIONS

Canine rabies continues to be a threat to human health throughout northern Africa. There have been considerable efforts made to combat the disease including through PNLRs. However, mistakes were made, especially where public awareness and dog population estimates were concerned. For example, the reasons for the low vaccination coverage in Tunisia, included the absence or lack of cooperation of dog owners, owned-dog aggressiveness and a high proportion of ownerless dogs. These problems were mirrored during the PNLR in Morocco. Lessons must be learned from these campaigns to ensure that future programmes are successful. An efficient surveillance and diagnostic network is essential in all countries implementing control programmes, to monitor the ongoing success of the campaign and, to ensure that the incidence of rabies is not underestimated.

References


CHAPTER 15

EPIDEMIOLOGY AND ECOLOGY OF FOX RABIES IN EUROPE

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Summary

An attempt is made to link epidemiological observations on the 20th Century fox rabies epizootic with information on rabies virus biology and fox ecology. It is essential for rabies survival that an infected fox transmits the virus during a period of excretion to an appropriate number of susceptible individuals. For this to occur, lyssavirus strains must be adapted to the physiological traits and population biology of their hosts. They must have a host specific pathogenicity and pathogenesis. During the passage from the site of entry through the central nervous system to the salivary glands and into the next susceptible individual, viruses may also experience a number of population bottlenecks and subsequent clonal growth under different selective constraints, during which they must maintain their genetic integrity and overall adaptation to their host's biology. Attempts to interrupt the disease transmission within fox populations have had variable success. It was exceedingly difficult to reduce fox population densities to levels at which social transmission networks ceased to operate. In contrast, it appeared relatively easy to vaccinate a sufficiently large proportion of foxes to interrupt the spread of the disease, a finding that was predicted intuitively.

Keywords: epizootic, rabies, raccoon dogs, red fox

INTRODUCTION

Rabies was seen predominantly in domestic dogs in past centuries, though there is a sufficient number of reports indicating wildlife involvement. The disease disappeared from large areas of Europe in the first decades of the 20th Century for reasons that are not fully understood. During the Second World War a new rabies epizootic began spreading from Russia and Poland toward the West. The majority of cases were observed in red foxes (Vulpes vulpes). For a while there was some debate as to whether this species was really responsible for the maintenance and spread of the disease, or if it was only the predominant victim or sentinel of an epizootic carried by another species. The hypothesis that the principal host species was to be found among the rodents had considerable support (95), especially from epidemiologists in Eastern Europe, while the idea that small mustelids were the real culprits was imported from North America (63). Investigations in the late 1960s and early 1970s did not bring substantial evidence for such claims. To the contrary, epidemiological analyses, laboratory studies, and modelling suggested that the recent rabies epizootic in Western Europe was propagated and maintained by a single species, the red fox (Vulpes vulpes) (2, 26, 104, 120). This statement is not necessarily correct for eastern and northern Europe, where Arctic foxes (Alopex lagopus) and introduced raccoon dogs (Nyctereutes procyonides) may be implicated in sustaining the chain of infection. This chapter focuses on the association between Vulpes vulpes and rabies virus in Europe.

THE RED FOX IN EUROPE

The species Vulpes vulpes is a small canid of 4.5 to 8 kg body weight. Males are 10% to 20% larger and heavier than females. Red fox morphology and biology are described in some detail (7, 70, 117), the ecology and population biology of red foxes in North America is summarised by Ables (1) and Storm et al. (98). A female fox is called a vixen; a male fox is often called a dog fox.

The species is widely distributed over temperate and subarctic regions of the Northern Hemisphere (42, 117) and also in Australia, where it was introduced in 1864 (70). Red foxes exploit a wide variety of terrestrial habitats from the seashore to alpine meadows, including peri-urban and urban developments.
Population densities in rural areas of Europe are estimated to be mostly between 0.4 and 1.8 adults km\(^2\) (70, 99, 110). Density assessments are based on extrapolations from hunting records, litter observations, radio-telemetry studies, or a combination of different methods and their accuracy is not very high. Relative densities and distribution were studied using questionnaire surveys (87), spotlight sightings (82) and standardised hunting (21). A tracking station methodology developed in the USA for estimates of coyote densities (73) has been used for foxes in Europe with limited success (5, 17, 29). The treatment of hunting records as indicators of population densities and dynamics must be viewed with caution. Hunting pressures change with the chances of hunting success (55, 91) and with the presence of diseases (rabies, sarcoptic mange) in the target population.

Observations on fox nutrition, particularly on the identifiable components of fox faeces, abound in the mammalogical literature (70, 85, 86, 92, 117). Foxes are omnivorous and opportunistic in their diet selection. In densely populated and developed Europe, foxes scavenge primarily on the refuse of farms and households (116). Rodents, primarily of the genera *Microtus* and *Arvicola*, rank second even in rural areas, at least in studies that are based on stomach content analyses. Rabbits are a frequently consumed prey where and when they are available (43, 70). Foxes prey on ground-dwelling birds, including domestic chickens. The impact on prey populations is sometimes considered significant (78, 94). Earthworms and insects are eaten frequently and occasionally in great amounts in summer and autumn. Fruit (mostly cherries, plums, prunes) and berries are consumed in large quantities when available.

The reproductive biology of European red foxes is fairly well understood (4, 6, 80, 102, 109). Red foxes are seasonal breeders and have one litter per year. Spermatogenesis intensifies in late autumn or early winter in the north of Europe, later than in more southerly regions (71). The oestrus usually lasts a few days. Mating takes place mostly between mid-December and March. In continental Europe about 90% of vixens examined during March and April are either pregnant or lactating (72). Cubs are born after a gestation of 51 to 53 days, mostly between mid-March and mid-April, in southern latitudes earlier than in northern, and at lower elevations earlier than in the mountains (71). The number of implanted foetuses recorded in pregnant vixens varies between 1 and 12, at an average of 5.4 in Switzerland, 6.2 in Bavaria, 6.0 in the Netherlands and 5.5 in Wales (72). The average litter size as observed in dens in the Canton of Bern in Switzerland is 4.67 cubs. This is significantly lower than 5.20 foetuses per pregnant vixen recorded in the same geographical area (120). Very large numbers of cubs are likely to be the pooled offspring of two (related) vixens. Reproductive performance varies with food availability in areas where foxes depend on less consistent resources, such as the cycling rodent and lagomorph populations in subarctic Scandinavia (44, 45). In the Swiss plateau area, the cubs are raised in earth dens, probably mostly dug by badgers (*Meles meles*). In more mountainous areas, natural caverns and the spaces under raised wooden floors of traditional farm buildings are more frequently used (110). Newborn foxes are without teeth, with closed eyes and ears, and a dark grey to brownish woolly fur. Birth weights are between 90 and 120 gm. The eyes open after two weeks. The first milk teeth erupt around day 18, the last ones at day 26. Cubs receive milk for their first few weeks, but they are also provided with solid food (rodents, lagomorphs, birds) from approximately three weeks of age. From April to July the cubs gain approximately 200 gm per week. They reach sexual maturity at approximately 10 months. Foxes ear-tagged as cubs and released at the capture site are usually recovered less than 1 km away from the tagging location during summer and early autumn. Sub-adult foxes emigrate from their parents’ home range between mid-September and the end of October. Recovery of foxes ear-tagged as cubs is then usually more than 3 km from the tagging site. The distribution of dispersal distances is skewed; most animals move less than 10 km, fewer between 10 and 50 km (46, 48, 62, 70, 77). Dispersal distances over 50 km are observed only rarely. Male foxes travel on average longer distances than females. Lloyd (70) suggests links between home range occupancy, mortality, and dispersal patterns. Carr and Macdonald (31), Doncaster and Macdonald (41), Trewella et al. (106), and in a more general context Gittleman and Harvey (52), discuss the interrelationships between habitat (resource distribution and density), social organisation, and dispersal. Higher resource densities permit higher population densities, resulting in smaller home ranges and shorter dispersal distances.

The social use of space by foxes appears to be highly flexible. Studies in North America (90) and in rural areas of Europe (81) suggest that adult foxes live in pairs with their young of the year in exclusive territories or only slightly overlapping family home ranges. Investigations in urban and suburban Britain paint a different picture. Here, foxes may roam in non-exclusive home ranges (58) or may form adult territorial groups rather than monogamous pairs (39, 40). Dominance hierarchies are established within...
social groups. Macdonald (74, 75, 76) observes that in the extended groups not all adults reproduce, and that non-breeding vixens help to care for the cubs of the dominant female. However, post-mortem examinations of vixens during the reproductive season indicate that non-breeding females are rare in rural Britain and in continental Europe (72).

A number of publications describe the age and sex composition of foxes collected in particular areas and under particular circumstances. The prenatal sex ratio is 1:1. Males predominate between 3:2 and 6:5 over females in most samples of sub-adult and adult foxes (72). Males prevail also among rabid foxes collected in winter in Switzerland, while female rabid foxes predominate in summer samples. The relatively high rate of reproduction suggests that the population turnover is rapid (99, 100). This appears to be confirmed by the large proportion of young animals among killed foxes. From early autumn to early spring samples of foxes killed by hunters and trappers typically consist of 60%-70% animals below one year of age (44, 57, 70, 111). Using the annual cement deposit layers on the roots of teeth for estimating ages one finds individuals up to about 12 years old. However, these are rare exceptions. There are significant problems with the interpretation of such data (111). The fact that samples grouped according to causes of death differ significantly in age structure and sex composition may indicate that sampling techniques are non-random. More important is the observation of an equally high proportion of the youngest age class among foxes killed in winter as that just after whelping, which suggests the unlikely conclusion that cub mortality is less than that of adults.

A large number of mostly canine infectious and parasitic diseases have been documented or suspected to occur in foxes. However, in recent decades only rabies and sarcoptic mange were seen to cause significant mortality. Other significant mortality factors are road traffic, hunting and trapping, and possibly intentional poisoning where this has not been outlawed. The parasite fauna of the species is quite well known (19, 24, 54). The occurrence of Cestoda is in good correlation with the frequency of prey species consumed and their infestation with larval stages (116). The widespread occurrences of *Echinococcus multilocularis* and *Trichinellaspp.* are of zoonotic importance.

**The behaviour of rabies viruses in individual foxes: pathogenesis**

The pathogenesis of rabies has been studied in experimentally infected laboratory rodents, and to a lesser degree in its principal carnivore hosts. Recent reviews of rabies pathogenesis (12, 33, 53, 60, 105, 107) link molecular biology, immunohistochemistry, and pharmacobiology to clinical disease. Rabies has a peculiar pathogenesis that is characterised by virus dissemination within nerve fibres rather (69) than by blood and lymph, the rapid expansion of the infection within the central nervous system (CNS) after a variable, but generally long incubation period, virus excretion in saliva towards the end of the incubation period, and the almost invariably fatal outcome of the CNS infection.

Rabies virus may be transmitted by several different means among mammals. Inoculation of infective saliva by bite is viewed as the predominant method of rabies virus transmission. This mode of transmission depends on close social encounters that may be triggered by the abnormal behaviour of the infected animal. Rabies virions are unable to penetrate intact skin, but they may infect mucous membranes. Infection by ingestion is therefore possible (16, 27, 34, 88). Yet, foxes are at least 100,000 times less susceptible to oral challenge than to intramuscular injection with European fox rabies isolates (27, 96). The susceptibility of different species experimentally exposed to rabies virus aerosols is high (123). Infectious aerosols have been observed only under exceptional circumstances in a North American cave harbouring extremely large numbers of bats (37) and in laboratories when they have been either deliberately or accidentally created (124, 125).

Red foxes are highly susceptible to virus injected by the intramuscular route (18, 27, 83, 96, 126). Sikes (93) demonstrated marked differences in susceptibility to intramuscular injection of street rabies isolates among North American mammals. The virus doses necessary to successfully infect 50% of the inoculated animals was less than 5 MicLD₅₀ for foxes, 500 MicLD₅₀ for skunks, 1,000 MicLD₅₀ for raccoons, and more than 80,000 MicLD₅₀ for opossums. Several authors confirmed the very high susceptibility of red foxes to American and European fox rabies isolates injected into the masseter or neck muscles (18, 23, 27, 96). Choosing a different inoculation site, Winkler et al. (126) were unable to induce disease in foxes given
250 MicLD<sub>50</sub> into the gluteal muscle. The outcome of exposure is not only dependent on the host species and the inoculation site, but also contingent on the properties of the infecting virus variant. Foxes were susceptible to low doses of a canine rabies virus from North Africa, but resisted the injection of higher doses and became immune in experiments conducted by Blancou et al. (25). Parker and Wilsnack (83) found that foxes and skunks were equally susceptible to a skunk isolate. The basis for species differences in susceptibility and how susceptibility is linked to specific properties of virus variants is not understood. Baer et al. (11) postulated that the abundance of nicotinic acetylcholine receptors at the entry port could explain the contrast in susceptibility between opossums and foxes. Blancou and co-workers (22) established the susceptibility of a number of European wildlife and domestic species to European fox virus. It is remarkable that the red fox is followed in susceptibility by species that only play insignificant roles in the epidemiology of rabies in Europe, such as the European hare (Lepus europaeus).

The time between exposure and first appearance of clinical signs of disease may range from days to years, but the majority of incubation periods observed after experimental inoculation are between three and six weeks (27, 83, 93). The length of the incubation period is inversely related to the amount of virus injected, and depends on the virus variant and possibly other properties of the inoculum, such as the presence of non-infectious rabies virus antigen and defective interfering particles. It is probably influenced by characteristics (innervation) of the inoculation site. By injecting a standardised inoculum at a well-defined site, it is possible to obtain reproducible incubation periods in foxes (27). However, surgical inoculation of very low doses into a single long digital extensor muscle still resulted in very variable incubation periods in striped skunks (35).

At the inoculation site virus replication can be detected in myocytes or in other cells. It is unclear if this is a necessary step before the virus gains access to the nervous system or if direct entry into peripheral nerves is the rule (32). That the virus binds with its glycoprotein trimers to nicotinic acetylcholine receptors is well documented (12), but it is also clear that these cannot be the only binding sites controlling rabies pathogenesis (33, 105). After experimental inoculation transport to the CNS may occur in motor and/or sensory fibres (33, 69). The transport of rabies virus in peripheral nerves is via the axons by retrograde axoplasmic flow. It is generally assumed that combined active and passive immunisation very shortly after exposure mediates the elimination of the virus before it enters the nervous system. In laboratory rodents it is possible to interrupt the transport to the CNS by amputation of the inoculated limb or by neurectomy within a short period after inoculation (13).

In the CNS the virus replicates in the cytoplasm of neurons. In the perikaryon of infected neurons accumulations of nucleocapsids can be seen as the pathognostic Negri bodies. Other cell types are only sporadically infected. The transmission of virus from one neuron to another is probably mostly by budding, followed by endocytosis on or near synaptic junctions (34). There is also some virus budding into the intercellular space. Viral dissemination within the CNS is due mainly (exclusively) to retrograde axonal transport (69). The pathology and the distribution of rabies virus antigen in the CNS are well described (32, 84). Antigen distribution is quite variable. It depends on the stage of virus dissemination within the CNS, but also on the site of inoculation and possibly on the infecting virus variant, and may also be more visible in certain (large) cells. The clinical signs resulting from CNS infection are certainly the expression of damaged neuronal functions. However, not all behavioural changes are easily explained by the areas of the CNS most obviously affected.

The period from the first clinical signs until death is relatively short in foxes. Sikes (93) reported morbidity periods of one to three days, Richards (89) five to 13 days, Parker and Wilsnack (83) one to 17 days, and Atanasiu et al. (8) one to nine days. In all studies short morbidity periods are common, while long ones are the exception. Clinical signs are variable (51, 89, 101, 126). The observable disease in experimentally infected foxes may begin with loss of appetite, loss of characteristic activity patterns, hyperactivity, tremor, hypersensitivity, increased and abnormal sexual behaviour, or sudden aggressiveness. Aggressiveness is not always prominent. Convulsions and paralysis are common late signs. They lead to death almost without exception. Disease-related alterations of social interactions and territoriality in free-ranging foxes is incompletely understood. Foxes inoculated with rabies, radio-collared and released at the site of capture changed their activity patterns a few days before their death, but died within or not far from their original home range (3).
Virus replication in the CNS proceeds to a centrifugal spread of the infection to peripheral organs. Again the virus moves passively inside axons. Rabies virus antigen can then be detected in most organs (14, 34, 38). Often it is limited to nerve fibres and ganglia. Replication in extraneuronal tissues is evident in salivary glands, in some other exocrine glands, adrenals, and occasionally in other organs such as tonsils and cornea. A possible connection between non-nervous tissue infection and virus excretion by clinically healthy ‘carrier state’ animals and survivors of CNS infection is discussed by Fekadu (49). Naturally infected rabid foxes, badgers (*Meles meles*), and stone martens (*Martes foina*) collected in Switzerland all yielded between $10^{3.5}$ and $10^{4.5}$ MicLD$_{50}$/g of brain tissue, while there were remarkable species differences in salivary gland infectivity. In 93% of the rabid foxes and in 83% of the rabid badgers virus was found in submandibular salivary glands, with median titres of approximately $10^5$ MicLD$_{50}$/g of tissue. In comparison, only half of the rabid stone martens had infected salivary glands with a low median titre of $10^3$ MicLD$_{50}$/g of tissue (119). Because of its neuronal spread, it is very unlikely that virus reaches the salivary glands before having replicated in the brain. However, salivary gland infection and virus excretion are occasionally seen in experimental cases before clinical signs become obvious (23).

In foxes and most domestic animals there is usually no measurable immune response to rabies during incubation, except when animals are inoculated with relatively high doses (including massive amounts of dead antigen) of a virus variant adapted to a different species (25, 59). Several factors may contribute to the suppression of measurable immune responses: low antigenicity of the inoculum and rapid sequestration within peripheral cells and nerves, the immunosuppressive effects of rabies virus (122), the immunodepressive effects of saliva (108). A measurable immune response is probably induced only when a large number of infected cells exhibit viral antigen on their surface and virions are released into the intercellular space. This does not happen before the virus starts to replicate in the CNS. Then, antibody and cellular immunity may become detectable. Animals and humans surviving clinical disease or who are chronically infected exhibit high antibody titres, not only in sera, but also in the cerebrospinal fluid (15, 49, 50). The scarcity of documented survival of clinical disease in experimentally and naturally infected animals contrasts with frequent reports of neutralising antibody in sera collected from wild animals in North America (30). There are several possible explanations:

a) the survival of clinical disease in nature is more common than implied from observations of domestic animal and experimental wild animal rabies, this being probable in some species such as bats and Caribbean mongoose (see below)

b) the antibodies are not the result of clinical rabies, but reflect the immune response to abortive peripheral infection and other (oral) exposure to rabies antigen

c) the observed neutralising or haemagglutination inhibiting activities are not specific or not even due to antibody. A comparison of rabies virus neutralising properties of sera from foxes from rabies-infected and rabies-free zones in Switzerland indicates that animals acquiring immunity during an outbreak, including survivors of clinical disease, are indeed rare in this species (119).

**Rabies in fox populations**

While rabies was seen predominantly in dogs in earlier times, red fox rabies emerged as significant epizootics in Europe and North America in the middle of the 20th Century. In North America the spread was predominantly north to south, in Europe it was east to west. The viruses circulating in European and in North American fox populations are distinct, though both are members of the ‘cosmopolitan branch’ (Chapter 19, Nadin-Davis *et al.*). The features of the epizootic expansion in Western Europe have been described and analysed by numerous authors (28, 68, 79, 96, 104, 118). Initial outbreaks lasted for about one year, usually followed by a period of several months to two years with no reported cases, and then by an oscillating prevalence over many years. These patterns varied from area to area (61). It should be noted that any observed prevalence pattern is highly dependent on the size of the geographical window through which an epizootic wave is moving. The hugely popular epidemiological compartment models (2) have ignored the spatial dynamics of the disease and have provided, therefore, only incomplete explanations of prevalence patterns.

As long as the epizootic was expanding, it had the following characteristics:
– the first rabies cases recorded in newly affected areas were almost always in foxes
– the epizootic front advanced in a wavelike fashion with a speed of approximately 25-60 km per year
– frontwave advances were usually preceded by a high case density in the area of origin (28)
– the case density in newly affected areas was usually very high (up to 5/km²/year)
– in areas with good surveillance foxes constituted between 60% and 85% of all diagnosed rabies cases of the initial outbreaks
– during an outbreak about 86% of the foxes killed because of abnormal behaviour were rabid, while rabies virus as the aetiologic cause was found in only 60% of abnormal badgers (Meles meles) and 21% of diseased stone martens (Martes foina)
– larger rivers, lakes, and high mountain chains functioned as obstacles to the spread. Rivers were usually crossed where bridges were available
– intensive fox destruction campaigns may have stopped the spread in a few privileged locations. That rabies did not invade the Danish peninsula is probably the result of successful fox population reduction
– where rabies alone, or in combination with fox control, brought fox population density below a certain level, rabies disappeared not only in foxes, but also in all other species (except bats). In Germany and Switzerland this low density threshold is reflected by 0.3 or fewer foxes killed by hunters per km² and per year (96)
– the progress of epizootic waves came to a standstill in areas where a proportion of the fox population was immunised through oral vaccination (9, 67, 97, 112, 114, 121). However, the progression also stopped in northern Italy and in the middle of France without any significant disease control interventions.

Rabies prevalence in animals sent to diagnostic laboratories and the spread into previously uninfected areas were at a minimum in April, May and June (28), immediately after the whelping season, when fox population densities reach their annual peak. This coincides with the observation that the youngest age categories were significantly under-represented among foxes diagnosed rabid from April to September; that is, during a period when they comprise the bulk of the population. In addition, only small proportions of young animals submitted for diagnosis in spring and summer were found rabid. They reached adult levels of infection only in late autumn (96, 119). Male animals almost always prevailed among rabies-negative foxes, only being a majority of rabies-positive cases in winter. In summer the Swiss Rabies Centre received greater numbers of rabid vixens (66).

**Fox rabies virus in other species**

In Western Europe, case clusters suggesting chains of intraspecific transmission were occasionally seen in badgers (Meles meles), the only species other than red fox perceptibly reduced in population density by the epizootic. The east Asian species, raccoon dog (Nyctereutes procyonides), that is expanding its range from an area of introduction into the western United Soviet Socialist Republics in the first half of the 20th Century, is likely to share responsibility with the red fox for the spread of the disease in northern and Eastern Europe (36). Similarly, the arctic fox (Alopex lagopus) and domestic dogs appear to participate with the red fox in the propagation of arctic rabies or ‘Polar madness’ (64, 65), though the epidemiology is not well understood in these thinly populated areas with incomplete surveillance.

Rabies is detected with different frequencies in a wide variety of other species. Such cases are usually in close spatial and temporal proximity to fox rabies cases, but often separated from other occurrences in the same species. The incidence of rabies in particular species is dependent on their susceptibility and the probability of potentially infectious encounters. Animals that inspect or attack a paralysed fox, such as roe deer, cattle and other domestic ruminants, are more prominent in rabies statistics. Highly susceptible European hares (Lepus europaeus) are hardly ever found rabid, possibly because they manage to avoid contact with abnormally behaving foxes, a species they usually experience as a predator.
One may wonder why some carnivores, such as domestic cats and dogs, badgers, martens and weasels play only insignificant roles in maintaining and spreading the disease. Stone martens (*Martes foina*) and free-roaming farm cats at least, reach population densities that equal or exceed those of red foxes (113). The combination of high susceptibility and high frequency of profuse excretion with saliva that facilitates transmission in foxes may be absent in these species (20). In the other species the population structure (contiguity, metapopulation structure), population dynamics, and behavioural traits may not be conducive to virus circulation.

**A brief comparison with rabies epizootics in a few other species**

Probably under the influence of the pioneering work of Keith Sikes (93) and Parker and Wilsnack (83) on the high susceptibility of foxes and skunks to rabies viruses propagated by these species in North America, we speculated that rabies virus adaptation to its principal hosts is always characterised by high pathogenicity and high levels of virus excretion in saliva. This concept was reinforced by observations on the European fox rabies epizootic. Jean Blancou and his team at the ‘Laboratoire d'études et de recherches sur la rage et la pathologie des animaux sauvages’ in Nancy, France, established the susceptibility of, and the rate and magnitude of virus excretion for, many European species. They found that the red fox has indeed the highest susceptibility to the European fox rabies virus. However, when inoculated with a North African dog rabies virus, red foxes may develop immunity, rather than disease. Rabid foxes also excrete more virus in their saliva than do most other rabid animals infected with the European fox virus. From these observations the French team developed the concept of viral biotypes. A particular biotype is a virus variant adapted to a particular principal host species by especially high pathogenicity for this species, by a high rate of excretion, and by low immunogenicity (22). In addition, the high efficiency of transmission and the high lethality does not generate any substantial herd immunity (119, 120). We might be tempted to view rabies viruses as perfectly adapted to persist in large populations of species with high intrinsic growth rates, that are capable of recovering rapidly after an epizootic wave has reduced the population density to a level at which the reproductive rate of the disease (disease transmission) falls below unity. This appears to fit well with the observation that the Carnivora serving as principal hosts all have similar life history traits and population characteristics. Red foxes, jackals, domestic dogs, striped skunks, and raccoons are all opportunistic, medium-sized species with a wide distribution and contiguous populations of relatively high density. They also have high reproductive rates that permit rapid population recovery.

We attempt to explain the epidemiological patterns of fox rabies with the very high transmissibility (high susceptibility and high rate of excretion) and high lethality. Also, using such disease characteristics and parameters of fox population biology and ecology in theoretical models can result in plausible outcomes (10), (Chapter 21, S. Harris et al.). However, this type of association between a parasite and its host is fairly uncommon. One might expect to observe other blueprints for rabies virus survival in other host species. This is fairly obvious for species with completely different life history traits such as bats (Chiroptera), but important digressions can also be found in Carnivora.

A significant deviation from the high susceptibility pattern is exemplified by raccoon rabies in eastern North America. Raccoon rabies emerged in the early 1950s in Florida and is spreading along the Atlantic coast and through the Appalachians northward. A distinct rabies virus variant is propagated in raccoon populations. One has to inoculate over \(10^8\text{TCID}_{50}\) by the intramuscular route to achieve 80% mortality in raccoons. This is a striking difference to red foxes, which need less than \(10\text{ TCID}_{50}\) for a lethal infection. One may speculate that not every encounter between a rabid and an uninfected raccoon results in disease transmission, and that the low susceptibility is keeping the transmission rate in balance with the behavioural ecology and population biology of this species.

While the biotype concept stipulates that a virus adapted to its host species achieves a high efficiency of transmission and high lethality and does therefore not generate any substantial herd immunity, this is not necessarily true in all situations. A well-described example is mongoose rabies in the Caribbean. Small Indian mongooses (*Herpestes auropunctatus*) were introduced from South Asia into the Caribbean islands in the second half of the 19th Century for rodent control in sugar cane plantations. They were recognised as important rabies vectors in the 1950s (103). Everard and co-workers documented a correlation between the number of diagnosed rabies cases in mongooses and the prevalence of rabies antibodies in this species.
on the island of Grenada (47). One may speculate that the observed pattern of susceptible, infected, and immune individuals is reflecting a configuration that permits the persistence of the virus-host association in these island host populations of limited size.

High transmissibility and high lethality as seen in fox rabies in Western Europe are not indispensable preconditions for the continued existence of rabies viruses. We also should keep in mind that the high pathogenicity/high susceptibility, high susceptibility/high excretion, low immunogenicity/low survival triad, does not cover all virus adaptations necessary for the survival of a virus in a species with a habitat-dependent population density, turnover and structure; and with specific patterns of behaviour and social interaction.

**INTERPRETATION AND CONCLUSIONS**

It is essential for rabies survival that an infected fox transmits the virus during a period of excretion to an appropriate number of susceptible individuals. For this to occur, lyssavirus strains must be adapted to the physiological traits and population biology of their hosts (10, 113, 115). They must have a host-specific pathogenicity and pathogenesis (length of incubation period, duration and magnitude of virus excretion, duration and extent of clinical illness). During the passage from the site of entry through the CNS to the salivary glands and into the next susceptible individual, viruses may also experience a number of population bottlenecks and subsequent clonal growth under different selective constraints, during which they must maintain their genetic integrity and overall adaptation to their host’s biology.

While the population biology of rabies virus clones in individual hosts and in host populations is hardly understood, one may venture into an interpretation of the epidemiology. Attempts to link epidemiological patterns with fox population parameters have been the primary topic of many attempts to model the virus-host association (2, 10) (Chapter 21, S. Harris et al.). Rabies transmission is usually thought to be density-dependent, though one may easily conceive scenarios that are mostly density independent. Density dependence can explain the observed prevalence oscillations. The deterministic prevalence models make no attempt to explain spatial dynamics. However, field observations show that rabies epizootics move slowly across the countryside in a wave-like fashion, rather than having synchronised incidence undulations over large areas. Field data from well-surveyed areas indicate that the disease invades vulnerable fox populations by transmission from an infected individual to its susceptible neighbour, rather than through regular dispersal movements or disease-induced long distance journeys. Radiotelemetric observation of rabid foxes and the peculiar age and sex distribution patterns suggest that foxes occupy their regular home range during the incubation period. When they become clinically ill, they may venture into their neighbours’ ranges or otherwise provoke a hostile encounter with a nearby resident fox. Adults, and in particular offspring-defending females in summer, are obviously more likely to attack an abnormally behaving intruder, while juveniles or sub-adults may avoid such contacts.

The epizootic wave leaves behind a largely depopulated area in which rabies prevalence is very low or nil. Low fox population density rather than high herd immunity explain the disease disappearance. Reduced fox populations recover within two to three years, making them vulnerable to disease reinvasion. The non-synchronous rates of population recovery and disease re-invasion are mirrored by temporal prevalence patterns that vary from location to location. The spatial variation is, in our interpretation, a reflection of habitat conditions dictating varying fox population characteristics (social use of space), though spatial rabies virus variation causing distinct disease patterns cannot be fully discounted. The asynchronous or chaotic prevalence patterns behind the front-wave are probably a significant basis for the prolonged persistence of the disease in larger areas.

Attempts to interrupt disease transmission within fox populations have had variable success. It was exceedingly difficult to reduce fox population densities to levels at which social transmission networks ceased to operate. In contrast, it appeared relatively easy to vaccinate a sufficiently large proportion of foxes to interrupt the spread the the disease, a finding that was predicted intuitively.
References


CHAPTER 16

DOG RABIES, PAST AND PRESENT, IN THE MEDITERRANEAN BASIN

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Summary

The Mediterranean is an area of recorded ancient history, and from the beginning we find rabies mentioned by poets or described by scientists. Of course, the presence of rabies requires the presence of its natural hosts, canids. Throughout the Mediterranean Basin cases of rabies have decreased to the present time. In some countries rabies has been eliminated; in some control measures are underway, and in others, where financial resources are limited, the aim is co-existence with rabies with minimal consequences. It is therefore improbable that rabies-free status will be extended to all regions of the Mediterranean Basin. This chapter will use the Mediterranean Basin as a scenario, and its history as a background, in order to try to understand the evolution and the present situation of rabies in the area.

Keywords: dog, Mediterranean, rabies

INTRODUCTION

In the Mediterranean the most frequent host of rabies was the dog in its different forms (domestic, semi-domestic and wild), always in close contact with humans. We estimate that in 12,000 years there have been approximately 500 human generations and 3,000 dog generations.

Despite being a highly fatal disease, which might have threatened the survival of the host species, rabies virus has been able to survive throughout history because of some limiting factors, i.e. difficult transmission (limited to bite, not always efficient) and a long incubation period. It may be presumed that in 12,000 years about 150,000 passages of rabies virus have taken place. The occasional infection of man may be considered an accident in the life cycle of the virus as man is a dead-end host for rabies.

THE MEDITERRANEAN BASIN – THE SCENARIO

The Mediterranean basin, i.e. the scenario of our analysis, has general features which led it to be considered a focal point for zoonoses, rabies included, as reported in a publication by the World Health Organization (WHO) Mediterranean Zoonoses Control Centre. The area extends over a surface of approximately 8,000 km in length and 5,000 km in width. Nowadays, it comprises some 30 countries with approximately 400 million inhabitants. The number of dogs is calculated to be 35-45 million, with a similar figure for cats.

Wild canids are present in all areas: wolves are rare and live in limited territories; jackals and foxes are numerous and widespread. In northern Europe foxes are associated with wildlife rabies (2, 4, 6, 8). Within the region, six major climatic types are found as are different environmental zones, with conspicuous differences in rainfall (from less than 500 mm to more than 1,000 mm annually). The climatic sectors alternate with and repeatedly cross well-defined macro- and micro-flora and fauna. Both extensive and intensive agriculture are traditionally practised. Agricultural activities began in the Mediterranean approximately 7,000 years ago and appear to have led to a variety of practices associated with epidemiologically important elements: such as trade, urbanisation and the development of armies. Also, important human movements (migrations, tourism, pilgrimages...) have occurred and are occurring in the
region, often involving movements of dogs (and cats). One form of migration is transhumance, in which seasonally moving flocks are followed by dogs (also wolves, jackals and foxes).

In addition, the Mediterranean has been the cradle of three of the major monotheistic religions, and of enlightened thought. These elements, which are consistent with civilisation in the Mediterranean, accepted the presence of dogs and their control (in case they should prove harmful). In general, religions have allowed (in some cases tolerated) human-dog coexistence, neither favouring the proliferation of dogs nor opposing their destruction. In many instances enlightened thought favoured the application of scientific findings (vaccination, epidemiology). Recently, trends favouring animal protection have emerged. Dogs have been allowed to maintain sufficient numbers and freedom of movement to sustain a rabies enzootic. However, with regard to rabies, no objections were raised against control measures based on a reduction in dog numbers.

The Mediterranean proved to be a suitable area for the coexistence of different ecological environments, populations, animals of different species, pathogenic agents and susceptible populations. Since the beginning of Mediterranean history, dogs have lived with humans and have been selected for special roles such as hunting, guarding and attending sheep flocks, and cattle or pig herds. We know also about free-living dogs, including those which had access to unburied cadavers or abandoned infants. Pastures have always been a source of food (placentae, dead animals) and consequently a meeting point for dogs and wild canids. It should be appreciated that some confusion would have existed over the correct identification of canid species among the dogs, wolves and jackals (sometimes also foxes). In addition, it should be considered that, while we know about those dogs which lived with humans, no information is realistically available on free-living dogs. Limited data might be obtained from indirect, mostly literary sources.

EARLY TIMES – THE EMERGENCE OF THE PROBLEM

Even if very few reports are available, we may deduce that free-living dogs, were present in ancient times, along with domestic dogs, remembered for their services and fidelity to humans. One of the rare references to free-living dogs comes from Egypt and dates to approximately 2000 BC: ‘Wild, semi-wild and vaguely domesticated dogs roam in the desert, in the fields and on the roads. According to an officer assigned to a far post, the only living things are flies and dogs. There are 200 large dogs and 300 wolf-dogs, total 500, ready to attack man...’.

High dog numbers and their migration probably existed in the entire Mediterranean Basin throughout the ancient and middle ages until modern times, with variations in different areas, sometimes influenced by epidemics of canine distemper. We have no documentation on the variations in canine populations caused by changes in human populations, agriculture or forestry. Some confusion between free-living dogs, wolves, jackals and occasionally foxes has occurred and surely still occurs.

Homer (9th Century BC) seems to refer to rabies when, in Iliad, Hector insults Teucros and calls him a ‘rabid dog’. Plautus (11 BC) writes in Menaechmi (scene V) ‘He stated his wife was rabid like a dog’. The disease is also cited in the Bible (Chapitre 13, B.A. Yakobson et al.). Dog rabies was known long before human rabies (credible reports of canine rabies date back to 900 BC, whereas rabies in man was first described only in 377 BC). Democritus (5th Century BC) defines rabies in dogs as an ‘inflammation of nerves’ and does not mention human rabies. Also Xenophon (385 BC) describes only canine rabies in Anabasis (Chapter 1, J. Neville).

Rabies was very widespread and many writers such as Virgilius (71-19 BC) and Juvenal (1 AD) mentioned it. Most of the regions pertaining to the Roman Empire of those times were affected by rabies. However, according to Dioscorides, Rufus of Ephesus and Paul of Aegina, rabies was especially frequent in countries ‘with extreme climate, hot in summer and very cold in winter’, i.e. those sited in the northern part of the Mediterranean. It is possible that movements and concentrations of wild canids in search of food in winter favoured an increase in cases of rabies.

The physician Athenodon affirms that rabies was frequent in Italy in Asclepiades’ times. Artemidorus of Cidas and Aridreas of Carest (2nd Century BC) described human rabies. As to the nature of rabies, the
disease was long considered as being of supernatural origin because of its pathology and terrifying signs. This is why, perhaps, some physicians (before Erophilus and Erisistratus) did not attempt to prescribe treatments. The Alexandrian physicians were the first to have a ‘scientific’ view of rabies: Andreas of Caristes called the disease *kynolyssa* to stress that transmission occurred through the dog; Demetrius of Apamea knew about hydrophobia but mistook rabies for dyspepsia and classified it among chronic diseases. The Alexandrian School discussed the precise seat of the ailment. Gaius (disciple of Erophilus) recognised the importance of nervous disturbances; Gaius’s theories were accepted by most physician disciples of Asclepiades, the founder of Methodism.

Hydrophobia remained the main sign and the others were not taken into consideration. The seriousness of the disease in the dog was known, and Columella said it is ‘almost invariably fatal’. The first vague parasitic theory comes from Pliny; he calls rabies ‘*lyssa*’, a Greek word which means ‘rage’, ‘fury’, ‘frenzy’, but also ‘worm’.

In ancient times prevention and treatment of rabies were based on measures consistent with the culture of that period. Many internal and external substances were used to attempt a therapy, such as the excrement of hen, hyena and seal; gentian, sage, rosemary, thyme, aloe and leek; pieces of swallow nests; snake skin boiled in wine with male crayfish... It is possible that some of these remedies proved ‘successful’ as a consequence of the low transmissibility of the disease.

Mass reduction in dog numbers to control rabies has been applied since ancient times. The inhabitants of Delos, after the death from rabies of Trasius, son of Anius, king and priest of Apollo, ordered the complete destruction of dogs. In Argos, during the dog-days, a festival called Kynophontides was celebrated, during which all dogs were killed. It is possible that these practices, together with cynophagy and common dog diseases have contributed to the control of dog populations and therefore limited the incidence of rabies.

In the Middle Ages, no relevant contribution came from Arab, Byzantine or Christian medical professions. The only possible changes (we have no documentation) might have come from ecological and/or social changes influencing human-dog relationships. Following the customs of the time, and considering the failure of the therapy and prevention of the disease, the Catholic Church appointed saints as protectors against rabies and other associated ailments. Some of these saints are still worshipped in some areas. The most important of them, especially in Italy and France, are Saints Antonio, Benedetto, Domenico, Rocco, Hubert and Valentino.

**THE RENAISSANCE AND THE EIGHTEEN CENTURY – DISCOVERING THE AGENT**

During the Renaissance, Hieronymus Fracastorius (1478-1553) opened up new fields in epidemiology, proposing an advanced theory on contagious diseases and their transmission. In his *De contagione et contagiosis morbis*, Chapter 10 is dedicated to rabies, and the mode of infection and the prolonged incubation period are well described. This was the beginning of a very slow change in the attitude of scientists and the general public. Important research demonstrated the infectivity of the saliva of dogs and other animals, developed vaccines, and eventually demonstrated the filterability of the virus.

The changed attitudes of the general public and public administrators were verified by a series of edicts which contained prescriptions on dog welfare, and the control of dangerous and rabid dogs. An example is given of an edict issued in Mantova (Italy) in 1811: ‘No dogs are allowed in the streets unless kept on the leash. They must wear a collar bearing the name and surname of the owner. Guard dogs and aggressive dogs must be kept on the leash or left free only within the premises or dwellings of the owners. All dogs found without collar and free-roaming guard dogs will be killed. Any person who knows of a dog or any other animal affected by rabies or showing obvious signs of the disease must notify the Authorities. All shops along the streets (groceries, pharmacies, etc.) must keep a container with fresh clean water at dogs’ disposal’.
Until the 18th Century, public health problems, including animal diseases, were dealt with by the Public Health Authority. The borderline between medical and veterinary problems, both from the cultural and the professional points of view, was extremely uncertain with regard to epidemiological and public health problems. The opening of Veterinary Schools provided cultural and human backgrounds for a more specialised approach. This created the basis for the establishment of official Veterinary Services, which extended their activities to Veterinary Public Health. The attention given to zoonoses (especially rabies) control, confirms both the evolution and the level of concern for public health, on the part of Veterinary Services (1, 7). Dog control was also applied in cases of human plague and epidemics in domestic animals (rinderpest, foot and mouth disease and others).

A series of events influenced human-dog relationships and attitudes toward rabies. The appearance of extensive urban areas and changes in agriculture resulted in a difficult coexistence with those carnivores (free-living dogs included), able to attack man and prey on domestic animals. In the urban environment, it was necessary to find appropriate procedures to ensure the safe coexistence of human beings with dogs. During this period, the number of dogs was probably regulated by their economic exploitation (cynophagy, use of dog skin, etc.), by distemper and other diseases; and by the scarce availability of food.

MODERN TIMES – CONTROL INSTRUMENTS ARE DEVELOPED AND APPLIED

Nowadays, two main patterns may be distinguished in the Mediterranean. In the northern areas of the Mediterranean, the capture of stray dogs, dog registration, population control and other measures have limited the number and movements of these animals. Sometimes this was complemented by dog vaccination campaigns (3). In some areas, these measures have led to the eradication of canine rabies, with the status of freedom from canine rabies being preserved by surveillance, by measures intended to manage canine populations and by controlling the introduction of animals from infected areas (5). As a consequence of reduced dog control measures and increased acceptance of dogs by humans, stray dogs are abundant in some areas which had been free of rabies for some years. Wildlife rabies is present in some of these areas or in bordering ones, but the two problems are distinct. It should be recognised that these areas have enjoyed a long period of peace and have had efficient Veterinary Services. The background is such as to permit a recrudescence of canine rabies, should these two conditions deteriorate.

In contrast, in the southern and eastern areas of the Mediterranean, populations of free-roaming dogs are still abundant, although drastic measures are often taken. The control of canine populations was initially based on measures such as poisoning and shooting; then, in most areas the practice of capturing roaming dogs and detaining them in dog pounds (followed by euthanasia) prevailed. Recent findings in dog ecology call for new approaches to dog population (and rabies) control. The introduction of dog vaccination has provided another important instrument for the control of canine rabies. Modern research aims to reach free-roaming dogs by oral vaccination, thus limiting the problems associated with dog elimination.

Veterinary Services have been able to eliminate rabies in some countries of the Mediterranean. This has enhanced the interest of other countries in becoming rabies-free. The elimination of rabies has radically changed the human-dog relationship and other important aspects of human life in the areas in which it has been accomplished. In the presence of rabies the relationship between dogs and humans is conditioned by fear. Persons generally avoid close contact with dogs; children are taught to avoid them. Urban veterinary legislation used to be called ‘anti-rabies legislation’ and the control of dog populations was based on drastic measures. Zoophilia and animal protection societies were limited by general attitudes toward dogs. Veterinarians specialising in small animal practice were rare.

Rabies-free status has strongly influenced the human-dog relationship, transforming it from one involving conflict to one of coexistence and proximity; thus allowing Veterinary Public Health authorities to transfer priority from rabies to other zoonoses. Rabies eradication in the Mediterranean Basin paralleled the development of vaccines against distemper and other canine diseases. The number of dogs has increased, reaching approximately 1 family dog per 10 persons, with a similar figure for cats. New methods of dog population control have been introduced, mainly based on fertility control. Dog registration is generally employed. The presence of neighbourhood dogs is widely accepted, and the tendency to limit or avoid the
euthanasia of captured dogs is gaining ground. Stray dogs, if abundant, are considered to be a public health problem to be dealt with, but not in regard to zoonoses alone.

Dog-related diseases that are important in the Mediterranean Basin and justify the management of canine populations are echinococcosis/hydatidosis, leishmaniosis, rickettsiosis (*Rickettsia conori*), dermatomycoses, and other minor infections. Other problems that justify dog population control are linked to safety, hygiene, vehicular traffic, etc. Veterinary clinics covering practically the entire region have been established, accompanied by the development of a veterinary profession which specialised in pet animals.

**CONCLUSIONS**

When examining the present situation of rabies in the Mediterranean Basin, important features are found which derive from the evolution of the region, from research, and from the organisation, (sometimes very efficient), of Veterinary Services in all countries. All countries are members of the WHO, the Food and Agricultural Organization (FAO) and the OIE and a number have joined the Mediterranean Zoonoses Control Centre (9).

It has been calculated that the dog population in the Mediterranean Basin is about 1 dog per 10 inhabitants. Depending on the country and area, a proportion of these is strictly domestic but many dogs, although owned, lead a relatively free life. Ownerless and free-living animals are in the minority. This situation applies in all countries, with marked variations according to local situations. Also, legislation on canine populations and human-dog relationships differs so that strong restrictions exist in some countries whereas others (generally rabies-free) are highly permissive (neighbourhood dogs, etc).

In varying degrees, the Mediterranean Basin exists as an area of exchange, travel and migration involving both people and animals. In many areas, rabies-free status is a prerequisite to growing tourism. In these areas, unpopular dog control measures cannot be applied. Effective vaccines are largely employed against rabies and the development of oral vaccines will also allow free-living dogs to be vaccinated, thus avoiding drastic, inefficient control measures. The incidence of rabies has diminished across the entire Mediterranean Basin. In some countries it has been eliminated for years, in others promising campaigns are in progress, while some nations carry out limited actions with the aim of co-existing with rabies with minimal consequences. When possible, rabies control is combined with dog-related veterinary public health activities, such as population control and programmes against other dog-transmitted zoonoses.

Other areas are encountering obstacles to the control of rabies. Resources are rarely sufficient. The problem is not considered a priority, especially where rabies is present in countries with poor economies. In the southern and eastern parts of some Mediterranean countries, vast territories are difficult to survey, and bordering countries do not consider rabies an important problem. The co-ordination of the control of rabies and other zoonoses by the Mediterranean Zoonoses Control Centre, the WHO, the FAO and the OIE is sometimes very difficult.

It is therefore improbable that rabies-free status can be extended to all territories of the Mediterranean Basin. Some regions might achieve a significant reduction in rabies prevalence without reaching, at least in the medium term, rabies-free status. Rabies-free or low-prevalence status can only be maintained by efficient Veterinary Services which maintain effective surveillance. Peace and well-being are necessary pre-conditions for the provision of essential resources with due attention to veterinary health services.

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**References**


CHAPTER 17
LYSSAVIRUS INFECTIONS IN EUROPEAN BATS

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Summary

Since the eradication of terrestrial rabies from most of western Europe, there has been an increasing recognition of rabies virus variants associated with insectivorous species of European bat. The epidemiology of European Bat Lyssaviruses in different European countries is the principal focus of this chapter. The importance of bat rabies virus variants in Europe and other continents, the epidemiology and effectiveness of current vaccines in providing protective immunity following exposure to a bat rabies virus variant is also reported.

Keywords: bat rabies, European bat lyssavirus

INTRODUCTION

Probably less is known about the Chiroptera (bats) than about any other mammalian Order. Bat species are more widely distributed than any other mammalian species except man. They are the only mammals able to fly; and among mammals the number of bat species is exceeded only by the number of rodent species. Bats inhabit most of the temperate and tropical regions of the world but are not found in the colder parts of either hemisphere beyond the limit of tree growth.

The order Chiroptera is divided into two suborders, the Megachiroptera and the Microchiroptera. The Megachiroptera are the Old World fruit bats and flying ‘foxes’, the single Pteropodidae family having 42 genera and 173 species, whereas the Microchiroptera are composed of 17 families with 144 genera encompassing 813 species (144). Bats may be insectivorous, frugivorous, carnivorous, fish-eating or flower-feeding, but only the haematophagous (vampire) bats feed by imbibing blood.

Rabies and the rabies-related viruses are now collectively known as lyssaviruses. However, as will be shown below, the lyssaviruses can be distinguished by serological and molecular characterisation into a number of different virus types (serotypes and genotypes) and it is now customary to refer to the serotype 1 viruses of bats in the Americas as rabies viruses, whereas all others are referred to as lyssaviruses.

