Marek’s disease

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Summary: Marek’s disease of fowls is a panzootic caused by a herpesvirus which induces tumorous proliferation of lymphoid cells in a large number of organs and tissues. It is a major economic threat to flocks of young adult fowls.

Symptoms depend on the localization of the tumours. Paralysis results from tumours in nerves. General illness and death is produced by tumours of the visceral organs.

The disease occurs throughout the world. Mortality is reduced considerably by vaccination. Spread of the disease is favoured by the high stability of virus excreted by skin cells. All birds can excrete the virus whether healthy or ill. Hypervirulent strains have been encountered in various countries. The appearance of tumours is linked to the special susceptibility of young, unvaccinated chicks, and to their genetic origin.

Diagnosis is based essentially on anatomical and histological examination of lesions. Detection of the virus or antiviral antibodies is not conclusive. Research on properties of the tumour cells is in progress.

Prophylactic measures are aimed at diminishing the risk of infection of very young chicks, vaccinating at an early age with an apathogenic strain suitable for countering the prevalent field strains, and enhancing resistance by selecting lines of fowl the least susceptible to tumour development.


INTRODUCTION

A number of viral diseases of birds are caused by herpesviruses. The most important of them are manifested by various signs: respiratory (infectious laryngotracheitis and pigeon coryza), digestive (plague or hepatitis of aquatic birds) and tumours (Marek’s disease). Marek’s disease (MD) is a panzootic affecting fowls. The diversity of its clinical signs is due to the occurrence of lymphoid tumours in a wide range of organs and tissues. Malignant evolution of the tumours leads to the death of affected birds.

It is a major economic risk for poultry flocks, not only because of its distribution throughout the world, but because it affects young adults about to be utilized for meat or egg production, reducing the profitability of an affected flock. The danger is permanent because the herpesvirus is excreted by healthy as well as sick birds. The economic losses, which have been calculated in some countries, justify the use of expensive, but fortunately effective vaccination in all large flocks (29).
The name "Marek's disease" is derived from the first clinical description by J. Marek in 1907 (22) of the characteristic nerve lesions in fowls. Subsequently the adoption of numerous other names based on the multiple distribution of the lesions created a certain confusion over the nature of the disease.

The history of scientific progress in our knowledge has been described exhaustively (7, 25, 29), demonstrating that the complexity of problems related to MD has led to profound research which has benefited the scientific community.

**CLINICAL ASPECTS**

As will be explained later, many factors modify the expression of MD. It is not the same from one individual to another, and may vary during spread within a flock, also between flocks and from one region to another. It is difficult to provide an overall description. This is why there is an "acute" form more severe in symptoms and lesions than the "classical" form which is close to the original description. Such descriptions are based on the disease as it occurs in unvaccinated flocks.

**SYMPTOMS**

**Classical MD** appears towards the age of 20-30 weeks in the form of progressive paralysis of the feet, wings and sometimes the neck. Affected birds have difficulty in gaining access to feed because of competition from the other birds, and they eventually die of cachexia after an illness lasting for 7-20 days. Other birds become affected in turn, showing similar signs. The proportion of birds ill at any one time is never high (less than 3%), but the disease continues to appear until the flock is culled. Since the birds affected are most often layers, total egg production falls considerably even though the unaffected birds remain in full production. Mortality ranges from 3 to 10% of the initial flock.

The **acute disease** appears earlier, and may commence between 7 and 16 weeks of age. Its evolution is quicker (2-5 days) and often the sick birds are not detected until they have died. When signs are observed, they take the form of a certain sluggishness without paralysis, and abnormal paleness of the comb and wattles.

During the final days extensive paralysis is evident. The proportion of birds ill at the same time is no higher than in the classical form, but the rapid appearance of new cases and the brief course of the illness leads to an overall mortality rate which may reach 90% of the initial flock in the case of layers. In flocks of broilers affected early at 7 weeks of age, the percentage of affected birds increases in the days just before slaughter (up to 8-10%). Skin tumours (leukotic lesions) are not detected until the feathers are plucked at slaughter.

In reality the clinical picture is not as clear cut as this. The onset may be an "acute", early and severe illness which becomes milder with time, changing to the "classical" form. Both classical and acute signs may occur simultaneously. Paralysis of pullets has been attributed to a collective hypersensitivity reaction (39).

When vaccination is practised it blurs the distinction between the two forms, diminishing the severity of acute forms and reducing considerably the mortality rate. If the vaccination should prove to be ineffectual, both clinical forms will recur.
Recovery is rare and is observed only under experimental conditions, when the sick birds can be isolated and protected from the other birds. Nevertheless a more frequent occurrence is regression of the initial lesions (25, 27).