Rabies in bats has a long history. Baer (19) cites examples of reports of human rabies due to vampire bats in the 16th Century and of cattle rabies epizootics due to vampires in the sixteenth, eighteenth and nineteenth centuries. Following an observation by Carini (30) that Negri bodies were present in cattle during an outbreak of undiagnosed disease in southern Brazil, which he suspected to be of wildlife origin, a relationship between rabid vampire bats and bovine paralytic rabies in the same area was later conclusively proven by Haupt and Rehaag, (45). Vampire bat rabies in cattle is the only disease of bats known to be of substantial economic importance.

Baer and Smith (20) drew attention to the fact that historians had frequently overlooked the virtually simultaneous discovery of rabies in insectivorous bats in Brazil during the 1920s and in frugivorous bats in Trinidad during the 1930s. A report by Pawan (101) which stated that of 69 infected bats captured, 64 were vampires, four were frugivorous and one was an insectivorous species seems to have aroused little interest. However, that was certainly not the case when a young boy in the United States of America (Florida) was bitten on the chest by a rabies-infected insectivorous bat in 1953 (130). The boy was given successful post-exposure treatment. However, when brain material from a woman who died in 1951 three
weeks after being bitten by a bat was retrospectively reviewed, Negri bodies were found (127) – an indication that the Florida bat was not the first rabid bat to bite a human in North America.

Within a decade of the Florida incident, rabies in insectivorous bat species was also reported from most Central and South American countries and from Canada. Today the virus has been isolated from all species of North American bats which have been adequately sampled (20). The Florida incident also sparked interest in bat rabies in other parts of the world; by the end of the 1950s in Africa rabies had been confirmed in frugivorous bats in Nigeria (25) and in Europe it had been found in insectivorous bats in Yugoslavia (91), Germany (71) and Turkey (128).

**BATS OF EUROPE**

Within the European Union, despite one third of the indigenous mammalian species being bats, little is known of their detailed distribution and numbers (114). Of the 31 bat species (from three families Rhinolophidae, Vespertilionidae and Molossidae), all of which are insectivorous, no fewer than ten are classified as endangered, whilst a further ten species are thought to be vulnerable. Interestingly from the bat rabies point of view, *Eptesicus serotinus* (serotines) and *Myotis daubentonii* – Kuhl (Daubenton’s) are not considered to be threatened. Legal protection of bats is afforded to all species in all EU countries and they are also protected in other European countries, but the level of protection varies greatly. In most countries government agencies may exercise their powers to move bats from unwanted areas or, in rare cases, to remove them because of a perceived disease threat to humans, but in practice this rarely occurs. Population recovery can only be slow because most bats produce a maximum of one young per year (114). Thus little or no disease-related research is carried out in European bat species. As is shown below, although representatives of a number of other bat species have been shown to be rabies positive, serotines, Daubenton’s and *Myotis dasycneme* (dasycnemes) account for the majority of all reported rabies positive bats in which the species has been properly determined.

Serotine (meaning ‘of the evening’, when they are expected to feed) bats have been by far the most frequently reported rabies positive (95% of cases). Serotines are distributed throughout Europe with the exception of Norway and Finland but only recently have they been found in Sweden. In Denmark their range appears to have spread northwards (18). Winter roosts are in hollow trees and buildings and, especially in areas with very cold winters, they occur in caves and mines. In summer, colonies are mostly found in urban buildings but also in hollow trees. In the Netherlands, they are found almost exclusively in buildings and in Denmark they are known as the ‘house bat’. They feed predominantly on large insects in open, sheltered urban and parkland areas, mostly in lowlands (114). In a recent study of serotine behaviour, it was shown that the maximum straight line distance to a feeding area was 7.4 km, the mean home range could be nearly 50 km² and there was a strong possibility of serotines from different colonies meeting in feeding areas within both home ranges and core areas (115).

The migratory bats of the *Myotis* genus are widely distributed, being absent only from arctic, subarctic and antarctic regions and on many oceanic islands (144). Within Europe, dasycnemes are found in Sweden, Poland, Czechoslovakia, Germany, Denmark (limited to Jutland), the Netherlands (Friesland, north and south-west Holland) and in the extreme north-east of France. They prefer riparian (river bank) habitats and usually feed over waterways. They roost in buildings in summer and caves, mines and cellars in winter, and nursery roosts and hibernacula are often 200-300 km apart (114).

In Europe, Daubenton’s have a somewhat wider range than dasycnemes and are also found in Spain, Portugal, Austria, Switzerland, South Scandinavia, North Yugoslavia, Bulgaria and possibly Romania and in the United Kingdom (UK). In Finland, they are found south of a line from Jakobstad to the border near Lieksa. They too are found primarily in riparian habitats and around ponds and lakes, often roosting under rock ledges or in scree, as well as in cellars, mines, caves, under bridges, in tunnels, in buildings and hollow trees. They feed over water often on emerging insects and summer and winter roosts may be widely separated (114).
BAT LYSSAVIRUSES IN EUROPE

‘On October 19, 1954 a young boy found a bat hanging in a tree in front of his house in Hamburg. The bat appeared to be sick and the boy took it into the house. In the course of the same evening the boy was bitten on the finger and the next morning the bat was found dead in its cage. The bat brain was examined for Negri bodies at the official veterinary examination laboratory in Hamburg with negative results. However, in accordance with German law in the case of human exposure, the bat brain suspension was injected into mice and all mice died. The mice brains showed numerous Negri bodies. The species of the bat was not determined. The boy received rabies post-exposure treatment and survived’. Although some of the details were from the PhD Thesis of Dennig (J. Cox, Tübingen, 1999, personal communication), this account by Schindler and Dennig (106) represents the first verified bat lyssavirus case in Germany and perhaps in Europe, although of course it is unlikely to have been the first infected European bat. No material has survived for typing.

‘Rabies’ in European bats was intermittently reported over the next thirty years and such cases were regarded as scientific curiosities (7). However, with a sudden increase in numbers in 1985 and occurring in a variety of countries, it became apparent that the disease in bats was of unsuspected significance. By the end of the century, just over 600 cases from 17 countries had been recorded (Table 17.1).

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Total: 676*  
* includes 3 humans and 1 imported bat;  
?? species unrecorded;  
RBE: Rabies Bulletin Europe Year/No
EVENTS IN COUNTRIES SPORADICALLY REPORTING BAT-LYSSAVIRUS CASES

Yugoslavia

In the early 1950s, several outbreaks of bovine paralytic rabies occurred in Vojvodina, but the appropriate vector could not be found. In 1955, 27 local bats, which included representatives of Nyctalus noctula, Eptesicus serotinus, Miniopterus schreibersi, Plecotus auritus, Myotis myotis and Rhinolophus ferrumequinum species, regardless of their appearance, were included in ecological surveys and three N. noctula bats were found to be infected (91), although they had shown no sign of illness. The virus (SM7) from one of these bats was intracerebrally passaged 20 times in white mice and at least 85 times in rabbits (48). Recently, an aliquot of SM7, although no longer viable, was subjected to real-time polymerase chain reaction (RT-PCR) techniques and proved closely related to a canine isolate from Morocco. To date, there is no satisfactory explanation for this finding, although the species is migratory and its distribution includes most of the Mediterranean islands and Morocco (114). Despite the continued but intermittent examination of bats (50 were examined between 1996-1999), no further lyssavirus-positive bats have been found (S. Stankov, Novi Sad, 1999, personal communication).

Turkey

A group of 71 Rhinolophus, Plecotus and Vespertilionidae bats from Diyarkakir and Bergama (in Izmir) were examined for the presence of rabies. None of the 19 bats from Diyarbakir was found to be positive, but one of 52 bats from Bergama, a Rhinolophus ferrumequinum (Greater horseshoe), showed Negri-bodies in the brain (128). No material remains for further examination and no further bat lyssavirus cases have been reported from Turkey.

Greece

During 1969-1971, from the ‘Cave of Cyclops the Polyphemous’ in the neighbourhood of Maronia, Prefecture of Rodopi, 22 live insectivorous bats were captured and sent to the laboratory in Thessaloniki. Here, after euthanasia, each bat brain was aseptically removed and emulsified and the suspension inoculated into white mice. After 16 days, mice inoculated with one of the brains showed signs of paralysis lasting for 24 hours before death. In subsequent passages, the incubation period was reduced to 10-15 days and all mice died with Negri bodies in their brain. Control mice, which had been inoculated with a mixture of positive mouse brain and antirabies serum held at room temperature for 30 min, survived for 30 days, after which the experiment was terminated. ‘A rabies-positive diagnosis was confirmed by Professor Ercegovac of the Veterinary School in Belgrade. Further research was envisaged, but to date there have been no other reports of bat lyssavirus cases in Greece.

The above information was obtained from a report by M. Pina-Costoglou in the 1970s, sent to Germany by the late Dr Harald N. Johnson following a visit to Greece (Denny G. Constantine, California 1999, personal communication). It has not been possible to further authenticate the report.

Russia

On 8 May 1985 an 11-year old girl (‘Yuli’), while on the balcony of a multi-storey building in Belgorod, not far from the border with Ukraine, was attacked and bitten near her lower lip by a bat, which then flew away. The bleeding wound was treated with iodine but the patient did not seek other treatment and she died 27 days later, having shown typical signs of rabies for six days. Brain samples were negative but 3-5 day old mice inoculated with brain material developed symptoms of paralytic rabies 12-24 days later and these tested positive to the fluorescent antibody test (FAT) (110). Two or three further isolations of lyssavirus from Russian bats have been reported (52), but these were from the Asian parts of Russia, beyond the geographical range of this book and no further cases have been reported from the European parts of Russia.
Ukraine

In Kiev in 1964, a 35-year old man was bitten by a serotine in the cellar of his house. The bat survived for 25 days without clinical signs, but then died and virus isolated from its brain was confirmed as rabies by mouse inoculation and by a neutralisation test. The victim was given Fermi vaccine post-exposure treatment and remained healthy (104). No material remains for further examination. A second case occurred in the Ukraine when during the daytime a 15-year old girl in Voroshilovgrad was bitten on the finger. The bat flew away but the girl, who was not given post-exposure treatment, died 35 days later and lyssavirus was isolated from her brain (111). No material remains for further examination. In 1989, two dead bats, a N. noctula and a V. murinus, were taken from the hollows of tall trees on the bank of the Pripyat River in the Volynsky region of Ukraine, near the border with Poland. Following isolation by intracerebral inoculation of mice, lyssaviruses were characterised by anti-nucleocapsid monoclonal antibodies (Mab-Ns) as similar but not identical to the virus ‘Yuli’, isolated from a victim in Russia (109). No other cases have been reported from Ukraine.

Poland

Komorowski et al., (55) reported an incident of lyssavirus in a serotine from the area of Krakow but no material from this bat remains for further examination. In a second incident, on 27 May 1985 the Veterinary Investigation Centre in Gdansk received the carcass of a mature male serotine with a request for rabies examination. It was found in Gdansk, sitting on the leg of a three-year old child who was crying because of the pain from the clearly visible bat bites. The bat was caught and killed. How it entered the room was not established – it could have flown in through the open window, or it may have been brought in with dried linen from the loft. The bat brain was lyssavirus FAT positive, as were tests on the brains of mice after intracerebral inoculation of a suspension of its brain. In these mice the first signs appeared after four days and the first death occurred one day later (129). The child survived the incident. Of eleven further bat lyssavirus cases to be reported from Poland by the end of the century, one was in 1990, seven in 1998 and three in 1999.

Switzerland

In September 1992, the first case of lyssavirus in a Swiss bat was diagnosed by the Swiss Rabies Centre. The Daubenton’s had been found on a sunny afternoon, hanging on the grid of a ventilation shaft of a house in ‘Schwarzeze’, a community of Pfaffieien, canton of Fribourg. When someone tried to take the bat from the grid, it escaped and fluttered to the ground, from where it could be picked up. It tried to bite, but was already too weak to puncture the skin and it died within a short time. The person who had handled the bat was given full post-exposure treatment and survived. When using a fluorescent polyclonal antiserum, the Daubenton’s brain was only weakly lyssavirus positive, but was clearly positive when an indirect FAT was done with Mab-Ns. Suckling mice, inoculated intracerebrally with 20% brain suspension, died 10-12 days later. Using a panel of Mab-Ns, the virus was identified as a European Bat Lyssavirus (EBLV) (50). A second case, also in a Daubenton’s, occurred on 12 July 1993. The bat was collected in Versoix on Lake Geneva after having bitten two persons on a ship. Examination of its brain with a standard polyclonal conjugate yielded a weakly positive result, but indirect FAT using a Mab-N was strongly positive and suckling mice inoculated intracerebrally died from seven days onward (R. Zanoni, Bern, 1993, personal communication). No further cases were reported before the end of the century.

Finland

Finland had long been free of rabies, the last human and animal cases being in 1934 and 1959 respectively. However, on 9 October 1985, a 30-year old Swiss biologist was admitted to the department of neurology, Helsinki University Central Hospital, with ascending paralysis of the Guillain-Barré type and radiating pain in the right arm and neck. On October 10 he became very agitated with hyperexcitability, hyperventilation, and spasms. From the clinical picture and the patient’s history of multiple bat bites, rabies was suspected. The patient had never been vaccinated against rabies and he died on 29 October 1985. Post-mortem neuropathological and virological examination, including mouse inoculation, confirmed the diagnosis of rabies. From studies with Mab-Ns on material passaged through mouse brain, the virus appeared to be
related to rabies virus detected from bats in Germany (Hamburg 1968 and Stade 1970) (66). The victim had been bitten several times by bats while in Malaysia over four years earlier, in Switzerland one year earlier and, most recently, 51 days before the onset of neurological symptoms (22). Despite extensive examination of terrestrial animals and bats in the area, no other cases were found and no further bat lyssavirus cases were reported by the end of 1999.

Czechoslovakia

In 1989 a bat was reported to be lyssavirus-positive but no other details were provided. However, on 28 August 1994 a paralysed serotine was found in the loft of a house in the Uherské Hradiste district (South Moravia). It was taken into the care of a family and artificially fed, but despite this it died three days later. The dead bat was stored frozen for six days at the Health Department and then submitted to the State Veterinary Institute in Olomouc for lyssavirus examination. The brain and spinal cord were FAT-positive, but subsequent mouse inoculation tests were negative, as were attempts to isolate virus in cell cultures (67). Two further cases were reported from Czech Republic in 1999.

Slovak Republic

In 1998 a lyssavirus-positive insectivorous bat was reported but no further details were given and there were no further case reports before the end of 1999.

Hungary

One serotine was reported positive in 1999 but at present no other details are available.

The United Kingdom

In June 1996, an obviously sick Daubenton’s was seen flapping around the wall of a public house in Newhaven, a resort on the south coast of England. The local amateur bat group was alerted and the bat was taken to a nearby bat sanctuary where, whilst being handed over, it bit two women. The bat brain was rabies FAT-positive (146). Both bitten persons were given successful post-exposure treatment. Between 1986-2001, despite continuing surveillance of sick and dead bats throughout England, Scotland and Wales, this case remained the only lyssavirus FAT-positive of almost 2,000 bats examined. However, in 2002, two cases of bat lyssavirus infection caused by the bat variant, EBLV type-2 were reported. The first case was detected in a Daubenton’s bat (49) and the second case was the first recorded case of human rabies for 100 years in Great Britain (35).

EVENTS IN COUNTRIES REGULARLY REPORTING BAT RABIES CASES

Germany

Mohr (71) also reported the first bat lyssavirus case in Germany (see above) and in July 1963 lyssavirus was isolated from a serotine from Thüringen, although none of 25 other bats examined showed histological evidence of lyssavirus infection. On passage in mice, the incubation period varied considerably (103). Interestingly, Pitzschke considered that, ‘based on studies of the properties of the virus it was a (rabies) street strain, but there was little reason to suspect a rabies reservoir among the insectivorous bats of Germany’. A second isolation from a bat in Hamburg, 14 years after the first, occurred in 1968 when a university student found a bat lying on the ground with its mouth wide open. As she approached, it initially remained calm, but as she picked it up it began to hiss and screech, whereupon it bit her on the thumb with such force that a piece of wood was necessary to pry the jaws apart (108). Successful post-exposure treatment was given to the victim and the presence of lyssavirus in the bat in which ‘the biological properties of the virus isolated were found in part to differ considerably from known street virus infection’ was made by Wersching and Schneider (145). In neither of the two Hamburg incidents was the species of bat identified, nor was that of a third infected bat found in 1970 at Stade, about 30 km
west of Hamburg. Sporadic cases continued but with increased frequency after 1982 and by the end of the 2001, 136 cases had been confirmed. This figure does not include an *E. fuscus* bat introduced to Tübingen from Canada for research purposes and which in 1986 died of a serotype 1 lyssavirus strain (8).

**Denmark**

In September 1985 in Ansager, Jutland, a serotine that was found in a weak condition bit a teacher on a finger when she went to remove it from a schoolyard. The local physician was visited and the bat was submitted to the local veterinarian, who killed it and sent it to the State Veterinary Serum Laboratory, Copenhagen for rabies examination. The bat was FAT-positive. By the end of that year, 34 bats, all found in poor condition or dead, had been submitted for lyssavirus examination and of 20 serotines, 10 were positive (22, 72). After the owner of a garage at Hejnsvig, which contained a roost of 60-70 serotines, had found several sick bats, including a bat showing incoordination in flight, an attempt was made to capture the remaining members of the roost. All the exits from the building were sealed a funnel trap was placed at the bats’ normal exit, to trap them at dusk as they left to feed. Seven were captured by hand in the roost and these were lyssavirus-negative. One of two which flew into the trap was positive. In all, 17 bats from the roost, including the one trapped, were positive (54). During 1986, 112 bats were positive and in 1987 48, but thereafter reports of positive bats became more rare, although by the end of 2001 no fewer than 204 lyssavirus cases had been confirmed.

**The Netherlands**

Following reports of positive cases in bats in Denmark, in July 1986 a bat lyssavirus surveillance programme was started. By May 1987, 23 bats sent to the Central Veterinary Institute, Lelystad, had been found negative, but on 30 May 1987 the first positive case was found in the province of Friesland. Between 30 May and 22 September of that year, 1,047 bats were investigated, of which 71 serotines and two dasycnemes were shown by FAT to be lyssavirus-positive (92). The Netherlands has been one of the few European countries to actively survey for infected bats (Table 17.2) and by the end of 2001 250 positive cases were recorded.

| Table 17.2 – Bat Lyssavirus in the Netherlands 1987-1998 |
|-----------------|---------|---------|---------|
| Species         | Examined| Positive| % positive |
| *E. serotinus*  | 1,086   | 220     | 20.26    |
| *M. dasycneme*  | 106     | 5       | 4.7      |
| Total           | 1,192   | 225     | 18.88    |
| Total (all bats)*| 3,234  | 225     | 6.96     |

*: The following bats were also examined and found negative: *M. daubentoni* (n=94); *M. mystacinus* (n=14); *M. nattereri* (n=8); *Nyctalus noctula* (n=53); *N. Leisleri* (n=3); *Pipistrellus spp.* (n=146); *P. pipistrellus* (n=1378); *Plecotus spp.* (n=8); *P. auritus* (n=177); *Vespertilio murinus* (n=5); Undetermined (n=104)

In 1995 no speciation was done on 50 bats

**Spain**

In Valencia, on 18 August, 1987, a twelve-year old child was bitten on the back. The bat species was not identified, but its brain was rabies FAT-positive. On 21 September 1987 in Granada, whilst two children were playing with a bat, one was bitten on a finger. Again, the bat species was not identified, but the brain tested positive. Both children received immediate and successful post-exposure treatment. In response to these occurrences, epidemiological surveillance was initiated (99). During this surveillance, a serotine was captured on 6 June 1989 in the province of Huelva, Autonomous Region Andalusia. It was isolated and observed because of its strange behaviour; it died a few days later and the brain was lyssavirus FAT-positive (40). Four further positive cases were captured in the same area between 19 July and 27 July 1989 (41). In 1994, another positive bat which had attacked a person in Grenada was found (105). The bite victim survived and no further cases were reported from Spain until four more were found in 1999 and five in 2000, bringing the total to 17.
France

In the afternoon of 11th September 1989 a serotine was seen flying over a group of people in a garden. One person noticed that the bat, which was wailing, changed course when she whistled at it. This behaviour was repeated several times until the bat sat on the person’s leg and bit through her trousers. The bat was killed and on examination the brain and spinal cord were rabies-positive. The bite victim survived. Eighteen days later, an approximately five to six year old male serotine was seen behind a shutter of a pavilion. When touched with a stick, the bat cried and tried to bite into it. The next day it was again observed apparently paralysed, head raised and crying. It was captured and on 2th October 1989 was taken to the Natural Science High school at Nancy. Two days later at the laboratory in Malzéville the brain was shown to be lyssavirus-positive (21). Later that year another positive bat was found. Since that time single cases have been recorded in 1995, 1997, 1998 and 1999, five more in 2000 and three in 2001 (Table 17.1), bringing the total number of confirmed cases to 13, although the 1999 incident was Lagos bat virus in an imported frugivorous bat.

LYSSAVIRUS INFECTIONS

Clinical signs and laboratory diagnosis

It is probable that the majority of non-biologists go through life totally unaware of the presence of insectivorous bats, such is the normal bat lifestyle. Most European bats are at roost during the day and since they are relatively small, fast, almost inaudible crepuscular feeders as they ‘swim’ through the air, taking their insect food ‘on the wing’, they are not easily seen by the untrained eye. In almost all mammals, behavioural changes are one of the first signs of a lyssavirus infection and bats are no exception to this rule. To see a bat in its natural habitat during the daytime is an exceptional event and a warning that the bat may be sick, possibly infected with a lyssavirus.

Of the 17 European countries to have reported lyssavirus in bats to date, in only four (Yugoslavia, Turkey, Greece and the Netherlands) did the disease come to light through active surveillance programmes. It is unclear when and where the Swiss biologist who died of rabies in Finland became infected, but in ten of the other countries the first indication of the disease in bats was when a member of the public came into contact with an infected bat during the daytime. Although in Czechoslovakia no bat bite was reported, in eight of the other nine countries (Russia, Ukraine, Poland, UK, Germany, Denmark, Spain and France), a member of the public was bitten. In Switzerland, the bat tried to bite but was said to be too weak. In only two cases (Russia and France) could the victim be said to have been ‘attacked’, although in the French incident whistling at the bat may be considered as provocation. Biting cannot be assumed to be pathognomonic of lyssavirus infection, as bats unable to fly for other reasons may react in a similar manner.

When infected bats were found alive, they were sometimes described as paralysed, at times crying and quite often biting when approached. Observations by two bat workers show that lyssavirus infection may result in aggression. Near Osnabrück a bat was taken into care and observed for 36 days of the incubation period and 19 days of the clinical disease. It was reported:

The bat was taken into care on 2 February 1989. The weight was 18 gm. It gained weight up to 27 gm and seemed to develop well. On 10 March 1989 it refused to eat. During the nights there was vigorous movement. A few days later there was frequent aggression. The animal bit inanimate objects including its cage. It died 29 March 1989. The diagnosis was made with the direct immunofluorescence test at the State Veterinary Investigation Centre, Braunschweig. Characterisation with monoclonal antibodies carried out by the WHO Collaborating Centre for Rabies Surveillance and Research, Tübingen revealed serotype 4, Duvenhage (Europe) virus’ (12).

An incubation period of at least 36 days is cited above, but almost always a FAT-positive diagnosis was followed by the intracerebral inoculation of a suspension of the infected bat brain into suckling or weaned mice. Thereafter, data describing the course of infection in mice are scanty, but Nikolic and Jelesic (91) reported that in the first passage the incubation period was 6-10 days but in subsequent passages it
became increasingly shorter, until from the seventh passage onward it remained ‘fixed’ at five days. The first signs to appear were ruffled fur, arched back and inappetence, followed by rapidly increasing weakness. Total paralysis of both hind legs was noted in one mouse only and the clinical course of the illness was seldom longer than 36 hours. The same authors also noted that intramuscular and subcutaneous inoculation routes were not always successful and on average the incubation period was as long as 7 days and 9-10 days respectively. These results are in contrast to those of Lumio et al. (66), who found that impression smears of the original infected brain revealed small intensively staining granules concentrated in neuronal cells when tested by direct FA. When brain specimens containing the (genotype 6) virus were inoculated into newborn and 3-week old mice, the animals died with signs of rabies after 11-14 and 21-25 days respectively.

There are no descriptions of the pathological changes found in bat brains infected with European bat lyssaviruses. However, the basic lesion, a non-suppurative meningoencephalomyelitis, appears to be similar to that observed in rabies infected terrestrial animals. Most researchers have limited their findings to the absence of Negri bodies following FA staining, or to their size and quality of staining when they are present. A few reports describe an unusual fluorescence picture on primary diagnosis, but more frequent are reports of the pathological changes found in rodents (mice) which succumb following inoculation with a suspension of infected bat brain. In a more recent investigation, Bourhy and his colleagues (26) isolated virus from the brain, medulla, lungs and heart but not from a number of other tissues including the salivary glands of a serotine from France. Lyssavirus antigen was also detected by FAT or rapid rabies enzyme immunodiagnosis (RREID) in the brain, medulla, lungs and the tongue. FAT on cryosections also showed virus antigen in the filiform papillae of the lingual epithelium.

In Yugoslavia, Jelesic and Jovanovic (48) reported that histologic examinations of the central nervous system of animals used for passaging the agent showed a meningoencephalitis of viral aetiology with basophilic cytoplasmic inclusions but an absence of Negri bodies in the pyramidal cells of the Ammon’s horn (hippocampus) when stained by the Lenz method. In Turkey, Tunçman (128) observed Negri bodies in bat brain smears and also in rabbit brain passaged material. In these rabbits the incubation period decreased ‘by up to eight days’ by the ninth passage and lymphocytic infiltration was observed in their brains. Mice intracerebrally inoculated with the positive bat brain from Greece showed paralysis for one day before death after an incubation period of 16 days. In subsequent passages the incubation period was reduced to 10-15 days and all mice died with Negri bodies in their brain. In the German M. myotis bat rabies case, Henschke and Hellmann (46) reported isolation of the virus from the salivary glands and fat, in addition to the brain, and that subsequent passage through mice showed that the virus ‘possessed some properties unusual in a street strain’. However, it should be remembered that no material remains from the Turkish, Greek and German incidents, and that the passed Yugoslavian bat virus genotype does not now accord with the more recent genotype 5 and genotype 6 viruses isolated in other European countries.

**Experimental studies in bats**

Because of the protected status of bats in Europe, only one bat-to-bat transmission study has been reported. Botvinkin and his colleagues (24) intramuscularly inoculated the genotype 5 viruses Yuli and Stade and ‘an unusual’ genotype 1 virus (1150) from a *Vespertilio murinus* bat from Omsk into a mixed group of 100 Daubenton’s and eleven *M. brandti* bats and into 15-20 gm adult mice (Table 17.3).

<table>
<thead>
<tr>
<th>No. inoculated virus</th>
<th>Bats/mice</th>
<th>Died of rabies</th>
<th>Days to death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuli</td>
<td>25/25</td>
<td>6(24%)/8(32%)</td>
<td>18.4±4.0/8.5±0.8</td>
</tr>
<tr>
<td>Stade (1)</td>
<td>33/30</td>
<td>3(9%)/17(57%)</td>
<td>19.7±9.7/8.2±0.2</td>
</tr>
<tr>
<td>Stade (2)</td>
<td>28/28</td>
<td>0/18(64%)</td>
<td>NA/8.0±0.8</td>
</tr>
<tr>
<td>1150</td>
<td>25/25</td>
<td>15(60%)/10(40%)</td>
<td>35.2±4.0/5.3±0.7</td>
</tr>
</tbody>
</table>

*Stade (1): inoculated in May*
Their results showed that bats were less susceptible than mice to the genotype 5 viruses and that incubation periods were longer. Conversely, the susceptibility of bats inoculated with the 'unusual' genotype 1 virus was higher than that of mice, although the incubation period was significantly longer. They also noted that whereas 50% of the bats inoculated with the genotype 5 viruses showed aggressive behaviour and convulsions, all bats inoculated with the 'unusual' genotype 1 virus showed only the paralytic form of lyssavirus infection.

**Antibody production in infection**

Only a few reports of antibody production following natural infection have been made. In one serum sample from ten apparently healthy Danish serotine bats, nine of them from a lyssavirus-positive colony in south-east Jutland, the other from a bat trapped in a house where a positive bat had been diagnosed previously, revealed rabies FA titres of 100 in four bats, 10 in four bats and less than 10 in two bats (43). The authors did not specify the antibody test used, but it can be assumed to have been the rapid fluorescent focus inhibition test (RFFIT).

In another report, in southern Spain between September 1991 and September 1992, four serotine colonies were blood sampled to determine the prevalence of lyssavirus antibody (102). From one of the colonies (Villarrasa), in May 1989 a year-old serotine unable to fly had been found lyssavirus-positive and in July 1989, of four less than one-month-old positive pups, one was found dead but the others appeared to be in good health when they were killed.

Although three of the four colonies showed the presence of antibodies when sera were tested in a RFFIT against a cell-adapted serotine isolate from Villarrasa, results from only two colonies were included in the statistical analysis because of the low number of bats captured in the others. The authors considered that the prevalence of antibodies obtained in spring 1992 in the Villarrasa colony, together with the individual development of antibody titres showing a strong increase from the low titres of the previous autumn, could be interpreted as evidence for an epizootic. However, during the study period they registered a consistently high level of lyssavirus antibodies in only one serotine bat. The antibody test used was the RFFIT as described by Bourhy and Sureau (28).

**The viruses: antigenic and molecular diversity**

Despite their neurotropism, lyssaviruses, including bat lyssaviruses, will grow in a variety of mammalian cells but their adaptation is sometimes prolonged and difficult. During the development of a method for the adaptation of rabies viruses to growth in baby hamster kidney 21 (BHK21) cells (53) it was noted that, whereas the FATs of isolates from serotines showed many particulate nucleoprotein antigen granules and adapted easily, the Finnish- and *Myotis* origin virus antigen appeared as amorphous masses and the viruses adapted more slowly (King, unpublished data). This led to a suspicion that there may be more than one lyssavirus variant in European bats.

Reports of the variability of fluorescence staining in early cases of European bat lyssavirus disease, as detailed above, coupled to reports of observed strain differences, usually when a small number of Mab-Ns were used, led to a retrospective, unofficial and complicated nomenclature for the viruses; usually involving the name Duvenhage, or Duvenhage-like, or Duvenhage with an integer. This was despite the fact that cases of European bat ‘rabies’ had been reported some 14 years before the index case report of Duvenhage in Africa by Meredith (70). Subsequently, more broadly based panels of Mab-Ns were produced and were followed by in-depth molecular studies. From one of these latter studies (27), it was proposed that the viruses of serotype 1 (rabies, which includes the rabies viruses from bats throughout the Americas), serotype 2 (Lagos bat), serotype 3 (Mokola) and serotype 4 (Duvenhage) should be classified as genotypes 1-4 respectively and that isolates from serotines (or European bat lyssaviruses – EBLV 1) and *Myotis* species (or European bat lyssaviruses – EBLV 2) be classified as genotypes 5 and 6 respectively. This classification is now generally accepted, although the traditional serotyping of the genotype 5 and 6 viruses.
by protection tests in rodents has yet to be performed. Australian bat lyssavirus (42) has been accepted within the *Lyssavirus* genus as genotype 7 belonging to serotype 1 (69) (Appendix 1).

An example of Mab-N studies of the European bat lyssaviruses is as follows: A panel of Mab-Ns was prepared against the prototype viruses of Lagos bat, Mokola, Duvenhage, a Denmark bat virus and the Finnish virus (53). When this panel was used to test a substantial number of European bat rabies viruses, one of three anti-Duvenhage Mab-Ns did not react with genotype 5 or genotype 6 viruses; none of five anti-genotype 6 Mab-Ns reacted with the genotype 5 viruses and only two of five anti-genotype 5 Mab-Ns reacted with the genotype 6 viruses (Table 17.4). Anti-Mokola Mab-N 11 gave variable reactions with genotype 5 viruses, positive with some, negative with others (Table 17.4), suggesting the presence of more than one variant present in these viruses. Interestingly, four of the five anti-genotype 6 Mab-Ns also reacted with Mokola virus, whereas none of them reacted with any of several hundred terrestrial animal serotype 1 virus isolates, although they have demonstrated three variants among the eight Mokola viruses tested (53). The reservoir species of Mokola has not been determined and an African bat species cannot at present be ruled out.

**Table 17.4 – Reactions of 52 lyssaviruses with a panel of 19 Mab-Ns** (32)

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Mab-Ns</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>154, 41 various</td>
<td>+ + + + + + V</td>
<td>5 (EBLV-1)</td>
</tr>
<tr>
<td>8, 29, 30, 228</td>
<td>+ + + + + + + + + +</td>
<td>6 (EBLV-2)</td>
</tr>
<tr>
<td>6, 131, 139</td>
<td>+ + + + + + +</td>
<td>4 (Duvenhage)</td>
</tr>
<tr>
<td>LBV</td>
<td>+ + + + +</td>
<td>2 (Lagos bat)</td>
</tr>
<tr>
<td>MOKV</td>
<td>+ + + + +</td>
<td>3 (Mokola)</td>
</tr>
<tr>
<td>CVS</td>
<td>+ + + +</td>
<td>1 (Rabies)</td>
</tr>
</tbody>
</table>

+ = positive reaction; no symbol = negative reaction; V = variable, some positive, some negative

**Mab-N key:**
- 1 = D1; 2 = D3; 3 = D9; 4 = DB1; 5 = DB3; 6 = DB9; 7 = DB10; 8 = DB14; 9 = L20; 10 = M2; 11 = M7; 12 = M11; 13 = L3; 14 = L25; 15 = F1; 16 = F7; 17 = F3; 18 = F4; 19 = F5
- D = Duvenhage; DB = Denmark bat; L = Lagos bat; M = Mokola virus; F = Finnish virus

**Antigen key:**
- 154, 41 various = Yuli virus and 41 *E. serotinus* isolates from various European countries
- 8 = Finnish virus
- 29, 30, 228 = three *M. dasycneme* isolates from Holland
- 6, 131, 139 = the three known Duvenhage virus isolates
- LBV = the prototype strain of Lagos bat virus
- MOKV = the prototype strain of Mokola;
- CVS = Challenge Virus Standard

Several investigations of the molecular diversity of the *Lyssavirus* genus have been made (26, 27), but the most comprehensive study which used 47 European and two African (Duvenhage) virus isolates attempted to determine the evolution of European bat lyssaviruses (2). The viruses came from Denmark (n = 3), Germany (n = 13), Holland (n = 18), Poland (n = 3), Russia (n = 1), Ukraine (n = 1), France (n = 3), Spain (n = 2), UK (n = 1), Switzerland (n = 1), Finland (n = 1) and South Africa (n = 2). The species examined were *E. serotinus* (n = 37), *V. murinus* (n = 1), *M. dasycneme* (n = 4), *M. daubentonii* (n = 2), *Miniopterus* sp. (n = 1) unknown species (n = 1) and human bitten by bat (n = 3). Analysis of both the nucleotide and deduced amino acid sequence grouped the viruses into three clusters, genotype 4, genotype 5 and genotype 6, thus confirming previous results (27). The percentage of nucleotide and amino acid similarity between the two genotype 4 (Duvenhage) viruses was high, 98.7% and 99.2% respectively, but both genotype 5 and genotype 6 viruses were divided into two different phylogenetic lineages (a and b). The distribution of genotype 5a unites 29 samples from northern and eastern Europe (Denmark, Holland, Germany, Poland, Ukraine and Russia), whereas that of genotype 5b unites 11 samples from the western part of Europe (Holland, France and Spain). Five isolates from Holland and the UK constitute the lineage genotype 6a, and two isolates, from Finland and Switzerland constitute the lineage genotype 6b.

From these results, Amengual and her colleagues speculate that genotype 5 viruses have evolved at least into two genetically distinguishable groups following geographical drifting. Further, they speculate that these two groups were introduced into parts of northern Europe from two different
geographical directions, with genotype 5b being more recently introduced from North Africa. Too few genotype 6 viruses have been isolated to draw significant findings, but at least three foci have been identified, one genotype 6a focus in dasycneme bats in Holland, another genotype 6a focus in Daubenton’s bats in the UK, and a genotype 6b focus in a Daubenton’s bat in Switzerland. There may be a fourth focus in Finland, although it is not possible to establish whether the Swiss biologist contracted the disease in Switzerland or in Finland.

European bat lyssaviruses and human health

Are the European bat lyssaviruses rabies viruses? Following the discovery in Africa of viruses with unusual properties, Shope (112) introduced the term ‘rabies-related viruses’. It became fashionable to include European bat lyssaviruses within this grouping, as the fluorescence pictures from bats appeared to be somewhat different from those of classical rabies virus within the fox population and a relationship with the rabies-related virus Duvenhage had been established. However, both genotype 5 and genotype 6 viruses have caused death following clinical disease in humans which was indistinguishable from that caused by classical rabies (genotype 1) viruses. It may be that the disease in European bats is a result of a long period of adaptation and evolution of lyssaviruses within bat species, but there is no doubt that they are rabies viruses and should be regarded with the same respect as classical rabies viruses. It is time to lay to rest the historical term ‘rabies-related’.

Do current lyssavirus vaccines for humans protect against challenge with European bat lyssaviruses? In one of the first studies to investigate the immunobiology of the European bat lyssaviruses, Schneider (107) showed that the Pitman-Moore (PM) strain did not protect mice against challenge with a (genotype 5) virus isolated in 1970 from a bat from Stade (Germany). This was a significant finding, since the PM strain serves as the basis for the widely used human diploid cell vaccine (HDCV). Dietzschold et al., (33) investigated the capacity of various vaccine strains and a (genotype 5) Polish bat virus to induce protective neutralising antibody and anamnestic response. Primary immunisation of mice with one of the vaccine strains and with the inactivated Polish virus induced significant neutralising antibody against the genotype 5 virus, but mice immunised with the PM vaccine developed serum neutralising antibody against genotype 1 virus only. Further, mice primed with the PM vaccine and subsequently boosted with a PM strain of virus mounted an anamnestic response to the genotype 1 virus only.

In another experimental study in mice, Lafon and her colleagues (64) confirmed Schneider’s findings, but also showed that those vaccinated with a different genotype 1 vaccine strain (PV4) were protected. Also in 1988, Fekadu et al. (34) showed that mice immunised intraperitoneally with HDCV or animal vaccines (Rabisin and Rabiffa) were protected against challenge with a (genotype 5) Danish bat virus but the vaccines gave only partial protection against the Finnish virus isolate (genotype 6) thought to be of bat origin.

In 1986, Lafon and her colleagues (65) used serum from volunteers immunised with PM virus prepared in a variety of cell types and all were found to contain high titres of neutralising antibody against the (genotype 5) Stade virus. It was later shown that 73% of human patients given post-exposure treatment following exposure to suspect rabies terrestrial animals developed specific neutralising antibody against the (genotype 5) Stade virus, but 27% of the patients had no detectable neutralising antibody (47).

Studies of the immunobiology of the European bat lyssaviruses have been fragmentary, with individual genotype 5 isolates tested from only three countries and no genotype 6 bat isolates tested, although the genotype 6 isolate from Finland may be considered as of bat origin. Thus, although no animal study has provided a definitive answer to the protection question, to date no human death has occurred following full pre-exposure vaccination and no human death has occurred following the correct application of post-exposure treatment.

What have we learned, what needs to be done?

Apart from the well documented vampire bat rabies of Central and South America (44), which was visible because of its effect on the victim species (cattle), in the rest of the world until the second half of the last
century, rabies in other bat species was unsuspected. Since the early 1950s, bat rabies in the United States of America (USA) and in Europe have parallel histories, with some similarities but with more marked differences. In the USA, it quickly became clear that the disease was present in all bat species adequately sampled and it was shown not to be a new phenomenon. By 1984 the USA had reported several thousand bat rabies cases and in that year a peak of 1,038 cases, representing 20% of the 5,174 wildlife cases, or 18.4% of the 5,630 total number of cases was reported (3). In the same period Europe reported only 14 bat rabies cases. After 1984 the number of reported cases in USA bats diminished a little, but in 1998 the number of positive bats at 992, although at a lower proportion (12.5%) of the total 7,961 cases, was the highest proportion since 1990 (63). Between 1951 and 1999 the number of human deaths attributable to bat rabies in the USA was 34, of which 20 were in the 1990s, although eight of these latter cases had no history of bat contact (J.S. Smith, Atlanta, 2000, personal communication). By the end of 2001, Europe had recorded only 672 bat rabies cases, including three human deaths (by 2003 there were 720 bat rabies cases, and human deaths had risen to four).

In the year following the peak (1038) of bat rabies in the USA, European bat lyssavirus was reported in Denmark for the first time—an event which was to change our perspective of the disease in European bats. A relatively large number (20) of serotine bats was found positive, to be followed by 105 in 1986 and by 48 in 1987. These 163 cases in three years were followed by only two cases over the next six years (Table 17.1). Was this an actual decline in disease incidence or was there a change in policy, perhaps influenced by a perceived threat to loss of rabies-free status? Interestingly perhaps, a further 29 cases were reported in the last three years of the century (Table 17.1). Events in Denmark triggered action in the Netherlands and surveys began which continue to this day. Their results provide our best incidence figures in that over an eleven year period, 20% of the sick or dead serotines examined were rabies-positive (Table 17.2) but this does not, of course, tell us the prevalence of disease in the bat population. Indeed, it is unfortunate that we currently know little about the prevalence of disease or of antibody status in free-flying European bats. The only other country to have reported a substantial number of positive bats (136) is Germany, where there have been no peaks or troughs but a low number reported in almost all years, with maxima of 17 in 1990 and 14 in 1999.

CONCLUSIONS

Without doubt the species most frequently reported positive in the second half of the 1980s was the serotine, but since that time most national reports to the WHO Collaborating Centre for Rabies at Tübingen contain case numbers only and it is by no means certain that all of the bats were serotines. Also, too few cases have been reported in Myotis spp. bats to draw conclusions concerning the geographical range of genotype 6 viruses. It is interesting to note that serotines and Daubenton’s are the only two of the 31 European bat species considered by Stebbings and Griffith (114) to be ‘not threatened’ by extinction, although this category for Daubenton’s is questioned and dasycnemes are considered to be endangered. Which ecological factors might influence rabies incidence in these species? As serotines are not considered to be endangered, presumably their population density is sufficiently high to withstand sharp decreases arising from adverse conditions, including lyssavirus infection, although even in normal circumstances population level recovery can only be slow due to the period necessary for biological reproduction. Yet the disease is able to persist. In the early years a few cases in other species were reported (Table 17.1) and it is too soon to rule out the possibility of other reservoir species. A more critical survey of European bats is required if we are to understand the lyssavirus disease within them.

Where USA and European bat lyssaviruses differ the most is in the virus types. In the USA the genotype 1 bat viruses differ from but are closely related to those found in terrestrial animals. In addition, there is a much greater diversity at the molecular level than is found in European bats (J. Smith, Atlanta, 1999, personal communication). ‘Spillover’ of USA genotype 1 bat viruses has been shown to occur (20) but in Europe during the oral vaccination campaigns to eliminate fox rabies, several countries have used Mab-Ns to characterise all lyssaviruses from positive cases and no bat lyssaviruses have been reported among them. However, in 1998 a sheep in Denmark died of a genotype 5 lyssavirus infection (13) and this event was followed by the death of two other sheep which died in the same vicinity, although they also showed evidence of listeriosis (14). Until 2000, this remained the only evidence of ‘spillover’ of bat lyssavirus to terrestrial animals (other than man) in Europe and thus must be considered an extremely rare event. On
the other hand, the immune status of wildlife species and pet animals in Europe is currently very high; in future years when the population immunity level falls, there may be a greater opportunity for spill-over to occur.

Is European bat rabies a ‘new’ phenomenon? If the North American experience is anything to go by, probably it is not. There, the extent of the disease was quickly realised, but early cases in Europe were regarded as little more than scientific curiosities. In the 1970s and early 1980s, most European countries were heavily involved with terrestrial animal (wildlife) rabies. Is it a coincidence that the country to record the highest number of bat rabies cases in 1985/1986 (Denmark) was a rabies-free country? From time to time there have been reports of rabies in Asian bats (data not shown) and since 1996 lyssaviruses have been found in all four of the major species of fruit bats in Australia and also in at least one species of insectivorous bat (K. McColl, Geelong, 1999, personal communication). We have learned in the last half century that the disease in bats is present in most parts of the world, if it is not ubiquitous, and it seems most reasonable to assume that European bat rabies is not a new phenomenon but one that has existed unrecognised for a very long time.

We have learned little of the transmission mechanisms and course of the disease in European bats. Similarly, our knowledge of the prevalence in general and within colonies in particular, as well as our understanding of its immunobiology, are limited and fragmentary. Although the WHO Collaborating Centre for Rabies at Wusterhausen collects statistics and occasionally publishes reviews of the subject, there is no Europe-wide programme of research. Bats are gentle creatures which are of great benefit to man. We have a duty to ensure their survival. But we also have a duty to protect the public from dangerous lyssavirus infections and to accomplish that we need to investigate and understand European bats and European bat lyssaviruses. An opportunity to achieve this may arise when terrestrial animal rabies is eradicated from Europe. Indeed, such knowledge may then become critical for the continued control of lyssavirus disease in Europe.

Acknowledgements

We record our thanks to Dr Kenneth A. McColl of the Australian Animal Health Laboratory, Geelong, for his critical reading of the script and helpful suggestions, and to Drs Winfried W. Müller and James H. Cox, of the WHO Collaborating Centre for Rabies Surveillance and Research, for the provision of statistics and some of the background information.

References


Chapter 17

Historical Perspective of Rabies in Europe and the Mediterranean Basin

Chapter 17


**Addendum**

Since the drafting of this chapter, Dr Arthur King has passed away and many of his suspicions have been confirmed.

In the UK, the second isolation of a European bat lyssavirus type-2 (EBLV-2) from a Daubenton’s bats (*Myotis daubentonii*) occurred in September 2002 and a bat conservationist died in November of the same year in Scotland from rabies caused by EBLV-2. The human death, the first recorded case of human
rabies contracted in Great Britain for 100 years, suggests either that EBLV-2 may be endemic in British bats or that transient epizootics may occur. EBLV-1 was also detected in a stone marten in Germany in 2001.

Four additional rabies-related viruses have been isolated recently from bats in Eurasia: Aravan virus, Khujand virus, Irkut virus and West Caucasian Bat virus. The last occurred 150 km from the eastern Turkish border. The emergence of these new lyssaviruses represents a clear threat to human and animal health, indicating that Europe needs to remain vigilant.

### Appendix 1

<table>
<thead>
<tr>
<th>Phylogroup</th>
<th>Genoserotypes</th>
<th>Species (tentative species)</th>
<th>Abrev. (ICTV)</th>
<th>Geographical origin</th>
<th>Potential vector(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1 – 1</td>
<td>Rabies virus</td>
<td>RABV</td>
<td>World (except several islands)</td>
<td>Carnivores (world) bats (Americas)</td>
</tr>
<tr>
<td>I</td>
<td>4 – 4</td>
<td>Duvenhage virus</td>
<td>DUVV</td>
<td>Southern-Africa</td>
<td>Insectiv. bats</td>
</tr>
<tr>
<td>I</td>
<td>5 – ?</td>
<td>European bat lyssavirus type 1</td>
<td>EBLV-1</td>
<td>Europe</td>
<td>Insectiv. bats Eptesicus serotinus</td>
</tr>
<tr>
<td>I</td>
<td>6 – ?</td>
<td>European bat lyssavirus type 2</td>
<td>EBLV-2</td>
<td>Europe</td>
<td>Insectiv. bats Myotis sp</td>
</tr>
<tr>
<td>I</td>
<td>7 – ?</td>
<td>Australian bat lyssavirus</td>
<td>ABLV</td>
<td>Australia (Philippines ?)</td>
<td>Frugiv./insectiv.bats Megachiroptera</td>
</tr>
<tr>
<td>II</td>
<td>2 – 2</td>
<td>Lagos bat virus</td>
<td>LBV</td>
<td>Sub-Saharan Africa</td>
<td>Frugiv. bats Megachiroptera</td>
</tr>
<tr>
<td>II</td>
<td>3 – 3</td>
<td>Mokola virus</td>
<td>MOKV</td>
<td>sub-saharian Africa</td>
<td>Unknown (isolated from shrews)</td>
</tr>
<tr>
<td>?</td>
<td>? – ?</td>
<td>West Caucasian bat virus</td>
<td>WCBV</td>
<td>Caucasus region</td>
<td>Insectiv. bat (isolated from Miniopterus schreibersi)</td>
</tr>
</tbody>
</table>
CHAPTER 18

RABIES VIRUS VARIANTS AND MOLECULAR EPIDEMIOLOGY IN EUROPE

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Summary

Molecular epidemiology continues to be an important tool for rabies surveillance, epidemiology, risk analysis and research into disease pathogenesis. The re-emergence of classical rabies virus strains and the emergence of other lyssaviruses, particularly those isolated from bats, can be detected and characterised through continuing vigilance, routine testing and the use of molecular phylogeny. The virus isolate genetic databases that exist, not only in Europe but throughout the world, will be invaluable tools when considering these continuing threats to human and animal health.

Keywords: molecular epidemiology, phylogenetics, quasispecies, surveillance

INTRODUCTION

Rabies disease is an encephalitis provoked by viruses belonging to the Lyssavirus genus. Lyssaviruses are considered to be capable of infecting all mammals, but host susceptibility may be dependent on the virus variant involved. The level of susceptibility of a particular reservoir species is thought to involve virus adaptation to that host, resulting in what is often referred to as a virus ‘biotype’. In the case of classical rabies virus (RABV, genotype 1) host mammals are usually small- to medium-sized carnivores all over the world and also bats in the Americas. The other lyssaviruses (six additional genotypes previously known as rabies-related viruses – RRVs) appear to have a species ‘barrier’ which generally restricts them to circulation in a variety of bat populations. The reservoir species for Mokola virus (MOKV genotype 3), however, is unknown. In general infection of non-reservoir species by lyssaviruses is known as a ‘spillover’ event. These cases are not unusual, but limited spread or lack of maintenance in the new host population often characterise them. However, it is possible that lyssavirus evolution and adaptation occur during these spillover events. On rare occasions a virus may adapt to a new species, thus potentially creating a new virus biotype that would then be stable in that host species. The resultant outcome of this strategy is the current situation where multiple biotypes of virus can be observed circulating in different geographical areas and reservoir species (43), for example RABVs in dogs, foxes and raccoon-dogs in parts of Europe.

The focus of this chapter are the lyssaviruses endemic in Europe: rabies viruses (genotype 1: RABV) and European bat lyssaviruses of type 1 (EBLV-1, genotype 5) and type 2 (EBLV-2, genotype 6) and relevant genes in relation to their use in molecular epidemiology in order to explain disease progression and possible elimination of rabies viruses throughout parts of Europe. The phylogeny of RABV in red foxes, raccoon-dogs and other terrestrial mammals is examined in some detail, as is that of the European bat lyssaviruses (EBLVs).

LYSSAVIRUS GENES

The Lyssavirus genome is composed of a single strand of negative sense RNA (around 12 Kb) comprising five discrete genes plus the vestigial non-coding pseudogene (psi). From the 3’ to the 5’ end these genes encode for the nucleoprotein (N), the phosphoprotein (M1 or P), the matrix or membrane protein (M2 or M), the glycoprotein (G), psi, and the RNA-dependent RNA polymerase (L) (Fig. 18.1). The G and N gene products are the major stimuli involved in eliciting an immune response in vaccinated animals (73).
and therefore have been the focus of much research. Detailed molecular information for the first of the RABV genes became available in 1981 when the G gene was cloned and subject to nucleotide sequencing (2). In general, the highly variable regions of the genome are more likely to represent the natural evolution of the virus outside any external selective pressure and the most suitable for differentiating closely related isolates. In contrast, the conserved regions are suitable for typing distantly related lyssaviruses.

Molecular studies using sequenced regions of the genome have investigated geographical virus diversity on global, national and regional scales and also chronologically. This type of molecular work began in the early 1990s using the N and psi genes (15, 16, 51, 52, 58). It has continued in more detail (1, 33, 66) with the most recent data focusing on N, G and P genes (17, 46; Chapter 19, Nadin-Davis et al.). Figure 18.1 is a schematic diagram of the RABV genome and the various regions sequenced for phylogenetic studies.

Figure 18.1 – Rabies genome and schematic representation of some genomic regions which have been studied

The N gene has been the main focus of molecular epidemiology studies for several reasons. Firstly, because the results could be related to the findings of monoclonal antibody characterisation of viruses. Secondly, because of its role in immunity (particularly against heterologous virus challenge) and thirdly, because it encodes an internal protein involved in the regulation of transcription and replication and could therefore be an important factor in host adaptation (33). Last but not least, it has been conserved over time due to structural constraints, thereby allowing evolutionary studies to be undertaken (16). Initially the full length N gene was studied, but later it was shown that 400 bp of the 3’ end of the gene were sufficient for phylogenic analyses (17, 33). Recently, an added advantage has been the large number of sequences available in various databases which allows detailed virus isolate and geographical and temporal comparisons (1, 6, 17, 38). The pseudogene has also been used in molecular epidemiological studies because it is the most divergent genomic area, and as such the most sensitive ‘clock’ for measuring virus evolution (51, 52).

In a recent study, a partial G gene sequence (690 bp at the 5’ end of G) was also targeted for analysis (17). This was because it encodes the surface glycoprotein and therefore is subject to a high level of antigenic pressure (7), has an important role in pathogenicity and immunogenicity (6, 22) and it also interacts with cellular receptors for lyssaviruses (32). The latter suggests it may be involved in determining host range (62, 64). Using the nucleotide sequence from the ectodomain of the G gene, phylogenetic trees have been drawn suggesting that genotypes 1 and 4-7 form a phylogroup I and genotypes 2 and 3 form a phylogroup II (6, 37). The databases for G gene sequences are somewhat smaller than those available for the N gene, but they are expanding at a rapid rate, providing an important resource for molecular epidemiologists.

An overriding reason to conduct molecular epidemiological research on wildlife (sylvatic) lyssavirus variants has been that most RABV vaccines are still derived from isolates obtained between 50-100 years ago (52). Such strains are unlikely to take into account the genetic variation of the virus in the field accompanying the spatio-temporal fluctuation of reservoir species. Vaccine failures are rare but do occur (35, 56) and may in part be explained by differences between vaccine and street strains. The phylogenetic information now accumulating should allow for the detection of genetic divergence of the wild virus from the vaccine strains. These new variants may require the development of new vaccines.
Point mutation is the most likely mechanism involved in rhabdovirus evolution and because of proof-reading errors associated with the RNA polymerase, the level of mis-incorporation of bases is potentially high (61). This dictates that RNA viruses exist as heterogeneous populations or ‘quasispecies’. The quasispecies are thus a population of mutants having an equilibrium distribution as a result of mutation, selection, ‘fitness’ and adaptation to a new host (70).

**QUASISPECIES – RABV POTENTIAL FOR ADAPTATION AND EVOLUTION**

The concept of quasispecies is widely accepted but it has been difficult to confirm their existence in virus samples. One difficulty in virology and particularly in molecular epidemiology and phylogeny is that the methods used select a single (or few presumably dominant) isolate from a virus population and therefore other variants would be overlooked. Indeed, nearly all virus studies are selective in that they examine a subset of viruses that lead to disease or fatalities. Field isolates, particularly from wild animals, which fail to infect the nervous system or are clinically silent and fail to kill the host are hardly detected and are therefore excluded from these analyses.

Benmansour and co-workers (7) have suggested that quasispecies exist in RABV using the glycoprotein sequence. A high level of intrinsic heterogeneity has been directly observed during the adaptation of a human RABV isolate to growth in cell culture (7). The human RABV isolate cultured from saliva had only five amino acids difference (1%) from a canine isolate, an indication of their close relatedness. Using G gene sequence, a street RABV isolate from a dog was compared with that of the Challenge Virus Standard (CVS) displaying a 10% divergence in overall amino acid composition. These differences could have originated during transmission from dog to dog, dog to human, or during isolation on cell culture; they do nonetheless demonstrate genetic evolution of street RABV. This evolution was further evidenced by the selection of cell-adapted virus variants which displayed new amino acid substitutions in the glycoprotein, one of which (Arg333) was associated with neuro-virulence in mice (7). This intrinsic heterogeneity was further demonstrated by sequencing molecular clones of the G gene, which revealed that only one third of the viral genomes present in the brain of a rabid animal (dog) had the consensus sequence. These ‘quasispecies’ provide the virus with the permanent potential to adapt quickly and easily to new environmental conditions.

The occurrence of RABV quasispecies has also been shown to have implications in disease pathogenesis. Two virus variants of the ‘fixed’ CVS-24 strain have also been described that differ genotypically (ten amino acid differences in the glycoprotein) and phenotypically. One is dominant in neuronal cells, the other in non-neuronal cells, both in vitro and in vivo (murine model) (41). Other factors which may be involved in generating sequence heterogeneity in RABV, include duration of infection, route of transmission, virus load, and virus host protein interactions (34).

Kissi and co-workers (34) examined the potential for variation in a wild RABV isolate from a fox and studied mutations in several genes following passage in mice, dogs, cats and cell culture. Substitutions in the glycoprotein again were at a higher rate. However, passage (2-3) in animals other than mice was not sufficient to produce a new dominant variant from the quasispecies population. It has been suggested that two mechanisms of genomic evolution of the RABV quasispecies exist during adaptation to environmental change. Firstly, a limited accumulation of nucleotide mutations with no replacement of the master protein sequence (conservative changes) and secondly, a less frequent but rapid selective overgrowth of favoured protein variants where advantageous mutated amino acid has occurred (34).

In the field, genetic variability has been especially evident at wave fronts of disease spread, an observation that reflects and supports the quasispecies concept; that is, the hypothesis that virus populations evolve most rapidly in a new environment. After a few ‘passages’ most fit variants are stabilised rapidly and the corresponding mutations are fixed (23, 26). Despite the obvious potential for random mutation, overall high levels of genetic conservation are found in wild RABV. This suggests that substantial selective pressures do operate. RABV genomes appear to become trapped at local fitness optima, therefore adaptations to new hosts or the adoption of other transmission strategies requires overpassing of strong structural and functional constrains on the virus. Several simultaneous co-adaptive changes may be
required in order to effect host species transfer (70) as appears to have occurred with the wolf to dog and fox to raccoon-dog examples described below.

**Epidemiology of Rabies in Europe**

Rabies in Europe provides excellent examples of temporal change both in the reservoir species and through geographical spread. The disappearance of wolves and the reduction in the number of stray animals had minimised two ancestral reservoirs for rabies in the 1900s (48, 74) leaving central Europe free of rabies for several decades. The disease, however, had not entirely disappeared as new hosts such as wild carnivore species became infected (52, 71). The epizootic of rabies in the red fox began in 1939-1940 on the Russian-Polish border and in northern Poland (57, 75; Chapter 2, J. Blancou). Following a period of apparent host adaptation, the disease spread in foxes to the rest of Europe moving west and south at 20 km-60 km/year. The progression of disease was well documented from 1945 (63), reaching France by 1968 (3, 9) and northern Italy in the early 1980s (27, 28) (Fig. 18.2). The main reservoir host species of lyssaviruses in Europe are the red fox, raccoon-dog and bat species (Fig. 18.3). Rabies in companion animals (pets) in this part of the world has largely been controlled (with the exception of Turkey and the Russian Federation) and is being radically reduced in foxes due to vaccination programmes (43).
MOLECULAR EPIDEMIOLOGY AND PHYLOGENY OF RABV IN EUROPE

Rabies in continental Europe represents an ideal opportunity to undertake molecular analyses because several strains of RABV (genotype 1) co-circulate within this region and infect a range of mammalian species. Data on the molecular epidemiology and evolution of lyssaviruses in Europe (1, 17, 38) are summarised below. It has been shown that two distinct, but related patterns exist; viruses from the same geographical area group together as do isolates taken from the same reservoir host species. A recent study (17) examined sequences from 245 virus isolates, 86 of which were from Europe. The European isolate dates ranged from 1972-1996 and included 51 red fox, 13 raccoon-dog and 13 other mammal isolates, from 15 different countries. The phylogenetic analyses indicated that there was a gradual dispersal of rabies from the north-east to the south-west across Europe (further details below), confirming other non-molecular epidemiological data (12). One barrier that appears to have disrupted the fluidity of virus transmission in Europe is the Vistula river in Poland (69). It has been suggested that this might be due to restrictions in movement of infected hosts, since virus isolates in central-eastern Europe have a strong geographical clustering (17).

During the westward and southward movements of RABV across Europe it also appears that two changes in host species took place. Phylogenetic evidence suggests that the first was a spillover from dogs to foxes occurring in Eastern Europe. The second host change appears to have occurred in north-eastern Europe when fox RABV colonised raccoon-dogs (17). The G gene sequence also highlighted three virus strains from humans, red fox and cattle in Eastern Europe that represent divergent lineages. They appear to have been derived from dog RABV isolates and may represent spillover infections.

All RABVs in Europe are not equally able to infect dogs, foxes and raccoon-dogs (10, 11). Therefore cross-species transmission into a new host in nature is probably due to a small number of genetic changes, involving minimal amino acid replacement in the viral genome (34, 65). It was found that very few amino acid changes accompanied the change in transmission from dogs to foxes or raccoon-dogs, the N and G proteins were strikingly conserved among the isolates studied by Bourhy and others (17). One possible explanation is that key mutations may reside in gene regions other than those sequenced and these have enabled the adaptation of RABV to different host species.

The phylogenetic trees using complete (1350 bp) and partial (400 bp) N sequences, allowed four European virus biotypes, sharing amino acid changes and preferentially infecting one or two species, to be identified (17). Just 10 amino acid positions in the nucleoprotein appeared to be critical for the distinction of the four groups. Two fox and one raccoon-dog biotypes appear to have evolved from RABV adapted to dogs. A third fox biotype was derived from an earlier fox strain. A precise geographical distribution of these biotypes was also determined, one in each of East Europe (EE), Central Europe (CE) and two in West Europe (WE). The Northeast Europe (NEE) group contains virus isolates from both the red fox and the raccoon-dog. Using partial (690 bp) G sequence produced a similar tree, the groups were separated into locations: EE, CE and WE, but there was only one WE group not two, and the NEE fox-raccoon-dog group were again removed from the remainder of the fox lineages (17).

Molecular sequence analyses were made, using the whole (and partial) psi hypervariable region for 12 (six fox and six other animals; cats, stone martens and a sheep) RABV isolates from three regions of north-eastern France (52). The wild isolates exhibited an intrinsic stability with only 2%-3% diversity but together they were divergent (15%) from the vaccine strains. No correlation was observed between the isolate genetic diversity and the animal host from which the virus was obtained, indicating that the red fox, in France, was responsible for transmission to other species. A good correlation between genetic and geographical criteria was noted indicating a slow evolution of the wild virus in parallel with the spatio-temporal progression of the epizootic. These data confirm, at a molecular level, the biological level observations by Aubert et al. (4) as outlined below.

Recent studies examined 400 bases of the 5′ end of the N gene sequence for classical RABV (n=57), EBLV1 (n= 7) and EBLV2 (n=6) in Europe (38). Figure 18.4a illustrates a phylogenetic tree indicating that
five RABV sub-groups exist in Europe and that there is very significant phylogenetic distance between these and the EBLVs. These were distinct from the vaccine strain CVS (Vaccine 2). The Europe 2 (E2) group containing fox and raccoon-dog isolates from the Baltic regions may be equivalent to the NEE group previously described by Bourhy et al. (17).

**European Genotype 1**

**Figure 18.4a** – Phylogenetic tree indicating the European RABV sub-groups and EBLVs
Similarly, the E1 dog/human group probably equates to the EE group, whilst the E4 fox group may mirror the WE group and the E3 fox group may represent the CE group. The E5 group is a canine biotype from Turkey. The map in Figure 18.4b shows the locations of our group isolate groupings (E1-E5), whilst the isolates used to generate the tree and map are listed in Table 18.1.

Table 18.1 – Origin of 70 rabies viruses used to generate Fig. 18.4a

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<td>Netherlands Bat</td>
<td>1987</td>
<td>Genotype 6</td>
<td>RV 228</td>
<td>Netherlands Bat</td>
<td>1989</td>
<td>Genotype 6</td>
</tr>
<tr>
<td>RV 33</td>
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<td>1987</td>
<td>Genotype 6</td>
<td>RV 594</td>
<td>Switzerland Bat</td>
<td>1989</td>
<td>Genotype 6</td>
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<td>RV 146</td>
<td>Germany Bat</td>
<td>1986</td>
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<td>1989</td>
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<tr>
<td>RV 147</td>
<td>Germany Bat</td>
<td>1986</td>
<td>Genotype 6</td>
<td>RV 628</td>
<td>England Bat</td>
<td>1996</td>
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</tr>
</tbody>
</table>
European red fox (*Vulpes vulpes*) rabies is one of the best described epizootics (9, 12, 60). The frontal wave of rabies migration across Europe, with mortality in foxes of between 20%-60% at and behind the front, halted despite available hosts in the middle of France and northern Italy, for reasons that have not been explained. Disease perpetuation is dependent on host species density of >1 km\(^{-2}\). The spatio-temporal dispersal patterns of rabies appear to follow a micro-epidemic model (54). Normal foxes are territorial animals and as a rule will not enter a neighbouring territory. In contrast, rabid foxes which become disorientated may travel long distances or may wander into a new territory. When this occurs, territorial disputes involving biting and scratching are common. As a result of the behaviour modification associated with disease, the rabid fox will potentially transmit disease. Generally, disease spread is from home range to home range, and occasionally over longer distances. The progress of an epizootic is stopped in zones of low fox density or where more than 60% of the fox population is immunised through oral vaccination (70). Different temporal patterns of prevalence are recorded in different geographical areas, with seasonal variation (autumn-winter peak at a time of high social contact) and differences in social behaviour of juveniles and adults (70).

An interesting hypothesis concerning a modification and adaptation of RABV isolate has been raised to explain the natural slowing and even regression of the rabies epizootic in Europe since 1978 (4). In an experiment where two groups of foxes were infected with RABV strains collected from naturally infected foxes in France from either 1976 or 1986, it was shown that all became rabid and transmitted RABV to their non-inoculated cage-mate. The difference detected was that the interval between the death of the inoculated fox and that of the cage-mate was significantly more variable with the earlier strain (1-33 days) than with the latter strain (10-14 days). The reduction of the time interval between infection and death could reduce the efficacy of RABV transmission and explain the decrease of the spread of disease (4).
Interestingly, many intangible factors have been attributed to the reduction of rabies in Europe including the lack of a suitable host. Rabies control strategies have focused initially on the use of strict quarantine laws and in the 1970s by using oral vaccination (5). Both strategies have been highly successful in preventing virus spread and altering the epidemiology of disease in Europe. Briefly, oral vaccination field trials were first reported in Switzerland in 1978 using a live-attenuated RABV strain (Street Alabama Dufferin-SAD). During the 1980s and 1989-2000, many European countries participated in oral vaccination programmes which resulted in the elimination of fox rabies in several European countries, with an overall 99% decrease of reported rabies cases (43). Both live-attenuated RABV strains (SAD B19, SAG1, SAG2) and a recombinant vaccinia virus expressing the rabies G protein were used as oral vaccines.

ARCTIC FOX RABIES

Rabies appears to be endemic throughout the Arctic region, and several epizootics have been documented in the last 30-40 years (49). A monoclonal antibody (anti-nucleocapsid (N) Mab P-41) has shown that RABV isolates from the arctic fox (*Alopex lagopus*) epizootic are distinct from those of the red fox epizootic (19). Outbreaks of disease in Finland and Russia were also caused by RABVs that react with this specific Mab epitope (47). The periodic occurrence (every 3-5 years) of arctic rabies is somewhat unique to arctic and sub-arctic regions and may be linked to the density of arctic foxes cycling in parallel to that of lemmings (19). Migration of arctic foxes can extend over long distances compared to that of red foxes and this may explain the spread of the disease around the arctic regions. Such a phenomenon is thought to explain the first recorded outbreak of rabies in the Svalbard islands of Norway (49).

RACCOON-DOG RABIES

At the end of the 1960s, the role of the wolf (*Canis lupus*) and the raccoon-dog (*Nyctereutes procyonoides* Grey) in the ecology and epidemiology of rabies in the United Soviet Socialist Republics (USSR) increased rapidly. This was caused by a lack of attention to wolf control and the introduction of the raccoon-dog into the European part of the USSR (18). Rabies in raccoon-dogs has continued to be diagnosed, mainly in European Russia, Estonia, Poland, Finland, Lithuania and Latvia, since the early 1980s (13, 17, 25, 33, 53). An epidemic that occurred in raccoon-dogs between 1988 and 1989 in Finland when numbers were above 1 km⁻² was eradicated by oral vaccination. Monoclonal antibody testing (Mab P-41) revealed that the virus was an arctic-type strain (50).

Available data suggest that foxes were the original source of raccoon-dog rabies virus. In Poland, there are four phylogenetic groups of RABV, a fox-raccoon-dog and three different fox virus variants (53). In addition, the NEE group of viruses in foxes and raccoon-dogs would suggest that the source of the raccoon-dog rabies (biotype) might be the fox (17). Figure 18.4b shows that, with the exception of one isolate, the two raccoon-dog viruses examined belonged to the Baltic geographical group (38).

The question remains whether or not the raccoon-dog is a genuine distinct biotype reservoir species or a spillover host. Countries such as Estonia, Lithuania, Latvia, Poland and the Russian Federation, which have rabies in their raccoon-dog populations, still report the main proportion of disease in foxes (43). This latter report assumes that raccoon-dog rabies is dependent on the presence of the fox as a vector. Such a situation exists for the fox-dog biotype overlap in the Russian Federation (43). The raccoon-dog hibernates and is known to harbour virus over winter, possibly maintaining rabies virus infection in areas of low fox densities or where vaccination campaigns would otherwise have eradicated it (39). It remains unknown whether these animals represent a new threat in terms of rabies disease dispersal as raccoon-dogs spread westward. Molecular epidemiological surveillance will continue to be essential as rabies can also be expected to undergo continued adaptation to local mammals.

RABIES IN OTHER TERRESTRIAL MAMMALS IN EUROPE

Some rabies-susceptible wild carnivore species reach population densities higher than those of foxes and raccoon-dogs, but do not support independent rabies epizootics. It has been suggested that they and domestic animals represent self-limiting spillover infections. Badgers are the only animals whose numbers
are noticeably reduced during a rabies disease epizootic. However, population density recovery is very slow and thus they are not able to support rabies over a prolonged period. The only country where badger densities alone are high enough to maintain infection is in the United Kingdom (UK), which remains rabies free. Examples of rabies in animals other than domestic mammals, pets and those mentioned above include hedgehogs, water voles, roe-deer, martens, voles, stoats and weasels (17, 52, 59, 70). Individual virus isolates have been analysed by molecular methods but numbers are low, making it difficult to draw epidemiological conclusions.

**BAT RABIES IN EUROPE (EBLVs)**

All European bat species are insectivorous and some species are reservoirs of rabies viruses (specifically, genotypes 5 and 6); within the past two decades more than 650 cases of bat rabies have been reported (44; Chapter 17, A.A. King et al.). The degree of threat to humans, domestic and other animals of rabies from a bat source is unclear. However, the risk appears to be low since only three human deaths and one case in a sheep have been reported so far (24). Few cases of bat rabies were reported before 1984, but since 1985 the disease has been recognised in bats of many countries. Of the 376 EBLV cases reported during 1985-89, 363 (96.5%) were recorded in Denmark, Germany and the Netherlands and of these, 339 (93%) were in *Eptesicus serotinus* (serotine) bats; the virus involved subsequently became known as EBLV1. Other countries that have now reported bat rabies are Poland, Yugoslavia, Turkey, Czechoslovakia, France, Spain, Switzerland, Slovakia, Ukraine and UK (Chapter 17, A.A. King et al.).

Initially these European bat lyssaviruses (EBLV1s) were characterised with Mabs, placing them in serotype 4 as a Duvenhage-like virus (21, 30, 31, 40, 55). A second group of bat lyssaviruses was identified in Denmark from *Myotis dasycneme* and *Myotis daubentonii* bats (8) and a human case (probably of bat origin) in Finland (36). By 1990, EBLVs were characterised as two distinct biotypes EBLV-1 and 2 (genotypes 5 and 6) (6, 15, 40).

Genetic analyses of these bat lyssaviruses began in 1992 based on whole and partial N gene sequences (15, 16, 33, 58). They allowed the genetic classification of lyssaviruses to expand from four to six genotypes (16). Kissi and co-workers (33) showed that there is a limited heterogeneity (3.3%) between EBLV and classical rabies N genes. A more comprehensive study was carried out by Amengual et al. (1), when 47 EBLV isolates and two African insectivorous lyssaviruses (Duvenhage viruses) were compared at the molecular level in order to evaluate their evolutionary relationships. Their phylogenetic study was based on the 3’ partial N gene sequence. Both nucleotide and amino acid sequences placed the viruses into three separate clusters, namely their respective genotypes, genotype 4 (Duvenhage), genotype 5 (EBLV-1) and genotype 6 (EBLV-2). They also showed that there was a low intrinsic heterogeneity between EBLV-1 and 2 and that both EBLV groups had evolved into at least two genetically distinguishable lineages (EBLV-1a or b and EBLV-2a or b) during geographical dispersion. The authors speculated that the different lineages of EBLV-1 were introduced into parts of northern Europe from two different directions, EBLV-1a being the more recently introduced strain from North Africa via the south of Spain. EBLV-1a exhibits a west-east European division whilst EBLV-1b has a north-south distribution. All isolates were from serotine bats with the exception of one from a *Vespertilo murinus* bat from the Ukraine (1993). Thus, EBLV-1a and 1b may represent two variant groups adapted to the same host. The Netherlands is the only country from which both EBLV-1a and EBLV-1b have been isolated.

Epidemiological studies have also shown that there are at least three foci of EBLV-2. The first, an EBLV-2a in *M. dasycneme* in The Netherlands, the second from a human case of an EBLV-2b in Finland, (although it was not proven that the victim was bitten by an infected bat in Finland) and the third an EBLV-2b focus in *M. daubentonii* in Switzerland. There have been only two other cases of EBLV-2b, therefore it is not possible to associate the virus with either species of *Myotis* (1). The lyssavirus isolated in 1996 in the south of England from a *M. daubentonii* (72) is phylogenetically closest to EBLV-2a. In 1997, an EBLV-1a was also found in a frugivorous bat in a Danish zoo. This isolate was identified using sequence analyses of the N (partial) and G genes (67).
The complete glycoprotein sequences of EBLV-1 and 2 have recently been published and compared with those of representatives of the other 5 genotypes (6). The authors suggested two lyssavirus phylogroups, one containing genotypes 1 and 4-7 and the other genotypes 2 and 3.

POSSIBLE FUTURE PROBLEMS AND THREATS FROM LYSSAVIRUSES

The fox oral vaccination programme is not only eliminating rabies from the target fox population, it is also reducing the number of spillover cases and, as the reservoir of disease is diminished, the disease itself disappears. As the number of European countries that are declared terrestrial animal rabies-free continues to grow, continued surveillance becomes of paramount importance. Surveillance before and during vaccination has been and is still satisfactory, but the need for continued surveillance during and after rabies elimination has not always been recognised. Complacency is the very problem that hampers final eradication of disease (42). Residual foci of infected animals can and do lead to new outbreaks or re-infected areas. This can be overcome with sufficient funds to guarantee regular (2-3 per year) distribution of sufficient vaccine baits on a large and long enough scale (45) as has been the case for France and should soon be in Germany. A potential problem may be that once fox rabies is eradicated, there may be a new niche for another spillover event, for example EBLVs to other mammal hosts. Molecular epidemiology will have its role to play in the on-going surveillance required by all countries, those that are either rabies-free, those in the process of eliminating disease, or those that remain endemic. Phylogenetic studies will also continue to be important in terms of potential mutation of viruses and the re-emergence of disease or its introduction into new hosts.

With the diminishing numbers of disease cases in Western Europe, the situation in Eastern Europe becomes accentuated. Eastern Europe still has large endemic areas, many with increasing numbers of reported rabies cases (68) and no current vaccination programmes. Social problems and civil unrest mean that, even if a thorough vaccination campaign could be funded, it is unlikely that the disease would be eliminated. Rabies ignores administrative, state and country borders (14) and as such will continue to present a threat to Europe as a whole.

Other threats that exist are:

(i) the adaptation of viruses to new reservoir/host species, and
(ii) our lack of understanding of and the absence of a means of controlling the rabies-related viruses in bats (including EBLVs).

Firstly, the occurrence of rabies in wildlife remains an under-studied area. Generally it involves a dead-end/spillover situation from foxes, dogs, raccoon-dogs and bats to many wildlife species, domestic animals and humans according to contact rates (43). Evolution of a highly pathogenic new biotype or quasispecies may be generated and result in a new disease outbreak. If the raccoon-dog biotype does prove to be independent of those of the fox it may be difficult to control since raccoon-dogs hibernate and are omnivorous. Secondly, there has been increasing attention paid to the subject of bat lyssaviruses in the past ten years and this is likely to continue as they emerge from relative obscurity, not just in Europe, but all over the world. Little is known about classical rabies viruses in bats (common in the Americas), but even less information is available on the bat (European and Australian) lyssaviruses. In addition, bat species are afforded protection in Europe and some other parts of the world making bat rabies in the native host difficult to study. This situation will also influence control strategies and eradication of rabies if required. In conclusion, surveillance and epidemiology will play a significant role in monitoring the situation as research improves our understanding of the disease and associated risks.

CONCLUSIONS

Molecular epidemiology continues to be an important tool for rabies surveillance, epidemiology, risk analysis and research into disease pathogenesis. The ability of evolutionary trees to establish speciation, geographical correlations and identification of common ancestry makes this an ideal tool to study the spacio-temporal evolution of the Lyssavirus genus. Today, they are seven recognised genotypes distributed
in two phylogroups (see Annex 1 in Chapter 17) and new ones have to be expected with the recent isolations of bat lyssaviruses in Eastern Europe and Central Asia. Genotypes 2 and 3 (phylogroup II) are the most genetically distant from the classical rabies virus strains used in vaccine production. Residue variation tends to vary with genotype implying that changes have occurred along the separation of viruses into discrete groups and are not due to immunological pressure from the host. Moreover, molecular analysis helps at understanding the dynamics of transmission from the animal reservoirs, and thus enables vaccination campaigns to be targeted to the appropriate animal species. A thorough knowledge of the epidemiology of rabies in a specific region is therefore an important pre-requisite for the implementation of control policies.

The genome region encoding the viral nucleoprotein N has been the most popular sequence used in analysing members of the *Lyssavirus* genus. Its strong genetic stability has led to the development of diagnosis methods by PCR that are capable of identifying all known lyssaviruses. Together with the large number of published nucleoprotein sequences, this makes the N protein an attractive region to study. However, other genome regions are also of great interest to study. The gene encoding the phosphoprotein P, because of its great variability and the functional importance of this protein in the viral transcription/replication complex. Most importantly, the gene encoding the glycoprotein G because of the predominance of this protein for lyssavirus immunogenicity and pathogenicity. Comparison of the amino acid sequence of vaccine strains with wild-type viruses allows us to highlight significant residues that constitute the molecular basis of their functional difference.

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Chapter 18


CHAPTER 19
EUROPE AS A SOURCE OF RABIES FOR THE REST OF THE WORLD

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Summary

A rabies virus lineage which appears to be associated with that of European strains is widely dispersed throughout several parts of the world. Phylogenetic studies have demonstrated a large cluster of genetically linked strains originating from around the world, which has become known as the ‘cosmopolitan lineage’. The isolates of the ‘cosmopolitan lineage’ all appear to have originated from the same progenitor virus. It is speculated that the colonisation of Africa and the New World by Europeans played a significant role in its dispersion. The time frames of the emergence of the cosmopolitan group, predicted from evolutionary clock analyses, compares well with historical records of rabies cases. During the first half of the 18th Century urban rabies emerged in Europe from sylvatic rabies due to the increasing dog populations associated with large human settlements. In the latter half of the 18th Century, rabies-infected dogs, travelling with their human masters, brought rabies to new colonies on other continents. Rabies, once established in the dog populations of these colonies, then spread as colonists extended their territories.

Keywords: colonisation, cosmopolitan lineage, evolutionary clock analyses, phylogenetics

INTRODUCTION

Advances in molecular epidemiological methods over the past 10 years have revolutionised our capabilities to track and monitor infectious diseases and these techniques have been widely applied to the study of rabies viruses. These advances include the development of the polymerase chain reaction (PCR) (54), which allows for the specific amplification of one or more selected regions of the rabies virus genome (85), as well as improvements in the acquisition of nucleotide sequences. Variations in the precise nucleotide sequence of a rabies virus gene can provide a molecular fingerprint with which to trace the origins of an isolate; Smith et al. (94) reported the use of such methods to implicate various exogenous dog rabies strains in three human rabies cases in the United States of America. Moreover, nucleotide sequence data can be employed to assess the evolutionary relatedness of viral strains through the application of specialised algorithms which can now be accessed on personal computers. The application of these techniques to:

– rabies viruses of global origin
– rabies virus strains from geographically distinct areas
– large numbers of rabies virus isolates from relatively restricted areas

has delineated the phylogeny of the lyssavirus genus, identified rabies virus lineages associated with distinct areas of the world and examined rabies virus variant emergence at local levels (92). Indeed, molecular epidemiological analysis is now a valuable complement to antigenic methods for rabies virus typing. The goal of this chapter is to briefly review the history of rabies around the world and to examine the phylogenetic evidence that viruses associated with different parts of the world have evolved along independent paths. Particular emphasis will be placed on the African and American continents since these regions are best represented in terms of historical data and the availability of rabies virus isolates for study. As will become apparent, a particular rabies virus lineage which appears to be associated with that of European stocks is widely dispersed throughout several parts of the world. The extent to which historical accounts of rabies in those areas can be correlated with the phylogenetic data will be explored.
THE HISTORY OF RABIES

Africa

It is likely that dog rabies has been present in northern Africa for millennia, since human civilisations in this area have communicated with those in the Middle East and southern Europe where rabies was reported in ancient times (5). However, the first recorded indications that rabies existed in North Africa date from the late years of the 19th Century when Pasteur Institutes were established in Algeria and Tunisia partly with the objective of producing rabies vaccine for treating people bitten by dogs (76, 112). Despite control efforts rabies has been maintained in dogs in this region ever since (8, 21).

In southern Africa, early records of the occurrence of rabies are conflicting. Two early explorers, Barrow (7) and Livingstone (63), noted the absence of the disease in their travels around southern Africa. On the other hand, several other authorities from between the 1770s and 1880s record cases of what they considered as rabies in dogs and people in South Africa (24, 47). Edmonds (32), in describing the outbreak of rabies which started around Bulawayo (Zimbabwe) in 1902, states that some of the old people at the time remembered a similar disease in their younger days. In Namibia, rabies was thought to have occurred in 1887 among dogs and livestock (87) and in Kenya, Hudson (52) was of the opinion that some of the local people there had recognised the disease before the advent of Europeans.

The first authenticated outbreak of rabies in sub-Saharan Africa was confirmed in dogs in 1893 in Port Elizabeth, on the south-east coast of South Africa (53). Domestic dogs were the predominant species involved, with some cases reported in cats and cattle. The outbreak was traced to an Airedale terrier imported from England into Port Elizabeth in September 1892 (18). After limited geographical spread of the outbreak, control measures, including the imposition of tie-up, leashing and muzzling orders and the destruction of unsupervised dogs, were implemented and the outbreak died out at the end of 1894.

In 1902, an outbreak of rabies in dogs was reported around Bulawayo, in the western part of Zimbabwe. According to Edmonds (32) this outbreak was thought to have come from north of the Zambezi River. Communications had increased with that area and rabies was known to occur there, as indicated by the fact that the Lozi ruler, Chief Lewanika, had ordered the destruction of dogs in western Zambia at around the same time. From Bulawayo the epidemic quickly spread throughout most areas of the country (32). Drastic control measures were brought into effect, including destruction of dogs, muzzling and leashing orders and dog taxes. The disease did not spread into neighbouring South Africa, possibly due to dog control efforts along the northern border of that country (42). However, it appears to have entered Mozambique, as the first record of rabies there was in 1908 from the middle regions of the country (114), including Tete, which is not far from the Zimbabwean border. The last case of this epidemic in Zimbabwe was reported in 1913 (91) and the region south of the Zambezi River remained essentially free of dog rabies until the 1940s.

Rabies was not confirmed again in South Africa until 1928 when two boys died of the disease after having been bitten by a mongoose (48). However, there had been several reports of unconfirmed rabies in the twelve years before this time (24). Most of these involved people dying of conditions resembling rabies following bites by yellow mongooses (Cynictis penicillata), genets (Genetta genetta) or domestic dogs. Once the disease was known to exist, more cases were confirmed on a regular basis and a greater understanding of its epidemiology was established. From early on it was recognised that rabies in mongooses was a different entity from the dog strain, in terms of its host pathogenicity and epidemiology, such that Snyman (99) referred to the two as the ‘mongoose type’ and the ‘European type’.

Recent antigenic and genetic analyses have determined that southern Africa hosts two distinct biotypes of terrestrial rabies (see below). One biotype is transmitted in domestic dogs and wild canid species whilst the other biotype is associated with various herpestid (Cynictis penicillata, Galerella sanguinea, Suricata suricatta) and viverrid (Genetta genetta) species. The distinctive viruses of the second biotype exhibit a high degree of genetic and antigenic variation (59, 116), thereby implying that the herpestid biotype has been circulating within this host for centuries, if not millennia, and thus may be indigenous to the region. It is quite
possible that at least some of the sporadic cases of rabies reported in early southern African literature were of this biotype.

North of the Zambezi River the status of rabies in the early colonial period is less certain due to the scanty surveillance prevailing at the time. However, it seems probable that dog rabies did occur sporadically. As mentioned above, Chief Lewanika of Barotseland (western Zambia) ordered the destruction of his people's dogs around 1902 as rabies was present in them (32). Rabies was first reported by the veterinary authorities in Zambia in 1914 (39). In Angola, it was reported from before 1930 (31). In East Africa rabies was reported for the first time in 1912 (52, 105), in dogs in Kenya. The neighbouring countries of Tanzania and Uganda reported their first confirmed cases in 1936 and 1935 respectively, although in both countries the veterinary authorities had suspected the presence of the disease in preceding years (51, 64, 81). Once confirmed, rabies tended to be reported more frequently, but was usually localised and sporadic. With time it became more frequent and widespread in every country, although in some countries, an apparent decline in prevalence was due to declining surveillance. In all these countries domestic dogs were the principal host species, although in Kenya during the 1930s and 1940s, jackals (species not indicated) constituted a significant proportion of cases, in some areas exceeding the reported cases in dogs. Small numbers of rabid jackals were also reported in Tanzania and Zambia (39, 84). The disease in other wild carnivores was rarely reported.

In West Africa, rabies showed a similar historical trend, with sporadic unconfirmed reports in the early years of the century followed by authenticated cases in most areas in the 1920s and 1930s; following this the disease tended to be reported more widely and frequently. Dogs have always been the principal host species throughout this area. In Mali, unconfirmed cases were reported from before 1906 and cases were confirmed in dogs soon afterwards (14). Senegal reported cases of rabies in dogs from 1910 (45). In Nigeria, rabies was first reported in two humans in 1912 but was only confirmed in dogs in 1928, since which time the disease has remained present in the country (15, 113). Annual reports of the Veterinary Department of Sierra Leone from 1949 to 1956 indicate that rabies was present during most of these years. In Ghana, reports of the Veterinary Department (1918-1955) indicate that rabies was not identified initially but was confirmed in 1929 (104) after which it appears to have become enzootic in dogs. In the Democratic Republic of Congo rabies in dogs was confirmed in 1933 but cases thought to have been rabies were also reported as early as 1914 (17). In the Congo (Brazzaville), the disease was first reported in 1921 (13).

In Sudan, rabies was reported in the 1870s, and subsequent cases were reported during and after 1904. As in other regions of the continent, initial reports were sporadic and it was not until after 1925 that the disease was consistently reported (43). Domestic dogs were the principal host species.

On the island of Madagascar, rabies has been present from before the 1880s at least (82). The Institut Pasteur de Madagascar was established in 1898 to investigate the disease and to produce vaccine for human treatment. The disease has been present ever since and is maintained in domestic dogs (71).

Following the disappearance of rabies from Zimbabwe in 1913, the disease in dogs, (but not mongooses or genets), for many years did not invade the subcontinent south of the Zambezi River and northern Namibia, despite the regular occurrence in, for example, southern Zambia. This restriction probably resulted from the presence of two barriers to dog migration. Firstly, the west-east lying Zambezi Valley, which separates Botswana, Zimbabwe and southern Mozambique from Zambia and Malawi in the north, apparently acted as an effective barrier to the southward progression of rabies. This could be due to the wide Zambezi River which flows through it but is more likely due to heavy infestations of trypanosomiasis, to which dogs are susceptible, and which was present in the valley until the tsetse fly host was eradicated in the 1980s. Secondly, the north-western part of the subcontinent (southern and central Namibia and western Botswana) is extremely arid, with low human and dog densities.

Dog rabies eventually invaded southern Africa in the 1940s via the north-west, from Angola. Rabies cases in dogs were present in the extreme north of Namibia, on the border with Angola in the 1920s and 1930s (115). Cases of dog rabies were confirmed in this area in 1938 and again in 1947. From northern Namibia, dog rabies spread into northern Botswana (50) and from there along Botswana's eastern border where the main human and dog populations resided (27, 28). In 1950, the disease entered south-western Zimbabwe
from where it spread within four years to almost the entire country (11). Dog rabies also entered northern South Africa in 1950 (67) and this focus subsequently spread into southern Mozambique and Swaziland. In the 1960s, and again in the 1970s, the epidemic spread southwards along the east coast of South Africa. To this day, dog rabies in South Africa has remained confined to the eastern seaboard.

After the second major introduction into southern Africa in the 1940s, rabies started appearing in new principal host species. The black-backed jackal (Canis mesomelas) was affected in significant numbers in Namibia in the late 1940s (115), in northern South Africa in the 1950s (107) and in Botswana and Zimbabwe in the 1970s (2, 12). Cases in side-striped jackals (Canis adustus) were reported in Zimbabwe soon after the entry of dog rabies in the 1950s and in the 1960s the first of several large epidemics occurred in the Mashonaland area of Zimbabwe (12). In the 1960s, the bat-eared fox (Otocyon megalotis) of the Cape area of South Africa also became a maintenance host (107). Antigenic and genetic studies (59, 116) have shown that the viruses of these cycles are closely related to each other and to the viruses from domestic dogs. Rabies was reported in wild carnivora in other parts of Africa, but apart from reports of jackals in Kenya, which for some years exceeded the number in dogs (52), the domestic dog appears to have been the principal maintenance host species throughout the rest of Africa.

At present, dog rabies is widespread throughout Africa wherever human populations of sufficient density occur, except in parts of the western region of southern Africa. Jackal rabies cycles occur in Namibia, Botswana, northern South Africa and Zimbabwe. Bat-eared foxes are the principal reservoir host in western South Africa. Mongooses, particularly the yellow and slender mongooses (Cynictis penicillata and Galerella sanguinea respectively), are the principal host species for the mongoose biotype around most of the southern African subcontinent.

Apart from rabies, Africa is also host to other lyssaviruses. Lagos bat virus (lyssavirus genotype 2) was originally isolated from fruit bats (Eidolon helvum) in Nigeria in 1956 although it was only recognised as a ‘rabies-related virus’ some years later (90). Further isolates were made in South African fruit bats (Epomophorus wahlbergii), West and central African fruit and insectivorous bats, and cats (106). In 1970, a new virus was isolated from a human in South Africa and it was presumed to have been of bat origin as the man had a history of a bat bite. This virus was recognised as being similar to but divergent from rabies virus and was named Duvenhage virus, after its human victim (70) and was later designated as genotype 4. Only two subsequent isolates have been made, both in Microchiropterid bats (Nycterus thebaica and Miniopterus schreibersii) (106). Mokola virus (Genotype 3) was first isolated from shrews (Crocidura sp) and humans from Nigeria and subsequently, mainly from domestic cats in southern Africa and Ethiopia (117). All three non-rabies lyssaviruses are indigenous only within the African continent.

The Americas

Canada and the United States of America

As in many parts of the world the earliest records of rabies in North America document the urban cycle, the involvement of sylvatic rabies being fully appreciated only after dog rabies was brought under control in the mid 20th Century (102). Prior historical reviews refer to rabies in dogs as early as 1753 in the state of Virginia whilst the first major recorded outbreak in the United States of America (USA) occurred in Boston in 1768 (58, 98). By the 1780s the disease had spread to dogs in most major towns and cities of the mid-Atlantic states and rabies is reported to have been commonly encountered in dogs in the Mississippi valley by 1860. Subsequently dog rabies appears to have followed the westward movement of migrants and their animals across the continent and by the turn of the century it had reached the west coast of the United States of America (USA).

A review of the history of rabies in Canada (108) described the first recorded human case; in 1819 the Governor-in-chief, the Duke of Richmond, succumbed to the disease close to the site of the present-day capital, purportedly after being bitten by a fox. A second human death, reported in Quebec city 20 years later, was linked to the bite from a rabid dog. Although these two reports demonstrate the presence of rabies in animals in the Dominion at that time, the reservoir hosts involved are unknown since there is little other information on the extent of the disease until the 20th Century. In 1905, sporadic dog cases
were reported in southern Saskatchewan, probably due to spillover from the state of North Dakota where rabies had been recognised some time before. Several subsequent limited outbreaks in central and western provinces are known and in many cases the disease was traced to dogs originating from the USA. In addition to several isolated cases, three major and distinct epizootics of dog rabies are documented in Ontario and Quebec between 1907 to 1945. The first outbreak, which resulted from a rabid dog which crossed into Ontario from New York state at the Niagara peninsula in 1907, lasted ten years and spread throughout southern Ontario before disappearing. The second outbreak, believed to have been initiated by hunting dogs imported from the USA, was identified north of Hull, Quebec in 1926. This epizootic spread into eastern Ontario and into eastern Quebec, including the city of Montreal, before subsiding by 1934. The third epizootic which infected several counties in south-western Ontario lasted just over three years (1942-1945).

Since the 1940s and especially after the Second World War, dog control measures such as muzzling, stray animal control and dog vaccination campaigns effectively brought urban rabies under control (102). Sylvatic rabies then emerged as the principal source of this disease for humans and their domesticated animals, although there had been indications that rabies was spread by wildlife much earlier. For example, an epizootic involving dogs, wolves and foxes was noted in Ohio in the early 1800s; in addition rabies was reported to be spread by foxes in Massachusetts in 1812 and in Alabama in 1890 (58). In 1940, an outbreak of fox rabies in Georgia was recorded following an incident in which a hunting dog, subsequently found to be rabid, bit two wild foxes during a hunt (57). The disease became epizootic in foxes (both gray *Urocyon cinereoargenteus* and red *Vulpes vulpes*) and within a few years this outbreak had spread to neighbouring States including Florida, which reported several cases from 1953-1958 (56). By 1960 fox rabies occupied the entire southern USA as far west as Texas and contributed substantially to the high level of fox rabies prevalent in the country at that time (120). Fox rabies levels have since declined although the disease still persists in gray foxes in parts of Texas and a geographically separated and distinct population of gray foxes in Arizona (61).