**LESIONS**

The **anatomical** lesions are principally **neoplastic**. They are particularly evident in older birds after a slow evolution of the disease. The tumours affect practically **all organs** and tissues, altering their appearance (general hypertrophy or deformity, change in colour and consistency). A simplified list of these localizations would be: liver, spleen, lungs, ovary, testes, kidneys, muscles, peripheral nerves of muscles and organs; also skin, retro-orbital tissue, thymus, cloacal bursa. In very young birds affected by the acute form, lesions consist solely of hypertrophy of **certain organs** (liver, spleen, kidneys, gonads). An individual carcass might show only one lesion, or a small number of tumours in different places. However, examination of a number of dead birds from the same flock will reveal the complete picture of tumour implantation.

The variations in frequency of the tumours in each organ or tissue are related to the virulence of the virus and the genetic susceptibility of the birds. This takes into account only those tumours large enough to see. It seems that the organs most often affected by tumours are the peripheral nerves, liver, gonads, kidneys and spleen (7, 25).

**Tumorous lesions** bring about atrophy in certain lymphoid organs — the thymus and the cloacal (fabrician) bursa. The latter normally undergoes regression with the onset of sexual activity, but in MD it shows premature atrophy, transforming it into an empty pocket. The thymus, normally present until 6 months of age, may have atrophied by 6-10 weeks. These types of atrophy are related to the number of tumours.

The **histological appearance** of tumorous organs has been described amply (19, 22, 24, 26), consisting of an invasion of healthy tissue by a population of leukocytes made up of many types of cells: small and medium lymphocytes, lymphoblasts, plasma cells, hyperbasophil cells and polynucleated pseudo-eosinophils. This invasion compresses and pushes back the normal cells of the tissues. There may be differences in the populations of abnormal cells between one organ and another in the same subject. Kinetic studies of the nerve lesions have revealed histological and cytological variations at different times after virus inoculation, types A, B and C having been described in peripheral nerves (26, 27). Such variation is not so easy to detect in other organs. Certain images are frankly neoplastic, composed of just one type of cell (acute form). Other images suggest a fusion of neoplastic elements with cells of the immune defence system.

Microscopic lesions are often found in macroscopically normal organs of sick birds. Less often, small accumulations of lymphoid cells are seen in the tissues of birds which neither show clinical signs nor present lesions of the disease, whether they have been vaccinated or not.

**Cytological examination** provides additional precision in identifying cells present in tumours. In fact most of the lymphocytes in tumours are type T (thymus dependent) (14). It is significant that cell lines established from these tumours are also of type T. Nevertheless, B-lymphocytes (bursa-dependent) can also be identified in a variable proportion among lymphoid tumours of the heart and ovary.
The relative pleomorphism of the lesions of MD reflects the operation of immune responses aimed at causing regression of the tumours. In certain birds the initial early lesions, probably initiated by intracellular multiplication of the virus (in Schwann cells, lymphocytes, etc.) undergo changes when the various leukocytes which participate in immunity are attracted towards the lesions. If the immune response is lacking, the T-lymphocytes transformed by virus present in tumour cells rapidly invade the affected tissues.

**EPIDEMIOLOGY**

**DESCRIPTIVE EPIDEMIOLOGY**

Marek's disease was adequately described and identified, although under various names, until 1936, when it became confused with other tumorous processes under the name "avian leukosis". Research published in 1961 (4, 6) made it possible to separate MD from the lymphoid leukoses caused by retrovirus, and then the *herpesvirus* responsible was characterized (8), providing a basis for vaccination (9, 40). Widespread vaccination has completely altered the epidemiological aspects described hitherto (29).

The disease is distributed throughout the world. Identified in Europe in 1907, it soon appeared in North America and then in other countries, depending on the thoroughness of health surveillance, which was best on large, modern poultry farms and in specialized abattoirs.

There has always been a diversity of clinical forms and lesions. Nevertheless, at the flock level the disease retains a certain uniformity in its evolution. By contrast, it can be very different from one flock to another, sometimes even on the same farm. Moreover, when a given batch of chicks is distributed to different premises, the evolution on each premises is also very variable.

However, the recent finding that premises may be at high risk despite vaccination (41) has explained the apparently haphazard nature of the appearance of the disease.

At the national level, vaccination against MD has considerably reduced the frequency of severe infection, as the statistics show. Nevertheless, the prevalence of mild forms in flocks is difficult to detect because of diagnostic problems. When disease surveillance is strict, a few cases of MD may be identified, but, in general, they are not accounted for, being included under a general heading for mortality.

A partial conclusion is that the disease persists in almost all infected flocks as a persistent endemic, the economic severity of which is alleviated by vaccination. An analysis of the causes will help to explain this epidemiological situation.

**ANALYTICAL EPIDEMIOLOGY**

The principal cause of MD is the specific virus first isolated in 1968 (8), which is a *herpesvirus* belonging to the family *Herpesviridae*. Viruses of this family occur throughout the animal kingdom, often being responsible for persistent and recurrent infectious diseases. Some are capable of producing lymphoid tumours having some
similarities to those of MD, such as monkey lymphoma, Burkitt’s lymphoma and human nasopharyngeal cancer. However, MD virus cannot multiply in human beings and other primates (35).

The virus is actually the sole pathogenic agent of the disease in fowls. It is possible to rear flocks which are free from the virus and from other pathogens, and the disease does not occur in such birds, although experimental infection with MD virus produces the disease.