The far north has also proven to be a major source of rabies spread by the arctic fox (*Alopex lagopus*) (25). The presence of a disease resembling rabies had been reported in canids in Greenland in the late 1800s and from 1907 onwards many other reports of canine and human rabies came from Alaska and northern Canada (58). By the middle of the century, the laboratory identification of infections in foxes and wolves from Alaska and several parts of northern Canada (80) had established the role of wild canids in spreading the disease to sled dogs. Several epizootics originating from arctic regions are known to have spread into more southerly areas of Canada, e.g., into Manitoba in 1951 and into Alberta from Fort Smith (North West Territories) in 1952 (108). However, neither of these outbreaks persisted for more than a few years. The most extensive and long-lived of these epizootics appears to have originated from Baffin island and moved to the community of Sugluk in northern Quebec where, in 1950, a large number of sled dogs succumbed to rabies after having been fed fox carcasses for much of the previous season. The disease, which was spread almost exclusively by red foxes, then moved southwards and reached northern Ontario by 1954 and the southern part of the province by 1956. A few scattered cases also suggest that there was concurrent movement of this epizootic into Labrador and Newfoundland. Reports indicate that the epizootic spread eastwards from Ontario into Quebec and then to New Brunswick as well as into the northern States of the USA. In most areas the disease died out but it became enzootic in the red fox population in southern Ontario, from whence it periodically spilled over into neighbouring regions of Quebec and New York State. Whilst the red fox is believed to have been the principal host the striped skunk may act as a secondary reservoir since, despite extensive control measures involving oral vaccination of foxes (65), pockets of this enzootic continue to this day, especially in skunks (A.I. Wandeler, personal communication).

Skunks are known to have been a source of rabies in the Americas as early as 1826 when spotted skunks (*Spilogale putorius*) were reported to transmit the disease to humans in California (58, 78). Rabies was also known to afflict skunks in the western and mid-western USA in the late 1800s and early 1900s, since significant numbers of human deaths from rabies are known to have occurred following skunk bites (122). Since the 1940s however, skunks have been recognised as a major wildlife rabies source (22, 46). An outbreak of skunk rabies in the mid-west occurred in Iowa in 1945, subsequently spreading to several north central States before entering Manitoba, Canada in 1959. The outbreak continued to spread westward as far as Alberta by 1971 and persists to this day in the north central region of the USA and
western Canada. Another focus of skunk rabies occurs in the south central States including Texas and neighbouring states (61). The striped skunk (*Mephitis mephitis*) is by far the most frequently reported species although other species which are less commonly encountered by humans (e.g. spotted skunk) may be involved in disease maintenance (58).

Raccoons (*Procyon lotor*) were not generally recognised as a source of rabies until the emergence of a localised outbreak in this species in Florida, with the first case reported on the eastern coast in 1947 (69). During the 1950s, this outbreak spread throughout the Florida peninsula and became established as an enzootic. By the 1960s, raccoon rabies had spread to the northern portion of the state and entered southern Georgia in 1962. This northerly movement continued through Georgia in the 1960s and entered South Carolina in 1972. Whilst this south-eastern epizootic continued to move northward, reaching North Carolina in 1992, a second raccoon rabies epizootic, probably inadvertently introduced into the mid-Atlantic region by translocation of infected raccoons, had been identified in Virginia in 1977 (121). The mid-Atlantic epizootic spread quickly into the north-east reaching the District of Columbia in 1982, New York in 1990 and the states of Massachusetts and New Hampshire in 1992. Since 1990, the raccoon has been the wildlife species most frequently reported rabid in the USA (20). By 1997, a continuous band of raccoon rabies stretched right down the eastern seaboard of the USA and cases in Ohio were being reported as the epizootic moved westwards across the Appalachians (62). In July 1999, the outbreak broached the St. Lawrence seaway and invaded the province of Ontario, Canada (118).

In 1988, the strain of rabies responsible for dog rabies in the US/Mexico border area caused an epizootic in coyotes (*Canis latrans*) in southern Texas (23). Subsequent dog/coyote transmission resulted in a significant outbreak in this region which is now being effectively controlled by Texan authorities through oral vaccination (62).

Insectivorous bats of several different species have been recognised as rabies reservoirs in North America since the first case (a rabid yellow bat) was diagnosed in Florida in 1953; the first rabid bat was identified in Canada in 1957 (6). Bat rabies case reports for these two countries have since increased to several hundred per year due to increased surveillance and human/bat contacts. Despite the occasional spill-over of bat rabies virus strains into terrestrial species, these viruses are epidemiologically quite separate from those of terrestrial mammals with distinct viral strains associated with particular bat host species (see below and Fig. 19.1). A recent summary of all the wildlife rabies reservoirs currently recognised throughout the USA is provided by Krebs et al., (62); some information on the situation in neighboring countries is also provided.

**Latin America and the Caribbean**

Since early colonial times, two distinct epidemiological cycles of rabies circulating in dogs and bats have been recognised in Latin America. Dog rabies is suspected to have been present in Mexico since 1709 (66) whilst records in South America date to the early 19th Century (101). Rabies was first reported in Peru in 1803 when it entered the country from the north and spread southwards, reaching the southern town of Arequipa by 1807. Lima itself was spared the epizootic through extensive dog control but the disease has remained enzootic in the country ever since. Dog rabies was introduced into Argentina in 1806 by sporting dogs owned by British soldiers (37). The disease invaded Uruguay in 1807, Colombia in 1810 and Chile in 1835; in each case dogs imported from Europe were implicated as the source (9, 101). Since that time dog rabies has been endemic in most South American countries and remains a significant public health problem to this day (1). In the latter half of the 20th Century particularly high numbers of cases were reported by Mexico and Brazil with Ecuador and Colombia reporting slightly lower numbers, although incidence based on human population levels are actually higher in other central American countries (36). Indeed, the high incidence of rabies in Colombia was noted in the 1940s during a veterinary survey conducted by the US Public Health Service in countries traversed by the Pan American Highway (100).

The danger of bat bites to both human and livestock health was recognised relatively early by Spanish colonists and soldiers, deaths in cattle following bat bites having been recorded in Guatemala (1576), Ecuador (1745) and Trinidad (1858) (9). Carini (19) was the first to report the deaths of large numbers of cattle in Southern Brazil but the nature and source of the disease was not established as vampire bat rabies
for another decade (44). An outbreak of a similar disease, both in cattle and humans, occurred in Trinidad in the 1930s and the presence of vampire bat bites on many of the succumbing animals suggested the role of these bats in disease transmission. An investigation identified rabies in several bat species in the area, especially in vampire bats of species *Desmodus rotundus* (79), thus confirming the source of infection. It is now recognised that throughout their range vampire bats are an important reservoir of sylvatic rabies and this results in frequent outbreaks of bovine paralytic rabies responsible for annual losses totalling thousands of animals per year in most Central and South American countries (4). Furthermore, this rabies epizootic continues to spread (e.g. southwards through Argentina) presumably as the vampire bat host extends its range, perhaps as a consequence of increased cattle populations in these areas (9). Paralytic bovine rabies was first reported in Colombia in 1940 (100), in Surinam in 1967, where no dog cases were reported, and in Peru since 1968 (9). In addition to the large cattle losses resulting from this rabies reservoir, significant numbers of horses and other equine species are also lost to this disease. Species of insectivorous bats, for example *Tadarida* species which migrate between North America and Mexico, are also known to harbour and transmit rabies (66, 97). Many other wildlife species have been reported rabid within Latin America. In Mexico, rabies outbreaks associated with wolves and coyotes have been reported at various times in the 20th Century and skunks, first reported rabid in 1952 (66, 84), have recently been associated with an enzootic focus of rabies in San Luis Potosi state (3). During this outbreak, which involved both hog-nosed (*Conopetus leucomotus*) and spotted species of skunks, just one other animal, a bobcat (*Lynx rufus*), was reported rabid in the area. Antigenic and phylogenetic analysis of skunk isolates from Baja California Sur identified several rabies viruses that formed a distinct branch of the north central and Californian skunk rabies virus lineage (30). In addition, a Mexican bobcat isolate was most closely related to those of the Arizona gray fox, thereby suggesting that this reservoir extends further south than had been previously recognised. Also, rabies has been reported in coyotes in Costa Rica, in foxes in Colombia in 1907-1908 (9) and in foxes in both Colombia and Venezuela in the mid 1950s (66); the importance of these animal populations as rabies reservoirs remains to be determined but it can be anticipated that additional wildlife rabies reservoirs will emerge as dog rabies is increasingly reduced and successful wildlife populations expand with changing ecological conditions.

Dog rabies was also known in the Caribbean during colonisation by Spain in Barbados (1741), Guadeloupe (1776), Dominican Republic and Jamaica (1783) (66); multiple introductions of the disease to the Caribbean islands is likely (101). Subsequently another rabies vector, the mongoose (*Herpestes auropunctatus*), has been recognised. This species was introduced from India in the 1870s and 1880s, originally to Jamaica and then subsequently to many other Caribbean islands, for the purpose of controlling rodents on sugar plantations. Mongoose populations in Cuba, Grenada, the Dominican Republic and Puerto Rico are currently known to be rabies reservoirs (34). In Cuba, a human death in 1948 has been ascribed to rabies in a mongoose and rabies was subsequently identified in captive mongooses in 1950 (66); dog rabies is also a significant problem on the island. Puerto Rico experienced its first major mongoose rabies outbreak in 1950, although historical records show that the disease may have been present on the island, presumably in dogs, as early as 1841 (110); the significant numbers of dogs reported rabid during the 1950 outbreak are attributed to the mongoose reservoir. Similarly in Grenada, although the first confirmed case of rabies was not diagnosed in a mongoose until 1952, there is anecdotal evidence to suggest that the disease had been present on the island either in mongooses or domestic animals in the 1940s and possibly earlier that century (33). Debate regarding the original source of mongoose rabies suggests either that it was brought to the islands from India with the original mongooses or that these animals acquired the disease from dogs subsequent to their transportation. On the basis of genetic analysis, which distinguished the viruses according to their origins from different Caribbean islands, Smith and Seidel (96) argued against a single point introduction and proposed that their data were more consistent with the latter mechanism.

The Middle East, Asia and Oceania

Although rabies has clearly been a long-standing problem in many parts of the Asian continent, historical details are sketchy. A historical review of rabies (101) mentions several early reports of note, including rabies in dogs in Turkey in 1586. In the early 1850s, in the town of Adalia in the Turkish territories, a major incident occurred when a rabid wolf attacked over 100 people, several of whom subsequently ‘went mad’ and died some weeks later. An epizootic of dog rabies is noted in the Ukraine in 1813 and in St.
Chapter 19

Petersburg, Russia, a major epizootic occurred in the 1860s – 1870s in which 47 people are reported to have died. Rabies was probably extensive in other parts of Russia at that time concurrent with some major outbreaks in many parts of Europe. Today wildlife reservoirs including foxes and wolves are known to be important rabies vectors throughout much of Russia, Siberia, the Middle East and other parts of northern and central Asia although, in many regions the dog still represents the major threat to humans.

In 1857, rabies was reported for the first time in Hong Kong when an English bloodhound transmitted rabies to one man; in 1860 in Canton, China, a man was also reported to have died of rabies. Several indigenous Chinese living near Peking were reported to have died of hydrophobia caused by mad dog bites in 1861; subsequently two Europeans died of similar symptoms and rabies was recorded as common amongst dogs owned by Europeans, suggesting that the disease could have been introduced through infected dogs of European origin. Another report, in 1869, mentions a rabid Scottish terrier which bit a water buffalo which later died. However, 'hydrophobia' was apparently well known to the Chinese medical community in much earlier times since a list of known 'cures' was already established during this period.

A more systematic study of the rabies problem in Asia began at the start of the 20th Century with the establishment of Pasteur Institutes in many countries, primarily for the treatment of exposed humans. Information on the extent of the problem became more readily available with the advent of annual surveys initiated in 1959 by the Veterinary Public Health Unit of the World Health Organization (WHO) (109). Between 1959-1968, five countries of the region were considered rabies-free: Hong Kong (last case in 1955), Taiwan (since 1959), Japan, Malaysia and Singapore (last case in 1953). In Malaysia, rabies had been enzootic since at least 1924 (prior records were lost) and spread of the disease caused an extensive outbreak in 1952 in Kuala Lumpur (119). Subsequent control measures eliminated the disease and the country has essentially been rabies-free except for occasional cases on the northern border with Thailand, a country with significant numbers of rabies cases. Japan had recorded many rabies cases each year, at least since 1906, including an epidemic of dog rabies in 1924 with 235 human deaths reported that year (89). By the early 1930s incidence was much reduced due to control measures but further outbreaks occurred in 1943 and 1948 after the end of the Second World War. Since 1956, when six cases were recorded, Japan has been rabies-free. The rabies-free status of Hong Kong was interrupted for a brief time in 1981-2 when dog rabies spilled across the border from southern China (102).

India and the Philippines currently report the largest numbers of rabies cases although poor surveillance, as for much of south-east Asia, undoubtedly underestimates the extent of the problem. Other countries reporting significant numbers of cases include Thailand, Indonesia (except for the eastern islands which are presently unaffected), Sri Lanka and the countries of IndoChina (109). Throughout the region the dog is the principal reservoir and indeed in the Philippines, where it has been estimated that 25,000 dogs die of the disease each year, wildlife surveys have failed to identify other rabies reservoirs (10). However, in other regions rabies has been associated with certain wildlife species, notably wolves (Iran), jackals (Afghanistan, Pakistan, Nepal and India) and mongooses (India) and these may constitute disease reservoirs. In Thailand, reports that rabies circulates in rodents and bats remain to be confirmed (92, 93).

The islands of the Pacific as well as Australia and New Zealand have generally managed to avoid the introduction of dog rabies. Australia did report a rabid dog in Tasmania in 1867, which may have spread to a child that died subsequently of suspicious symptoms (9). McColl et al., (68) reported the death of an immigrant child from rabies in 1990, an infection most likely to have been acquired prior to entry into Australia. More recently, Fraser et al., (38) identified a group of lyssaviruses associated with flying foxes; these viruses, which are now referred to as Australian Bat Lyssaviruses (ABLVs), can cause rabies in humans but they are phylogenetically distinct from genotype 1 rabies viruses (Fig. 19.1). Guam reported its first rabies outbreak in 1967 but after an extensive control campaign it was eliminated within a year; dogs from southeast Asia are regarded as the likely source of the infection but no strain identification was undertaken (9).

THE PHYLOGENETIC DIVERSITY OF LYSSAVIRUSES

Since the lyssavirus genome comprises a single negative-sense RNA strand which must be transmitted in its entirety to generate viral progeny (unlike the multi-segmented RNA viruses which can generate
reassortment genomes), phylogenetic analysis of lyssaviruses is independent of the genetic target. Thus, conclusions obtained from different parts of the genome should be complementary and the only limitation on subsequent interpretation is that the sequence data is of sufficient length and diversity to generate trees with a high confidence level. Thus in the following summary, conclusions have been drawn in many instances from several different studies.

The earliest phylogenetic study of the Lyssavirus genus employed the entire N-gene sequence (16). The Old World lyssaviruses, Lagos Bat virus, Mokola virus and Duvenhage virus, were assigned genotypes 2-4 respectively, a grouping in accord with their prior serological classification (88). European bat lyssaviruses of groups EBLV-1 and EBLV-2 (Chapter 17, A.A. King et al) were designated genotypes 5 and 6 respectively; as predicted genotype 2 and 3 viruses were the most distant from classical rabies virus (genotype 1). Subsequent studies which included the Australian bat lyssaviruses (ABLVs) classified these isolates as a seventh genotype (40). Whilst the rabies-related viruses appear to be restricted in their geographical distribution to Africa (genotypes 2-4), Europe (genotypes 5-6) and Australia (genotype 7), rabies virus (genotype 1), in contrast, is distributed throughout most of the world.

Additional studies focusing primarily on rabies viruses have employed complete or partial N-gene sequence windows (29, 30, 55, 60, 73, 74, 95, 97), segments of the G-gene and the neighbouring G-L intergenic region (75, 83, 112, 116) or the complete P-gene (S. Nadin-Davis, manuscript in preparation). The study of Kissi et al. (60), in which a particularly large sampling of African isolates was included, permitted some appreciation of the complex rabies situation on this continent and the following description employs the nomenclature described in their work. Three quite distinct African lineages denoted AFRICA 1-3 were described. AFRICA 1, which was subdivided into two subgroups, was localised to Algeria, Morocco and Tunisia in northern Africa and Ethiopia (group 1a) and to several countries of southern Africa and Nigeria (group 1b). Several central and eastern African countries and Somaliland harboured AFRICA 2 viruses. Whereas most of group 1 and 2 isolates were from canids, or humans bitten by dogs, AFRICA 3 isolates were comprised of only Herpestid species, principally yellow mongoose (Cynictis penicillata), from the Republic of South Africa. Indeed, the situation in South Africa was examined in more detail by von Teichman et al. (116) with the characterisation of rabies viruses associated with four main animal reservoirs: the dog in the eastern coastal region, the black-backed jackal in the northern tip, the bat-eared fox of the Cape region and mongooses, particularly the yellow mongoose, of the central plateau. The latter region physically overlaps to varying degrees with the other enzootic areas. Two phylogenetically distinct viral groups were defined:

a) a group associated with canids (dog, jackal, bat-eared fox) which was relatively homogeneous (>95% sequence identity), exhibited <15% divergence from the PV reference strain and which presumably represented AFRICA 1b;

b) a group associated with herpestid (mongoose) isolates which were quite heterogeneous (about 88% sequence identity) and highly divergent (>24%) from the PV strain and representative of AFRICA 3. A fourth African lineage may be defined by a single isolate from Egypt which segregated distinctly (60).

The situation in some other parts of the world appears rather less complex. Specimens from central and southern Europe and the Middle East (red fox, dog, wolf) consist of isolates differing by less than 10% and thus are considered to form a single lineage (60) although regional variations are often evident, as illustrated by a study of isolates from Israel (26). However, specimens, primarily of raccoon dogs (Nyctereutes procyonoides) and foxes, from arctic regions including northern Europe, the former Soviet Union, northern parts of Asia (Nepal and India) and northern areas of North America (arctic fox, red fox), formed a distinct ARCTIC lineage. In contrast, isolates of South East Asia are quite distinctive and regionally segregated. A single isolate from Thailand included in the study of Kissi et al. (60) formed a distinct lineage named ASIA, whilst of the six main lineages identified by Smith et al. (95) groups II, III, IV and Va,b originated from several Asian countries, including Thailand, the Philippines, Indonesia and Pakistan. An additional study on 27 isolates from Thailand indicated their monophyletic nature and confirmed their distinctness from most other rabies viruses with the most closely related isolate originating from China (55). In addition, a distinct lineage (SW ASIA) associated with dog samples from Sri Lanka and southern India has been identified (S. Nadin-Davis, manuscript in preparation) but its relationship to the other Asian lineages described by others is presently unknown. The Komatsugawa
strain, derived from a rabid dog in Tokyo, Japan, just after the Second World War, clusters as an outlier of the ARCTIC clade, thereby suggesting that the outbreaks experienced by that country just before rabies elimination was due to the incursion of a strain of the ARCTIC type. (A ‘clade’ is a group of organisms believed to have evolved from a common ancestor).

The complex rabies situation in the Americas, where rabies persists in multiple species of both terrestrial mammals and bats (97), comprises the following lineages:

a) the ARCTIC cluster which presently occupies Alaska and New York, USA, Ontario and northern Canada
b) a group including rabies from the gray fox in Texas and Arizona, from dogs in Mexico and from dogs and coyotes along the Texas-Mexico border region
c) viruses circulating in skunks of California, the USA mid-west and Canada and mongooses from Puerto Rico (USA).

Dog rabies isolates of Latin America segregate phylogenetically to a limited degree according to their geographical origins whilst very distinct rabies viruses are associated with: vampire bats (principally Desmodus rotundus) in much of Latin America; several species of North American insectivorous bats including the big brown bat (Eptesicus fuscus), for which at least two separate clades have been identified; also bats of the Myotis genus, the Lasiurus species, particularly hoary (L. cinereus) and red (L. borealis) bats, the silver-haired bat (Lasionycteris noctivagans), the eastern pipistrelle (P. subflavus), freetailed bats (Tadarida brasiliensis) and insectivorous bats of undefined species of South America. These chiropteran strains, together with the distinctive south central (SC) skunk and raccoon strains of North America, constitute the ‘American indigenous’ (AI) clade which is phylogenetically segregated from all other members of the genotype 1 family.

The phylogenetic tree (Fig. 19.1) uses P-gene sequence data to illustrate the evolutionary relationships between all lyssavirus genotypes and many of the rabies virus clades described above. Whilst many of these clades segregate according to host species and geographical distribution, e.g., as in the indigenous American cluster, a large cluster of genetically linked rabies viruses originating from around the world is evident, as has been noted previously (60, 95).

Figure 19.1 – Lyssavirus phylogeny based on the P gene sequences of 78 members of this genus
The complete P gene sequences of these rabies virus isolates were aligned using CLUSTALX (49) and then analysed by a Neighbor Joining algorithm, with bootstrap resampling, using the PHYLIP 3.5 package (35). Trees were converted into a graphical output using Treeview (77). Lyssaviruses outside of the classical rabies group (genotype 1) are indicated by genotype only; see text for more detail. Rabies virus clades are labeled according to their groupings as described in the text or according to their host reservoir and country of origin. The bar at bottom indicates the nucleotide distance scale.
This cluster, which has come to be known as the cosmopolitan lineage, is represented in this study by 46 rabies virus isolates as detailed in Table 19.1 and is illustrated in greater detail in Fig. 19.2. Several notable properties of this lineage include:

- the close phylogenetic grouping of strains from geographically isolated parts of the world
- the varied range of species which act as hosts to viruses in this clade, although the dog is highly prominent
- the relatively small genetic distances between isolates of these strains, indicating that evolutionary divergence has been operating for a limited period.

The isolates of the cosmopolitan lineage all appear to have originated from the same progenitor virus since support for the monophyletic nature of this clade is very high (bootstrap value of 100%) (see Fig. 19.2).

Table 19.1 Rabies virus isolates used for phylogenetic analysis in Figure 19.2

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<th>Year</th>
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<td>Canada</td>
<td>1993</td>
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<td>1741.WC.SK</td>
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<td>1992</td>
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<td>Mongoose</td>
<td>Puerto Rico</td>
<td>1990</td>
</tr>
<tr>
<td>ARC5.FX</td>
<td>Dog</td>
<td>Canada</td>
<td>1993</td>
</tr>
<tr>
<td>B1.DG</td>
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<td>1993</td>
</tr>
<tr>
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<td>Mouse</td>
<td>Beijing, China</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>V015</td>
<td>HEP-Flury</td>
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* the species suffix applied to each specimen indicates the presumed host reservoir; in some cases the species from which the isolate was recovered is different
THE ‘COSMOPOLITAN LINEAGE’

There has been significant speculation regarding the historical events leading to the emergence and distribution of the cosmopolitan lineage, including proposals that the colonisation of Africa and the New World by Europeans played a significant role in its dispersion (95, 96). The extent to which the documented history of rabies in various parts of the world, as summarised in the preceding sections, supports these ideas is explored below.

An important aspect of these investigations is an attempt to apply absolute time frames to the emergence of specific lineages within the cosmopolitan group. The inclusion of selected Canadian ARCTIC specimens as an outlying cluster in the tree (Fig. 19.2) serves to provide a time scale since, as detailed above, the Ontario enzootic (ONT specimens) was introduced from Northern Canada (ARC specimens) in the mid-1950s and these viral populations have evolved independently since that time (74). Based on the genetic distances between these samples (K) and the time period of their separation (T=40 years) the rate at which genetic distance accumulates (r) can be calculated by applying the formula T=K/2r (41). The application of this value of r together with observed K values for other groups of isolates, corresponding to the nucleotide distance values illustrated by branch lengths within the tree (Fig. 19.2), thus provide an estimate of the length of time which has elapsed since their divergence. It should be stressed that this simple calculation makes a number of assumptions which are almost certainly not observed in the field. Thus, for example, it is assumed that the rate of genetic change is a constant which is independent of the strains compared and, furthermore, that this value remains unchanged when a virus adapts to a new host or environment. Such constancy in this rate of change is unlikely in practice; indeed it is more likely that a virus adapting to a new host undergoes relatively rapid evolution to reach an optimal host/parasite balance and this is then followed by long periods of relative genetic stasis.

Figure 19.2 – Phylogenetic analysis using P gene sequence of 46 rabies virus isolates of the cosmopolitan lineage

Analysis was performed as detailed for Fig. 19.1. The numbers contained on branches within the tree are the bootstrap values indicating the number of times out of 100 that the samples to the right of the branch were grouped together; values of 95% are regarded as providing very high support for the monophyletic nature of the group. Three members of the ARCTIC lineage were included to help define the time scale described in the text; the 058.BBB isolate, a member of the AI clade, was used as an outlier.
On this basis, one might predict that the method proposed here might overestimate evolutionary periods involving adaptation of viruses to new hosts, although in fact, in some cases it would appear that divergence times are underestimated based on historical accounts. Notwithstanding the limitations of this process, the application of this time scale to the cosmopolitan lineage provides some interesting insights. For example, the European/Middle Eastern clade (Fig. 19.2) appears to have evolved from a progenitor virus circulating in 1914, a period when rabies was widespread throughout the region but surveillance and control were limited due to political turmoil. In addition, estimates of the age of the entire cosmopolitan group based on the greatest distance between two isolates (V266LY and V217CO) suggest that this viral population emerged a little over 200 years ago (1794), an estimate which, given the simplicity of these calculations, agrees reasonably well with most of the historical data provided above.

The Middle East

Due to the relatively close proximity of middle eastern countries to Europe, it is not surprising that the rabies virus strains found in both areas are generally closely linked phylogenetically. Two specimens, one from Iran and another from the Russian state of Kazakhstan were of the same lineage and, of all the viruses studied, were most closely related to current European stocks. Interestingly, a second dog isolate from Iran segregated to a distant place in the tree together with a Peruvian isolate (Fig. 19.2), strongly indicating that current viral populations of Iran have emerged from two distinct European stocks. A group of four Israeli fox isolates clustered on a separate branch within this same clade and were thus more divergent from the viruses of Europe.

Africa

All the African isolates of the canid strains examined, with the exception of the Nigerian viruses (see below), cluster with high confidence (bootstrap value of 96%) into one large clade within the cosmopolitan group, with subdivisions according to country and region. The isolate from Tunisia, together with the four Ethiopian viruses, comprise one main branch (AFRICA 1a); whilst the viruses from southern African countries, including Tanzania, form a second main branch (AFRICA 1b). The six Tanzanian viruses form a well defined sub-branch whilst those from South Africa, Namibia and Zimbabwe are less clearly segregated, indicating, in agreement with historical accounts (see above), a close association between these countries in the introduction and spread of rabies.

The situation in Nigeria is particularly complex and appears to reflect a distinct colonisation history from many other parts of Africa. Two Nigerian isolates were placed on separate branches of a highly heterogeneous clade (VACCINE 2) that includes a Texas fox specimen and two fixed strains: CVS and HEP-Flury. This clade is well removed from those cosmopolitan clades associated with other African countries and interpretation of these results is presently unclear. In addition, a Nigerian RABV strain (AFRICA 2) outside of the cosmopolitan lineage was represented by two isolates (Fig. 19.1).

Time scale estimates suggest that the progenitor virus which evolved into the strains currently circulating in Tunisia and Ethiopia was extant in the mid-1920s whilst the progenitor of all cosmopolitan viruses currently circulating in Africa is estimated to date back to 1896. Whilst temporally limited introductions of canid rabies certainly occurred prior to this date (see above), the strains responsible may not have persisted. The viruses presently in sub-Saharan Africa, specifically Zimbabwe, Namibia, South Africa and Tanzania, appear to have diverged since 1958, a date which is rather later than that suggested from the surveillance history of the last rabies epizootic in the countries of Zimbabwe, Namibia and South Africa. Isolates from earlier rabies outbreaks in southern Africa may circulate only in localised areas or may no longer exist, thereby precluding their analysis by phylogenetic methods.

It is not possible to state with certainty the route of entry of the cosmopolitan strain of rabies virus into Africa. It appears that canid rabies was not present as a regular and widespread entity in sub-Saharan Africa before the appearance of the European settlers, but that the first authenticated cases of dog rabies were generally recorded not long after settlement in an area. Initially, dog populations were probably too small and dispersed to maintain sustained cycles of rabies, but some populations were capable of...
supporting temporally- and geographically-limited cycles. As colonisation progressed, animal population increases and ecological change brought about by altered agrarian practices provided conditions such that domestic dogs, jackals and bat-eared foxes could now maintain long-term rabies cycles, which previously they were not able to do. Dog rabies may have been introduced to sub-Saharan Africa from Europe, the Middle East or northern Africa by one or more of three routes:

a) via European maritime traffic along the west coast, which had been active since the first Portuguese explorers of the 15th Century

b) via the maritime traffic along the east coast of Africa, which had involved Arab trade since early in the first millennium, and trade between Europe and Asia after the 15th Century

c) overland from northern Africa.

Asia

As described above, most of Asia appears to harbour rabies virus strains which are phylogenetically distinct from viruses of the European/cosmopolitan group (see SW ASIA and ARCTIC clades, Fig. 19.1 and studies on the Philippines, Indonesia, Malaysia and Thailand [55, 95]). However, of two Chinese isolates characterised by Tordo et al. (111), one defined a distinct Chinese lineage and the other segregated to the cosmopolitan lineage; this latter isolate (C1.DG) also clusters within the very heterogeneous VACCINE 2 clade (Fig. 19.2). It would therefore appear that the cosmopolitan lineage is present in the People Republic of China but the extent of its spread within the Asian continent will remain unclear until further characterisation of isolates from this part of the world can be performed.

The Americas

In the Americas, the cosmopolitan lineage is represented by several distinct viral strains:

a) The isolate from Peru segregates distinctly from other South American dog viruses. Although this virus would appear to be more related to one of the isolates from the Middle-East, the bootstrap value for this association is very poor (35%)

b) A second grouping places the skunk isolates of Canada and the USA mid-west as relatively closely related, as expected due to their close physical proximity; whilst surprisingly, a mongoose isolate from Puerto Rico was also placed as an outlier in this clade with strong bootstrap support (98%). This would strongly argue that the same viral population was introduced separately into these physically and taxonomically separate wildlife populations. The progenitor virus responsible for yielding both the Puerto Rico mongoose isolate and the mid-west skunk strain (USA and Canada) is estimated to have circulated in 1875, a time at which mongooses were first being introduced into the Caribbean. At that time the viral host reservoir was most certainly the dog which, through co-transportation with humans, disseminated this strain to geographically separate regions and distinct hosts. The separate emergence of the north central skunk strain within Canada and the USA is estimated to have begun in 1908 at which time this strain was presumably already adapted to the skunk host. This would place the introduction of rabies into these skunk populations at a time far earlier than expected from reporting data. The availability of just a single isolate from Puerto Rico for this study precludes any estimate of when the mongoose-adapted strain made the transition from dog to mongoose, although from the limited reporting of dog rabies on this island in the first half of the 1900s it appears likely that this occurred well before the enzootic status of the disease in mongooses was recognised. Another distinct clade (VACCINE 1) is composed of two laboratory-adapted virus strains, PV and SADB19, the close grouping of which was unexpected due to their distinct documented histories. The SAD isolate was originally recovered from a dog in Alabama, USA, in 1935 (86) and, is thus logically placed in this clade together with other wildlife strains likely derived from American dog viruses whilst the PV strain was originally derived by Pasteur from a street isolate in France. The PV strain is surprisingly distinct from current French isolates (60, 83) and moreover has a nodal position within phylogenetic trees inconsistent with its ancestral relationship to this wild type strain (Figs 19.1 and 19.2). Based on these observations, it has been suggested that stocks of the PV strain, which
were widely distributed throughout the 20th Century, were mislabelled and that many current preparations of this strain do not represent the original Pasteur isolate; indeed the viruses now identified as PV, SAD and ERA appear to be representative of essentially the same viral stock (83).

c) Another clade (VACCINE 2) includes a gray fox isolate from Texas which is grouped with fixed strains (CVS, HEP-Flury), two Nigerian viruses and the Chinese isolate. An outlying branch of this clade includes a Mexican dog isolate (which is representative of several Mexican dog specimens) and a group of three viruses from different species but representative of the dog-coyote-adapted variant presently circulating in Texas and along the Texas/Mexico border. The branching pattern of this group supports the notion that the Texas coyote strain evolved from the Mexican dog virus, an event which is estimated to have occurred around 1986 in close agreement with the first reports of coyote rabies in 1988 (23). The isolate (M29) from Mexico city is estimated to have diverged from the viruses of the Mexico/USA border region over a 95 year period.

d) A distinct branch represented by two dog isolates, one from Brazil and one from Paraguay, suggests that the introduction of dog rabies into these two South American countries was epidemiologically linked but yet separate from the epizootics which infected other parts of the Americas. Indeed the progenitor of dog rabies in Brazil and Paraguay is estimated to date back to 1885 whilst viruses of Paraguay and Peru appear to have been evolving distinctly since 1835, a date soon after the time when historical records confirm the presence of rabies in Peru. The separation of dog isolates from Latin American countries to several distinct branches within the cosmopolitan cluster indicates that separate introductions of rabies into this region undoubtedly occurred over a prolonged period.

Note added at press time: Since the preparation of this manuscript a paper providing for a more thorough investigation of the time scale for the cosmopolitan lineage was published (Badrane H. & Tordo N. (2001). – Host switching in Lyssavirus History from the Chiroptera to the Carnivora Orders. Journal of Virology, 75, 8096-8104). In this study the authors used dated isolates to estimate the average rate of evolution of the lyssavirus G gene to be $4.3 \times 10^{-4}$ synonymous substitutions/site/year. On this basis, together with their observations that all lyssavirus lineages exhibit similar rates of evolution, they determined that the cosmopolitan lineage diverged between 284-504 years ago. These values are rather longer than those estimated by the analyses presented here but may indeed be more accurate given the more detailed treatment of the data and its good concordance with certain historical records.

CONCLUSIONS

The time frames predicted from phylogenetic data generally compare well with historical rabies case records and thus the following account of the emergence of the cosmopolitan group can be proposed. During the first half of the 18th Century, urban rabies emerged in Europe from sylvatic rabies (of unknown species) due to the increasing dog populations associated with large human settlements (Chapter 2, J. Blancou). In the latter half of the 18th Century, rabies-infected dogs, travelling with their human masters, brought rabies to new colonies on other continents. Rabies, once established in the dog populations of these colonies, then spread as colonists extended their territories. Subsequent to introduction of the disease into new geographic areas, the virus may then have been transmitted into new wildlife host reservoirs within which the virus persisted and over time accumulated mutations to evolve into distinct strains. Parts of the world colonised prior to the emergence of the cosmopolitan group (eg Oceania) were generally spared the introduction of this disease. Whilst this time frame for the emergence of the cosmopolitan group is consistent with much of the recorded history of rabies in the Americas and Africa, there are a few cases in which rabies reports in the colonies significantly pre-date the late 1700s, eg the report of rabies in Mexico in 1709. Such an outbreak could be due either to an indigenous rabies reservoir (e.g. bats) or another imported canid line which did not manage to survive and spread. It is quite possible that rabies viruses circulating prior to the progenitor of the cosmopolitan group were transported overseas but that after a short outbreak in the colonies these viruses disappeared because there were insufficient numbers of susceptible animals to sustain the strain.
As previously indicated by Smith and Seidel (96), certain properties of the rabies virus facilitated this dispersion of the cosmopolitan group. The first is the ability of the rabies virus to adapt to different host species and hence be maintained in distinct host reservoirs over a significant time period. Several such adaptations have been documented, e.g. in the transmission of dog rabies to foxes in the USA in the 1940s (57, 96) and in the more recent transmission from dogs to coyotes in the Texas/Mexico border region (23). This phenomenon is also proposed to account for the emergence of fox rabies in Europe in the early 20th Century (103). The second important viral characteristic is the relatively long incubation period which is often observed for this disease; thus, animals infected with the rabies virus prior to the start of a lengthy journey had a chance of reaching their destination before clinical signs became evident. However, as discussed above, in addition to introducing the cosmopolitan biotype capable of infecting domestic dog populations, to new countries, the colonisation process was responsible for introducing political, industrial and agrarian change to these new lands. Enormous social and ecological changes followed. Medicine and food security brought high population growth rates and urban populations were created. Livestock diseases (e.g. trypanosomiasis in Africa) were increasingly controlled, thereby allowing more extensive settlement in rural areas. The larger human populations sustained a denser and more widespread population of dogs. Agricultural practices turned from being almost entirely subsistence to include large-scale commercial enterprises and commercial livestock farmers exterminated many unwanted predators. The new farming practices altered the ecology of the land in ways that increased the carrying capacity and population turn-over for certain wildlife species. Thus, habitats conducive to the establishment of rabies in new host species were generated in many distant parts of the world. However, the global importance of the cosmopolitan lineage should be placed in perspective. This group of rabies viruses is just one of many which currently circulate in different regions around the globe. As improved surveillance and strain identification methods reach more remote areas, additional strains of rabies viruses, possibly of relatively ancient lineages, are likely to emerge as testament to their adaptability and opportunistic nature.

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CHAPTER 20
COMPUTER ANALYSIS OF THE FOX RABIES EPIDEMIC

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Summary

The ability to process epidemiological data has been revolutionised by the introduction of micro-computers. This has enabled improved data storage, the processing and presentation of information at both national and international levels, which have greatly enhanced the coordination of efforts to control fox rabies in Europe. The following chapter details the development of software to visualise the rabies epidemic in Switzerland and a visit to the Swiss Rabies Centre website provides an impressive demonstration of the results of this work. It concludes by posing a number of questions that are relevant to the continuing problem of fox rabies control in Eastern Europe.

Keywords: epidemiology, fox rabies, geographic information systems (GIS), Switzerland

INTRODUCTION

The current rabies epidemic in Europe started some 50 years ago at the Polish-Russian border and has since infected roughly 2,000,000 km² of Central and Western Europe. In the 1960s and 1970s, when Western European countries experienced the first rabies infections, the only control measure applied was the culling of foxes, which had little effect on the spread of the disease. In most areas, the incidence of rabies oscillated for several decades, until oral immunisation of red foxes became effective. At the time, epidemiological models of rabies were already available (1, 2, 11, 17, 18), but they had little influence on the development of control strategies. Vaccination campaigns were empirically designed, and the parameters defined during the first field trials have since remained surprisingly unchanged (8).

The tools available not only to chart and report rabies data, but also to analyse the epidemic and to develop models, have considerably changed during the most recent 30-40 years’ history of rabies in Europe. At the beginning, data storage, analyses, mapping, and reporting were tedious manual work. Epidemiological data on distribution were collected and reported mainly at regional or national levels. However, the need for international reporting – more urgent when an increasing number of countries joined the fox oral vaccination campaigns – was satisfied with the publication of the Rabies Bulletins Europe (WHO Collaborating Centre at Tübingen, Germany) which started in 1977. In the early 1980s, the first micro-computers with database applications were used to store, sort, and list rabies cases. Then, basic graphic programs allowed the plotting of simple maps (20). During the 1990s, more sophisticated software packages to process spatial data became more widely available and at the same time became easier for non-specialists to use. Computers can not only support the handling of data and accelerate the reporting, they can also facilitate the communication within the ‘rabies community’, between practitioners and theoreticians. An example is the presentation of rabies data on the Internet, e.g. WHO’s ‘RabNet’.

Nevertheless, there are still many bottlenecks and shortcomings with regard to the collection of computer-compatible data. There is a significant difference between the practice of data collection and the power of current analytical tools. In this chapter we use examples from the Swiss dataset to demonstrate how the use of computers can influence epidemiological work in rabies from the daily routine work to the design of control strategies. We will focus on geographic information systems (GIS), which have a high application potential because they can support a variety of tasks, from data storage and plotting of simple maps to the most sophisticated statistical analyses and development of models (13).
Context for the analysis of the fox rabies epidemic

The primary objective of epidemiological analysis is to describe disease prevalence in relation to possible underlying factors. In an applied context, epidemiological work aims to control a disease. In the case of rabies, it took some time before epidemiology provided effective diagnostic and immunological tools which allowed the development of the respective control strategies. The central role of the red fox as vector species for terrestrial rabies in Europe had been obvious for a long time and led to the qualitative assumption that reduction of the fox population would eliminate the disease. Consequently, early rabies epidemiology followed a qualitative approach (4, 28). As Bacon (3) stated, only the failure of fox culling as a control strategy promoted the development of a scientifically based framework to:

- collect detailed quantitative information,
- process and analyse the data at various stages and
- use the resulting knowledge to improve the control strategies.

Computers are now used at all levels within this framework. When a system for the collection of samples is established, the amount of data will rapidly grow. Further processing of the data is much more efficient when the information is stored in a database. All steps following data storage can be seen as a continuum from descriptive documentation to sophisticated analysis (Fig. 20.1). The most basic level consists of the summation of data in tables and visualisation in maps, serving mainly reporting on a regular basis. At this level, grouping of data and selection of cartographic techniques already imply analytical components, as detailed in the following section. Between simple documentation, and quantitative or correlative data analysis, we propose computerised data animation as a valuable tool. This technique, not commonly used in epidemiology, corresponds well to the dynamic character of rabies spread. It is suitable to describe a dataset over a longer period, and may often provide surprising insights, enabling new hypotheses for further investigations.

Figure 20.1 – Steps in the analysis of a rabies epidemic and relevant control measures

The graph illustrates how information from all levels influences the decision-making process for control strategies. Predictive models are based either on retrospective analysis of epidemiological data ('statistical models') or knowledge from associated fields ('scientific models'). Shaded boxes show the steps that are dealt with in more detail within this chapter.

The output from static and animated visualisation has already had a significant impact on the decision-making process. Nevertheless, the methods mentioned so far do not provide tools to differentiate between the general features of the rabies system and local or random components. Selection of control strategies, based on these tools alone, is somewhat arbitrary. It would however be a cost-intensive and time-consuming process, if specific experiences needed to be regained in different areas or under different conditions. It is much more desirable to have models that allow prediction of the response of the epidemic to a certain strategy.
We classify models according to their inductive or deductive approach:

\textit{a)} The inductive approach begins with the description of single components of the rabies epidemic system, mainly data from the fields of virology and wildlife biology, such as the mechanism of infection, incubation period, or fox population turnover. From this description, it proceeds to predictions relating dependent and independent variables in mathematical formulas or in simulations. This is also referred to as a ‘scientific model’.

\textit{b)} In this chapter we focus on ‘statistical models’, which follow a deductive approach to describe the relationship between dependent and independent variables, e.g. between incidence rates and control strategies. Statistical models assume that the validity of such relationships extends beyond the dataset under analysis.

The two types of models complement each other. On one hand, statistical modelling provides the basis for the verification or falsification of scientific models. In such a process, characteristics predicted by the scientific model, e.g. formation of clusters, are compared to those observed in the retrospective analysis. On the other hand, the deductive approach is essential to model the rabies epidemic in relation to habitat factors (11). Data from wildlife biology on fox dispersal and contact rates – needed as input into scientific models – are not available for all varieties of habitats. Statistical modelling can help to adapt a scientific model, originally designed to run in a homogeneous space, to real landscapes. For rabies it is essential to study first the intrinsic patterns associated with characteristics of the virus and the disease, before we can judge any of the ecological factors. In this chapter, however, we concentrate on examples of pattern analyses and neglect ecological studies (Fig. 20.1).

The steps described for data processing used to be done with different types of software, such as databases, spreadsheets, statistical packages, or graphics programs. Software development today tries to implement the different applications under the same interface. This is especially true for GIS, which combine tools for the collection, storage, visualisation and analysis of geographic data (12). Basic functions especially for mapping can be used without specialised knowledge. In addition, more sophisticated functions are accessible through the implementation of scripting languages. In the following sections, we present and discuss examples of visualisations and analyses from the Swiss dataset. The examples cannot reflect all significant aspects of the epidemic. For instance, it is almost impossible to show the temporal dynamic in printed form alone. We encourage the reader to consult the animated visualisation of the rabies epidemic in Switzerland while reading the following sections. The animation is available under http://ubexc.unibe.ch/ivv/rabies.htm.

**METHODICAL ASPECTS**

Rabies persisted in Switzerland from March 1967 to September 1996. Visualisations and analyses in this chapter are based on samples collected from January 1967 to December 1996. During this time, 12,542 foxes were diagnosed positive for rabies, compared to 38,467 negative samples. The origin of all animals was registered at the level of political communities. The record for every sample included the X-Y coordinates of the spatial centre of the respective township. For implementation into a GIS, we used either the stored coordinates, or we assigned a random location to every case within the community borders. A geographic dataset with the polygonal outlines of the Swiss communities provided the basis for randomisation. Firstly, random numbers were drawn for X and Y coordinates within the minimum rectangle bounding a community. If a resulting point fell outside the polygon of the community border, the process was repeated. For some analyses, all parts of the community above 2,000 m were excluded. These zones were derived from a gridded digital elevation model with grid spacing of 250 m.

For the analyses of spatial patterns in rabies occurrence, we considered only foxes diagnosed positive for rabies. The location of each fox was randomised in the zone below 2,000 m. We calculated smoothed density surfaces using the normal Kernel estimator (23) on quarterly pooled data. The output of the Kernel estimation is to be understood as probability, referred to as percentage values (0 \% < f(x) < 100\%). If not stated otherwise, the bandwidth (smoothing parameter) for Kernel estimations was arbitrarily set to \( h = 5 \) km. For the assessment of temporal patterns we calculated Kernel distributions for
successive quarterly periods. All analyses were done by means of the GIS ArcView 3.1 (ESRI Inc., Redlands).

**DOCUMENTATION AND REPORTING OF THE STATUS OF RABIES**

Practical epidemiological work in rabies starts with detecting, storing, and reporting of rabies cases. Sensible reporting is done by means of maps showing the distribution of positive cases and perhaps of a negative control sample for the given period. Plotting maps is a typical basic task for a GIS. All GIS incorporate database facilities, but are also able to work with standard database software. A specific situation can be displayed with different cartographic techniques, emphasising various aspects of the situation shown. Cartographic techniques fall broadly into two categories:

a) dot maps which show the location for every record of a positive or negative sample

b) choroplethic maps which use graduated fillstyles (hatches, colours or shades) to represent relative values for spatial subcategories, usually for administrative units. The technique is mainly suitable to show ratios (prevalence rates, case densities).

Figure 20.2 represents two situations of the rabies epidemic in Switzerland, from the Swiss Plateau (Fig. 20.2a, b) and from the Alps (Fig. 20.2c, d), as dot maps (a, c) and as choroplethic maps (b, d). Apart from their reporting function, these maps reveal some interesting epidemiological situations and limitations of the data available. Rabies started in north-eastern Switzerland and spread concentrically. In March 1969, the epizootic reached the rivers of Limmat and Aare (Fig. 20.2 a, b), but did not cross these barriers. Both maps (Fig. 20.2a, b) illustrate how the rabies cases were concentrated along the eastern shores of the rivers. However, in the dot map (a), cases were randomly distributed within the boundaries of a community, and consequently, the map does not depict the authentic distribution of the cases. The use of central coordinates of the respective townships as maximum spatial precision was sufficient for large scale reporting, for example a map of all Switzerland, but limits more detailed analyses. The choroplethic map (Fig. 20.2b), which represents the case density, does not have this shortcoming, but lacks the information on numbers of cases per community (24).

The example from the Alps (Fig. 20.2c, d) demonstrates even more clearly how epidemiological information gets confused if administrative or reporting units do not match ecological boundaries. The valleys are separated from each other by high mountain ridges which acted as barriers to the spread of rabies. As a consequence, the disease persisted in each valley independently of neighbouring valleys. This
Effect cannot be seen in a choroplethic map (Fig. 20.2d), as the common borders of the communities follow the ridges, nor could it be shown in a dot map with randomised distribution of the cases. However, additional knowledge about case densities in relation to habitat factors can help to solve the problem. In Switzerland, no rabies case in wildlife has ever been reported from an altitude above 2,000 m. If, as shown in the dot map of Fig. 20.2c, all areas above 2,000 m are excluded for the random assignment of the rabies cases, the effect of the ridges becomes obvious. Although such a procedure is arbitrary, the result represents the reality better than any systematic distribution of the cases within the borders or around the centre of a community.

Figure 20.2 – Two situations of rabies in Switzerland
(c) and (d) show a sector of the eastern Alps in the canton of Grisons for the period April 1971 to March 1972
Identical situations are illustrated as dot maps (a, c) and choroplethic maps (b, d) respectively

- bold grey lines = rivers
- thin black lines = borders of political communities
- shaded area = zone above 2000 m

PATTERN ANALYSIS OF THE RABIES EPIDEMIC IN SPACE AND TIME

Spatial prevalence patterns of sylvatic rabies vary in correlation with local geographical factors. However, the life history of this directly transmitted infectious disease would evoke clusters even in a homogeneous space. The red fox is highly susceptible to the virus (22, 25). Transmission of the virus occurs mainly between foxes living in neighbouring home ranges (31). In Switzerland, 94% of fox rabies cases were less than 5 km from any other case registered during the previous 12 months (15). Mortality rates are estimated to be above 80% (27, 29), causing a reduction of the local host population. Consequently, rabies spreads rather steadily through the landscape. Case densities in the initial frontwave are high and fall sharply after some time. Subsequent re-infections usually cause oscillating density patterns with less distinct peaks (10).

Such dynamic effects become visible when rabies cases are mapped for successive periods. Steck et al. (26) illustrated the development of rabies in Switzerland from 1967-1978 by means of 11 yearly maps. If the extent of vaccination areas is included in the maps, the efficiency of control strategies can be disclosed (7, 15). When rabies occurrence is mapped with increasing temporal resolution, the visualisation of rabies distribution can be animated. The performance of modern personal computers allows two different approaches to the production of animations (16).

a) Temporal and spatial data for each case are read out of a data file and every case is plotted on the computer screen in real time. After a certain time period, (three to six months have been used with good results), the cases are removed from the display. Map composition (background, feature symbols)
can be adapted according to the aspects to be shown each time the program is run. Standard GIS software packages in the past have not been able to update this kind of map fast enough to produce the desired ‘film effect’. Specialised software had to be bought or programmed individually. Currently, new versions of GIS packages offer better capabilities for on-screen animations of maps, because of the growing use of the global positioning system (GPS) that increased the ability to track locations of many kinds of moving objects.

b) Frame-based animations are produced once and can then be played independently of the underlying data. Single maps, representing the desired time windows, are composed within the GIS and then exported into bitmap format. Many software tools are available that can merge bitmaps into a single movie file (14).

DELINEATION OF SPATIAL PATTERNS

Although typical patterns of rabies distribution become obvious through the animation, it is not sufficient as an analysis of the characteristics of the spread. Data from rabies surveillance include random errors and biases, since the proportion of animals sampled is known neither for positive nor for negative animals and may vary between political and geographical regions (19). To remove this noise and create smoothed density surfaces, we used a Kernel estimator. Fig. 20.3 shows the same situation as Fig. 20.2a, b, with overlaid contours of identical case densities. Inner contours with high-density values depict foci of the rabies situation, contours with low density values outline the entire area infected. Two main foci are visible in Fig. 20.3, one south of the river Rhine, the other north of the river Limmat. Steep slopes in the smoothed surface are visualised through small distances between contour lines. They are caused by the rivers acting as barriers. Due to the smoothing character of the estimator, the exact location of the barrier cannot be presented. Right of the southern focus, well apart from the big rivers, the tight contours bent to the north indicate another barrier, the densely populated area of Zurich. At that time, urban areas were not inhabited by foxes and hardly any rabies cases were detected there during this first wave of rabies. Probability distribution maps as shown in Fig. 20.3 reveal rabies distribution patterns. If they are superimposed onto geographical maps, they also help to explain the diversity observed.

Figure 20.3 – Identical situation as Figure 20.2 (a) with randomised dots representing rabies cases in red foxes and overlaid contours of identical relative case densities

Density calculation is based on a normal Kernel estimator
- bold black lines = density contours at intervals of 5% from 5%-100%
- bold gray lines = rivers
- thin black lines = borders of political communities
- hatched area = zone above 2,000 m

MOVEMENT OF SPATIAL PATTERNS IN TIME

So far, we have looked only at spatial patterns for a preset time window. In this section, we demonstrate how frontwaves shift forth and back as time passes, and how case densities fluctuate at a specific point. The calculation of Kernel probability surfaces can be repeated for successive time periods, allowing the recording of probability values for each period at given locations in the study area. Fig. 20.4 shows the chronological changes of density values at six points placed at 5 km intervals along a transect. The transect was oriented at right-angles to the main expansion of the rabies front (points A’!F in Fig. 20.4). The graphs demonstrate how the frontwave propagated and where it was stopped at barriers. The first front, approaching from the north, reached point A in the 4th quarter of 1967 (67-IV) and reached its peak there
in 68-I. Within the following quarter the peak reached points B and C, and, in 69-I, finally reached point D. Altogether, the frontwave took slightly more than one year to cross the distance of 15 km between A and D. At each of these four points, case densities of >0 were found during 2-3 consecutive quarters. The first frontwave was not able to cross the river and is missing in the histograms E and D in Fig. 20.4. During the subsequent 17-18 quarters, no cases were found along the transect north of the Limmat.

The next cases originated from two separated fronts approaching the area. Firstly, rabies had crossed the barrier formed by the Limmat system about 80 km further east, and now approached from the south. Secondly, the area north of the river Limmat had been re-infected. On this occasion, the river was crossed from the north without obvious delay, and the two rabies waves merged near point D. Points A to B demonstrate the different shapes of initial and follow-up infections. While the first peak of the epidemic showed high case densities and disappeared after a short time, the later waves typically showed fewer cases per time, but lasted longer. Not only the intensity, but also the shape of a rabies wave over time seems to be determined by fox density. When an area is re-infected, fox densities have rarely recovered to initial densities. At points E and F, even the first wave showed no distinct peak. The failure of rabies to cross the river at the first event was believed to be a result of the then intensive fox population control measures (31). The reduced intensity of the first rabies infection at points E and F can be explained accordingly with low fox densities.

SCALE PROBLEMS

Figure 20.5 represents a series of rabies developments at three points along the river Rhine and its tributary the Hinterhein of the canton of Grisons in the Alps (see also Fig. 20.2c, d). The first row of histograms (bandwidth 2.5 km) shows similar characteristics to those in Fig. 20.4: short periods with rabies (1-4 consecutive quarters) alternate with longer rabies-free periods (up to 16 quarters). The graphs in the 2nd and 3rd row (bandwidths 10 and 30 km, respectively) are based on the same dataset, but computed from a Kernel estimation with higher bandwidths. As a consequence, peaks are less pronounced and seem
to last for several years. The choice of the bandwidth determines the strength of the spatial smoothing for a specific quarterly dataset. This effect allows for a mathematically controlled removal of random noise. However, larger bandwidths also produce an undesired increased blurring effect, in respect of both temporal and spatial patterns (9).

A rabies epidemic is a dynamic event in space and time. A wider spatial window consequently includes different stages, which would, if projected to an ‘ideal point’ with no spatial extent, follow one after the other. The combined effect of both temporal and spatial blurring is especially obvious in the Alps, where rabies followed the main course of a valley but often spread independently in two neighbouring valleys. The distinct development can only be shown if the width of the spatial window used does not incorporate adjacent valleys, nor areas in a different epidemiological stage further up or down the valley. Point C in Fig. 20.5 demonstrates this problem best. Starting with a bandwidth of 10 km, an additional rabies peak becomes visible in 1983 that in fact never reached point C, but belonged to a focus evolving in the valley between points A and B.

Figure 20.5: Development of rabies case densities over successive quarters of a year from 1970 to 1979 at points in valleys of the eastern Alps in the canton of Grisons

Values from Kernel density estimations with varied bandwidths of $h=2.5$ km, $h=10$ km, and $h=30$ km. The inserted map shows the geographical location of the points.

We have to compromise between precision and sample size. Usually, we only have enough data (rabies cases) to perform a certain quantitative analysis, if we open the spatial and/or temporal window and hence blur the effect under examination. The effect of the spatial window has practical relevance, when analyses are linked to administrative units of varying sizes. Jackson (6) described differences in rabies prevalence patterns that may be an effect of blurring as a consequence of different sizes of the units under consideration. Problems associated with the pooling of data at different scales or into different zones are known as ecological fallacy (5, 21, 24, 33). They are inherent to analyses studying characteristics at an individual level, when in fact data are only available for zonal units.

CONCLUSIONS

In modern life, computers are ubiquitous. In everyday work in rabies epidemiology, we use computers to do things that the rabies pioneers of the 1960s could not have dreamed of. Now, as the rabies epidemic in Western Europe comes to an end, we finally have the instruments to store, analyse, and report rabies cases and epidemiological situations with practically no time lag. Furthermore, we have the tools to analyse huge datasets and to include in these analyses information from fields relevant for epidemiological research, such as biology or geography. We can repeat computer-aided interpretations with little effort and thus
incorporate them into the daily routine. We can, for instance, link a database containing rabies cases with a programme-controlled visualisation device and immediately distribute it over the Internet. Thanks to the Internet, we can also link regional or national databases to ensure that international borders are no longer barriers to information flow.

With regard to the interpretation of epidemiological data, computers provide tools to quantitatively analyse complex spatio-temporal data. Where only some years ago, subjective interpretations based on personal experience was the only or at least the most rational way to handle such complicated series of data, we can today perform statistical analyses and hence replace the ‘qualified guesses’ with quantitative methods. To support control measures such as oral vaccination campaigns, we can start to build complex and yet realistic models that take into consideration not only information from rabies epidemiology and fox ecology, but also ‘real’ landscapes and habitats. The ultimate goal would be to develop models that can simulate the spread of rabies, the response of the vector population and the effect on both of control measures in a given geographical area.

We have the theory and the computers to build such models. What we still lack to some extent, however, are reliable estimators to feed the models. One way to estimate such parameters is the retrospective analysis of rabies data. To do so, we must solve two problems:

\( a \) all data on rabies and the vector population incorporate a sampling bias (30, 32) which we must overcome, and

\( b \) rabies prevalence is defined by intrinsic patterns (rabies epidemiology, fox biology), local aspects (habitat, topography, geographical features), and stochastic events.

To estimate parameters, we need to distinguish these factors. Unfortunately, the quality (spatial resolution) of the data available often does not permit detailed analyses. Rarely, for instance, do we know the place of origin so exactly that we can link it to a certain habitat type.

How can we specifically profit from computers in rabies epidemiology? Obviously, we already have the means to eradicate rabies, as can be seen from the example of Switzerland (32, 34), soon to be followed by other Western European countries. Some questions, however, remain: why have oral vaccination campaigns been successful in some cases, but failed in others? How can we generalise our experience and transform it to other epidemiological or geographical situations? Last, but not least, did we reach our goals in the most economical way? To answer these questions, we need to re-analyse the epidemiological records of Western Europe. Moreover, we must start to collect rabies data in a computer-compatible way. Computers are not only tools to help us to do the same work more efficiently, they should alter our thinking and influence our basic approaches. So far, a rabies case is identified according to the place an animal was diagnosed positive for rabies. In a GIS based epidemiological system, a rabies case will first be an event in a specified location at a given time, thus emphasising, among other aspects, the importance of recording the precise location.

The application of GIS will not only influence the precision, but also the strategy of sampling. Locally gained high-resolution data can be easily extrapolated over other areas, if the underlying mechanisms are understood. In future, we may sample data of high quality in representative test sites, and then use such information to calibrate low-quality data over larger areas. Such a strategy would allow us to combine in an economical way the surveillance of other zoonoses (e.g. echinococcosis) and the monitoring of vector species.

Rabies in Western Europe will soon come to an end. As a result, the motivation to invest in new systems and models might decrease. Nevertheless, the countries that have led in rabies epidemiology and control in the past 30 years should continue their work in order to help to solve the problems caused by rabies elsewhere in the world. These countries have not only the knowledge, but also the data to perform retrospective analyses to assist in the understanding of rabies epidemiology. We can continue to learn from our rabies experience with regard to other wildlife epidemics.
Acknowledgement

This chapter is based on data collected over a period of more than 30 years by many co-workers of the Swiss Rabies Centre, University of Berne, especially F. Steck, A. Wandeler, A. Kappeler, and R. Zanoni. F. Wandeler and A. Kappeler created the first versions of a computerised animation of the rabies epidemic. The Swiss Federal Office for Education and Science funded research within the EU-FAIR-Project CT97-3515 (BBW-No. 97.0586). Additional funds came from the Swiss Rabies Centre. The Swiss Federal Statistical Office and the Swiss Office for Topography provided the geographical datasets for political communities (© BfS GEOSTAT), waters (© BfS GEOSTAT/L+T) and elevation (RIMINI – © BfS GEOSTAT).

References


CHAPTER 21

EPIDEMIOLOGICAL MODELS

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Summary

Epidemiological modelling offers a method of predicting the development of a disease and the possible outcomes of human intervention. The following review provides a thorough explanation of the theory behind a range of models developed to address the problem of fox rabies. It then discusses the many attempts to model this disease within continental European or the scenario where rabies is introduced into a rabies-free area such as the United Kingdom. This provides interesting insights into the possible speed at which rabies could spread within a fox population and the relative merits of vaccination versus culling.

Keywords: deterministic models, stochastic models, fox rabies, vaccination

INTRODUCTION

The use of models is a significant area of research within the field of epidemiology. Models can be used to either mimic what is actually happening in real life, or to predict what is likely to happen. They help us to understand why specific temporal or spatial patterns of disease occur and allow us to investigate various scenarios of disease spread and control.

THE ROLE OF MODELS IN WILDLIFE EPIDEMIOLOGY

Epidemiological models generally take one of two forms. The most common type of approach is that based on deterministic, compartmental mathematical models, as first proposed by Anderson and May (1). These models operate in continuous time and are deterministic in the sense that their predictions are determined solely by the initial values of the parameters included in the model and thus, for each unique combination of parameter values, there is just one solution.

Under the basic deterministic model structure for disease-host interactions proposed by Anderson and May (1), the total population of a host, N, consists of three compartments of individuals: X, uninfected or susceptible; Y, infected and Z, immune. For some diseases there may be a distinction between latent and infectious phases, but in the simplest form of these models, all infected individuals are capable of transmitting infection. For a direct infection, the rate at which the infection will be acquired by susceptible animals will be proportional to the number of encounters between susceptible and infected animals and will be equal to $\beta XY$ where $\beta$ is a transmission coefficient (the proportion of contacts that result in infection). The mortality rate for infected animals is $b + \alpha$, where $\alpha$ is the disease-induced mortality which operates in addition to the natural mortality, $b$. There is also a recovery rate, $\nu$, that is the development of immunity. Recovered animals are initially immune, but this immunity can be lost again at a rate $f$.

These assumptions give the following general equations that describe the population dynamics of the disease-host interaction in terms of the constituent susceptible, infected and immune individuals:

- $\frac{dX}{dt} = \alpha(X + Y + Z) - bX - \beta XY + fZ$
- $\frac{dY}{dt} = \beta XY - (b + f + \nu)Y$
- $\frac{dZ}{dt} = \nu Y - (b + f)Z$
From these equations, further more applied equations can be derived. The two most relevant are the following: If $r$ is substituted for $a - b$ (i.e. $r$ is the intrinsic population growth rate) then if:

$$a > r \left[1 + v/(b + v/(b + f))\right]$$

the disease has the ability to regulate the host population. If not, the population will continue to grow in the presence of the disease. The second equation relates to the threshold population density ($NT$). This is the density of hosts that is required for a specific disease to persist in a population, and is therefore of key importance in predicting the spread and control of an infectious disease. The threshold population density is given by:

$$NT = (a + b + v)/\beta.$$ 

The mathematical relationships that can be obtained between different epidemiological parameters represent one of the strengths of this deterministic modelling framework. However, these models also have various drawbacks.

The first of these is that they assume that the host population is homogeneous and freely mixing. This means that each infected host has an equal opportunity of transferring the infection to any other individual in the population, whether it is living close by or far away. For some disease-host systems, this assumption may be a satisfactory approximation to reality. However, some vertebrate hosts in particular display marked heterogeneity in their distribution at various scales, e.g. being distributed in relation to resource availability or living in groups occupying distinct territories. For these host species, the assumption of a homogeneous freely-mixing population will be violated. Movements of animals such as migration may also confer an additional dynamic temporal element to this spatial heterogeneity.

A second assumption made by these models is that all host individuals behave identically. This is also not going to be true for vertebrates living in complex societies. For example, some individuals may take more responsibility for territory defence and therefore be the ones mainly responsible for the spread of infection to adjacent territories. Other individuals may concentrate on rearing young and therefore be more responsible for the spread of an infection to other members of the same group. Different status animals may show sex- or age-related grooming preferences and this will also affect the detailed pattern of infection. Different individuals may also show differences in terms of their susceptibility to infection. For example, immunity may be partly determined by other external factors such as nutritional status, and some degree of immunity may be genetically linked as well.

The final assumption made by the non-spatial deterministic disease-host models is that the disease itself is uniformly distributed in the environment. This is never the case in reality, and spatial heterogeneity is often found in the patterns of disease in natural environments. The reasons for these patterns are not clear in many circumstances and are the subject of current research. However, most deterministic models are unable to mimic these patterns because they have no spatial component. They are therefore also unsuitable for trying to understand why these patterns exist.

There are therefore many problems with the non-spatial deterministic approach to epidemiological modelling. However, the approach also has its advantages. These models can give an overview of a particular disease situation based on simple theory, and can provide an estimate of the likely rate of spread of a disease, or the reduction in host population density required to eliminate an infection. Over a large population, the various problems associated with them probably cancel one another out to an extent so that the overall picture that emerges is still at least crudely accurate. These models often suffice where many of the assumptions are not contravened too obviously, and have been important in formulating policy for the control of a number of wildlife diseases (2, 3, 10, 11). However, they make a number of assumptions about the behaviour of diseases and their hosts. They are not so well suited for use where there appear to be well-developed heterogeneities in the disease-host system, whether these are in the transmission interactions between the disease and the host, or the ecology of the host itself.

It is possible to overcome the inherently non-spatial nature of deterministic models by imposing a spatial structure on them. For example, Barlow (10) modified a classic deterministic disease-host model for bovine tuberculosis in New Zealand possum populations by considering two patches, one with disease
and the other without disease. Within these patches, standard differential equations were used to describe the dynamics of the possum population. He found that incorporating disease aggregation into the model improved its predictions relative to the standard non-spatial model. However, the nature of this approach, i.e. conferring patchiness a priori on to the system rather than considering patchiness as an emergent property of the system, precludes any understanding of how patchiness originates or is maintained. Thus, this type of spatial deterministic model may provide more realistic predictions in terms of control, but it will not help greatly in our understanding of the processes operating to determine spatial heterogeneities within the disease-host system.

The main problems with all non-spatial deterministic-based approaches arise where control strategies are required for particular locations or in particular circumstances, when the general overviews produced by homogeneous deterministic models is inappropriate. For example, when control is required, we need to know not only how intensive it needs to be overall (i.e. a percentage cull or vaccination rate), but also where it should be applied. Because of their non-spatial nature, most deterministic models assume it will be applied uniformly across an area, but this may not be desirable or even possible. They will also predict that it will either be successful or not. In reality, we are more likely to be interested in the probability of success.

Because of these various problems with deterministic models, there has been increasing attention given to spatial, stochastic modelling approaches. Since they are constructed to reflect the biological characteristics of specific populations, there is no general conceptual framework for spatial stochastic models. Stochastic models operate on the basis of probabilistic events. The basic compartmentalisation of the host population is similar to that used for a deterministic modelling framework. Thus, for a simple directly transmitted microparasite, the host population may be divided into susceptible, infected and immune individuals. However, the difference between the deterministic and stochastic approaches is that whereas in the deterministic approach, transfers of individuals between different compartments within the population are determined analytically, in the stochastic approach, these transfers are determined probabilistically.

In the stochastic approach, a susceptible individual therefore has a defined probability of becoming infected through contact with an infected individual. Because these stochastic models are generally based at the individual animal level, the overall likelihood of a susceptible individual becoming infected will depend on the number of infected ones around it and the other characteristics of these individuals. It is possible to include different probabilities relating to different transmission (or other) pathways. Thus, an individual may have a probability, pw, of picking up infection from an infected individual in the same group but a different probability, pb, of picking up infection from an individual in a different group. Similarly, the probabilities of transmission may vary between different sex or age individuals within the same group. Through these differences in probabilities of transfer between different states, an implicit structuring of the stochastic disease-host model becomes apparent. However, this structure can also be made spatially explicit by considering the distribution of the host population in space.

The most common approach to this, and one which is particularly suited to territorial species, is to use a spatial grid, within which a social group of individuals occupies one or a number of distinct cells (31, 38, 48, 49). Interactions between groups are therefore made spatially explicit through the relative juxtaposition of other groups (or cells). The probability of contact between immediately adjacent cells is likely to be greater than that between cells further apart, and this can be built in to the model via probability-distance functions. Because of their probabilistic structure, spatial models may be extremely complex. This can be an advantage in that for well-studied populations, the models can incorporate many different properties of the population, such as age structure and different behaviour patterns. However, this complexity also accounts for some of the problems of the spatial stochastic approach, principally their analytical intractability.
FOX ECOLOGY AND BEHAVIOUR IN RELATION TO RABIES TRANSMISSION

Models represent a simplified version of reality. They should contain only those parameters which are considered to be immediately relevant to understanding the system under investigation. For a directly transmitted viral infection such as rabies, the key parameter in terms of disease transmission will be the rate of contact between infectious and susceptible individuals. Not all contacts will result in transmission of infection, but transmission will be proportional to the number of contacts. In deterministic models, both the likelihood of encounters and the likelihood of transmission during these encounters are incorporated within the transmission coefficient $\beta$. In stochastic models, they can be incorporated either as separate probabilities, or a single combined probability.

The frequency of contacts between susceptible and infectious individuals is the rate-determining step in the spread of directly transmitted viral infections such as rabies. The probability of disease transmission is therefore a direct consequence of the social behaviour of infectious individuals. Contact rates are extremely difficult to measure in the wild, especially for nocturnal and elusive species such as foxes. However, we can gain considerable insight into the pattern of contact behaviour within a host population by considering its social organisation.

Foxes live in family groups, each of which occupies a more or less exclusive territory. This pattern is normal throughout the geographical distribution of the red fox (27, 45). Apart from dispersing foxes, the exclusivity of territories breaks down temporarily only in the breeding season when male foxes make extra-territorial forays into neighbouring territories in search of mating opportunities (45, 47). In low density populations or areas with high levels of mortality, the groups consist of just an adult mated pair and their cubs, but in higher density populations or areas with lower mortality, several adults may be present in each group. The subdominant animals are usually females from previous litters, but in some instances males may also stay behind on their natal range rather than disperse.

As in any spatially structured and hierarchical society, contact rates will not be equal between all individuals. The maintenance of sociality requires some level of communication within a group. This communication may be effected by indirect means (scent marking, vocalisations) as well as by direct means (encounters). However, direct encounters are likely to be important in cementing social bonds between group members. White and Harris (47) found that this did indeed appear to be the case, with foxes from the same group meeting up significantly more frequently than could be expected by chance. In contrast, encounters between individuals from neighbouring groups may be costly (20) and would therefore be expected to be relatively infrequent. White and Harris (47) also found that foxes from neighbouring groups tended to move in such a way as to avoid encounters with one another. Within a group, there may also be differences in contact rates relating to dominance status, which may also be linked with dispersal behaviour. For example, subdominant animals may avoid contact with dominant ones, since increased aggression from dominant animals is associated with dispersal in foxes (21, 22, 47).

A fox population is therefore structured at two distinct levels; firstly, processes operating within groups and secondly, processes operating between groups. However, these two levels are not mutually exclusive as links between them will be formed by dispersing foxes. Dispersing foxes may provide an efficient means by which infections can be transferred from one group to another. Some authors believe that in low density fox populations, as are found throughout most of continental Europe, aggressive encounters between infectious sub-adult foxes dispersing from behind the rabies front, and susceptible foxes in the rabies-free zone ahead of the front, are primarily responsible for the spread of the disease (5). However, Artois and Aubert (6) found that young foxes 5-13 months old contracted rabies less frequently than older ones, suggesting that perhaps the role of dispersing foxes may be overestimated and that inter-group encounters between neighbouring adults may be at least as important. Indeed this is the situation in high density fox populations, where it is believed that contacts between foxes of neighbouring groups are the primary means by which the disease is spread (29).

One of the major problems with building models of infectious disease is that the contact behaviour of the hosts may be modified by their infection status. This is a significant problem for rabies, for which changes...
in the behaviour of infected hosts will affect the likelihood of transmission. However, the problem is exacerbated by the acute nature of the infection. Individuals remain infectious for only up to ten days (29) so monitoring the behaviour of naturally infected animals is difficult. Andral et al. (4) inoculated three wild-caught foxes with rabies virus and released them. Their results showed that the rabid foxes showed no alterations in their activity area, but that they did move more, and that prior to their death they remained immobile near the border of their home range for some time. These results suggest that monitoring the behaviour patterns of healthy foxes may be at least a reasonable indicator of the potential contact rates of infectious individuals (47, 50). However, rabies may increase the ratio of aggressive to non-aggressive encounters.

A REVIEW OF RABIES MODELS FOR EUROPE AND THE MEDITERRANEAN BASIN

The principal epidemiological models produced for rabies in Europe since 1980 are listed in Table 21.1. This table also summarises the basic structure of the models, their area of reference, their aims and their main conclusions. Of the 19 models shown, nine were deterministic (2, 7, 16, 25, 28, 32, 33, 34, 35) and ten were probabilistic or stochastic (9, 14, 18, 24, 31, 36, 37, 38, 41, 50). Of the nine deterministic models, most operated in continuous time, but three (7, 16, 28) used discrete time steps. All the stochastic models incorporated a spatial element, whereas only two of the deterministic models (7, 16) did so.

Table 21.1 – Rabies models for Europe and the Mediterranean Basin

<table>
<thead>
<tr>
<th>Type of reference</th>
<th>Main concern</th>
<th>Area of reference</th>
<th>Main conclusions or points of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2) Deterministic</td>
<td>To explain observed patterns of rabies</td>
<td>Europe and Britain</td>
<td>Disease shows cycles with periodicity of 3-5 years for density of 1-4 foxes km⁻². Period of cycle determined by growth rate of fox population. Due to high pathogenicity, rabies will only persist in fox populations at low prevalence (3-7%). Prevalence higher in higher density fox populations. Damped oscillations of fox density and prevalence over time. Vaccination better than culling with higher vaccination rates required to control higher density fox populations. Combined strategy of culling and vaccination likely to be most effective. If rabies became endemic in Britain, culling alone would not be sufficient to control it.</td>
</tr>
<tr>
<td>(14) Stochastic</td>
<td>Progression of enzootic disease in time and space</td>
<td>Europe</td>
<td>Rabies only progresses if density of foxes &gt;1 fox 160 ha⁻². New pockets of rabies behind the rabies front produced by young dispersing backwards once population recovered in those areas. Rabies front moves at 42 km per year. First wave followed by further waves, cyclical population density with about a 3 year periodicity. Seasonality of rabies – more cases associated with dispersal and mating. Two key areas for control – one immediately ahead of rabies front, the other in areas behind where population densities recovering to close to threshold.</td>
</tr>
<tr>
<td>(28) Deterministic</td>
<td>Effects of contact rate on dynamics of disease</td>
<td>None</td>
<td>Changes in contact rate affect disease dynamics, in particular periodicity of cycles.</td>
</tr>
<tr>
<td>Type of reference</td>
<td>Main concern</td>
<td>Area of reference</td>
<td>Main conclusions or points of significance</td>
</tr>
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</tr>
<tr>
<td>Discrete time</td>
<td></td>
<td></td>
<td>Based on observed 3-4 year cycles, contact rate of 1.9 gives best results</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contact rate is most sensitive factor in the model and therefore the parameter of overriding importance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vaccination more likely to succeed in controlling rabies than culling</td>
</tr>
<tr>
<td>(25) Deterministic</td>
<td>Characteristics of rabies front and the width of control area required</td>
<td>Britain</td>
<td>Wave speed about 50 km per year</td>
</tr>
<tr>
<td>Non-spatial</td>
<td></td>
<td></td>
<td>Outbreak of rabies in Southampton will reach Bristol/London in 3 years and Leeds in 7.5 years</td>
</tr>
<tr>
<td>Homogeneous</td>
<td></td>
<td></td>
<td>15 km wide control band with intensive control about 80% required to stop spread of rabies</td>
</tr>
<tr>
<td>Continuous time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(9) Stochastic</td>
<td>Effects of group size on rabies spread and control</td>
<td>None, but based on British fox data</td>
<td>As group size increases, rate of spread of disease increases and proportion of foxes infected increases</td>
</tr>
<tr>
<td>Spatial</td>
<td></td>
<td></td>
<td>Group size of 3 represents the threshold population density for disease persistence</td>
</tr>
<tr>
<td>Homogeneous</td>
<td></td>
<td></td>
<td>Culling may cause perturbation, thus increasing contacts and disease spread</td>
</tr>
<tr>
<td>Discrete time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(31) Stochastic</td>
<td>Use of spatial models in understanding patterns of disease</td>
<td>None</td>
<td>Epizootic splits up into an enzootic pattern of wandering patches of infection</td>
</tr>
<tr>
<td>Spatial</td>
<td></td>
<td></td>
<td>Proportion of vacant sites much smaller than predicted from non-spatial models</td>
</tr>
<tr>
<td>Homogeneous</td>
<td></td>
<td></td>
<td>Spread of infection from single focus is initially fairly regular but patches develop later</td>
</tr>
<tr>
<td>Continuous time</td>
<td></td>
<td></td>
<td>Periodic fluctuations e.g. in population size or prevalence may only be due to the small size of the simulation area rather than genuinely cyclical as in the non-spatial models</td>
</tr>
<tr>
<td>(35) Deterministic</td>
<td>Temporal dynamics of enzootic disease and control through culling or vaccination</td>
<td>None</td>
<td>Rabies regulates fox population to level very close to threshold population</td>
</tr>
<tr>
<td>Non-spatial</td>
<td></td>
<td></td>
<td>Low equilibrium prevalence of infection (&lt; 4%)</td>
</tr>
<tr>
<td>Homogeneous</td>
<td></td>
<td></td>
<td>Rabies induces oscillations in fox density that may or may not dampen out</td>
</tr>
<tr>
<td>Continuous time</td>
<td></td>
<td></td>
<td>Culling rates may have to be high to eradicate disease: 40% cull will eradicate rabies, but culling has little effect on fox population density where rabies is enzootic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A vaccination rate of 40% will eradicate rabies, but a vaccination rate of &lt;10% may actually increase rabies incidence</td>
</tr>
<tr>
<td>(16) Deterministic</td>
<td>To quantify incubation period and dispersal behaviour</td>
<td>Europe</td>
<td>Mean dispersal distance less than 8 km and mean rabies incubation period greater than 25 days would fit with empirical observations of rabies in continental Europe</td>
</tr>
<tr>
<td>Spatial</td>
<td></td>
<td></td>
<td>With these parameters, population recovered within about 6 years</td>
</tr>
<tr>
<td>Homogeneous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discrete time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(33) Deterministic</td>
<td>Spread of rabies epizootic in a fox population</td>
<td>England</td>
<td>Rabies front would move at speeds of up to 100 km per year and reach Manchester within 3.5 years</td>
</tr>
<tr>
<td>Non-spatial</td>
<td></td>
<td></td>
<td>Cycles of disease occur with periodicity of 2-7 years</td>
</tr>
<tr>
<td>Homogeneous</td>
<td></td>
<td></td>
<td>Disease would reappear in southern England about 6 years after wave had passed, and then periodically after that</td>
</tr>
<tr>
<td>Continuous time</td>
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<tr>
<td>Type of reference</td>
<td>Main concern</td>
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<tr>
<td>Stochastic</td>
<td>Impact of rabies on urban fox populations and effects of control</td>
<td>Britain</td>
<td>A rabies break established ahead of the front through vaccination to reduce susceptible population to below the threshold would need to be 15 km wide. Vaccination has considerable advantages over culling.</td>
</tr>
<tr>
<td>Spatial</td>
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<tr>
<td>Homogeneous</td>
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<tr>
<td>Discrete time</td>
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<td>(37)</td>
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</table>

| Stochastic        | Pattern of spread and efficacy of different urban fox populations | England | Variance in speed of travel of rabies front greater for heterogeneous fox populations, some small pockets of infection preceding rabies front. Probability of success decreased with fox density. Rabies outbreaks in dispersal period less likely to be controlled. Increasing size of control zone increased probability of successful control. Mean velocity of rabies front = 1.2 km per month (14.4 km per year). Low rate of spread thought to be due to high density of foxes. High probability of success for high density cities only achieved with control efficiency of 87% or more. Increasing efficiency of control was more effective than increasing area of control. |
| Spatial           |              |                   |                                          |
| Heterogeneous     |              |                   |                                          |
| Discrete time     |              |                   |                                          |
| (38)              |              |                   |                                          |

| Deterministic     | Effect of immunity on speed of spread and effectiveness of different forms of control | Germany | Immunity has little effect on speed of propagation of first wave. Immunity means that secondary outbreak fronts occur less frequently. Immunity decreases oscillations in fox population. Wave speed increases with population density. Vaccination may be useful in establishing breaks since break widths required are slightly smaller. Break widths of 10-50 km required under most conditions, and break width required increases with fox density. |
| Non–spatial       |              |                   |                                          |
| Homogeneous       |              |                   |                                          |
| Continuous time   |              |                   |                                          |
| (32)              |              |                   |                                          |

| Deterministic     | Control of rabies in Germany by vaccination of foxes | Germany | Because immunisation causes an increase in fox density, then number of available baits per fox decreases. Need to increase density of baits for foxes continued effective rabies control, at least in some parts of Germany. |
| Non–spatial       |              |                   |                                          |
| Homogeneous       |              |                   |                                          |
| Continuous time   |              |                   |                                          |
| (34)              |              |                   |                                          |

<p>| Stochastic        | To investigate effects of vaccination on rabies control in specific English cities | England | Rate of rabies spread through standard 19 km radius control zone greater during vaccination than poisoning. At low fox density, no difference between effectiveness of poisoning or vaccination. At high fox density, vaccination much less successful than poisoning. For low density urban or rural fox populations, a ring vaccination policy would be most appropriate with a very small poison area. |
| Spatial           |              |                   |                                          |
| Heterogeneous     |              |                   |                                          |
| Discrete time     |              |                   |                                          |
| (36)              |              |                   |                                          |</p>
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<tr>
<td>(50) Stochastic Spatial Heterogeneous</td>
<td>Effects of real contact rate data on rabies Spread and control in specific English cities</td>
<td>England</td>
<td>For high density populations, a relatively large poison area is still required</td>
</tr>
<tr>
<td>(18) Stochastic Spatial Homogeneous Discrete time</td>
<td>Mechanisms responsible for wave-like pattern of spread</td>
<td>None</td>
<td>Wave-like pattern of spread emerges from model Foci in front of and behind the wave for models with inter-group infection and dispersal Fewer parameters make the model more manageable than many spatial rabies models and therefore able to produce predictions based on basic insights</td>
</tr>
<tr>
<td>(7) Deterministic Spatial Homogeneous Discrete time</td>
<td>Influence of dispersal and rabies-induced mortality on rabies spread and control</td>
<td>Europe</td>
<td>Increase in dispersal distance leads to increased speed of rabies spread Vaccination rate of 75% needed to eradicate rabies As rabies-induced mortality increases timing of second rabies wave is later If fox population continues to grow, an even higher proportion of foxes will need to be vaccinated</td>
</tr>
<tr>
<td>(24) Stochastic Spatial Homogeneous Discrete time</td>
<td>Effect of dispersal in Generating large-scale rabies patterns</td>
<td>Europe</td>
<td>Wave-like pattern produced for a wide range of parameters First wave velocity is 27.1 home ranges per year (about 54 km per year) Distance between first and second wave is 93.2 home ranges (both values in range of empirical observations) Suppressing dispersal leads to disappearance of wave-like pattern Wave pattern is result of interplay between dispersal and neighbourhood infection Very rare long-distance dispersal events are sufficient to influence large-scale spatial patterns of disease</td>
</tr>
<tr>
<td>(41) Stochastic Spatial Homogeneous Discrete time</td>
<td>Persistence of rabies in immunised fox populations</td>
<td>Germany</td>
<td>Low level rabies persistence can occur for all immunisation rates of 60%-80% Persistence characterised by spatio-temporal moving clusters of infection Suggest that sporadic rabies incidences are caused by lasting seats of infection rather than immigrating foxes from non-immunised regions Frequency of low level disease persistence increases up to 74% immunisation rate, then declines. Even after immunisation rates of 70% and 5 years of repeated vaccination, eradication cannot be guaranteed; at least 6 years of 70% mean immunisation rate required for high chance of successful control</td>
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The models can also be divided into two broad categories relating to their purpose. The first category is where the main aim is to explain a particular temporal or spatial pattern of disease or understand how certain key parameters relating to epidemiology or control give rise to specific disease patterns. The second category is where the main aim is to make predictions of disease spread and/or control for specific locations. There was a general trend for the deterministic models to be primarily concerned with the former and the stochastic models with the latter objective. However, the distinction between the two is not clear-cut. Thus, models belonging primarily to the first category include the deterministic models (2, 7, 16, 28, 32, 35) and the spatial stochastic models (9, 18, 24, 31). Models belonging primarily to the second category include the deterministic models (25, 33, 34) and the spatial stochastic models (14, 36, 37, 38, 50).

In terms of the emergent temporal and spatial properties of rabies in Europe, the models have been used to consider aspects such as the rate of spread of the rabies front, the frequency and separation distance between successive rabies waves, the level of control required, the type of control required (culling or vaccination), the width of control area required and the effects of immunity on rabies persistence and control. The models have also been used to investigate the effects of inherent characteristics of fox behaviour and rabies infection on these patterns. These inherent characteristics include fox contact rates, dispersal distance, the incubation period of the disease and the implications of heterogeneity in the fox population.

The wave-like progression of rabies in foxes is one aspect of the disease that has received much attention, specifically the nature and speed of travel of the rabies front. Anderson et al. (2) were concerned purely with the large-scale temporal aspects of this pattern and showed how the periodicity of rabies was determined mainly by the rate of growth of the fox population but also by fox population density and the incubation period of the disease. At lower fox population densities and shorter incubation periods, cycles had a shorter periodicity and at fox densities of less than about 5 km⁻², oscillations disappeared completely.

David et al. (14) predicted that rabies in continental Europe would move at 42 km annually, that the front wave would be followed by further waves, and that the fox population would become cyclical with approximately a three year periodicity. Jeltsch et al. (24) estimated that the front wave of rabies in Europe should move at a speed of about 27 home ranges annually. On the basis of an average range size of 4 km² for foxes in central Europe (44), this equates to about 54 km annually. Both these estimates fit closely with empirical data showing rates of spread of rabies in continental Europe of 30-60 km annually (42).

Researchers referring to continental Europe have empirical observations of the spread of rabies on which to base their estimations and refine their models, and so a high level of agreement would be expected. However, for researchers concerned with predicting the rate of spread in a country such as Britain, where there are no empirical data on which to base such parameters, there is, not surprisingly, much less agreement.

With reference to Britain, Källén et al. (25) estimated a front wave speed of approximately 50 km annually, and on the basis of this, predicted that an outbreak of rabies in Southampton would reach Bristol and London in three years and Leeds in just over seven years. Murray et al. (33) stated that the rabies front would move at speeds of up to 100 km annually, that an outbreak on the south coast would reach Manchester within 3.5 years and that the disease would show cyclicity with a periodicity of 2-7 years. They also predicted that once the disease had passed, it would then reappear in southern England after about six years, and periodically after that. Both these sets of authors had used deterministic approaches to model rabies spread in Britain, but neither of the models incorporated a spatial element. However, other models have shown that the spatial element may have significant implications for the spread of the disease. Smith and Harris (38) used a spatial stochastic model, adapted from that of Voigt et al. (46) for rabies in Ontario, to examine the pattern of spread of rabies in specific cities in Britain. They predicted that the mean speed of the rabies front under British conditions would be only about 14.4 km annually.

The main reason for this difference is that Smith and Harris (38) were modelling the disease in both space and time and that therefore each potential transmission process such as inter-group contact or dispersal was spatially explicit. This is of great importance for a disease such as rabies existing in a spatially structured host population. Thus, transmission via inter-group infection and dispersal will be spatially
restricted. The reason why this seems to have such a significant impact on model predictions in Britain, compared with the situation in continental Europe, is that fox population densities in urban areas in Britain are much higher than those found in Europe. As population densities increase, home ranges become smaller, and so inter-group rabies spread is spatially increasingly restricted. Thus, at high fox population densities, the rate of spread measured in terms of social groups will be high, but the rate of spread measured in terms of distance moved will be relatively low. Smith and Harris (38) showed that population densities similar to those found on continental Europe gave rise to a much higher rate of rabies spread. Jeltsch et al. (24) were specifically concerned with understanding the relative importance of dispersal and inter-group contacts in generating the wave-like pattern of rabies spread. They found that suppressing dispersal resulted in the disappearance of the wave-like pattern of spread and that random walking foxes alone could not replicate this wave-like pattern. They concluded that the wave-like pattern was a result of the interaction between dispersal and inter-group contacts in transmitting infection. Most transmission occurs by inter-group neighbour-neighbour contact, but occasional dispersal of infectious foxes causes sudden advances in the main rabies front, these dispersing foxes setting up foci of infection ahead of the main front. Inter-group contacts then act to consolidate the disease behind the front, before dispersal events again cause a sudden advance. Behind the main wave, empty ranges are colonised by healthy foxes dispersing from uninfected groups both ahead of and behind the wave, causing a build-up of susceptible individuals which will then form a second wave of rabies. Jeltsch et al. (24) also demonstrated that long-distance dispersal events only have to occur very rarely for the typical wave pattern to emerge. Of all the parameters involved in the epidemiology of rabies in foxes, the contact rate is the one that is most difficult to quantify. One of the advantages of continuous time deterministic models such as those in (2, 33, 35), is that it is possible to derive the contact rate mathematically from other parameters. However, since the models themselves are spatially unstructured, and therefore not very representative of the fox-rabies interaction, the actual figures produced for contact rate may be relatively meaningless in terms of fox biology. Contact rate is a key parameter in terms of its effects on the dynamics of the disease-host interaction. Macdonald and Bacon (28) demonstrated that contact rate had a considerable effect on the periodicity of rabies cycles, with higher contact rates lengthening the periodicity. Higher contact rates also resulted in the disease having a much more dramatic effect on the fox population, such that at a contact rate of 2.9 both the disease and the fox population were extinct within seven years. Macdonald and Bacon (28) found that the contact rate was the most sensitive parameter in their model and concluded that it was the single most important factor in the epidemiology of rabies in foxes.

Measuring actual contact rates in the field for any host population is extremely difficult, and only White et al. (50) and Smith (36), using data from White and Harris (47), have incorporated real contact rate data into their rabies models. White et al. (50) used data in Trewhella et al. (44) and White et al. (51) to formulate a relationship between home range size and fox population density. They then used behavioural data on encounters between healthy foxes at one population density in combination with simulation-modelling of individual movement patterns, to quantify relationships between contact probability (the probability of contact between individual foxes) and population density, for a range of population densities during different seasons of the year. They then used these data to revise the model of Smith and Harris (38). White et al. (50) found that the rate of rabies spread was lower under the revised model (about 12 km annually), mainly due to the lower inter-group contact rates derived from the empirical behavioural data, and that this effect was especially pronounced at lower fox densities. There are insufficient data on the behaviour of infectious animals to determine the extent to which contact behaviour changes with infection, but it is likely that rabies will increase contacts slightly, especially the likelihood of transmission during contact. The true rate of rabies spread would probably therefore be slightly higher than that predicted by White et al. (50) on the basis of the contact behaviour of healthy animals.

One of the main purposes of modelling infectious diseases is to simulate various control strategies and compare their relative effectiveness. It is therefore not surprising that many of the rabies models have focused on control as one of their principal objectives. Anderson et al. (2) compared the relative effectiveness of culling and vaccination for the control of rabies. They found that vaccination was more effective than culling in controlling the disease. At a density of 2 foxes km\(^{-2}\), they estimated that a 50% vaccination rate was required, but that above 10 foxes km\(^{-2}\) this increased to 90%. They concluded that an
integrated strategy involving both culling and vaccination would be the most effective. Macdonald and Bacon (28) and Murray et al. (33) also predicted that vaccination would be a more effective strategy than culling.

Empirical observations of rabies spread and control in Europe have indicated that, for fox densities equivalent to those found on continental Europe, vaccination is much more effective than culling. Indeed vaccination has been successful in controlling the spread of the disease throughout much of continental Europe (8). However, the situation for potential rabies spread and control in Britain is slightly different. In Britain, rabies would be in the form of a point source infection rather than a broad front as is the situation in Europe. In addition, the high density of foxes in urban areas leads to practical problems in conducting and evaluating a vaccination campaign. In Britain, the principal means of control in rabies contingency plans has therefore been culling through the use of poison baits (19). However, the level of culling also needs to be high to ensure effective control of the disease. Smith and Harris (37) found that more than 75% of foxes had to be culled in order to significantly reduce the duration of a rabies incident. Smith and Harris (38) found that a high probability of success for controlling a rabies outbreak in a city with a high fox density would only be achieved with a control efficiency of 87% or more, although White et al. (50), using revised contact rate data, estimated that an equivalent probability of successful control could actually be achieved by 5%-15% lower fox control.

As a result of the effectiveness of vaccination in containing rabies in continental Europe, renewed attention has been given to the incorporation of vaccination into British rabies contingency plans. In contrast to the situation at low fox densities, Smith (36) found that at high fox densities, such as occur in some British cities, vaccination on its own was much less successful than culling in controlling rabies. However, he also found that by using an integrated control strategy combining culling with vaccination, equivalent levels of control could be achieved as with culling alone. Thus, for a high density city (Bristol), ring vaccination around a central core area of culling led to a slightly higher success rate than culling alone, although the success rate of control generally declined as the area covered by culling was reduced. This type of ring vaccination strategy would be beneficial for some instances due to the decreased use of poison baits and the consequent increase in safety and reduction in labour requirements (36).

Other authors have been primarily concerned with the location and size of the control area required. David et al. (14) identified two key areas for control, one immediately ahead of the rabies front and the other in areas behind the front where fox populations were recovering and close to the threshold levels for disease persistence. Källén et al (25) calculated that a 15 km wide control band ahead of the rabies front, with 80% control would be required to halt the spread of the disease in Britain. Murray and Seward (32) stated that a break width of 10-50 km would be required under most conditions in Europe. The control area proposed for Britain is a 19 km radius around a presumed point source of infection (19, 36). This area might seem relatively small, but this difference in size reflects the impact of higher fox densities resulting in a decreased rate of spread of the disease measured in pure distance terms. White et al. (50) suggested that the heterogeneity of urban landscapes might result in a lower contact rate than would be observed between foxes at similar densities in rural areas, and that this would further exacerbate the slower rate of spread of the disease in urban areas. Therefore, one of the potential problems in the event of a rabies outbreak in Britain is that should the disease escape beyond the urban areas into the countryside, fox population densities will be much lower there, and the rate of rabies spread could increase (50).

Despite the existence of clear spatial patterns of rabies in Europe, only some of the models have incorporated space explicitly. However, even those models that have included space have tended to do so in a relatively simplistic manner, by assuming that the fox population is homogeneously distributed throughout the environment. This means that there are therefore no variations in fox population density occurring within the area being modelled. For example, (7, 9, 14, 18, 24, 31, 35, 41) all assumed that home ranges were equal in size and shape. Only Smith and Harris (38) and White et al. (50) have explicitly considered the effects of heterogeneity in the fox population on the spread and control of rabies. However, these authors have found that the influence of heterogeneity can be considerable. In particular, Smith and Harris (38) found that heterogeneity resulted in greater variability in the speed of travel of the rabies front and that this heterogeneity can also disrupt the rabies front, resulting in some small pockets of
infection preceding the front. This disruption to the rabies front has since also been observed by Grimm et al. (18) and Jeltsch et al. (24) in their homogeneous models.

Although the spread of rabies has been successfully controlled in much of Europe by oral vaccination of foxes, this leads to further problems when the fox population starts to recover towards the threshold level required for rabies persistence. Some of the more recent models produced for rabies in Europe focused on the consequences of recovering fox populations for the continued control of rabies. This is of particular relevance since some countries such as Germany are now considering reducing their expenditure on rabies control (41). Schenzle (34) used a deterministic model to investigate whether rabies could be controlled in Germany by vaccination of foxes, and found that for continued control, there was a need to increase the density of baits. Similarly, Artois et al. (7) concluded that if the fox population continued to grow, a higher proportion of foxes would need to be vaccinated to maintain the current success rate. Tischendorf et al. (41) found that even after five years of repeated vaccination at a rate of 70%, eradication could not be guaranteed, and that at least six years of control with a 70% immunisation rate were required for a high chance of successful control.

One of the other problems associated with immunisation is the fact that rather than completely eradicating the disease, immunisation can actually lead to the disease being maintained at very low prevalence levels in an endemic situation. Anderson et al. (2) concluded that due to its high pathogenicity, rabies would only persist endemically in fox populations at very low prevalence (3%-7%). Tischendorf et al. (41) found that this low level persistence could occur even for high immunisation rates of 60%-80% and that it was characterised by clusters of infection that moved in time and space, in a similar way to the ‘wandering patches’ observed by Mollison and Kuulasmaa (31). However, these patches seemed to be associated with long lasting seats of infection rather than infected foxes migrating from non-immunised areas.

PROBLEMS AND LIMITATIONS OF THE RABIES MODELS

The previous section has shown that models have contributed much to understanding the spread and control of rabies in Europe. However, there are some general issues that it is necessary to address in order to assess the real value of these contributions.

Rabies is the most frequently modelled wildlife disease, with rabies models accounting for 15 of the 35 wildlife disease models discussed by Barlow (12). One of Barlow’s (12) criticisms of many wildlife disease models was that they offered no evidence that a model’s output was realistic. For rabies models for Britain, this testing is not possible because a rabies outbreak is a hypothetical event. However, most of the rabies models for continental Europe that are reviewed here were developed in the light of an existing endemic rabies scenario. The fact that they provide realistic estimates of rates of spread for the disease is therefore unsurprising. However, the models varied widely in both their structure and their transmission pathways, especially regarding whether or not dispersal and/or inter-group contact were included as transmission pathways. This has significant implications for the mechanisms underlying the wave-like pattern of disease.

In deterministic models where rabies spread occurs by the diffusion of rabid foxes (25, 33), resurgence of rabies occurs because the susceptible population recovers to the threshold population required for disease persistence. The presence of extremely small numbers of infectious individuals, termed ‘atto-foxes’ by Mollison (30), allows the disease to erupt once more. In spatial stochastic models, disease is re-seeded into the recovering fox population by infected foxes dispersing from the rabies front (14). As Barlow (12) points out, only one of these mechanisms is likely to be correct. The more recent models (24, 41) have shown that the spatial mechanism is of vital importance in creating this wave-like pattern. However, dispersal alone is not sufficient, and the pattern appears to be a result of the interplay between long-range dispersal and inter-group contact.

As the discussion in the previous section showed, contact rate remains one of the most significant unknown parameters in rabies epizootiology (28). In most of the rabies models discussed in this chapter, contact rate is assumed to be proportional to the density of infectious and susceptible hosts, and therefore
proportional to the total population. Thus, contact rate is highest in high density populations and lowest in low density populations. However, this assumes that contact behaviour is not affected by changes in host density or with perturbations to the host population such as may be caused by culling. In reality, the relationship of contact behaviour with host density may be more complex.

As host density decreases, home range size will increase (44). However, increases in home range size mean that animals will be ranging more widely and also that they will be unable to defend larger territories as completely as smaller ones. White and Harris (47) showed that foxes from neighbouring groups at high densities moved so as to avoid one another close to their territory boundaries. This means that at high densities, although potential contact rates are higher, actual contact rates may be significantly reduced due to avoidance behaviour. At lower densities, the relative lack of boundary surveillance will mean that incursions into neighbouring territories may be more frequent. Although the chances of actually meeting a neighbouring fox will be reduced by the larger home range size, the probability of a physical encounter following detection of another fox may actually be increased. It is therefore very unlikely that the relationship between contact rate and population density is linear over a wide range of densities. However, the precise nature of the relationship would be extremely difficult to quantify in the absence of extensive fieldwork at different population densities. White et al. (50) predicted that contact rate would increase in a general linear manner with population density for most of the year, but that the nature of the relationship would show seasonal differences, such that in winter, it would be more asymptotic. They suggested that the nature of the relationship between contact rate and population density was a key factor in predicting rabies spread for different density fox populations, and that it might also have significant implications for disease control strategies.

In addition to the predictions of theoretical models (31), empirical observations of rabies and other microparasite diseases such as bovine tuberculosis have shown that disease shows distinct spatio-temporal clustering (10, 48). This spatial structuring implies an important difference in the internal structure of transmission pathways used by different models since in a spatially structured population, an infectious individual will encounter far fewer susceptible individuals than in a homogeneous mixing model.

For chronic diseases such as bovine tuberculosis, it has been shown that homogeneous mixing models cannot adequately recreate the behaviour of the disease (3, 13) and that some degree of spatial structure in the host population is required (10, 39, 48). However, for acute diseases such as rabies, there is much closer agreement between the predictions of the homogeneous mixing models and their spatially explicit counterparts. The reason for this is probably that the spread of acute diseases is much more rapid and therefore, homogeneous mixing, although a gross oversimplification of reality, does not contrast with the real situation to such an extent as for chronic diseases. Nevertheless, since many of the parameters for the non-spatial deterministic models are tuned to fit in with empirical observations, this does raise the question of whether they may be providing the right results for the wrong reasons. This also raises questions over their use as analytical tools for determining the relative importance of different parameters. The simplicity of the deterministic homogeneous mixing models and their consequent analytical power is frequently cited as one of their main advantages (2, 25, 32, 35). However, it is dangerous to put too much faith in analysis using simple models built on invalid assumptions.

CONCLUSIONS

The future role of models for rabies in Europe

One of the significant areas for contribution of any model of infectious diseases is that of disease control. This is an area where models have been of considerable value in policy formulation for rabies in Europe. The two principal options for rabies control have been culling or vaccination of foxes. Until the 1970s, culling was the only method available, but only two outbreaks in Europe can be said to have been eradicated by fox culling (26). The main problems with culling are the high reproductive rate of the foxes and the disruption to the remaining individuals in the population (9), which may exacerbate problems of disease spread. Indeed, Aubert (8) reported that in some Départements in France, intensive culling of the fox population had actually resulted in longer lasting rabies episodes than in areas where the fox populations had remained uncontrolled. A similar problem has been found with respect to the control of
bovine tuberculosis in Britain by the culling of badgers (40, 49). However, even without the inclusion of perturbation to the fox population, the earliest rabies models showed that vaccination would be a more effective strategy (2, 28).

Since the 1970s, efforts to control foxes on continental Europe have concentrated on the use of vaccines, and oral vaccination has been successful in controlling the spread of the disease. However, the eradication of rabies from the European continent remains some way off. The main reason for this is the fact that fox populations are starting to recover to higher densities once more and become re-infected by remaining pockets of infection. Models have shown that in order for control to continue to be effective, vaccination campaigns must remain in force for some time (7, 34). If rabies is to be eventually eradicated from continental Europe, then the predictions of these models should be addressed by policy makers considering the future of the oral vaccination programme in parts of Europe.

Any mathematical model should be biologically realistic, yet it should also be mathematically tractable. The problem with many spatial stochastic models is that they are extremely difficult to analyse mathematically. Thus, it may be difficult to interpret the predictions of the model in terms of the contributions of the various individual parameters. Nevertheless, the greater biological reality of these models, especially for spatially heterogeneous or limited populations, has meant that their popularity has increased over the years for modelling ecological processes within such populations. The fact that the predictions of these models may differ considerably from those of deterministic non-spatial approaches, (33, 38, 50) has led some authors to incorporate spatial approaches into their deterministic models, (7). This has undoubtedly improved the biological realism and predictions of these models.

The models (38, 50) represent the ultimate reductionist approach in that they are individual-based. However, this means that they are also the most complex. As a result, the relative sensitivity of the models to different parameters is harder to determine, and simple relationships such as those between contact rate and host density are also harder to quantify. As a result, some of the more recent models have combined a probabilistic, spatial approach with group-based rather than individual-based functions, (e.g. 18, 24, 41). Even for these models with their relatively reduced complexity, sensitivity analysis is extremely complex (24). However, the development of these models has been important in yielding further information about the mechanisms behind certain disease patterns and therefore increasing our understanding of the disease. These types of models may be particularly important in quantifying the level and location of control efforts to counter the threat posed by recovering fox populations in some parts of Europe.

One of the principal aspects to emerge from the above discussion is the importance of heterogeneity in the dynamics of rabies. Heterogeneity may operate at many levels: at a landscape level in determining fox population distribution and abundance; at a territorial level determining the dynamics and nature of contacts between neighbouring groups and, within social groups determining the level and type of contacts between individuals of the same group. For an acute disease such as rabies, the within-group level may not be so relevant. However, a comparison of the models developed to date suggests that the other levels are likely to be quite significant.

In conservation biology, metapopulation theory has increasingly been applied as a framework for understanding spatial and temporal heterogeneities in populations. Metapopulation dynamics reflects the dynamics of processes within patches and links between patches, and primarily focuses on the role of interactions between the patches in promoting the continued existence of a population. Recently, there has been a growing interest in applying metapopulation theory to infectious diseases, both on a theoretical level and also empirically (15, 23). The gap between theoretical and empirical studies is a concern in wildlife disease research (12, 43), but a metapopulation approach may provide a useful way of bringing these two strands of research together (17). This type of approach has yet to be applied specifically to the epidemiology of wildlife diseases. However, since the nature of the remaining questions and problems surrounding many wildlife diseases, including rabies, is inherently spatial, such approaches are likely to become increasingly important in the future.
References


CHAPTER 22
FOLKLORE, PERCEPTIONS, SCIENCE AND RABIES
PREVENTION AND CONTROL

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Summary

Rabies has profoundly touched the human imagination for millennia. Yet, it was only during the late eighteenth and nineteenth centuries that public anxieties about the disease reached their zenith and began to manifest themselves in an extreme fashion. Other terrible afflictions such as syphilis and cholera that affected people throughout Europe during this period were linked to depravity and class distinction. There was a clear connection between changing codes of conduct and anxieties about contagion. In the case of syphilis, this meant that, during the 16th Century, people no longer wished to so freely associate with others, particularly those of lower and thus more questionable status, not only for dread of contracting the disease, but also for fear of ‘social pollution’. Human anxieties about rabies have been embodied by and embedded in the folklore and notions that have surrounded the disease since antiquity. This chapter will examine why rabies has struck such terror into the hearts and minds of people throughout the ages and how this has been translated into efforts to prevent and cure the disease.

Keywords: folklore, myths, post-exposure treatment, rabies, treatise

INTRODUCTION

Rabies is probably the most notorious and feared zoonosis known to humankind. Throughout the course of history, this disease has deeply affected the human condition, inspiring not only great fear and trepidation, but also considerable disagreement and seemingly irrational prejudices about how and between whom it may be spread.

Firstly, human fear of rabies will be analysed in general terms. Two alternative, yet interrelated, explanations for humankind’s age-old dread of the disease will be considered: the fear of rabies will be contemplated as perhaps being the fear of the de-civilising effects which the disease has on its human (and canine) victims, and the intimate and long-standing relationship of humans to the archetypal agent of transmission, the dog, will be examined.

Secondly, the folklore and ideas that have for centuries manifested dread about rabies will be dealt with more explicitly. A brief history of fear, extending from ancient times up until the 19th Century will be outlined and the various ways in which people have attempted to prevent, cure or control rabies will be explored.

The third and final part of the chapter will examine the rise of new scientific explanations and strategies for the control and prevention of rabies. It will consider how scientific knowledge gradually superseded erstwhile folklore and practices and led to the attenuation of fears about the disease.

BECOMING A HUMAN ANIMAL

Historically, there has been some dispute as to the origins of the term rabies. An early 17th Century source suggests that the ancient word ‘rabiem’ may have been derived from ‘raviem’, the ‘madness’, or the ‘hoarseness of the voice’ (due to the fact it was said that an afflicted dog cannot bark). But it instead goes on to argue that the term rabies may come from the word ‘rapiendo’, since when a dog is smitten it will become irritable, bite anything it encounters and often begin to run back and forth, or roam aimlessly (25). Modern accounts, however, claim that the Latin word for rabies derives from the Sanskrit rhabas that
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means ‘to do violence’ (22). Whatever the case, all definitions point to the consequence of infection: uncontrolled and violent conduct. The following passage, taken from an account of a patient who died of rabies in 1976 in a British hospital after having been admitted due to stomach pains and operated upon for appendicitis, clearly depicts the shocking and devastating effects of the disease on its human victims:

‘After the operation he started mumbling loudly and then became hysterical... He was given a sedative which had no effect and his body began to twist about and his legs thrash about in the air. Exhibiting the classic symptoms of rabies, he was moved to a side room. But before he was moved... the patient, thrashing about in agony bit a nurse... [who] told how, after a routine operation, the patient began growling and howling, disturbing the whole hospital. Drugs had no effect and he suffered convulsions and he was violently sick. Saliva began foaming from his mouth and he was unable to control his movements. He tried to hurl himself from the bed and before she could catch him and stop his head hitting the floor, he bit her.... By then six members of staff were trying to restrain him and he appeared to be asking for water. When offered a glass he spat water out and went mad.’ (12).

Unbeknown to the physicians who treated him, the deceased – of Bangladeshi origin – had been bitten by a dog during a visit to his homeland the previous year.

As the above description suggests, the furious stage of the disease is characterised by a radical change in the patient’s behaviour; a change which would undoubtedly perturb all those in attendance. The violent ‘madness’ that embodies the final stages of rabies has a far deeper social and metaphorical significance, even for those who are not immediately confronted by a rabid person; hence, perhaps, the universality of the fear of the disease. In rabies, humanity itself is seemingly brought into question, for the individual is unavoidably reduced to a wild, uncontrolled, animalistic state. A rabid person breaches the gap between humans and other animals, thus opening the floodgates to fear, fantasy and folklore. In this way, rabies has been blown up out of all proportion, for it has appealed to peoples’ imaginations and inflamed their senses of danger and disgust.

This supposition may well explain why rabies has been enshrouded in a veil of mystery for millennia. As earlier chapters in this volume have already demonstrated, the disease is in fact one of the oldest of the known infectious diseases. Since ancient times, allusions to rabies have been found in mythology, poetry and prose, legal documentation and medical treatises. From the earliest accounts it is clear that the causal link between the disease and the saliva accompanying a dog bite had been made, and multitudes of outlandish practices were used to protect individuals against the disease (Chapter 1, J. Neville).

Descriptions of rabid animals and humans, plus a variety of cures, emanated from European and also celebrated Arabic physicians such as Rhazes and Avicenna, throughout the first millennium AD. References to rabies continued to appear in legislation, which suggests that outbreaks of the disease were taken very seriously. For example, in 1026 the disease is mentioned in the laws of Howel the Good of Wales. Here the occurrence of the disease is treated as a notable event, recording a rabies epizootic amongst dogs that same year (9). Earlier Alamannic law (ca. 718) also required partial compensation from the owners of dogs that killed people. Interestingly, this suggests that dogs might have been thought to have the capacity for reason and intent, thus their owners were spared full responsibility for their actions. It is unclear whether these laws refer to death caused simply by a vicious animal or one that was rabid, but it is certain that owners were required to take a degree of responsibility for their animal’s conduct, be it in sickness or in health. This sentiment was also echoed in the laws of the Visigoths (ca. 476-654), Burgundians (ca. 483-532) and the Lombardians (ca. 643-755) (19).

It appears though that prior to the Middle Ages, rabies epizootics were most uncommon. The cases recorded generally related to singular cases where people had been bitten by rabid dogs, or sometimes by wild animals. Around this period, however, tales of rabid beasts attacking humans began to emerge. The first significant recorded outbreak of the disease occurred in Franconia during the year 1271, when rabid wolves reportedly invaded human settlements, attacking both domesticated animals and people. At least thirty people are said to have died after having been bitten during this lupine onslaught (22).

In light of the increasing casualties from the disease, rabies continued to be a worthwhile and weighty topic for medical discussion during the Middle Ages. For example, an 11th Century Anglo-Saxon text ‘The Medicine of Quadrupeds’ attributed to a certain Sextus Placitus – borrowing from classical tradition
advices that an individual bitten by a rabid hound should be given the head and liver of the affected animal. Furthermore, offering a variation on Pliny's worm theme, he recommends that the worm, or rather severed membrane, should be placed by a fig tree (20). During the 13th Century, the celebrated -- and later canonised -- Christian encyclopaedist and natural philosopher Albertus Magnus (ca. 1193-1280) identified hydrophobia as being the most serious disease to afflict the canine species. In De Animalibus, he clearly recognises the highly contagious nature of the disease, noting that it can be transmitted to other dogs and humans by the bite of an infected animal. In view of this, he advises that 'when a dog becomes hydrophobic or rabid' it should be isolated 'immediately from the rest of the pack, lest it infect its kennel mates by biting them'. He reports the claim that dogs can be cured of rabies by mixing chicken manure with their food (1). However, he also goes on to outline a far more radical, and rather barbaric, solution to the problem:

‘According to the writings of Ameria, the King of Valentia, a rabid dog should be immersed in a tank of hot water, suspended by its forepaws so that the hind feet barely touch the bottom; and the entire length of its body should be submerged for nine days. After removal from the water, its head and body should be shaved, even to the extent of scarifying the skin. Then, it should be smeared with beet juice and re-dipped in the tank for additional immersion. If the dog eats at all during this period, its food should be marinated in beet juice and mixed with the pitch of black elder, because the latter is also beneficial. However, if no favourable results are obtained in the next seven days, the dog should be slain, for it will never be cured.’ (1).

Whilst this treatment for rabies might seem rather drastic, it is clear that its diagnosis was likely to have instilled great fear and trepidation in the hearts of mediaeval folk. Moreover, that there was any attempted cure at all for this dreaded disease – albeit an extremely unpleasant one – evidences the value of dogs to their mediaeval owners and the esteem in which they were held. If the animal survived this therapy at all, it was unlikely to have been suffering from rabies in the first place. As modern veterinary medicine shows, if a rabies suspect is still alive after having been kept in isolation for ten days (from onset of the clinical signs), the disease can in fact be eliminated as a diagnosis.

As the years passed, the body of literature on rabies gradually grew, providing increasingly more detailed descriptions of the disease and innovative cures for it. Yet it seems that very little progress in preventing or curing rabies had been made, much of that recorded being ground in superstition or hearsay. For example, in The Noble Arte of Venerie or Hunting published in 1576, George Tuberville held that the time of breeding influenced an animal's susceptibility to madness. He wrote that procreation should only be permitted after the full moon, preferably under the zodiacal signs of Gemini and Aquarius, so that more progeny are male and less prone to becoming mad (20). From a modern perspective, we can surmise that such commentary failed to expand the frontiers of medical knowledge.

The need for effective control of the disease is clearly reflected in the increasing numbers of outbreaks recorded in pre-modern Europe. For example, in 1500 canine rabies is said to have raged throughout Spain; and in 1586 further canine epizootics were reported in Austria, Flanders, Hungary and Turkey during the plague epidemic. By 1604, rabies amongst dogs was said to have been widespread and to have caused great alarm in Paris (22). Wherever dogs are affected there is cause for human concern.

In addition to increasing numbers of outbreaks, the sixteenth and seventeenth centuries also saw an expansion in the body of European literature relating to rabies, though as the above suggests, the remedial and preventative measures suggested were most certainly the result of existing medical and superstitious beliefs. Astrology, folklore and the humoral theory of disease inherited from classical scholars often went hand in hand at this time, and consequently influenced people’s view of the disease (5). Often, writers would suggest that there were more causes for rabies than simply infection from the bite of a rabid animal and several varieties of ‘madness’ were often described. It was also during this period that one of the most significant and influential works on natural history appeared. The Historia Animalium was penned by the Swiss-born naturalist Conrad Gesner (1516-1565) and published in 1587. A version of this work in English was produced by Edward Topsell in 1607 (25). The Historie of Foure-Footed Beasts provides a wonderful overview of both classical and contemporary wisdom pertaining to the characteristics, habits and diseases of every species imaginable. Topsell (1572-1625) devotes considerable space to describing the dog and its afflictions, the most significant of which he identifies as being rabies. Akin to many of his
contemporaries, much of the description of remedial measures and many of the tales he presents are based on superstition or hearsay. For example, he reports that:

‘A man bitten with a Mad Dog, falleth mad presently when he cometh under the shadow of a com-
tree; as it is affirmed by most Physitians, for that shadow seteth the poyson on fire: but a man falling
mad, of all creatures avoideth a Dog, and a Dog most of all falleth upon men. There are many things
which ingender madness in Dogs, as hot wheaten bread dipped in bean-water, melancholy bred within
them and not purged by Canaria, or other herbs, the menstruous pollutions of Women, and the pain of
his teeth. Their madness is most dangerous in the Dog-days, for then they both kill and perish
mortally; for at that time their spittle or fome, falling upon mans body, breedeth great danger; and that
if a man tread upon the Urine of a Mad Dog, he shall feel pain by it if he have a sore about him: from
whence it came to pass, that a stone bitten by such a Dog, was a common proverb of discord.’ (25)

Interestingly, Topsell understood that not all bites inflicted by a rabid dog will necessarily be deadly. He
thus wrote that ‘sometimes a mad Dog hath bitten, and there hath followed no harm at all, whereof this
was the reason, because poyson is not equally in all his teeth; and therefore biting with the purer and
wholesomer, the wound became not perilous’ (ibid). However, Topsell did believe that dogs – in addition
to their wild relatives, wolves and foxes – were inclined to go mad by nature, whereas other species would
only be afflicted by madness once they had been bitten. He put this down to the nature of the dog’s teeth
that are sharp and saw-like, unlike those of other species. Belief in the spontaneous generation of rabies in
dogs was popular at this time and persisted even until the late 19th Century when Fleming, in his major
work on the malady, curiously states that although the main cause of rabies is contagion, the disease may
occasionally occur spontaneously (10).

In 1613, a book entitled ‘A declaration of such grievous accidents as commonly follow the biting of mad
dogges’ appeared. Written by Thomas Spackman, an English physician, this publication is believed to be
the first work to have been specifically devoted to the topic of rabies. Spackman distinguished clearly
between the canine and human forms of the disease, stating that rabies was specifically the madness of
dogs and hydrophobia the human consequence of being infected by rabies. Although he recognised
contagion as the cause of the malady in cats, wolves and horses, Spackman held to the belief of
spontaneous generation in dogs, noting that the ‘inward causes’ of rabies in the dog were an excess of heat
and cold, insufficient water, and a ‘peculiar and natural propensity’ of dogs to go mad. Adding a number
of ‘external causes’, he noted that contagion could occur through being bitten, from feeding on carrion or
animals which have died from plague or rot, or have been killed by lightning. To this list, he even included
the grief that a dog might suffer at the loss of its master as a cause. Spackman also suggested that black
and red coloured dogs were more prone to the disease, as were similar hair-coloured men and women
(21). The notion that an animal’s colour may denote its constitution was echoed in other works emanating
from this period. The much published and influential, though later much maligned, veterinary ‘expert’
Gervase Markham (1568-1637) was also fond of this idea and applied it frequently in his works on farriery
(23).

In Countrey Contentments, Markham also turned his attention to the topic of rabies, promoting the following
cure for dogs that have been bitten:

‘If your Hound have beene bitten with another madde Dogge, which is a disease exceeding dangerous
and mortall, you shall presently wash the place so bitten with Sea water, or a very strong brine, and it
will save and cure him, or els take the hearbe called Yarrow and beate, a handfull thereof in a morter,
with a handfull of wheate till it come to a salve, and then lay it to the sore, and it will heal e it, and if
you poure into his stomacke as much methidrate as a hasellnut, dissolved in sweet wine, and it will
wonderfully scoure and preserve him from the infection of the inward poison.’ (15)

It is noteworthy that during this period the disease was most commonly associated with dogs, although it
had by then been clearly established that other species could be affected by it. With regard to this, in 1677,
the German naturalist Christian Francis Paullinus remarks in Cynographia Curiosa that this most serious and
incurable disease was generally known as ‘Rabies Canina not because it is inflicted by dogs alone, or
because dogs only are seised by this disease... but because dogs are much more subject to it and to a
greater degree than all other animals, and because, living along with us as domestic animals, they all the
more easily communicate the evil to us.' (3).

The late sixteenth and seventeenth centuries witnessed the growing popularity of the belief in religious
marvels. The best example of this is the miracle of St. Hubert, the patron saint of hunters, which enjoyed
particular favour in 17th Century Belgium where a shrine to him is situated. It is rumoured that people
visiting this shrine as early as the year 825 were miraculously cured of their madness, but it was only
centuries later that the cult of St. Hubert became truly popular. Writing in 1872, George Fleming reveals
that the custom of visiting the shrine was still being practised well into the 19th Century (10). The legend
of St. Hubert pertains to a stole which was given to the saint by an angel whilst he worshipped at the
tomb of St. Peter in Rome. It was believed that this stole would work miracles, as would also a golden key
that would afford special powers over evil spirits. This key was in fact an iron that was applied red-hot to
the wounds of those bitten by rabid dogs. St. Hubert was also apparently venerated in both Liège and
Utrecht, where the iron takes the form of a ring and a cross respectively (ibid). Another religious artefact
popular at this time was attributed to a St. Lambert, whose cape and cross were supposed to have certain
medicinal benefits for treating those afflicted by rabies (6). Topsell also mentions the ‘miraculous fiction’
of the door key of the church of St. Bellius, situated near Rhodigium, which was believed, if held red-hot
in the hand of a mad man, would deliver him from his fits forever (25).

The mystique surrounding rabies continued to prevail well into the 19th Century, its very real terrors and
symptoms being greatly heightened by popular ignorance and superstition, not to mention endless
scientific speculation about its spontaneous propagation and cure. Why is it that rabies, in essence a rare
affliction, has occupied so unique a position in disease history; when other perhaps more common
diseases, which also have terrible manifestations and produce aberrant behaviour in the victim, have
struck without provoking such a vehement response? As Thomas Dolan, a 19th Century physician
implored, why, for example, should 'a death from rabies... be considered more terrible than a death from
tetanus'? Dolan’s last word on this subject, although it skirts the issue, will be my own. Quite simply, he
writes, that ‘it is fortunate for humanity that other diseases have not been treated in the manner... [of]
hydrophobia.’ (8).

Notwithstanding the fact that other maladies may also produce similarly disturbing symptoms, at times
even being confounded with the disease, the manifestations of rabies possess a particular sociological
significance, perhaps in common with other afflictions such as epilepsy, tetanus and various neurological
conditions. In short, the disease seems to involve what may be best described as an involuntary ‘reversal’
of specific behavioural standards which have been learned by the individual and are common to the
society in which he lives. A person afflicted by the disease thus experiences a sudden and undesirable
degeneration in his capacity to exert control over his own actions. This loss in self-control will, in turn,
distress those around him who may not comprehend his change in behaviour. To a certain extent, this can
also be said of the canine victims of the disease, which during the excitative phase display radical and
anomalous changes in behaviour, which eventually turn the generally tractable dog into an uncontrollable
whirlwind that will attempt to bite anything that moves, often inflicting severe damage to its own teeth
and oral tissues (24). The domesticated dog is thus also reduced to an uncivilised and highly dangerous
state, quite shocking to humans who are generally unaccustomed to witnessing savage canine behaviour. It
is no wonder that the Victorian middle classes were reluctant to accept that their well-bred and genteel
pets were as susceptible to the disease as the aggressive curs and fighting dogs kept by the lower classes.

The human fascination with rabies has also meant that the disease has been remarkably well documented.
A consequence of this is that it is evident that the clinical manifestations of the disease have changed little,
if at all, for over 2000 years. This is highly unusual for a viral disease, since viruses tend to mutate over
time producing different symptoms, thus being difficult to accurately identify from historical records (27).
Scientific treatises on the disease which began to appear from the early 17th Century onwards, however,
often suggested that many of the cases which were deemed hydrophobia were in fact cases of acute
insanity, tetanus, 'brain fever', cardiac disease or pericarditis. Given inconsistencies in symptoms, not to
mention that some of the instances recorded full recovery from the disease, many of the cases were
deemed spurious. In fact one English physician, Robert White, wholeheartedly denied the transmission of
rabies canina to humans, even going so far as to inoculate himself with the saliva of a rabid animal to
prove his point! (18, 26). Further to this, it was suggested that many of the therapeutic measures adopted
throughout the centuries to cure ‘hydrophobic’ patients may have done more harm than good, perhaps being more responsible for their demise that any virus (8).

Scrutinising case studies of supposedly hydrophobic persons, one is struck by the graphic accounts of the patient’s demeanour. References are often made to the spontaneous and violent movements of the patient, most strikingly to their attempts to bite those tending them. Consider, for instance, the following excerpt from a report made by an English surgeon, G. Battcock, in 1809:

‘... at noon his countenance materially altered; the teeth and gums of the upper jaw were constantly exposed, and frothy saliva ran out at the sides of his mouth – he begged me to kill him at once; stamped on the floor with violence, became furious, and could scarcely be held by the attendants. He was now confined to bed with a straight waistcoat – he wished to be confined when it was proposed – he now attempted to kick and bite every one who came near him – occasionally requesting to be held fast, lest he should bite or injure others. The vessels of the tunica conjunctivita in the eyes became filled with red blood, which, added to the way in which his teeth were shewn, and the foaming at the mouth, gave his mouth a frightful aspect; in this state he continued till near one o’clock p.m. and expired.’ (26).

The uncontrolled behaviour, of which the above patient appears to have been partially aware, has a certain animalistic character. Biting is a defence mechanism instinctive to carnivorous animals, and is certainly one which humans are, from a very early age, dissuaded from adopting. As Robert James pointed out in his treatise on canine madness in 1760, unlike dogs, the natural weapon with which a man defends himself is the fist. This, he explains, is the reason why dogs infect humans with rabies, but humans do not infect one another with such terrible afflictions. He argues:

‘When a dog... in delirium picks a quarrel with any thing he imagines offends him, he bites the antagonist, and some of the saliva enters the wound, or scratch, a very little of which is sufficient to excite the same distemper in the wounded animal. A man in the same situation gives a slap on the face, a box on the ear, or a pinch, by which no wound is made, and none of the excrementious juices discharged from the sick person is convey’d into the habit...’ (13).

The rabid patient is, however, as we have already seen, not always capable of producing such socially appropriate responses. When one considers other popular fantasies about vampirism and werewolves, both of which bridge the gap between the human and the animal world, it is not hard to comprehend why, combined with other aspects of rabies, such biting behaviour provoked disgust and fear in people. Another curious ingredient of many case studies, not wholly supported by 20th Century accounts, is the strange dog-like noises which patients are reported to have made; presumably this is where the expression ‘barking mad’ originates. The earliest English language publication devoted entirely to the disease, penned by Thomas Spackman in 1613, recounts:

‘The venome... in the processe of time getteth up to the braine, where it perverteth and corrupteth the imagination, reason and memorie. Yea sometime it so infecteth the synowes, as hee is vexed with grievous crampes, and cruell convulsions, and in the end forceth him so far out of his wits, as hee will offer violence both to himselfe and all that he is in companie withall, especially with his teeth like a dog, and will howle and barke after and doggish manner, fearing the sight of water, or any bright thing, and (as some Writers affirm) imagining that therein hee seeth a dogge, which of all creatures hee feareth and abhorreth most.’ (21).

Such dog-like noises are most likely connected with the spasms of laryngeal musculature that the patient suffers, which produce a hoarseness of voice in addition to an inability to swallow. Battcock also remarks that ‘the coughing or convulsed motion in the oesophagus, throughout the whole disease, was so loud and remarkable, that several people in the neighbourhood (who knew nothing of the dreadful situation the man was in) said he was barking like a dog – the noise certainly resembled it’ (26). Fantasies of seeing or hearing dogs are also reported elsewhere; it is also said that in delirium the patient may also imagine that he is surrounded by people distant from him, whom he converses with or violently abuses (17, 31).
In short, the patient is, within a relatively short space of time, reduced to an apparently ‘inhuman’ state. So terrible was this fate that, until at least the end of the 18th Century, people afflicted by the disease were commonly smothered to death. This practice was apparently widespread for centuries, though received little publicity (28). In fact, one Irish case which did receive public and judicial attention, involved a teenage boy who was smothered between two feather beds by his friends whilst in the throes of hydrophobia. This led to an English commentator remarking that the Irish ‘did not regard it as a murder, but absolutely as a legal and meritorious act, to smother any person who had arrived at an advanced stage of hydrophobia.’ (8).

Popular ignorance and superstition about the disease had not only led to the notion that the disease could occur spontaneously, but also that rabies might be induced by the bite of a perfectly healthy animal. Such erroneous beliefs occasionally led to hysteria, particularly amongst women, who fancied that they were afflicted by this terrible disease and would soon perish horribly. As Grantley F. Berkeley recounted in 1874:

‘It is known to everybody how fond ladies are of their lap-dogs, or any of the canine race upon whom they lavish their care, or to whom they assign a companionship that, by constant use, becomes one of the amusements of their lives. In the course of my existence, it has come occasionally within my knowledge that ladies and their waiting-maids have been bitten by their canine pets, and when there has been any constitutional or nervous tendency in the mind – a species of morbid apprehension, needless in origin, but very difficult to combat – has sprung up, capable by its own chimeric and mental poison to produce, not the very disease that caused the unfounded dread, but a madness from the force of imagination, arising in and mastering the temporarily unhinged intellect, and which might ultimately produce death.’ (4).

In 1810, the French hospital administrator Bernard-François Balzac implored that patients suffering from ‘psychological hydrophobia’ must be protected from the age-old practice of smothering. Furthermore, euthanasia, although generally performed as a humanitarian act, he suggested, might be far too tempting an option for heirs or enemies of the ‘hydrophobic’ patient if ignored by the judiciary (28). Veterinarian William Youatt, however, pointed out that although ‘hydrophobia has been produced in the human subject by the power of imagination, or by strong excitement... the disease has materially differed from rabies in its symptoms, progress and termination.’ (31). True rabies and an imagined affliction should thus not have so easily been confounded.

HUMANS, HOUNDS AND HYDROPHOBIA

Historically speaking, the dog has been an active participant in human society for at least 12,000 years, if not more (7). The historical bond between dog and human should not, however, be romanticised as a consequence of present day affections for the animal. Until comparatively recently, the relationship between human and hound has often been, at best, ambivalent. Certainly dogs have always been a favoured species, but the adage ‘all dogs are equal, but some are more equal than others...’ more accurately describes the ambiguous and age-old human relationship with the species. Since ancient times, a hierarchy amongst dogs has existed in the eyes of humankind.

The first ranking position amongst the canine species has always been occupied by the greyhound. In mediaeval times, for instance, none under the social rank of gentleman or free-holder was even permitted to own such a beast (32). Other hunting and fowling dogs such as spaniels have usually occupied a second rank status in this canine hierarchy. Lap dogs, of no value for hunting pursuits, favoured by noblewomen and bourgeois ladies, have taken third place; less attractive, though nonetheless useful breeds, such as mastiffs and sheep dogs, have been regarded as being of yet still lower status. Finally, the currish cross-breeds kept by common folk have always found themselves at the bottom of the pile, often being regarded as ugly creatures of no real use to humankind. Dogs were thus generally ranked according to their importance to the elite. The breeds with the greatest hunting prowess and aesthetic beauty were placed far above the working and mongrel dogs kept by people of lower social standing. This ‘social’ ranking of the canine species persisted well into the 19th Century and is clearly reflected in ideas about rabies that existed at that time.
During the 19th Century, concern for animal well-being reached a new height. Dogs, or rather particular breeds of dog, began to be held in greater reverence, especially by the middle classes, acquiring a quasi-human status as cherished pets and family members. Dogs were thus seen to possess moral, human qualities and deserved to be treated – above all – with compassion. However, the allocation of a quasi-human status to non-human animals created somewhat of a dilemma when it came to the allocation of blame for the transmission of rabies. How could people possibly admit that their most cherished and faithful companions, as one commentator put it, ‘educated into the bosom of man’ could be ‘perverted into his most formidable enemy’? (16).

The answer, it seems, was straightforward. Just as the middle classes had laid blame at the door of the unruly working classes for the proliferation of other infectious diseases, the dogs most commonly owned by the lower classes were identified as the most likely culprits for the spread of rabies. As Harriet Ritvo describes in her fascinating book *The Animal Estate*, the legal conventions of the Victorian age bestowed a hierarchy of moral attributes upon dogs, associating both the calibre and character of animals with their owners. By attributing moral culpability to dogs, animals which were rabid could be perceived as being guilty for carrying the disease, rather than simply ill. By making a correlation between infection and moral deviance, Ritvo suggests, those responsible for keeping the disease under control would more easily be able to recognise, isolate and destroy potential carriers. So began a fanatical police-directed persecution of dogs, which would theoretically nip the problem of rabies in the bud but ultimately resulted in the destruction of hundreds of animals that were generally only guilty of being unattractive or suffering from epilepsy or distemper (18).

As early as the mid-1700s, well-intentioned judicial attempts to prevent the spread of the disease through the confinement of canines during a rabies epizootic resulted in the persecution of dogs found at large. As the physician Daniel Layard wrote in 1762, rewards offered for the destruction of straying dogs ‘prompted a licentious rabble to kill every dog they could meet, within their reach, with all the barbarity possible: and too often the number of real mad dogs was increased, by the violent pursuits and attacks of the giddy and unthinking populace’ (14). The pursuit of a fast shilling was, however, not the only motivation for canine persecution. Fear of the disease and the ignorance of the true signs and appearances of rabies canina were also largely responsible for the demise of multitudinous mutts. Not surprisingly, this persecution aroused considerable consternation within the veterinary profession of the day. John Woodroffe Hill, for example, a distinguished fellow of the Royal College of Veterinary Surgeons lamented that:

> ‘many unfortunate animals are condemned as rabid, through the ignorance of inexperienced persons... The cry of ‘Mad Dog’, nowadays, is quite sufficient to hunt down a poor harmless creature who has perchance lost his master, and in fear and excitement frantically seeks for him up one thoroughfare and down another. Panting and distressed, he at last falls exhausted, or is compelled to rest: truncheons, bludgeons, brooms, etc. or a revolver, are brought to bear on the luckless animal, and often brutal is the torture inflicted before the supposed mad dog is put out of danger’ (30). The most common problem was that epilepsy was continually confounded with rabies. This mistake, Woodroffe Hill continued, was rather unfortunate for the poor dog targeted; but was luckily ‘usually made, not by veterinarians, but by misguided policemen with the usual mob to back them up’ (ibid).

It in fact seems that pursuing ‘mad dogs’ became somewhat of a sport during the 19th Century. It was reported that, for amusement, children would often taunt dogs by launching projectiles at them. Provoked, these dogs would sometimes turn on their assailants, who, in a bid to secure their own safety and ‘a large modicum of sympathy’, would cry ‘mad dog’, thus passing a death sentence upon their poor victims (29). More disturbing still were the tales of animals deliberately being captured, driven into a frenzy and let loose to their peril. In the introduction to his 1874 publication, *Fact against Fiction*, Grantley F. Berkeley reports that:

> ‘In the cause of humanity, and in defence of the poor dog, I deeply regret to say that it has more than once become known to me, that, for the sake of a ‘lark,’ the lowest of the lower orders, when able to steal or entice a dog into their baneful possession, have anointed his limbs, or more sensitive parts of the frame, with a mixture denominated ‘horse oils.’ Then, if in a town or populous place, they have turned this poor agonised animal out of doors, for the time essentially mad, but no more mad, from any disease fatal to himself or any other creature, than a newly-born lamb. The appearance of this poor
animal, particularly when the mid of a population has been frightfully imposed on, then gives rise to a mischievously designed cry and to an exciting chase, always acceptable to the lowest of the low. Policemen follow in cabs, kill an innocent dog, and get cheered for their courage’ (4).

As the above quote explicitly shows, such conduct was attributed solely to the depraved lower classes. An article which appeared in the Edinburgh Medical Journal several years later echoes this. Its author, Andrew Wilson (a physician), describing the particularly brutal mob killing of a dog which took place in this Scottish ‘city of culture and education’ – wrote:

‘The dog – a black retriever – comes upon the scene pursued by a policeman. The official is accompanied by the usual retinue of message-boys and canaille, to whom any dog, pariah, or otherwise, is an object of extreme interest, as admitting a display of savage traits and hunting instincts which the said urchins have possibly inherited from their far-back ancestors, and which the progress of civilisation has not yet succeeded in eliminating.’ (29).

The public perception of the disease was that it was an alarmingly rampant one, whereas in reality it was demonstrated to be a far from common affliction. Post-mortem examinations often showed no signs of the disease in the butchered canine victims’ bodies (ibid). The 1887 House of Lords Select Committee, thus concluded that the truth about rabies and its appearances ought to be more widely circulated; the signs of the disease preferably being endorsed on dog licenses (2).

Whilst fear, ignorance and sadistic pleasure personified the public response to rabies canina, there was also a great deal of speculation amongst the learned about the nature of the disease. Although people were fully aware that rabies was generally communicated by the bite of an infected animal, theories abounded as to the spontaneous origins of the canine disease and the kind of animals most liable to contract it. It was, for instance, suggested that the disease was generated as a result of hot weather – the ‘dog-days’ of summer being the most dangerous period, warm spells thus being accompanied by increasing fears of rabies outbreaks. In his treatise *On Canine Madness*, William Youatt contemptuously describes a rather cruel experiment that he hoped would finally lay this hypothesis to rest. In short, a number of dogs were left standing by experimenters in the strong summer sun without shelter, food or water for a considerable period of time. All of the animals eventually expired, though none of them as a result of rabies, consequently proving that strong heat and sun did not produce rabies as had widely been believed (31).

Another fashionable theory, reported by John Gamgee (principal of the New Veterinary College, Edinburgh), was that canine rabies commonly originated spontaneously ‘from the restraint put on the animal’s sexual desires’. Gamgee cites a Parisian expert, M. Leblanc, on the subject who, to support his theory, claimed ‘that in a portion of the course of the Danube, the Christians on the one side of the river have chiefly male dogs, and there rabies is common, while on the Musselman side, where, as in the East generally, dogs of both sexes are left at liberty, the disease is unknown. Leblanc went on to add that ‘fancy and pet dogs, which are kept under most restraint in this respect, and are well fed, are those most liable to the disease’ (11). Interestingly, even George Fleming, the most learned 19th Century expert on canine rabies, acknowledged that there may well be a connection between sexual excitement and the production of rabies in dogs: although several years later, when pressed by the Select Committee on canine rabies, Fleming retracted all his earlier ideas about rabies being generated spontaneously on the basis of new foreign evidence and Pasteur’s new vaccine (10).

Aside from these theories of solar exposure and sexual repression, certain classes of dog were viewed as the most liable to develop and spread the dreaded disease. The dogs that were regarded with the greatest suspicion were the aggressive sporting and poaching dogs kept by the lower classes. It was believed that these animals, rabid or not, were generally vicious by nature and inclined to attack other dogs and humans. Such dogs posed a great danger for they were likely to both become infected and infect. This also added extra weight to the anti-cruelty campaign to outlaw dog-pits, which were also seen as hotbeds of crime and depravity in the eyes of the middle class. It was believed that the propagation of rabies was in no uncertain terms linked to, as Youatt put it, ‘the increasing demoralisation of the country’ (31). Youatt believed ‘that rabies is propagated nineteen times out of twenty by the cur and lurcher in the country, and
fighting-dog in the town’ (ibid). The only solution to this problem was that a tax should be levied on all ‘useless’ dogs, with extra penalties if they were found loose, or used for fighting.

More dangerous still, however, were the multitudes of stray and neglected dogs, generally mongrels, which roamed the streets and countryside, scavenging to survive. These vagrant animals were held in particular contempt and fear, for not only did they foul the environment and carry all manner of parasites, but they also were believed to be more susceptible to rabies than their pure-bred and well cared for canine counterparts (18). As mentioned earlier, the popular theory that stray animals were responsible for the propagation of the disease was proved unfounded by the experiences of those who dealt with them routinely. In 1877, in a letter to the Standard, the secretary of London’s Battersea Home for Lost and Starving Dogs stated that

‘since the establishment of the Home... 200,000 animals have been brought to the kennels. Not one of those dogs has been affected with rabies, although most of them were stray, starving or vagabond animals’ (8).

This information and the fact that no kennel staff or policemen bitten by stray dogs had ever developed hydrophobia was also submitted to the Select Committee in 1887. It led to the recommendation that suspected rabid animals should not be killed immediately, but instead be isolated and examined by canine experts who could appraise their condition more accurately (2).

More surprisingly perhaps, it was not simply strays and the ‘dangerous’ dogs of the lower classes that caught Victorian middle class attention. Harriet Ritvo argues that the excesses of the rich were equally epitomised by the dogs that they kept. The aristocracy did not adhere to the same degree of moderation and restraint in their conduct as the affluent middle classes, and were thus also singled out for their unruliness and lack of productivity (18). The pampering and over-feeding of ‘useless’, ‘inbred’ small dogs, was thought to give them a predisposition for contracting the disease. As Dolan asserts, the ‘pleasure dogs kept by the rich are scarcely less a source of danger and extravagance, for they appear very predisposed to rabies, whilst the food they consume forms no inconsiderable item of expense’ (8).

Dogs of foreign breed prized by the upper classes were also particular objects of contempt, their importation posing a particular danger, for they might contaminate both physically and metaphorically. Furthermore, akin to the working classes’ fighting dogs, the aggressive sporting dogs kept by the aristocracy were viewed as probable transmitters of rabies infection, thus posing a direct threat to law and order. The fox-hounds kept by the gentry were identified as the breed most responsible for rabies outbreaks. However, in contrast to the mutts of dubious social status, the elite were very quick to defend the moral character of their hounds. As Ritvo says, a ‘dog’s pedigree, cash value, or genteel environment might be cited as evidence of its respectability.’ Rabies infection in the kennels of the wealthy was thus generally blamed upon the incursion of unsavoury animals, such as cats and stray mongrels, into the throng of well-bred dogs, otherwise beyond reproach (18).

The apparently higher incidence of infection amongst dogs of morally reprehensible background appeared to more or less substantiate the argumentation put forward by the middle classes. But there were still exceptions to the rule for, as Ritvo points out, not all rabies suspects conformed to the stereotype of the aggressive mad dog which appeared from nowhere to wreak havoc amongst innocent human and canine populations: the revered family pet too may also become afflicted.

The premise that only dogs of morally questionable character and ownership were liable to infection lulled the middle class Victorians into a false sense of security. In reality, the intimacy which prevailed between human and cherished pet provided the ideal circumstances for cross-infection. It is far from unusual that a person will come into contact with the saliva of his treasured pet upon a routine basis. By simply displaying affection, licking its master, a dog could be at its most dangerous if contaminated by the rabies virus. In fact, one of the earliest clinical signs of the disease is that dogs which are usually rather highly strung may become far more affectionate towards those around them, whereas dogs which are generally affectionate may become more irritable than normal and shy away from humans (24). No wonder that, in his tract on hydrophobia, Dr John Murray commented that:
‘It is a matter of prudent precaution in everyone not to fondle strange dogs. There is a most reprehensible practice in some people of making pets of snarling puppies, pug dogs, or French poodles, and Italian greyhounds: and the lap of its mistress or a couch of down, clothed sometimes with silk or satin, must be the brute favourite’s place of repose. Of all the degrading and contemptible acts exhibited in the drawing-room or the parlour, this is at once the most reprehensible and dangerous, and it is from this source that numerous cases of the ill-fated disease have sprung. To recur only two of no very ancient date, we may advert to the fate of the beautiful and accomplished Mrs. Duff, sister to the Earl of Fife, who was bit by her lap dog, and whose fascinating and lovely form became the victim of this hideous disease. The other is that of the Duke of Richmond, Governor of the Canadas, who having cut himself with his razor, in the act of shaving, suffered a favourite dog to lick the wound, and fell a prey to his temerity’ (17).

**PROPHYLAXIS AND PREVENTION**

Towards the close of the 19th Century, scientific advances and government regulations appear to have attenuated public fears about rabies. During the 1880s, Pasteur’s experiments at last conclusively proved that the disease could only be transmitted by inoculation, ultimately dealing a deathblow to popular theories of spontaneous generation. The prognosis for those bitten by rabid animals was suddenly far less bleak, for the vaccine which Pasteur developed proved itself to be a reliable preventative remedy, if administered soon after the bite had been inflicted. The public clamoured for post-exposure prophylaxis, even though many who received it were in no danger of actually developing rabies. In fact, the vociferous anti-vivisectionists of the day, highly critical of Pasteur’s efforts, even suggested that patients may well leave the Pasteur Institute with more diseases than those with which they went in(18).

Prior to Pasteur’s discovery, middle-class rhetoric and scientific disagreement about the causes and transmission of the rabies virus had led to the institution of rabies control measures based more upon the stigmatisation of the classes of dogs and humans deemed most likely to contaminate, than upon public health science. Ritvo contends that the official measures introduced, the earliest of which being dog licensing in 1796, were designed as much to control owners as their dogs. Taxes imposed on ownership would, it was hoped, not only generate extra revenue, but would also discourage poor people from acquiring dogs for disreputable ends. Licensing meant that respectable people could give the assurance that their dogs were not a public menace; the poor, on the other hand, who generally did not have the means to pay up, would inevitably not meet this criteria of respectability. It was argued that people who could not afford, or were not prepared to pay for, a licence should not be allowed to keep dogs at all. As Ritvo (18) suggests, a new way had been found of controlling at least one aspect of the urban human and canine proletariat.

Muzzling dogs was the next measure to be adopted, since this was a more visible sign of control than the carrying of a license. Compulsory muzzling was implemented first in London in 1867 as a result of the Metropolitan Streets Act; other local authorities were later also empowered by the Rabies Orders of 1886 and 1887 to enforce this measure. Unmuzzled dogs were easier for the police to spot and deal with, although, as described above, they often embarked on this task with great zeal, inflicting great cruelty on those dogs unlucky enough to be apprehended. Such measures were particularly resented by those who kept working dogs, since they effectively disabled their animals and prevented them from performing their working tasks. Muzzles were also condemned as cruel and liable to cause pain and infections in the dogs forced to wear them (18).

The familiar stratagem of control through licence, muzzling, dog tags, destruction of strays etc. continued to be recommended in governmental investigations into controlling the disease. The Select Committee of 1887 suggested that such control should especially be exerted in metropolitan districts where the disease doubtless lurked amongst the most unsavoury canine populations which dwelled in the equally unsavoury urban slums. A more effective public health measure was to quarantine all foreign dogs during rabies outbreaks abroad (18). Quarantine was, in fact, the way to the future for rabies control in Great Britain. Pasteur himself had been rather perplexed by British interest in the large-scale application of his vaccine, for his proof that rabies was an infectious disease clearly provided a very simple solution to eradicating it from the British Isles. In 1887, Victor Horsley, a member of a British party sent by the government to
investigate Pasteur’s claims, was bluntly told by Pasteur that the British only had to ‘establish a brief quarantine covering the incubation period, muzzle all your dogs at the present moment, and in a few years you will be free’ (27). Horsley heeded this advice and was largely responsible for the legislative efforts – namely the Rabies Order and the Importation of Dogs Order of 1897, plus the Dogs Registration Act of 1898 – which finally resulted in the eradication of rabies in Britain by 1902. In spite of the vigilance of British customs officers, attempts to smuggle animals into the country in order to avoid quarantine resulted in a reintroduction of the disease, which again was wiped out by 1922.

CONCLUSIONS

Rabies is one of the oldest of infectious diseases and descriptions of the disease have been found in numerous ancient documents and medical treatises. Although the causal link between the disease and the saliva accompanying a dog bite had been made, it was not until the late 1880s when Pasteur proved that the disease could only be transmitted by inoculation, ultimately dealing a deathblow to popular theories of spontaneous generation. Although various practices were used by different practitioners to protect individuals against rabies, none proved to be fully effective. Pasteur developed the first reliable preventative vaccine treatment which, if administered soon after the bite had been inflicted, would elicit a protective immune response. The prognosis for those bitten by rabid animals seemed suddenly far less bleak.

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CHAPTER 23
HUMAN RABIES AND ITS PREVENTION

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Summary

Classical rabies is an invariably fatal disease once clinical symptoms have developed. However, there are fully effective pre-exposure and post-exposure vaccination and treatment schedules that prevent disease. Despite this the global number of human deaths each year is in excess of 50,000. In addition to medical intervention, it has been shown that the control of disease in animal hosts (vaccination) effectively reduces the number of human exposures. The number of human deaths from this ancient and terrible disease could be further reduced if resources were focused on regions with endemic animal rabies.

Keywords: human rabies, post-exposure treatment, vaccine

INTRODUCTION

Rabies is one of the oldest diseases of mankind. More than 4,000 years ago in the Eshuna Code of 2300 BC, it was recognised that the bite of a rabid dog could cause human death and policies for animal control were described. Celsus identified saliva as the source of transmission in AD 100 and he was the first to use the word ‘virus’ in this connection. Rabies prevalence in the human population depended upon the epidemic situation in animals, mainly dogs.

In the prevention of rabies, two periods of therapeutic effort can be identified towards the end of the 19th Century, one before and one after the introduction of rabies vaccination. Before Pasteur, attempts to treat rabies were by using medicine prepared from animals (e.g. powdered horns, heated gallstones), local wound treatment by cauterisation (as earlier recommended by Celsus), or by using chemicals or the insertion of hairs. It should also be noted that P.E. Galtier, a veterinarian from Lyons (France), did the first attempts towards vaccination before Pasteur. Thereafter, vaccination was used and from Pasteur (1885) until 1975 vaccines were prepared from neural tissue from the rabid spinal cords used by of Pasteur through the sheep brain of Semple (1906) to the suckling mouse brain of Fuenzalida (1955). However, in 1977, rabies post-exposure treatment (PET) with the first inactivated human diploid cell vaccine (HDCV) administered according to the Essen-scheme, together with rabies immunoglobulin (RIG) was recommended by the Committee for Immunization (Seiko) of the German Federal Health Agency (BGA). Such treatment was extended to the eastern part of Europe in 1990. Because of the expense of HDCV and difficulties with its preparation, other so-called ‘second generation’ cell culture vaccines were developed.

POST-EXPOSURE TREATMENT SINCE PASTEUR

Pasteur’s early experiments were carried out in dogs, which were given subcutaneously (s/c) suspensions of fragments of dried rabies virus-infected spinal cords, beginning with those dried for long enough to become avirulent, followed by more virulent suspensions. The dogs resisted challenge when they were subsequently given a virulent street virus intracerebrally (i/c). After 50 such pre-exposure treatments in dogs, without differentiating between the tested pre-exposure treatment and the post-exposure treatment, in 1885 Pasteur attempted the first human PET by administering daily injections in the abdominal region for 28 days to a nine year old boy, Joseph Meister.

Of 688 human dog-bite victims given PET, only one died, whereas 2 of 28 persons bitten by wolves died. Later, treatment failures were observed mostly in children bitten on the face or head, or who had received deep wounds to the extremities. Treatment for this group was given in the schedule as shown in
Table 23.1. In extreme cases of exposure, a complete series of treatments could be given in a single day and repeated on following days. In contrast, the standard treatment at this time was inoculations over a 10-day period beginning with material dried for 14 days and concluding with the five-day-old cord preparation. Pasteur followed the theory of multiple doses over the time period and to intensify protection he increased the initial dosage of vaccine, a method that is still in use today.

<table>
<thead>
<tr>
<th>Treatment (day)</th>
<th>Number of vaccine inoculations</th>
<th>Age of desiccated spinal cords (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>12, 10, 8</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>6, 4, 2</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
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<tr>
<td>4</td>
<td>3</td>
<td>8, 6, 4</td>
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<td>5</td>
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<td>6</td>
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<td>8</td>
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<td>2</td>
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<tr>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Pasteur’s method of treatment aroused great interest in the medical field and was rapidly accepted. The Pasteur Institute in Paris was founded in 1888 and within a decade others were established throughout the world. The original method of Pasteur’s PET was used in France and the French colonies up until 1952, despite the high rate of neurological-complications and vaccine failures which occur with neural tissue vaccines (NTVs). In other parts of the world many modifications of Pasteur’s NTV for PET were introduced, but for many decades after Pasteur scientists in the rabies PET field followed his principles.

Due to the extremely low and mostly non-standardised antigenicity of NTVs, multiple daily injections of large amounts of virus-containing tissue suspension of up to and sometimes more than 25 doses, with additional boosters on days 20 and 90, were necessary to induce protective immunity following exposure. This regimen was never questioned and systematic comparative trials aimed at dose reduction were rarely performed. On the contrary, the theory of ‘a necessary permanent antigenic stimulus’ was put forward, which did not take into consideration the class diversification of the humoral immune response or the cellular immune events.

In the conquest of rabies since Pasteur’s crucial work, there have been important developments. Understanding of the reservoirs of virus in wildlife species has increased and the use of anti-rabies immunoglobulin of human (HRIG) or equine (ERIG) origin for passive/active immunisation, with high immunogenicity and virtually no side effects has evolved. Safe and potent HDCV has made possible a considerable reduction in the number of vaccine doses (from at least fourteen to six) necessary for protection of naïve individuals (not previously vaccinated). The finding of antigenic differences among isolates of rabies virus has allowed the identification of variants, biotypes and genotypes of lyssaviruses that may influence the protective capacity of antirabies vaccines.

Since 1980, other important developments include the formulation of new cell-culture vaccines propagated in chicken fibroblast or Vero cells, which enable the mass production of vaccines of the same immunogenicity and safety as HDCV but at much reduced cost. The ‘Essen scheme’ of five or six visits over a period of 20 to 90 days is used worldwide and has proved to be protective when WHO recommendations are followed. Also, abbreviated regimens and intradermal (i/d) instead of intramuscular (i/m) administration of the vaccine have been introduced to meet the economical requirements of developing countries. This led to the approval of the 2-1-1 i/m and the abbreviated i/d regimen recommended by the WHO Expert Committee on Rabies (1). Exposure risk has been simplified into three categories (Table 23.2) and non-recommendation of NTVs by the WHO has helped in the reduction of their use. Cell culture vaccines (CCVs) are now also produced outside of Europe, in Brasil, India, the People Republic of China, etc. The primary chick embryo cell vaccine (PCECV) is the first cell culture vaccine, after rigorous worldwide clinical trials, to be produced on an industrial scale in India, and Thailand is the first country in Asia to use only CCVs since 1992.

Introduction of the Duck Embryo Vaccine (DEV), which was administered 14 times at daily intervals in the peri-umbilical region, with two booster doses given 10 and 60 days after the primary series, was an intermediate phase between NTV and CCVs. In comparison with NTVs, immunogenicity was improved but DEV caused local reactions in all patients and neurological reactions in about one in 25,000-100,000
cases. Moreover, the continuous daily administration of DEV, which resulted in a rather late IgM/IgG conversion, was a negative aspect. Since, in contrast to IgG antibodies, IgM class rabies virus antibodies do not provide immunity, DEV was not an optimal vaccine. However, it has been improved by purification and, according to the WHO, now offers the same safety and immunogenicity as other modern CCVs.

Table 23.2 – Guide for post-exposure treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Type of contact with a suspect or confirmed rabid domestic or wild animal, or animal unavailable for observation</th>
<th>Recommended treatment</th>
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<tbody>
<tr>
<td>I</td>
<td>Touching or feeding of animals, licks on intact skin</td>
<td>None, if reliable case history available</td>
</tr>
<tr>
<td>II</td>
<td>Nibbling of uncovered skin, minor scratches or abrasions without bleeding</td>
<td>Administer vaccine immediately. Stop treatment if animal remains healthy throughout ten days observation or if animal is humanely killed and found rabies negative by appropriate laboratory techniques</td>
</tr>
<tr>
<td>III</td>
<td>Single or multiple transdermal bites or scratches. Contamination of mucous membrane with saliva (e.g., licks)</td>
<td>Give RIG* and vaccine immediately. Stop treatment if animal remains healthy throughout 10 days observation or animal is humanely killed and found rabies negative by appropriate laboratory techniques</td>
</tr>
</tbody>
</table>

* Rabies immunoglobulin should be applied as follows:
  i) for all category III exposures, irrespective of the interval between exposure and the beginning of treatment
  ii) 20 IU/kg body weight HRIG or 40 IU/kg body weight purified ERIG
  iii) infiltrate as much as possible around the wounds, give the rest i/m into the gluteal region in a single dose, followed by a complete course of vaccine. Rabies immunoglobulin should never be administered without simultaneous application of a dose of cell-culture vaccine, because protection is only effected by simultaneous active and passive vaccination
  iv) postpone suturing of the wound; if suturing is necessary, ensure that rabies immunoglobulin has been applied locally as described above

Safety and protective efficacy of rabies vaccines lies in their production from cell cultures free from neural tissue and as free as possible from foreign proteins. Thus cell lines of human origin seemed ideal. However, vaccines were also prepared in non-human cells and one of these was the PCECV based on chicken fibroblasts, developed for dogs and later reformulated for human use by Barth et al. (3).

HDCV was the first vaccine to consist of virus particles and virus proteins only. After four years of clinical studies in thousands of human volunteers, the new vaccine was used in humans exposed to rabies infection. A new schedule for dose reduction and proper spacing of doses, based on earlier experiments in dogs, was devised (6). They demonstrated that the i/m application of partially purified inactivated rabies vaccine of only 4-5 doses every seven days resulted in an S-shaped antibody response curve within the first four weeks of immunisation. The curve was not altered by increased antigen or by additional doses. Therefore the ‘six-fold vaccination scheme’ was proposed and 46 persons who were bitten by laboratory proven rabid animals were vaccinated. The humoral immune reaction pointed to an early and long lasting immunity, when HDCV was given on days 0, 3, 7, 14, 30 and 90. All exposed vaccinees survived (they were checked for more than five years) and the success resulted in the approval of the Essen scheme by WHO. In Germany, the National Vaccination Advisory Committee recommended this scheme in 1977.

Later, it was shown by an ELISA technique that IgM/IgG conversion began with the induction of IgM two to three days after the first vaccination, followed by a pronounced IgG response beginning on day 5-7. The original ‘Essen scheme’ of six vaccine doses is still in use in many countries. However, the necessity of the day 90 booster was questioned and it is no longer recommended by the WHO nor applied in the United States of America (USA). The booster dose was recommended because it was shown that in
a few cases there was a rather rapid decline in antibody titre after the day 30 dose, but no vaccine failures have been observed even in heavily exposed persons when the day 90 dose was not given. The day 3 dose was applied since nearly 30% of the vaccinees experienced a low or late antibody induction in the first studies. It seemed that HLA-B7 and HLA-DR2 carrying persons were early and high responders, whereas HLA-DR3 carriers were late and low responders. Later, in Bangkok it was shown that the day 3 injection was especially beneficial when wounds were severe.

The combined use of HRIG or ERIG and vaccine in PET was introduced in 1950. Cabasso (4) standardised production of RIG and Bahmanyar et al. (2) used it together with HDCV and the Essen scheme for patients severely exposed by bites from Iranian wolves. The WHO Rabies Expert Committee (1) recommended the use of HRIG at 20 IU/kg body weight, although this dosage was based on experiments with DEV. Although some groups observed no suppressive effect of HRIG in combination with HDCV, in early studies other groups found that the vaccine antigenicity was rather low. Today, HRIG has little or no influence on patient antibody production, but when applying the 3-1 or 1-week scheme with very high initial antigen values for pre-exposure vaccination, some interference has been observed.

When the Essen scheme with HDCV was established as an efficient PET, efforts were undertaken in two directions – first to develop newer CCVs using non-human or permanent cell strains for virus multiplication, and second, to formulate regimens which would be economically more feasible but equally safe and protective. The first aim was reached with the development of the PCEC and Vero vaccines. The attempts took the following directions:

- a) a decrease in single clinical visits in the Essen scheme,
- b) an increase of first vaccine dose and application at least on both sides of the deltoid muscles, together with reduction of the total number of clinical visits and
- c) multi-site i/d injection of a reduced amount of vaccine.

Various groups studied alternatives to the Essen scheme, for example, changes in the spacing of doses, but no significant improvements in antibody induction were found. When HDCV was adjuvanted with aluminium hydroxide, the same antibody induction was observed but with one tenth of the adjuvanted vaccine, in comparison with the same but undiluted and non-adjuvanted vaccine. These studies were undertaken under simulated PET situations only.

A significant breakthrough occurred with the discovery that the dynamics of the antibody response could be altered (increased) by splitting the vaccine dose and applying it at several sites, a procedure first investigated by Turner (9) in the United Kingdom (UK). Such multi-site i/d injection of the vaccine was standardised by groups from the UK, Thailand and the USA and demonstrated the high efficiency of various i/d multi-site regimens. For 4-site injections of 0.1 ml vaccine, the left and right deltoid and thigh areas were used; for 8-site injections, the supra-scapular, thigh and lower abdominal wall area were added. When antibody induction of multi-site i/m administration was compared with i/d administration, the kinetics of antibody induction was nearly identical. WHO recommended one of these regimens as a new abbreviated PET regimen. It consists of one dose (0.1 ml), given at each of 2 sites, either forearm or upper arm, on days 0, 3, 7, and 1 dose at 1 site on days 30 and 90.

Vodopija and his colleagues (10) in Croatia introduced the multi-site i/m vaccination regimen. They administered two doses at different sites on day 0 and observed an early and high antibody induction. After different spacing, the vaccine was given on days 0 (2 doses) in the deltoid muscle of both sites and on days 7 and 21, one dose each. Day 7 proved to be superior to day 5. The last vaccination was given on day 21, not only to reduce the vaccination period, but even more importantly, day 21 precedes the maximum rate of the incubation period of 30 days in man. The patients that may benefit from this booster are the slow and late responders (see above). Moreover, the booster should maintain high levels of antibody after RIG application.

The WHO recommended further investigation of the 3-1 schedule, consisting of three i/m doses applied on day 0 and one dose on day 7. This one-week scheme, developed in Brandenburg during the time of
German unification, is now used for urgent pre-exposure immunisation. Immunity is early, fast and long lasting and comparable with the results of the Essen scheme.

INTERNATIONAL EXCHANGE OF KNOWLEDGE

It is worth remembering that regular symposia organised by the WHO, to include scientists of various disciplines (virologists, physicians, veterinarians, fox and bat biologists, ecologists, sociologist etc.) were not seen in any other narrow scientific area. They resulted in the fast development of vaccines for human and animal use and strategies for rabies eradication in Europe (Chapter 25, K. Bögel). These symposia yielded books and other publications that became landmarks of rabies progress. Charles Merieux, grandson of one of Pasteur’s assistants, must be mentioned as an initiator of these meetings. They took place in many countries of Europe and the Mediterranean basin. Other international forums now take place on a regular bases to facilitate exchange of scientific data. These include Rabies in the Americas (RITA), Rabies in Asia, Rabies in Europe and Rabies Bulletin Europe (RBE) and the Southern and East African Rabies Group Meeting (SEARG).

HUMAN SUSCEPTIBILITY

Humans are of relatively low susceptibility to rabies infection, but they can be infected by the saliva of any rabid animal (see below). When bitten, case fatality may range from 0 to 100%, dependent upon the location of the bite and the species of the biting animal. Human to human transmission is rarely reported, although two cases of mothers who were incubating the disease whilst in close contact (extensive kissing, saliva exchange) with their babies were observed in Kenya. Iatrogenic transmission of rabies has also been reported following corneal and solid tissue transplantation. Hospital personnel who have contact with rabies patients should be given pre-exposure immunisation.

INFECTION RISK BY DIFFERENT ANIMAL SPECIES AND PROTECTION BY POST-EXPOSURE TREATMENT

Rabies is a public health problem in human medicine insofar as, even today, approximately 50,000 humans die from rabies annually. However, it is widely believed that the disease is under-reported in many developing nations. Approximately 2.4 billion people live in 90 countries where the rabies reservoir is the dog. In these countries more than 95% of all human cases are caused by dog bites. In India, for example, the increase of the human population to 800 million and of the dog population to 18 million in 1992 resulted in a dramatic increase in bites and possible human exposure to rabies virus. More than 700,000 persons undergo PET and an estimated 30,000 die from rabies annually.

Apart from dogs, other animals may transmit rabies via a bite or infected saliva on excoriated skin or mucosa. One survey report in India by Seghal and Bhatia (7) stressed the possibility of rabies exposure by other domestic animals: of brain samples examined, 66.4% of those from cows and 12.5% from horses were rabies infected. Other animal species which are known to transmit rabies are dogs (93%), cows (1.4%), buffaloes (1.2%), jackals (1.02%), mongooses (0.6%), monkeys (0.4%), cats (0.4%), donkeys (0.2%), horses, asses and mules (0.12% each), goats, sheep, pigs and panthers (0.09% each species), camels (0.08%), foxes (0.05%), rats and bears (0.02% each), wolves, (0.007%) and lions, rabbits, jackals, hyenas, tigers, vultures, lizards and deer (<0.005% each). Other animals associated with rabies include bats, raccoon-dogs and members of the mustelid family. The proportions of disease in animal species differ widely depending on the country examined, annual returns for European countries can be found in the RBE. However, there have been no reports of deaths following bites of animals other than dogs, cats, foxes, jackals, wolves, mongooses and rats after correctly applied PET. Dog vaccination has been shown to be an effective measure to considerably reduce the risk to man.
INCUBATION PERIOD

Of 257 rabies cases in Ghana, seven with bites on the head or neck had an incubation period of 16-46 (average 31) days. Of 44 with bites on the upper limbs, the incubation period was 35-100 (average 68) days and of 28 with bites on the lower limbs it was 40-160 (average 100) days. Twenty-one cases with bites at more than one site showed an incubation period of 22-80 (average 51) days. Table 23.3 shows the intervals from bite to death of 707 cases in Thailand. Although the incubation period in general is up to three months, elsewhere an incubation of up to seven years has been recorded.

Table 23.3 – Interval from bite to death of 707 rabies cases in Thailand

<table>
<thead>
<tr>
<th>Interval (days)</th>
<th>Percentage of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-10</td>
<td>3.23</td>
</tr>
<tr>
<td>10-20</td>
<td>41.93</td>
</tr>
<tr>
<td>21-28</td>
<td>25.80</td>
</tr>
<tr>
<td>30-90</td>
<td>16.13</td>
</tr>
<tr>
<td>90-180</td>
<td>3.23</td>
</tr>
<tr>
<td>360+</td>
<td>6.45</td>
</tr>
</tbody>
</table>

RABIES INFECTION AND DISEASE

Initial nonspecific prodromal symptoms may not be suspicious of rabies. It is therefore important to ask the patient (or accompanying person) of any bite history or stay in a rabies endemic country. In cases of unclear neurological or psychiatric symptoms in connection with a bite history, rabies cannot always be excluded as a diagnosis. Some patients are confirmed as having rabies only after death at post-mortem.

Hours or days after the initial symptoms, the neurological illness may begin. For example, in Thailand two thirds of rabies patients may progress to an encephalitic form and the remainder to a paralytic form of rabies. The encephalitic form may last from seven days to two or three weeks before death. There are generally three main clinical symptoms during the acute phase, a change of consciousness, phobic spasm (hydrophobia) and dysfunction of the autonomous nervous system with confusion, excessive perspiration and a discharge of 1-1.5 l of saliva a day. The paralytic form is difficult to differentiate from Guillain-Barré syndrome. Phobic symptoms occur in fewer than 50% of the cases. The terminal state is characterised by clinical symptoms in the circulatory and/or respiratory systems. Dramatic blood pressure changes that in many cases cannot be adjusted may occur. Death occurs due to failure of the respiratory or circulatory systems. For a summary of the clinical symptoms that may be encountered, see Table 23.4 and Hemachuda (5). The clinical manifestations of rabies are difficult to interpret, especially during the early stages. *Intra-vitam* diagnosis is seldom conclusive. Often, only after death is a ‘clear cut’ diagnosis possible following, virus isolation, antigen or genome detection.

Table 23.4 – Summary of clinical symptoms in human rabies cases

<table>
<thead>
<tr>
<th>Clinical status</th>
<th>Clinical symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodromal</td>
<td>Fever, anorexia, nausea, vomiting, headache, malaise, lethargy, anxiety, agitation, depression, pain or paraesthesia at the site of the bite</td>
</tr>
<tr>
<td>Acute neurological phase</td>
<td>Hyperventilation, hypoxia, aphasia, paresis, paralysis, hydrophobia, pharyngeal spasms, in co-ordination or other signs of the CNS, confusion, delirium, hallucination, anxiety, agitation, depression, marked hyperventilation</td>
</tr>
<tr>
<td>Coma</td>
<td>Pituitary dysfunction, hypoventilation, apnoea, hypotension, cardiac arrhythmia, cardiac arrest</td>
</tr>
<tr>
<td>Death</td>
<td>Pneumothorax, intravascular thrombosis, secondary infections</td>
</tr>
</tbody>
</table>
Chapter 23

Historical Perspective of Rabies in Europe and the Mediterranean Basin

POST-EXPOSURE TREATMENT IN TROPICAL COUNTRIES

With the advancing eradication of rabies in Europe and the Mediterranean Basin, infection risk for the population exists mainly in visits to rabies endemic countries. Examples of human rabies acquired in the tropics include bites of dogs in India, Sri Lanka and Thailand. Recently, a visitor to the Caribbean, while sitting near a swimming pool saw something dark falling from the sky into the pool. He jumped in behind the black object, fished a bat out of the water and released it. He later returned to Germany and died from rabies, diagnosed only after death, as he was unaware that he had been bitten by the bat.

Human rabies can be prevented in nearly all cases by prevention of a bite (cave Canem), pre-exposure vaccination, PET including wound treatment followed by vaccine and RIG and by the prophylactic vaccination of animals. The prevention of a bite by walking with a thick wooden stick as a weapon against offending animals proved to be effective in reducing human rabies in a field trial in Tanzania. Prophylactic vaccination of dogs is necessary to reduce the risk of human exposure.

In the absence of a comprehensive national canine or wildlife rabies vaccination programme, PET is the only alternative. In India, about two million doses of PCECV are now produced annually. However, brain tissue vaccines are still used in many rabies endemic countries and even in India about 40,000 litres of sheep brain vaccine are produced annually. NTVs are dangerous for the health of the vaccinees and have low immunogenicity. They may induce severe nervous illness from their myelin content. Paralysis or death is caused in 1:1756 to 1:4000 patients. Due to low vaccine immunogenicity, low potency, fast degradation under cold chain conditions and low stability in temperatures above 8°C, vaccine failures may be as high as 20%.

Post-exposure treatment should be performed according to the three categories of infection risk, as defined by the WHO Expert Committee on Rabies (1) and summarised in Table 23.2. The combination of local wound treatment, passive immunisation and vaccination is recommended for all severe exposures (category III) of rabies. HRIG is expensive and not always available. However, ERIG is equally well tolerated, cheaper and used with great success, e.g., in Thailand. In all cases the most important first measure is the local wound treatment including washing with soap and water. Health authorities should train the populace on how to perform first-aid treatment that reduces the risk of infection.

It is advisable for an unvaccinated bite victim from a rabies-free country to visit a doctor in the country of contact to be given modern PET and, if available, HRIG. At present, Thailand was the first Asian country deciding to provide only CCVs. The best service in Thailand is available at the ‘Snake farm’ in Bangkok, known by every taxi driver. This WHO centre for rabies has by far the greatest PET experience in the world, because it treats many patients with possible rabies contact every day and has a clinic for rabies cases. The ‘Guide for Post-Exposure Treatment’ (Table 23.2) was formulated by this centre and accepted by the WHO Expert Committee for Rabies (1).

In India, CCV is administered at several health centres. Private doctors in larger cities may also have CCVs imported from Europe. Take care not to have turbid vaccines injected, as they may be NTVs or vaccines of unknown quality. It is better to leave the doctor’s office and, if no other possibility is available, to return home forthwith. In Germany we have observed increasing numbers of category III cases who return home with initial active immunisation but without RIG. Patients should be informed by their family practitioner about rabies contact risks and how to react.

Exposure to rodents, rabbits and hares seldom, if ever, requires specific antirabies treatment. For dogs and cats only, if they are apparently healthy or from a low-risk area and can be placed under observation, PET delay may be warranted. Except in the case of threatened or endangered species, other domestic and wild animals suspected as rabid should be killed humanely and their tissues examined using appropriate laboratory techniques.

The regimen of post-exposure vaccination with CCV, which is recommended by the WHO and is used worldwide is the ‘Essen Scheme’ (see above). Another acceptable regimen for i/m administration is the 2-1-1 Zagreb regimen. The i/d regimen is used in the WHO Centre for Rabies Pathogenesis in Bangkok. Vaccination should be started as soon as possible after exposure, without waiting for laboratory results.
Neither pregnancy nor infancy are contra-indications. Only active immunisation is necessary in case of category II exposure risk, if anamnesis is reliable.

**SAFETY AND IMMUNOGENICITY OF CCVS**

Rabies CCVs are the safest and most immunogenic vaccines. Many studies have shown the lack of neurological-complications and low local reactogenicity, with high immunogenicity and protective value. Recently we have shown not only high induction of humoral but also high cellular immunity after application of PCECV when applied by the Essen scheme.

To date, no rabies case has occurred after PET using CCV according to WHO recommendations. In India, none of 1000 patients given PCECV contracted rabies after bites from confirmed rabies virus-infected dogs. So far, only 29 cases of rabies following cell-culture PET (19 in India, 10 in Thailand) have been reported. These cases were not attributable to vaccine failure but to treatment flaws, such as – incorrect wound treatment, failure to infiltrate RIG locally, or no RIG administration (8).

Application of RIG one day before vaccination with CCV also caused treatment failures. Suppression of immunity by such treatment has been proven experimentally. When mice were treated 24 hours before active immunisation with anti-rabies monoclonal antibodies, 90 to 100% of them died, even if a high dosage of rabies vaccine was administered. On the contrary, the death rate was only 10% if RIG was not applied before active immunisation. Thus it is a medical error to apply RIG before active immunisation.

In a case of severe exposure, PET must include the simultaneous application of vaccine and RIG. To meet this mandatory condition, it is necessary to develop an efficient local vaccine storage system that enables immediate supply of vaccine to any location. Failures also occur if PET initiation is delayed. The population should be educated to visit the vaccination centre as soon after a bite as possible. Host factors such as immuno-suppression, use of immunosuppressive drugs (including anti-malarials) or underlying severe diseases may also be responsible for treatment failure. Furthermore, multiple wounds, short incubation periods of 9 to 34 (mean 23) days, or a combination of these factors may be responsible for rabies despite PET. Nevertheless, despite these few cases of PET failure, rabies CCVs are among the safest and most immunogenic vaccines known today. Although they are of effective high potency, it is necessary to maintain the potency by cold storage (+4 to +8°C), using reconstituted lyophilised vaccine as soon as possible. If some reconstituted vaccine remains, it can only be used later if it is stored at +4°C to +8°C and used on the day of reconstitution.

**LONG-TERM HUMORAL AND CELLULAR IMMUNITY**

Long-term immunity against rabies can be gained after vaccination with inactivated rabies CCVs only. CCVs are whole virion vaccines that contain all rabies virus proteins. Virus neutralising antibodies (VNA) in sera of vaccinees reflect protective immunity against rabies. However, in time they may become undetectable, although there is still a protective immunity as has been shown by dog challenge tests. In one of our studies, it was shown that after vaccination with either HDCV or PCECV, all of 18 vaccinees had antibody levels of >0.5 IU ml⁻¹, considered as protective, up to 14 years later. In general, the IU values of the rabies fluorescent focus inhibition test (RFFIT) test were lower than the antirabies virus IgG concentration measured by ELISA. This is most likely due to the fact that the RFFIT determines VNA against epitopes located on the virus glycoprotein (G) protein, whereas the ELISA also measures antibodies against additional epitopes of other viral proteins. Antibodies against all five rabies virus proteins were detected in all sera with the Western blot technique. Recent studies have demonstrated that the internal nucleocapsid also plays an important role in the induction of protective immunity in laboratory rodents and in cynomolgus monkeys. The ribonuclear protein complex (RNP)-induced protection is mediated by a complex interaction including antibodies and T-lymphocytes. In this study, we demonstrated that 17/18 vaccinees showed rabies virus-specific T-cell responses. Both vaccines induced a high degree of T-cell reactivity. The cellular response of our vaccinees’ peripheral blood mononuclear cells (PBMC) was especially directed against rabies RNP, since 16/18 vaccinees had a positive response, but only eight vaccinees showed a G-protein specific proliferation.
RNP is a major antigen capable of inducing T-helper cells. Immediately after vaccination, the cells obtained from vaccinees were of the helper/inducer class of T-lymphocytes and years after vaccination the majority of the proliferating cells were CD4 T-lymphocytes. Three of 18 control persons had a positive T-cell response to two antigens, especially RNP. No correlation was observed between their VNA titres and proliferation by the G-protein. It seems that the activity of T-cells differs from that of B-cells to the G-protein. Conversely, 9 of 10 tested vaccinees with anti-RNP antibodies also had T-cell reactivity against RNP of proliferation index (PI) >2.0, which is indicative of immunity. Therefore, we suggest that T-cells may especially recognise RNP and to a lesser degree G-protein. Again conversely, B-cells appear to react to both RNP and G-protein to the same extent. The differences between the group of vaccinees and the control population concerning their T- or B-cell reactivity to rabies virus proteins may be based on the stimulation of different T-helper cell classes, Th1 or Th2. We found that pre- or post-exposure rabies vaccination with inactivated cell culture vaccines induced a long-term B- and T-cell immunity.

The early and high immune response to rabies vaccination may be predictive of a long-term immunity, as was demonstrated in dogs. Dogs that were antibody negative at the time of challenge infection were protected against a lethal challenge if they had responded to one rabies vaccination with early and high antibody. On the other hand, dogs that were antibody negative at the time of challenge infection succumbed if they had shown no or only a minor response of short duration to the vaccination. In our study, all vaccinees had an early and high immune response after immunisation.

Human vaccinees that respond to pre- or post-exposure vaccination with an early and high immune response to the inactivated cell culture rabies vaccine may therefore be protected for several decades, if not for life. No death from rabies has so far occurred in cases of a re-exposure after one or two booster vaccinations. Such boosters lead to an immediate and high anamnestic antibody response.

**POST-EXPOSURE TREATMENT UNDER EUROPEAN CONDITIONS**

In principle, there are no differences between PET in tropical countries and in Europe. However, the epidemiological situation should be taken into account when evaluating the need for patient treatment. Due to a decline of rabies in the fox population in Germany and some other European countries, in recent years vaccination after bites has decreased by up to 90%.

**PROTECTION AFTER VACCINATION WITH CELL CULTURE VACCINES**

Protection is the ultimate indicator of the success of immunoprophylaxis. An analysis of more than 530,000 PETs revealed no rabies cases. Percentage protective efficiency is calculated from the equation $PE = (ARU-ARV)/ARU \times 100$, where $PE$ = efficiency of PET, $ARU$ = attack rate of persons without PET and $ARV$ = attack rate of persons with treatment failures. PE of current immunoprophylaxis with CCV is better than 99.999%, in contrast to less than 96.94% after vaccination with NTV. This means that protective efficiency is from 300 to >1000 times better with CCV than with NTV. This calculation assumes three treatment failures after 2 million post-exposure vaccinations with CCV and a theoretical infection ratio of 0.15 for rabies in untreated cases for NTV. On the other hand, the probability of a rabies case despite present immunoprophylaxis $1/n$ with CCV is a probability ratio that no vaccination failure occurs. That means that the confidence limit (95%) can be determined as one case per 320,000-5,500,000 treatments or 2-32 cases can be expected after 10 million PETS, according to present reports. These figures show that current immunoprophylaxis for post-exposure protection is comparable to the best pre-exposure vaccinations.

**PRE-EXPOSURE TREATMENT**

The WHO pre-exposure scheme consists of three i/m injections of one dose given on each of days 0, 7, and 28. This schedule induces an effective immunity. Neutralising antibodies are present in all vaccinees on day 35. Cellular and humoral immunity lasts up to 14 years and sometimes may be life-long. This result is in accordance with the observation that no individual given pre-exposure vaccination has yet been reported to have contracted rabies after exposure.
Another pre-exposure scheme is the 3-1 or 1-week scheme, whereby over one week three vaccine doses are distributed, with half doses in both deltoid muscles given on day 0 and one dose administered on day seven. Antibody response is very fast (a cellular immunity begins during the first day) and long lasting. All vaccinees have antibodies on day 14. Antibody induction is as good as that achieved after application of the five visit, five dose Essen scheme. Two studies with equivalent results were undertaken with PCECV in healthy students and with the Verorab vaccine in healthy Thai children. This schedule is especially useful for persons who need rabies immunity very quickly.

**RE-EXPOSURE PROPHYLAXIS**

In case of an additional exposure in a person with a history of previous rabies vaccination with an inactivated CCV, only one or two doses of vaccine are given on days 0 and 3. One vaccination may be sufficient, according to a study with healthy adults. The second is, however, recommended for safety reasons after severe bites. HRIG is contraindicated. If the potency of the previously administered vaccine is uncertain, post exposure immunoprophylaxis is performed according to the category of exposure.

**DETERMINATION OF IMMUNE STATUS AFTER VACCINATION**

Immunity against rabies virus is correlated with the presence of neutralising antibodies and cellular immunological parameters. Neutralising antibodies are determined by a neutralisation test, such as the RFFIT or the FAVN (fluorescent antibody virus neutralisation) test. ELISA test procedures are not recommended as they measure total antibody not just neutralising antibodies. Parameters of cellular immunity cannot be determined easily today. Neutralising antibodies at a concentration of 0.5 IU/ml serum are indicative of immunity. Such determinations should be carried out for persons at risk to decide if a booster is to be given.

**CONCLUSION**

Safe, effective vaccination and treatments now exist to combat rabies both in human and animal hosts, but as with many other diseases, control strategies for rabies require the input of resources, vaccine supply and education, to reduce the global burden of disease.

**References**


CHAPTER 24
EUROPEAN RABIES CONTROL AND ITS HISTORY

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Summary

The campaign for oral vaccination of red foxes against rabies has been practised in Europe since 1978 and has succeeded in greatly reducing the occurrence of this disease in the target species. This is an example of coordinated activity against a disease that affects both wild and domestic animals as well as humans. The decline in fox rabies has been mirrored by the decrease in spill-over hosts and its elimination over large areas in Europe. It draws the conclusion that oral vaccination is a powerful tool for controlling the disease. As the number of European countries that are declared rabies free (excluding bat rabies) continues to grow, the most important issue in maintaining this situation will be continuing surveillance and control efforts in those countries that remain endemic.

Summary: domestic animal rabies, oral fox vaccination, wildlife rabies

INTRODUCTION

The ultimate goals of rabies control are the protection of human health and the avoidance of economic losses and animal suffering; all can now be achieved by prophylactic vaccination of domestic animals. Yet a far more ambitious task is the control of the disease in the terrestrial rabies hosts such as domestic dogs, red foxes and raccoon dogs (11, 53). The authors of several chapters of this volume have recounted the history of human and animal rabies throughout Europe. However, one striking feature of their accounts is that although the disease may have been absent from some areas at particular times in history, at no time in recent centuries has the continent of Europe been entirely ‘rabies-free’. Nevertheless, as Wandeler (52) has pointed out, for unknown reasons rabies disappeared from Central Europe at around the turn of the 20th Century. This disappearance was unlikely to have been the result of intervention policies, since at that time knowledge of the conditions under which infection occurred were little understood. In this chapter, we briefly discuss the control of rabies in domestic animals and dwell in more depth on the events of wildlife rabies which have taken place since the epidemic of fox rabies began during the Second World War.

Domestic animal rabies

Historically in continental Europe, rabies appears to have been ever present in dogs, although other species may from time to time have been involved. Early attempts to control the disease in dogs centred upon hygienic measures such as the wearing of muzzles and the destruction of biting dogs. The practice of wearing muzzles, although well-known in Greco-Latin antiquity, does not seem to have been made obligatory anywhere in Europe until the 18th Century and although the destruction of biting dogs similarly was practised in antiquity it was not until the 18th Century that Germany, France and Spain, for example, passed legislation for the destruction of stray dogs. Even in those early days however, the destruction of stray dogs found little favour with the public.

When the infectious nature of rabies and the role of dogs in transmitting urban rabies were clearly recognised, several health measures, including quarantine, were taken to prevent the transmission of rabies by them. Some of these measures were already in place by the end of 19th Century (22) and some are still in use today. By the beginning of the 20th Century, urban rabies could be eliminated in most European countries by using health measures alone. For example, Nocard and Leclainche (41) do not mention...
vaccination of dogs as an alternative to culling or even as a tool to be used concomitantly in order to achieve dog rabies elimination. At this time vaccination against rabies was still a cumbersome process and there were still many stray dogs roaming in European cities. In fact, although Pasteur demonstrated the possibility of vaccinating dogs in 1885, it was only in the 1920s that domestic animal vaccination was developed and practised. Contrary to other European countries that relied mainly on the destruction of stray dogs and other hygienic measures for eliminating dog rabies, Austria reached the same goal by initiating a combination of these measures with dog parenteral vaccination (30). Even if preventive vaccination of domestic vector species (mainly dogs and cats) was introduced rather late, it rapidly proved to be one of the most efficient tools to eliminate rabies from a country, provided that at least 70% of all animals were vaccinated.

In summary, in many parts of the world, particularly in countries where human and dog populations are increasing, dog-rabies is a re-emerging zoonosis. Nevertheless, whether enzootic or epizootic, urban rabies can be controlled and even eradicated in a reasonable period of time, provided a comprehensive control programme is implemented (32). Such programmes require legal and financial support, planning, co-ordination and bordering country co-operation, animal vaccination and epidemiological surveillance allied to dog population control. Since the end of the Second World War and with the exception of Turkey, dog rabies has not been endemic in any European country.

WILDLIFE RABIES

In earlier times the wolf (Canis lupus) was the main sylvatic reservoir of rabies in Europe (37, 41). Rabies infection of wolves was associated with highly aggressive behaviour towards humans and domestic animals. This danger was the origin of the fear provoked by wolves and a reason for the voluntary progressive elimination of wolves from large parts of their previous range (Chapter 5, A. Botvinkin et al.). The wolf had been extinct in Belgium since 1873 (23) and also disappeared from France just before the Second World War, where specialised civil servants were in charge of its extermination (Compagnies de Louveterie) (20). In 1992, the wolf reappeared in France in the National Park of Mercantour, having migrated from nearby Italy (16), but its reappearance took place in a new context (absence of rabies) and it became a protected species.

As mentioned above however, rabies had virtually disappeared from central Europe at the turn of the 20th Century, but during the 1940s and thereafter, the disease became established in the fox population and spread inexorably southwards and westwards, eventually to encompass almost the whole of western Europe (Chapter 18, S.M. Brookes et al.). The earliest attempts at control of the disease in foxes focused on drastic decimation of the fox population. However, although theoretically rabies could be eliminated by this method, in practice it was nearly impossible to reduce those populations below a threshold where disease transmission ceased. Thus, more promising was the vaccination of the main host. But, as Wandeler so elegantly wrote, ‘... immunising free-living wild animals is not simple. The wild mammal does not follow an invitation to visit a veterinarian, and there is no owner to bring it there. It has to be lured by some trick to vaccinate itself. This method has to be simple and efficient, so that it becomes technically and economically possible to establish the herd immunity required to eliminate rabies’ (53). The control of rabies in the racoon-dog is also further complicated by the fact that they hibernate over the winter and may harbour virus during this time. Disease then appears to re-emerge in the spring as animals become active and breed (36).

ORAL VACCINATION

Many authors have described the development of oral immunisation techniques (56, 53, 59, 3, 15). It is worthwhile to note that ideas developed independently in both North America and Europe as attempts to control rabies in wildlife on both continents by population reduction had failed.

The first attempts to immunise foxes by non-parenteral routes were undertaken in the early 1960s, when live rabies virus vaccine strains were administered by stomach tube, but these failed to induce an immune response. However, a protective effect was achieved in 6/14 foxes when a killed rabies vaccine was ‘exploded’ in the foxes’ mouths by using ‘coyote-getters’, devices, hidden in baits, originally designed to
carry an explosive which would destroy the animals coming into contact with them (5). Given the danger that this and other devices (such as a vaccine-containing syringe propelled by a steel trap to parenterally immunise foxes) would pose to the public, these developments were not further pursued.

A breakthrough came (in 1971-73) when it was shown that after oral administration of live-attenuated Evelyn-Rokitnikii-Abelseth (ERA) vaccine strain foxes developed neutralising antibodies and were protected from a virulent challenge (6, 9, 19). Earlier, Black and Lawson (8) had successfully immunised foxes with the same vaccine applied by stomach tube, although it was later speculated by Wandeler (53) that immunisation may have been due to virus having been dragged unintentionally across oral mucosa. The first successful oral immunisation of captive foxes by vaccine-baits occurred shortly thereafter. Vaccine inoculated into eggs, vaccine-impregnated dog biscuits, and a commercial sausage containing a plastic tube filled with vaccine were used (18, 60, 61, 35). These experiments, along with the ERA seed virus generously provided by the Centers for Disease Control in Atlanta, USA, substantially promoted European efforts to further develop oral immunisation and finally to field applications of the system.

In the 1970s, research efforts were concentrated in three European facilities, the ‘Centre National des Etudes sur la Rage’ in Nancy, France, the ‘Staatliches Veterinäruntersuchungsamt’ in Frankfurt am Main, Germany, and the Swiss Rabies Centre at the Veterinary Faculty of the University of Bern, Switzerland. WHO strongly supported this work, sponsoring meetings where information could be exchanged and guidelines for future research discussed. Early work was not limited to the ERA strain – or Street Alabama Dufferin (SAD), as it was renamed at the request of the manufacturer of the commercial ERA vaccine (54) – but included various other live attenuated strains as well as inactivated vaccines (10).

FIRST FIELD APPLICATIONS

Prior to the field application of oral vaccines, the following goals had to be met:

a) a vaccine that efficiently immunised the target species under field conditions while posing the least possible risk to target species, other potential consumers and humans

b) a system that successfully delivered the vaccine to the oral mucosa

c) an attractive and species-specific bait to serve as a vehicle for the vaccine and

d) a temporal and spatial strategy for the distribution of baits, through which a sufficiently high proportion of the target species could be reached (53).

While the SAD virus successfully immunised foxes (24), its residual pathogenicity for small mammals raised fears about the release of the strain into the environment (53). Although wild rodents fed SAD in captivity could occasionally be infected with and succumb to SAD, laboratory results suggested that transmission from one such infected individual to another would be unlikely. To test this assumption, the first field trial in which live attenuated SAD rabies vaccine was released into the environment was carried out in September 1977 on a small island of 0.1 km² surface in the river Aare near Solothurn, Switzerland. Approximately 1,000 rodent-specific baits with SAD were distributed. Rabies virus could not be demonstrated in any of the 271 small mammals captured after the trial (55).

One year later the first campaign to orally immunise foxes against rabies took place in the canton of Valais, Switzerland. Relying on the barrier effect of surrounding high mountain chains, an attempt was made to stop an advancing rabies front by distributing vaccine baits in the path of the disease. The vaccination zone covered the valley over its whole width of only a few kilometers and to a depth of about 60 km. The baits consisted of chicken heads, which had given satisfactory results both in placebo field trials (39, 57) and when used to immunise foxes in captivity (24). The chicken heads, each containing a sachet made of plastic and aluminium foil with 1.8 ml SAD vaccine, as well as 150 mg of tetracycline to mark bait consumers, had to be thoroughly chewed by foxes which guaranteed that the container was punctured and vaccine released into the mouth.

Bait applications were repeated in the spring and autumn of the following years. Examination for tetracycline in bones from foxes killed in the vaccination zone revealed that up to 60% of the animals had
consumed baits. The immune belt was never crossed by the disease, and rabies began to disappear from the area, although sceptics of the method speculated that the fox density in the part of the valley located beyond the vaccination zone might not be high enough to support a rabies epidemic. This suspicion was allayed in February 1980 when an outbreak occurred behind the immune belt after, most likely, at least one rabid fox from a focus north of the Alps had crossed the mountain chain separating the area. After two vaccination campaigns the area was cleared (48). For the first time it had been possible to prevent the spread of rabies into an area by orally vaccinating its fox population and to eliminate rabies from a given area by vaccination only.

Taking advantage of the natural compartmentalisation of their country by high mountain ranges, lakes and rivers, the Swiss developed a strategy of treating one infected compartment after another until the disease had disappeared and, of protecting rabies-free but threatened compartments, by vaccinating animals in their points of entry. By the end of 1987 they had succeeded in eliminating the disease from the major part of the country and had thus shown that rabies control by oral immunisation of the vector species was feasible, safe and efficacious. Their experience provided solutions to problems of selection and definition of areas to be vaccinated; strategies to protect non- or no longer vaccinated areas; timing and frequency of vaccination campaigns; bait distribution patterns; bait density and placement; and campaign logistics and participation of hunters and other personnel (3, 26). Their methods were used by other European countries when they started their own programmes several years later.

In 1983, German workers started vaccination campaigns in Bavaria, Baden-Württemberg and Hesse using the SAD_{B19} vaccine strain, developed from the SAD_{Bern} strain at the WHO Collaborating Centre in Tübingen, and chicken head baits (46). Although they had found a more efficient way of producing chicken head baits, it soon became clear that an alternative to this labour-intensive method was essential. A decisive breakthrough was achieved with the development of bait based on vegetable fat and fish-meal suitable for semi-automated production and containing a blister pack similar to that used for the chicken head bait. Following placebo bait trials, the so-called Tübingen fox bait was first used in Germany in autumn 1985 and, beginning in 1986, was also widely used in many other European countries (44; Table 24.1).

To cope with the enormous task of distributing large numbers of baits manually, the Germans opted for the same system of bait distribution that had already proven efficacious in Switzerland, by having many people, mainly hunters, each distribute a limited number of baits, preferably in an area familiar to them. This concept was later to become known as the ‘Bavarian model’ (58). By 1987 all States of the Federal Republic of Germany participated in the field trials (45) and the number of rabies cases was considerably reduced throughout most of the country in the subsequent years.

In 1984, similar vaccination campaigns began in the northern province of Brescia, Italy and were further extended to the neighbouring provinces of Trento and Bolzano in 1986. By the end of that year rabies had disappeared from all of the Alpine valleys in Italy (7). In 1986, Austria joined the field trials, beginning with vaccination in Vorarlberg, near its borders with Switzerland and Italy, then in subsequent years gradually extended the campaigns over most of the country, with good results (28).

In the same year (1986) joint vaccination campaigns between Luxembourg, Belgium and France began, the treated zone centring around Luxembourg. The vaccinated area grew steadily over subsequent years and when a small number of rabies cases were recorded in terrestrial mammals in the southernmost part of the Netherlands, this country also joined the vaccination efforts for a short period (from 1988 to 1991). Cross-border collaboration between Switzerland and France began in 1987, when a small area in France adjacent to the Swiss vaccination zone was treated for the first time. Large-scale operations on the French side of the common border with Switzerland, however, began only in 1989, along with the general extension of vaccination zones in France.
Table 24.1 – Number and type of baits and vaccines used in oral vaccination campaigns in Europe, 1978-1999 (1)

<table>
<thead>
<tr>
<th>Country</th>
<th>First vaccine camp</th>
<th>Vaccine strains used</th>
<th>Bait types used (2)</th>
<th>In use from/to</th>
<th>No. of baits distributed</th>
<th>Method (3) of bait distrib.</th>
<th>Vacc. camp. in 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAG-1/SAG-2</td>
<td>Rabifox Oral</td>
<td>1995-1997</td>
<td>1,847,000</td>
<td>F, M</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAD P5/88</td>
<td>Rabifox Dessau</td>
<td>1998-1999</td>
<td>1,146,800</td>
<td>F (H)</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Belgium 1986</td>
<td>SAD B19</td>
<td>Tübingen</td>
<td>1986-1990</td>
<td>428,000</td>
<td>M, H</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V-1/G</td>
<td>Raboral</td>
<td>1989-1999</td>
<td>2,510,070</td>
<td>H (M)</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAD B19</td>
<td>Tübingen</td>
<td>1996-1999</td>
<td>390,000</td>
<td>F</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAD P5/88</td>
<td>Rabifox Dessau</td>
<td>1998</td>
<td>50,000</td>
<td>F</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Czech Republic 1989</td>
<td>SAD B19</td>
<td>Tübingen</td>
<td>1989-1992</td>
<td>1,435,00</td>
<td>M</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Finland 1988</td>
<td>SAD B19</td>
<td>Tübingen</td>
<td>1988-1999</td>
<td>951,000</td>
<td>(M 88-89)</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>France 1986</td>
<td>SAD B19</td>
<td>Tübingen</td>
<td>1986-1992</td>
<td>1,557,244</td>
<td>H (M)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAD P5/88</td>
<td>Chicken Head</td>
<td>1987-1988</td>
<td>5,000</td>
<td>M</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V-1/G</td>
<td>Raboral</td>
<td>1989-1999</td>
<td>6,011,913</td>
<td>H (M)</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Germany 1983</td>
<td>SAD B19</td>
<td>Chicken Head</td>
<td>1983-1985</td>
<td>476,000</td>
<td>M</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAD P5/88</td>
<td>Tübingen</td>
<td>1985-1999</td>
<td>32,707,000</td>
<td>F, M</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wusterhausen</td>
<td></td>
<td>1989-1990</td>
<td>717,000</td>
<td>M</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAG-1</td>
<td>Rabifox Oral</td>
<td>1996-1999</td>
<td>2,149,000</td>
<td>F</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAD P5/88</td>
<td>Lysvulpen</td>
<td>1996-1997</td>
<td>870,000</td>
<td>F</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rabifox Dessau</td>
<td>1997</td>
<td>23,000</td>
<td>F</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Italy 1984</td>
<td>SAD B19</td>
<td>Chicken Head</td>
<td>1984-1985</td>
<td>15,000</td>
<td>M</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAD B19</td>
<td>Tübingen</td>
<td>1986-1999</td>
<td>333,783</td>
<td>M</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Latvia (1) 1992</td>
<td>EVMTI</td>
<td>Chicken Head</td>
<td>1992</td>
<td>143,210</td>
<td>M</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VVMK-71</td>
<td>GKN Moscow</td>
<td>1995-1996</td>
<td>103,400</td>
<td>M</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vnukovo-32</td>
<td>Lysvulpen</td>
<td>1998-1999</td>
<td>66,100</td>
<td>M</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAD P5/88</td>
<td>Rabifox Dessau</td>
<td>1998-1999</td>
<td>50,000</td>
<td>M</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Lithuania (1) 1995</td>
<td>SAD-1</td>
<td>Rabifox Oral</td>
<td>1995-1997</td>
<td>519,000</td>
<td>M, F</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAD P5/88</td>
<td>Lysvulpen</td>
<td>1999</td>
<td>100,000</td>
<td>M, F</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rabifox Dessau</td>
<td>1998</td>
<td>100,000</td>
<td>M, F</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V-1/G</td>
<td>Raboral</td>
<td>1992-1999</td>
<td>815,000</td>
<td>H</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Poland (5) 1993</td>
<td>SAD B19</td>
<td>Tübingen</td>
<td>1993-1999</td>
<td>26,562,000</td>
<td>F</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>32/107</td>
<td></td>
<td></td>
<td>400,000</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Slovenia 1989</td>
<td>SAD B19</td>
<td>Tübingen</td>
<td>1989-1999</td>
<td>2,220,000</td>
<td>F (M89-94)</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAD P5/88</td>
<td>Lysvulpen</td>
<td>1998-1999</td>
<td>630,000</td>
<td>F</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Switzerland 1978</td>
<td>SAD P5/88</td>
<td>Chicken Head</td>
<td>1978-1990</td>
<td>1,326,119</td>
<td>M (H)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Sweden and</td>
<td>SAD P5/88</td>
<td>Tallow-SFE</td>
<td>1987</td>
<td>5,500</td>
<td>M</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Liechtenstein</td>
<td>SAG-1</td>
<td>Chicken Head</td>
<td>1988</td>
<td>4,220</td>
<td>M</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAG-1/SAG-2</td>
<td>Rabifox Oral</td>
<td>1991-1998</td>
<td>1,442,172</td>
<td>M (F)</td>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>

(1) This table does not include (early) field trials with locally developed vaccine strains and baits in Belarus, Latvia, Lithuania, Russia, and Ukraine, for which only limited information is available (Chapter 4, B. Westerling et al.).

(2) Bait types: Tübingen bait (=Fuchsoral), produced by Klocke Pharma Service, Weingarten, Germany; Wusterhausen, locally produced in former East Germany; Rabifox Desain (= Alstrofex 91), produced by Imfungreffwerke Desain-Tornau, Rusland, Germany; Raboral-VRG, produced by Rhône-Mérieux, Lyons, France; Rabifox Oral, produced by Laboratoires Virbac, Carros, France; Lysvulpen, produced by Bioveta, Ivanovice na Hani, Czech Republic; Kamark, produced by Meraik, Niira, Slovak Republic; chicken head baits were locally produced by veterinary services and hunters (see 35, for details on baits). The tallow-SFE bait used in Switzerland in 1987 was an experimental bait produced by the Swiss Rabies Centre (1).

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Total 151,465,503
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(4) Croatia received 4000 Tübingen baits in 1991; probably distributed in area adjacent to Slovenia. The country reports a vaccination campaign with 80,000 baits of unknown origin in RBE 1994/4. The figures for 1996-1999 are based on bait manufacturer's data; no data could be obtained from Croatian sources.

(5) Bait numbers according to bait manufacturer's data, no data could be obtained from Polish sources.

(6) Figures for Slovakia based on country reports in Rabies Bulletin Europe (RBE); campaigns reported up to spring 1999; no data could be obtained from Slovak sources.

In spring 1988, after 30 years without rabies, Finland recorded its first rabies cases, mainly in raccoon dogs (*Nyctereutes procyonoides*). In an emergency experiment, Tübingen baits with SAD-B19 were fed to captive raccoon dogs, most of whom developed neutralising antibodies against rabies and survived a subsequent challenge. Less than six months after the first field case, Finland embarked on its first oral vaccination campaign. In February 1989, the last rabies case was recorded, but vaccinations were maintained along the border with Russia (Chapter 4, B. Westerling et al.). Also in 1988, the first vaccination campaigns took place in Slovenia and in 1989 the Czech Republic and the former East Germany joined in, followed by Hungary and Slovakia in 1992, Poland in 1993, and Croatia in 1994.

In the early 1990s, both Lithuania and Latvia started vaccination campaigns with locally developed baits and a vaccine strain from Belarus, but adopted commercially produced vaccines and baits in 1995 and 1998 respectively (Chapter 4, B. Westerling et al.). Russia, Belarus, and the Ukraine also carried out limited field trials with their own vaccines and baits, but very few data are available for these experiments (29; Chapter 5, A. Botvinkin et al.). Thus, from 1978 until the end of 1999, oral vaccination campaigns with either SADBern strain and chicken heads or with commercially produced vaccines and baits were performed in 18 European states, including Liechtenstein (Table 24.1).

**NEW VACCINE STRAINS AND BAIT TYPES**

Concerns about the safety of live-attenuated rabies vaccines were certainly among the main reasons why many countries hesitated to release SAD into the field. Indeed, SADBern showed not only residual pathogenicity for small mammals, but was also isolated from three animals that had been killed with symptoms of rabies within the vaccination areas in the course of the Swiss field trials (56). Wandeler later found eight ERA vaccine-induced rabies cases in oral vaccination areas in Ontario, Canada and suspected ‘that perceived differences in SAD/ERA pathogenicity in the field are essentially phenotypic in nature (that is, the result of varying vaccine production protocols, vaccine titre, etc.), or are observational biases’ (54). When German workers began field trials in 1983 using SAD-B19, they were convinced that they had found a safe vaccine with respect to pathogenicity for small mammals, although this was later refuted (33, 50).

In 1984, the first genetically engineered rabies vaccine, V-RG, a vaccinia virus with the DNA sequence for rabies glycoprotein introduced into its genome, became available (27). This construct did not bear any of the risks associated with live-attenuated rabies vaccines, but concerns about the pathogenicity of the vectored vaccine and its release into the environment were raised. V-RG now has been more extensively tested in target and non-target species than any other oral rabies vaccine and has proven safe for field application (13). It was first used in Belgium in the autumn of 1988 (43) and from 1989 it was the only vaccine used in Belgium and Luxembourg and in most parts of France (3).

Flamand and her co-workers (21) were successful in reducing the pathogenicity of SADBern by selecting escape mutants not neutralised by specific monoclonal antibodies which were known to recognise an epitope crucial to virus pathogenicity. The first such vaccine strain was SAG-1 (34), which was later replaced by the genetically more stable SAG-2 strain (31). SAG-1 was first used in Switzerland in a small field trial with chicken head baits in 1988 (17). It found a wider application from 1990 in France, when it was marketed together with a bait (3) and in 1991 was adopted in Switzerland as the only vaccine in use. All other vaccine strains introduced elsewhere in Europe from 1989 onwards were directly derived either from SADBern or Vnukovo-32, without attempts to further reduce the parent strain’s pathogenicity by genetic engineering.
In the former East Germany, the first vaccination campaigns were carried out in 1989, using an SAD\textsubscript{Bern} derived strain SAD P5/88 (47). The Czech Republic began using SAD\textsubscript{Bern} in 1992, mainly because it was more economical to produce vaccine and bait in that country than to import it from abroad. In the same year, the Slovak Republic carried out its first field trial, using a Vnukovo-32-derived strain called Vnukovo 32/107 (49).

Along with the new vaccines came new types of baits. V-RG was used with bait originally developed for raccoons and subsequently modified for European field trials with foxes. It consisted of fish oil and fish meal bound by a synthetic polymer and contained the vaccine sealed in a plastic pouch (42). All other commercial baits introduced in Europe between 1989 and 1992 resembled the Tübingen bait and were based on animal or vegetable fat and fish meal, or meat and bone meal, containing a blister pack as a vaccine container (35).

France is the only country in which three different vaccine-baits (SAD\textsubscript{B19}, SAG-1 and V-RG) have been tested on a large scale. When given to caged foxes, all three vaccine-baits gave similar protection against challenge. Protocols for the dispatch of baits, fox sampling in treated areas, tetracycline and serum analysis were carried out by the same laboratory. Standardisation of protocols, areas of large size and variety, and repeated treatment with the same vaccine baits provided a valuable basis for comparison of the efficacy of vaccine-baits within various habitats, fox densities and rabies endemic status (some areas had been infected for a long time, others were newly infected). All vaccine-baits were effective in achieving a significant decrease in rabies incidence. However, nowhere did four campaigns using SAD\textsubscript{B19} succeed in the complete elimination of the disease. Early campaigns with SAG-1 were partially efficient, giving results similar to those with SAD\textsubscript{B19}, but efficiency was improved after stabilisers were added to the vaccine and the thawing point of the envelope was raised. V-RG vaccine-baits were found to be the most efficient and resulted in rabies elimination after only two campaigns. If bait uptake by free-ranging foxes was equivalent, the differences in the thermostability of the three vaccine-baits were the most likely explanation for the differences in field efficacy. Several further experiments on stability of the various baits in the field supported this interpretation.

**NEW STRATEGIES FOR NEW PROBLEMS**

Initially, the manual distribution of baits involved thousands of hunters who were relatively easily motivated to submit dead foxes for analysis, a prerequisite for the evaluation of the success of vaccination campaigns. On the other hand the increasing number of baits made the campaign logistics increasingly complex and alternative ways of bait distribution were sought. The first system for large scale aerial distribution of baits was developed in Ontario, Canada, long before 1985 when this province embarked on its first oral vaccination campaign (38).

In Europe, between 1978 and 1984 Switzerland used helicopters to distribute small numbers of baits in inaccessible mountain areas (25), but in 1988 France was the first country to use helicopters for large scale aerial distribution (4), a method later also used by Belgium and Luxembourg. Residual foci of rabies in boggy areas first prompted the use of fixed-wing aircraft in Germany in 1988 and in Finland in 1989 (45; Chapter 4, B. Westerling et al.). After it was shown that the efficiency of bait distribution from fixed-wing aircraft was as effective as but cheaper than manual distribution, this method became popular in Eastern European countries from 1990 onwards (40).

While the onset of oral vaccination campaigns often quickly resulted in a reduction in the number of rabies cases or even in the elimination of rabies from specific areas, most countries also suffered considerable setbacks over the years. Among the reasons for these setbacks were an over-optimistic interpretation of the initial success and inadequate funding, which led to the early reduction of vaccination zones, often followed by reappearance of the disease. Few countries have experimented with a single vaccination campaign per year, as is successfully practiced in Ontario, Canada. In Hesse, Germany, this strategy failed to produce the desired results in the late 1980s (45) and Belgium, after three vaccination campaigns in 1986/1987, experienced a dramatic setback in its efforts to control rabies when the country performed only one vaccination campaign in 1988. A minimum of two campaigns per year has since become standard for most countries.
A delayed implementation or even a lack of cross-border co-ordination of vaccination campaigns repeatedly led to the re-infection of areas previously cleared from rabies. The consequences thereof could be particularly dramatic in areas where the absence of the disease had allowed fox population densities to grow. In 1990, Switzerland was almost free of rabies when it became re-infected from across the border with France, where vaccination had only just begun. This led to a serious outbreak on the Swiss side, which three years later threatened to re-invade France, where in the meantime the adjacent area had been almost cleared of rabies (12). Similarly, a new focus that developed in Baden-Württemberg in early 1992 could be traced back across the river Rhine to a heavily infested area in France (3). Austria suffered a re-infection in Vorarlberg from a rabies outbreak in Bavaria, Germany, in 1991/1992 and in the border zones between Germany, France, Luxembourg, and Belgium, rabies foci moved across national borders several times in 1994/1995. In the late 1990s, both Austria and Slovenia experienced only sporadic cases along their borders with Hungary and Croatia respectively. However, the rabies situation in their neighbouring countries would oblige them to maintain vaccination zones along their border for several years to come, as was the case with several other countries (e.g. Finland).

COPING WITH INCREASING FOX DENSITIES AND NON-IMMUNE FOX CUBS

Fox populations in many European countries have been increasing over the last few decades, a phenomenon that was probably accelerated by successful rabies elimination. Mortality statistics (hunting, roadkills) increased 4-fold from 1984 to 1995 in Switzerland (12). Interestingly, the percentage of foxes positive for tetracycline did not change significantly over these years. Obviously, the absolute number of foxes that had not consumed vaccine-baits had increased considerably and this helped explain why areas previously freed from rabies were easily re-infected from neighbouring areas, as mentioned above. Data from France and Switzerland showed that after spring campaigns, 70% of adult foxes but only 20%-40% of cubs consumed baits, as revealed by tetracycline marks in their teeth or bones. In parallel, the proportion of individuals with rabies antibodies among those marked with tetracycline was lower in cubs than in adults. With two thirds of the fox population in spring being cubs, the key to a successful vaccination programme was to give cubs access to baits in order to immunise them.

Several methods to increase vaccination coverage of cubs have been tested. These include bait distribution at the entrance to fox dens, bait distribution in summer when cubs begin to disperse and bait distribution twice at a two-week interval during spring. Best results were obtained with bait distribution directly at fox dens in early summer, which increased the percentage of tetracycline-positive young foxes from 40% to 80% (12). However, vaccination at den entrances increased the costs per km² of spring campaigns by a factor of 2.3 to 4.5 in France (51). Whereas highly efficient when well planned, this additional measure is therefore only recommended for eliminating residual foci in limited areas.

COSTS -BENEFITS OF ERADICATING RABIES FROM WILDLIFE

Surprisingly, few attempts have been made to quantify the cost-effectiveness of wildlife rabies eradication, including situations where there was but a single reservoir species (the red fox). One such comprehensive study has, however, been carried out (2). The study, in France, included the costs associated with the vaccination of domestic animals; the reinforcement of epidemiological surveillance networks and the support provided to diagnostic laboratories; animal and economic losses associated with outbreaks of rabies; clinical observation of those animals which had bitten humans; and the prophylactic vaccination and post-exposure treatment of humans. A substantial percentage (72%) of the costs involved the prophylactic vaccination of domestic animals. Two main strategies for controlling the disease at the reservoir level, fox population reduction and the oral vaccination of foxes, were evaluated. The combined costs and benefits of both strategies were compared and included either the cost of fox culling or the cost of oral vaccination (baits, bait delivery and follow-up to ensure the efficiency of the vaccination). In France, the cumulative costs of both strategies remained comparative until the fourth year, after which the oral vaccination strategy was more beneficial. The expected benefits of oral vaccination had then been achieved and the strategy was shown to have been a good investment (14). Fox depopulation has only ever resulted in a transient lull in the occurrence of the disease, while oral vaccination has proved to be capable of eliminating rabies even in situations in which fox populations were increasing.
Zanoni et al. (62) estimated the direct costs of rabies per year in Switzerland at US$ 15,300,000 (CHF 25,780,000) when the disease was at its peak in 1977/1978 and at US$ 10,800,00 (CHF 18,169,500) in 1993, when oral immunisation campaigns had already eliminated the disease from most of the country. In these two periods, the costs of prophylactic dog vaccination accounted for 63.5% and 90.2% of the total respectively. In 1977/1978, the remaining costs were caused by human post-exposure treatment (PET) (15.5%), vaccination of personnel at risk (2.3%), vaccination of cattle (17.7%), and compensation for loss of livestock (1.0%). In 1993, 3.1% of the total costs were for vaccine baits and their distribution at US$ 2.15/bait (CHF 3.60/bait), 2.8% for surveillance of vaccination campaigns, 1.6% for PET, 2.2% for vaccination of personnel at risk, and 0.1% for loss of livestock. Even though there was no estimate for the total cost of the disease and its elimination, the long-term benefit is obvious, in particular since dog vaccinations are no longer mandatory as the country is officially free of rabies.

**CONCLUSIONS**

Even after several years of implementation, oral vaccination of wildlife is still considered an experimental control method that should be planned as a long-term strategy. The vaccination programme must be conducted and continuously monitored by a scientific team exclusively dedicated to this task. The team should be trained in field surveys and should use validated laboratory methods for rabies diagnosis, titration of vaccines, evaluation of bait uptake by the target species, and rabies antibody titration. The whole procedure, including bait distribution in the field, must be carefully processed under a quality assurance system.

With the support of the European Community, rabies control leading to elimination in western Europe has been a great success, as proven by the dramatic reduction in the size of the contaminated area (Table 24.2). Within a recent 12 years period (1989 to 2000) some points of the main rabies front have been pushed back eastwards more than 1,300km. The Netherlands, Belgium, Finland, France, Italy, Luxembourg, Switzerland, Cyprus, Greece, Iceland, Ireland, Denmark, Norway, Portugal, Sweden, UK – (2002-2003) have been free of rabies (excluding bat rabies) for two years or more. Large areas in Germany are rabies free, but Bavaria and North Rhine-Westphalia maintain two active foci in the west of the country. These areas constitute a possible source of re-infection (and concern) for the surrounding countries. Countries close to the main front such as Austria and Slovenia have recorded no cases for many months but are vulnerable from the east. The Czech Republic, Hungary, Poland and the Slovak Republic have initiated promising vaccination control programmes which bear a reasonable hope that the whole European peninsula will become free of terrestrial rabies early in the first decade of the twenty-1st Century.

In Switzerland, once the success of the initial field trials became evident, there was little incentive to deviate from strategies that had proven successful, thus there was little or no variety of experimental data produced to elucidate the importance of certain parameters of oral vaccination programmes (25). Similarly, in most other countries, opportunities for variation that could compromise any success achieved so far were very limited, because what had started as experiments soon became part of national strategies to eradicate the disease. Where, in later years, strategies were adapted to new conditions, the approach was pragmatic and it will never be known with certainty which changes were the most decisive and which had limited or no influence (12).

As Wandeler (54) pointed out, however ‘it is essential that we also look for alternative explanations [to vaccination of foxes] for the disappearance of the disease in treated areas. We should not find any that appear to be more probable. Of course as some reports may be ‘chauvinistically biased’, Wandeler would ‘like to caution against attributing too much weight to particular case histories’. But the elimination of rabies over large areas in Europe and Ontario allows the conclusion that oral vaccination is a powerful tool for controlling the disease. Considering that for centuries, rabies has been regarded as an ineluctable piece of the scenery, this new victory carries a great hope that, provided the method is able to be adapted to the dog, oral vaccination should help in eliminating rabies from where it is most dreadful: the urban habitat of developing countries.
### Table 24.2 – Prevalence of rabies before and after onset of oral vaccination campaigns and rabies status in December 2000

<table>
<thead>
<tr>
<th>Country</th>
<th>First vaccination campaign</th>
<th>Average No. of cases per year before vaccination (2)</th>
<th>Average No. of cases per year 1997-1999</th>
<th>Rabies cases in 2000</th>
<th>Number of major vaccination setbacks (3)</th>
<th>Rabies status 2000 Quarter with last case in fox</th>
<th>No. of months case in any species</th>
<th>w/o cases in foxes</th>
<th>w/o any rabies cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>1986</td>
<td>1,518</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2/00; isolated cases in border area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>1986</td>
<td>431</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>3/99</td>
<td>3/99</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Croatia</td>
<td>1994</td>
<td>364</td>
<td>620</td>
<td>917</td>
<td>1</td>
<td>rabies still endemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Czech.</td>
<td>1989</td>
<td>1,427</td>
<td>178</td>
<td>165</td>
<td>1</td>
<td>rabies still partially endemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>1988</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1/89</td>
<td>1/89</td>
<td>142</td>
<td>142</td>
</tr>
<tr>
<td>France</td>
<td>1986</td>
<td>2,450</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1/98</td>
<td>4/98</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>Germany</td>
<td>1983</td>
<td>8,332</td>
<td>81</td>
<td>182</td>
<td>1</td>
<td>residual foci in part of country</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>1992</td>
<td>955</td>
<td>470</td>
<td>398</td>
<td>1</td>
<td>rabies still endemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>1984</td>
<td>382</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4/95</td>
<td>4/95</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Latvia</td>
<td>1998</td>
<td>179</td>
<td>(173)</td>
<td>516</td>
<td>0</td>
<td>rabies still endemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td>1995</td>
<td>81</td>
<td>253</td>
<td>855</td>
<td>1</td>
<td>rabies still endemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luxemb.</td>
<td>1986</td>
<td>89</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>4/97</td>
<td>1/99</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Netherl.</td>
<td>1988</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3/88</td>
<td>3/88</td>
<td>147</td>
<td>147</td>
</tr>
<tr>
<td>Poland</td>
<td>1993</td>
<td>2,672</td>
<td>1321</td>
<td>2204</td>
<td>0</td>
<td>rabies still endemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slovakia</td>
<td>1992</td>
<td>290</td>
<td>392</td>
<td>351</td>
<td>0</td>
<td>rabies still endemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slovenia</td>
<td>1988</td>
<td>403</td>
<td>16</td>
<td>114</td>
<td>1</td>
<td>major focus in eastern-central part</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switz.</td>
<td>1978</td>
<td>1,277</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1/96</td>
<td>4/96</td>
<td>57</td>
<td>48</td>
</tr>
</tbody>
</table>

(1) omitting cases in humans, bats and imported animals

(2) average number of cases before onset of vaccinations is calculated as average of 1st year with vaccination plus 2 preceding years

(3) vaccination setbacks: periods of at least 2 subsequent years with a higher number of cases than the minimum number recorded in any year before, starting with the year after the first vaccination campaign or the minimum number recorded since the last setback

*Source of data: Rabies Bulletin Europe*

## Acknowledgements

We record our thanks to all those who generously provided information on the numbers and types of baits used in various countries. These include Drs. Reisenhofer (Austria), B. Brochier (Belgium), O. Matouch (Czech Republic), B. Westerling (Finland), A. Németh (Hungary), F. Mutinelli (Italy), J. Rimeicans (Latvia), A. Dranseika (Lithuania), A. Besch (Luxembourg), H.U.R. Nieuwenhuis (The Netherlands), Ales Brecelj (Slovenia) and in particular to Dr T. Müller, Federal Research Centre for Virus Diseases of Animals, Wusterhausen, Germany, for providing manufacturer's data on the number of
Fuchsoral and Rabifox baits delivered to Germany and to other countries. This chapter is dedicated to the memory of F. Steck and his pioneering work on the vaccination of foxes against rabies.

References


CHAPTER 25
INTERNATIONAL COOPERATION AND THE ROLE OF INTERNATIONAL ORGANISATIONS

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Summary

International cooperation and organisations such as the World Health Organization and others have been crucial in the dissemination of information, continuing improvements in research and in the surveillance and diagnosis of rabies. The result has been the reduction of human and animal rabies in many parts of Europe and other regions of the world, due mainly to the control of animal rabies by various vaccination programmes.

Keywords: eradication, international organisations, vaccination

INTRODUCTION

Over the past thirty years the control of rabies in Europe has been largely determined by new research findings and innovations in field operations. The origins of international collaboration arose from:

a) the rapid westward spread of rabies in wildlife into countries which had been cleared of canine rabies decades previously (2, 21)

b) revolutionary cell culture technology developed by research and production laboratories

c) a new generation of research workers.

These factors triggered activities in many national research centres, soon followed by universities and industries. The World Health Organization (WHO) Geneva, took the lead at the international level with a well organised research network (5, 30). From the beginning of the European wildlife epidemic it fostered the development of new epidemiological approaches and control methods (3, 4, 5). The Food and Agriculture Organization (FAO) of the United Nations assisted at the policy-making level of national ministries of agriculture and the Office international des Epizooties (OIE), Paris, became instrumental in stimulating and harmonising activities via national veterinary services. It should be noted that major progress was made in international cooperation in the 1970s and early 1980s, e.g., in epidemiological surveillance, despite the Iron Curtain and the Cold War climate between East and West prohibiting or restricting direct contact among scientists and administrators. International organisations, by organising numerous meetings under their auspices, were instrumental in bringing together scientists from East and West (3, 4, 5, 37, 40).

INITIAL CONDITIONS

Prior to the spread of rabies in wildlife, rabies had become an exotic disease in Central Europe. The last foci of canine rabies were fading away in Greece and southern Italy (10, 21). Experience in the field of rabies had been retained in the network of Pasteur Institutes and WHO Collaborating Centres, as well as in some specialised research laboratories. The World Surveys of Rabies, issued annually by the WHO, dated back to similar surveys of the Health Organization of the League of Nations in the first half of the 20th Century (2).

However, these had dealt with other parts of the world, where rabies remained rampant in various reservoir species (5). Until the 1970s, research coordination was largely restricted to the standardisation of laboratory techniques and the development of safer and more potent human vaccines. Adult animal nerve
tissue-derived vaccine was mainly used in human post-exposure treatment, causing severe paralytic vaccine accidents in 1 in 1,700 patients and death in about 1 in 11,000 persons (1).

Control in domestic animals was based on classic veterinary measures. The strategy overseen by the WHO Expert Committee on Rabies can be summarised as follows: the killing of suspected cases and unsupervised animals, movement restrictions and specific observation. Intensified fox hunting and gassing of dens became tools specific to the rabies reservoir in foxes (30). These measures appeared to be successful in Denmark, which was invaded by rabies in an erratic manner, the disease disappearing again from both sides of the Danish-German border (33). The actual impact of these measures, i.e., on the density and dynamics of fox populations, was unknown. In the United States of America (USA), the first attempts to immunise foxes with inactivated virus by automatic syringe-traps had been reported (29). In Europe, inactivated and live vaccine was administered under laboratory conditions (32). The results remained academic in nature.

THE ROLE OF INDIVIDUALS

In the first instance, attention should be paid to the initiatives of individuals in scientific and technical organisations and also in administration- who made significant progress, even against existing policies, so that the author of this chapter once entitled a presentation ‘Rabies, a history of mankind’ (22), as opposed to ‘The Natural History of Rabies’ by Baer (17), a book of outstanding scientific quality.

At the beginning of the fox rabies epidemic, rabies had almost been forgotten in Central Europe as the disease had been eliminated from dogs decades earlier. Knowledge was as exotic as the disease itself and the proliferation in foxes called for new approaches. It is almost 30 years since Günter Wachendörfer, a young scientist in Frankfurt am Main, Germany, advocated the vaccination of dogs and cats and was publicly accused of irresponsibility by the professional establishment, thus endangering his career (G. Wachendörfer, Frankfurt, 1968, personal correspondence). Vaccination in wildlife had not been considered and was strictly forbidden in dogs and cats in some countries. From that time it was only 11 years until Franz Steck, a young professor in Bern, Switzerland, after careful consideration of the results of WHO-coordinated research, had the courage to administer live rabies vaccine (including to wildlife) (36, 38). Franz Steck and his colleagues within WHO headquarters were denounced by governments and senior experts in France in particular, but also in Germany (see below); also by a world rabies expert in the USA, who requested that we immediately cease such irresponsible trials (K. Bögel, Geneva, 1980, personal records).

The scientists referred to above (Steck and Schneider), members of WHO Expert Advisory Panels, opened a new era of technical collaboration under the auspices of the WHO. Both had been trained in America and maintained close working relationships with colleagues there. This became a keystone of progress, initially between the Americas and Europe and gradually among European countries (23). However, some courageous administrators were equally important in triggering collaboration as the new generation of scientists. Initially, many decision-makers hesitated to accept that the human health sector, (i.e., the WHO and the ministries of health), should principally deal with the control of rabies in wildlife (the reservoir of infection) and domestic carnivores (the principal transmitters to people). Other bodies, such as the Food and Agriculture Organization of the United Nations (FAO) and some important national ministries of agriculture, were equally reluctant to make use of appropriate resources. Wildlife rabies was considered economically unimportant for the animal production sector (31).

Thus, the WHO took the lead, supported by some administrators in a few national and international services. In particular, Germany and France provided much support and funding for research, although, under the legal and scientific conditions of that time, both countries opposed the release of live virus vaccine in wildlife. Eventually Europe went down the path of Veterinary Public Health. The process of intersectoral collaboration extended far beyond the scope of rabies control.

The list of research workers, administrators and field officers who, with their ingenuity and enthusiasm, contributed to the success of wildlife rabies control would fill a whole page of this chapter.

In addition to those above reference is therefore made, to:
– George Baer and his team in Atlanta, USA, who found that foxes can be immunised against rabies by
the oral route (18) and continued to contribute to the European programme

– Lothar Schneider, who developed a machine-made bait for large-scale vaccination campaigns (11)

– Alexander Wandeler, who coordinated the work of wildlife ecologists (7) in many countries

– Louis Andral, who established the French rabies investigation laboratory at Nancy-Malzéville and who
hosted a number of workshops on mathematical models and oral vaccination (7) – despite the negative
attitude of it’s government.

Within the WHO and in many national services, mathematicians, ecologists, programmers, field managers,
foresters, wildlife officers, laboratory workers, even mechanical engineers and pilots contributed to the
technological advances which led to our current techniques. Franz Steck, who was responsible for the
first, successful rabies vaccination field trial, two other members of the veterinary team and the pilot, were
lost in a helicopter crash in the Rhone Valley, Switzerland and will never be forgotten.

INTERNATIONAL ORGANISATIONS

In 1968, the WHO Regional Office for Europe organised in Frankfurt am Main the First International
Conference on Surveillance and Control of Rabies (4). The success of this conference can be partly
attributed to the strong personalities of Dr Radovanovic, secretary to that meeting and Martin Kaplan and
his colleagues from the WHO headquarters in Geneva, who took responsibility for pursuing research and
development.

Political pressure of a particular nature, however, became apparent during the conference. At the national
level, that pressure was simply due to the fact that ministries had, for too long, blamed each other for
insufficient efforts in rabies control. At the international level, governments complained that the epidemic
entered their territory because their neighbours had not done enough to fight the disease. A member of
the Danish delegation added to the criticism by referring to the success of rabies elimination from her
country. The epidemic spread to Denmark for the first time in 1964, to Belgium, Luxembourg and Austria
in 1966 and Switzerland in 1967 (8, 26). There were good reasons for the conference accuse Germany. It
became clear, however, that control operations could not be assessed without a basic knowledge of fox
population density, the annual turnover of that species and its movement patterns. Moreover, as eminent
scientists claimed at that conference, the incidence pattern of three to four year cycles in foxes is evidence
of an underlying reservoir in another species. According to such ‘rules in natural foci of disease’ it would
therefore make no sense to apply control measures to foxes (22). In a search for a hidden reservoir, initial
findings in Czechoslovakia suggested that mice were responsible (37, 40).

Without doubt, both the mutual accusations at international level and the admission that knowledge about
control measures in wildlife was virtually lacking, greatly enhanced international collaboration. It was this
author’s privilege to be associated from the beginning in 1968 with a swift and fascinating development.

Multidisciplinary research

The spirit of Louis Pasteur, who cultivated non-discriminatory scientific collaboration, lived on in the
network of Pasteur Institutes as well as in other international institutions devoted to rabies research and
control. Certainly, this holds true for the rabies group in the WHO with its Collaborating Centres. This
was a key to success long before the terms ‘interdisciplinary’ and ‘intersectoral’ collaboration were re-
invented in modern science. In view of the particular experience in research coordination and the
outstanding performance of the WHO Expert Committee on Rabies, it was reasonable to entrust the
Veterinary Public Health Unit of the WHO headquarters in Geneva with the coordination of research in
the European region; a body ideally located for this task.

In 1968 and only weeks after the First Conference on Surveillance and Control of Rabies, two
WHO/FAO conferences were organised to plan research projects. Further steering conferences followed
in 1970, 1972 and 1975. Progress was rapid and thus, in 1977 the Second Conference on Surveillance and Control of Rabies was organised by the WHO Regional Office for Europe, to take into account the work accomplished since 1968 (8). In total 16 research teams had been mobilised in Czechoslovakia, Germany, France, Italy, Switzerland, the United Kingdom and within the WHO (20, 26). Between 1966 and 1977 the following areas were covered by these internationally collaborating teams:

- punch card (initially) and computer analysis of the spread of rabies (workshops in 1972, 1973, 1974 and 1975)
- telemetric studies of foxes (workshops in 1972 and 1973); economic consequences of wildlife rabies and its control (workshops in 1971, 1972, 1975 and 1976)
- rabies viruses isolated from rodents (workshop in 1971)
- epidemiological surveillance (workshops and conferences of national Chief Veterinary Officers of European countries in 1975, 1976 and 1977)
- oral immunisation of foxes against rabies (workshops in 1972 and 1975).

On average, 20 persons participated per workshop. These figures give an idea of the scope of work of the WHO, and particularly, an indication of the enthusiasm which brought together so many scientists and countries. Funding was mainly based on national/local resources and on extra-budgetary contributions of Member States to the WHO. Approximately 100 scientific publications resulted from this initial nine-year period, although laboratory and field work advanced at such a rapid pace that scientists lagged far behind in publishing their findings, relying instead on their workshop records. Two papers exemplify the situation:

In the first example, the annual turnover of fox populations was studied, using the same field technique, in the United Kingdom, Denmark, the Netherlands and Switzerland. Data were processed by a special team set up within the WHO (7). The results were fairly consistent in all study areas. In order to reach a common conclusion and report, the WHO requested that one of the scientists visit all teams and write a joint publication. This procedure was not easy and was singularly unusual, as it was the custom at that time, especially for biologists and ecologists, to publish individually. The joint publication became the undisputed model for the development of control strategies, including those for population reduction and later on for the vaccination of foxes. Epidemiological modelling has been based on these findings for more than two decades with no indication of failure.

The second example concerns research on the mechanisms of spread of rabies in wildlife. A number of studies and papers contributed to the final concept. Over 3,000 animal cases recorded during the southward spread of the epidemic in southern Germany were analysed for time and space distribution in relation to the density of fox populations, control measures and the ‘front-line of the epidemic’ (27). The definition of that steadily moving front-line for computer application required a group of specialists within the WHO. These studies resulted in a basic understanding of disease transmission, population dynamics and densities, seasonal influences and species involved. The phenomenon of a threshold density of foxes for maintaining the chain of infection was identified and quantitatively determined. All this became ‘standard knowledge’ for the assessment of risks and control operations (25).

Yet, in 1976, there was only a faint vision of live vaccine application in wildlife. However, for some years, consistent failures in reducing fox populations over large areas, called for other measures (37). The late Franz Steck wrote in his research review for the Second European Conference: ‘Despite the fact that wildlife rabies still escapes our control efforts, the strict application of proven methods of prevention of rabies in domestic animals and man could reduce the occurrence of human rabies in Europe and other parts of the world (37).

The culmination of the research efforts must undoubtedly be the oral vaccination of foxes (Chapter 24, P.-P. Pastoret et al.). The prerequisites for the release of the vaccine in the first field studies were complex and technologically difficult. An appreciable number of institutes and scientists joined the research activities in subsequent years. Their activities involved refined mathematical modeling, marker studies of
vaccine strains, the ecology of the wild boar and competition for the vaccine bait, aerial baiting, the principles of cross-border collaboration and measures preventing the spread of rabies through tunnels. Such projects received the recognition of the WHO, and have largely become associated with the WHO Collaborating Centres in France, Germany, Italy, Switzerland, Russia, UK and other countries. Towards the end of the century the research institutes returned to their previous independently organised and autonomous research programmes but with much closer relationships now existing among their many scientists.

The completion of the WHO/FAO-coordinated research programme on wildlife rabies in Europe was celebrated at WHO headquarters in Geneva 22 years after its inception. On this occasion the WHO Assistant Director-General and the author of this chapter presented an award to 42 team leaders, in recognition of their contributions to international collaboration (25).

**Innovative surveillance**

As early as the 1970s it became clear that rabies control in wildlife called for an effective surveillance system, permitting the accurate mapping of individual cases by village or geographical coordinates. Information on rabies cases needed to reach authorities beyond local administrative boundaries and national borders promptly, so that control strategies could be adapted to epidemic phases and local conditions. This also meant a departure from classical control measures which were applied to cases and their distribution over rigidly defined periods. As the idea of vaccinating foxes on a large scale developed in the minds of the scientists, government administrators began to construct a new rabies surveillance system in Europe.

In a series of WHO meetings, Chief Veterinary Officers began to overcome technical difficulties and political hesitation. Countries had different systems of recording geographical coordinates. The North Atlantic Treaty Organization coordinates were found to be the most useful, since they were available from most of the countries. Tourist-dependent countries saw problems in reporting rabies cases by village. The German Democratic Republic (GDR) and other countries beyond the Iron Curtain had difficulties in sending their scientists to WHO meetings at Tübingen, West Germany, where the surveillance centre was to be established under WHO auspices with the financial support of the Federal German Republic (FRG). In some instances other international organisations assisted in establishing working relations. Eventually, the GDR joined the programme, after cordial discussions between Professor Cherkassky, Director of the WHO Collaborating Centre for Epidemiology in Moscow and the Vice-Minister of Agriculture of the GDR. As well, it was the untiring staff at the WHO Collaborating Centre at Tübingen which expanded the services of the quarterly 'Rabies Bulletin Europe' (9), now covering almost 40 countries and territories (12, 24).

**Oral immunisation of foxes**

Whereas the first ten years of international cooperation provided insight into the epizootic process and the efficacy of ‘classical’ control measures, the second ten years provided one of the greatest success stories in the history of disease control. Never before had a live virus vaccine been used in wildlife, nor had a vaccine been tested so thoroughly by international collaboration before its widespread use. Never before had anyone ventured to release individual vaccine batches without the prior testing of multi-host transmission. Finally, never before had a surveillance programme been set up with such speed and precision as this, a programme which remains in use in Europe today. Fundamental to the planning and assessment of local and international operations was the development of confidence between the research and control authorities during the first ten years of the international collaboration under the auspices of the WHO.

From the beginning, research tasks on oral rabies vaccination were planned and divided among the participants of the WHO workshops (6, 8). Selection of the virus strain was made in collaboration, although there was some competition between the WHO Collaborating Centres in Tübingen and Bern. The largest series of agreed testing concerned ‘forced’ chains of infection by alternating the route of application orally, intracerebrally and/or intramuscularly. The WHO Collaborating Centre at Nancy,
France, concentrated its studies in foxes kept in captivity. The Centres in Bern, Tübingen and Frankfurt shared the work in other wildlife carnivores, laboratory rodents, muskrats and mustelids. Meanwhile, ecologists studied the uptake of bait by different wildlife species under well controlled field conditions. The most important phase of collaboration concerned the decision on the strains to be used in the field. At that stage, the German team had to withdraw temporarily from the field studies, since, for legal reasons, their authorities required a test clearly differentiating vaccine from field virus. Thus, the laboratory at Tübingen continued to work on a genetic marker in collaboration with the Wistar Institute in the USA and others. When this was achieved in the first half of the 1980s (11, 34, 35) the door was opened to the field application in virtually all European countries. The rabies vaccinia-recombinant vaccine (VRG) developed in France met this requirement per se (16, 19).

The only field trial which was planned at a strictly national level, (although regularly reported to the WHO workshops), concerned the massive application of vaccine virus by Franz Steck and Alexander Wandeler on a river island populated by rodents and insectivorous mammals (37). It was decided that the entire island would be burned if infection from vaccine virus occurred in the rodents. Specimens were taken from these populations for more than a year before the conclusion was drawn that the vaccine virus strain was suitable for testing under open-field conditions. The subsequent application of the attenuated virus under ‘natural’ conditions is a milestone in science (12, 24). Thousands of chicken-head baits containing the virus were distributed by hunters and wildlife officers on sites clearly marked on maps (38, 39). As a result, the rapidly moving epidemic was prevented from spreading into the large Rhone Valley in Switzerland.

One decade later, when technology proved to be reliable with respect to safety, potency, stability, genetic marker and large-scale application, the Commission of the European Community (EC) in Brussels took an active role in the international collaboration. Funds were made available and plans developed to ensure vaccination in non-European Union (EU) countries bordering the immunised territories of EU countries. The competence and enthusiasm of the international staff of the EU were very important, if not crucial, to the success of the continuing programme.

**BAT RABIES IN EUROPE**

A bat rabies epidemic in Denmark which started in 1985 and peaked in 1986, together with subsequent reports of increasing numbers of cases in Germany and the Netherlands, triggered further international collaboration through the WHO in relation to the diagnosis and surveillance of the disease; and as well as to the ecology and protection of bats and the classification of the serotypes of the genus lyssavirus in general (13, 14; Chapter 17, A.A. King et al.). Bat rabies continues to be an emerging threat to public and animal health as new viruses are described and others are detected in previously lyssavirus-free locations (28).

**CONCLUSIONS**

In conclusion, it would be reasonable to assume that the development of such a politically sensitive and scientifically complex technology as that of mass live rabies vaccination in wildlife would not have taken place without the coordination and support of international organisations. It would probably also not have happened if there had not been a new generation of rabies workers in Europe, as referred to in the introductory paragraph. All heads of the research centres involved and, their team members in particular, were relatively young, less than 40 years of age on average when they initiated their projects; thus, providing fertile ground for innovation.

To an extent, political pressure and the interactions and/or competition among scientific communities enhanced the international collaborative effort, which was outstanding for the number of disciplines and research teams involved. This collaboration paved the way for further research beyond the original targets, e.g., on related rhabdoviruses and their molecular biology. Refined methods of virus strain characterisation and diagnosis by monoclonal antibody became routine in the laboratory (14). Details of the methods and experience of fox ecologists have subsequently been supplied by the WHO for the study of dog populations in developing countries, with remarkable results. The earlier approaches to dog rabies control
had to change (15, 41), but it may take decades before all the innovations are reflected in national policies and practices.

In spite of all the enlightenment in rabies wildlife control and the involvement of so many scientists, a miracle remains within the success of the programme. When the chicken-heads containing vaccine virus were prepared and distributed by hand over large areas, Veterinary Services organised the programme and paid the costs, wildlife services, foresters and private hunters voluntarily distributed most of the vaccine and the health sector benefited in health and economic terms. Normally, such a scheme probably would not have been expected to work anywhere in the world. However, it did work, at least until fox rabies control was thought to have caused an undesirable increase in the fox population, an hypothesis which has not yet been proved.

Other areas of international cooperation and the organisations involved include: the WHO rabies collaborating centres, the OIE rabies network, Rabies Bulletin Europe and international conferences dedicated to rabies research and diagnosis. The role of these groups and other collaborations by many internationally recognised rabies groups ensure that there is a continuing effort to improve our understanding of rabies and an improvement in the world health situation involving this infectious agent.

References