Certain characteristic properties of this herpesvirus throw light on the epidemiology of the disease. Extensive research on multiplication of the virus in tissues of fowls has shown that blood cells, particularly lymphocytes, and tumour cells contain the virus and are capable of transmitting the infection to healthy birds (5, 7, 31). Nevertheless, the virus is so closely associated with these cells that death of the cells leads to destruction of the virus. Research has shown that such cells possess viral information, but the virus fails to multiply actively in vivo, although it can multiply in vitro. Suppression of infection with a fragile virus does not explain the mode of natural transmission in a flock.

From another aspect, transmission by means of skin scales and feather debris shows that the virus can survive for a long time in these materials (3). Consequently attention has been directed to multiplication of the virus in skin cells at the level of feather follicles. Electron microscopy has confirmed the abundant multiplication of virus in cells undergoing keratinization (7, 23), and the discharge of particles having a special structure and surrounded by an envelope. Such enveloped particles are infective. By contrast with virus associated with blood cells and tumours, enveloped virus is very resistant to various physical and chemical agents. The particles leave the body during natural desquamation of the epithelial cells, particularly the cells which surround the base of a growing feather. Excretion of virus commences 2-3 weeks after infection and persists for the life of the bird, regardless of development of the tumorous form of the disease. Apparently healthy vaccinated fowls can excrete contagious virus in the same way as sick birds.

There is little individual variation in susceptibility, expressed in terms of morbidity and mortality, when a given strain of virus is inoculated into a group of birds uniform in age, sex and breed.

However, fowls do not develop tumours in the same way under natural conditions. This observation, made a long time ago, was formerly interpreted as evidence of different diseases, although it is in fact a single disease rendered variable by host factors.

It is interesting to note that a variation in the resistance of genetically different lines of fowl was demonstrated as early as 1932 (1). Subsequently, sensitive and resistant lines were established by selective breeding after experimental infection of chicks. In some such lines a variation in the genetic basis of resistance is correlated with erythrocytic histocompatibility markers of the fowl. In particular, the marker of allele B21 of group B is associated with strong resistance to the tumorous form of MD following experimental infection of homozygotes (20), and still some resistance in the heterozygous state. In lines carrying the allele B2, one subline (line 6) was found to be more resistant than another subline (line 7). This difference in resistance was not expressed when chicks were infected at one day of age, but it was very pronounced at one month of age. A correlation was established between the resistance of line 6 and the presence of a group Ly4 allele carried by lymphocytes. This resistance is
related to immune responses expressed in fowls by group B. Other alleles among the
large number belonging to group B probably modulate the resistance. Research in
progress may shed further light on this situation.

Such an approach is very important because it can explain variations in the disease
associated with flocks or with individuals, as well as guiding selection for creating
resistant flocks.

**The age of birds** at the time of infection is an important determinant of the fre­
quency and severity of the disease. Experimental infection during the first few days
after hatching is usually more effective than later infection with a given strain of virus
(see above). Unfortunately, it is very difficult in practice to record the age of ex­
posure to infection, and then to relate it to the earlier or later appearance of clinical
cases. Almost all flocks become infected during the first few days or weeks of age,
but they are not all infected simultaneously. The virus multiplies rapidly in the first
birds to become infected. When, after 10-14 days, excretion of virus commences,
the remaining disease-free birds, which may be resistant to tumour development
because of their genetic make-up or as a result of active immunization, are exposed
to infection. The presence of specific maternal antibodies against the virus does not
completely halt multiplication of the virus.

**Sex** may be related to sensitivity to the disease. Numerous observations have
revealed a higher frequency among females than males. Some experiments have con­
firmed this, but the difference has not been very pronounced during an identical period
of observation. The problem is whether sexual activity constitutes a major risk factor.

**Environmental factors** are probably involved in the sensitivity of birds to tumours,
and there are numerous observations which bear this out. Stress of any sort (such
as long-distance transport, rehousing, sorting operations, vaccination, thermal shock,
appearance of another disease) may be followed by the start of an outbreak. A sug­
gestion that there may be coincident infection with retroviruses of the avian leukosis-
sarcoma group has not been confirmed.

Experimental investigation of the influence of these factors, taken singly or in
combination, is difficult and costly. It could provide valuable information, particularly
when resistance following vaccination is incomplete. Current developments in the
formation and modulation of immunity may provide a better knowledge of immune
mechanisms and the way in which they are influenced by environmental factors.

**The ways in which the disease is transmitted** are now well understood. For a long
time vertical transmission from the hen to her chicks has been suspected. Chicks
removed from their parents at hatching are often infected, and the virus can multi­
ply in experimentally inoculated embryos, resulting in MD after hatching. The
demonstration of infection by means of dust has raised doubts concerning the prob­
ability of vertical transmission. In fact, the herpesvirus has not been detected in
the organs of embryos in eggs laid by infected hens. When eggs laid by infected hens
are submitted to prompt and thorough antiseptic treatment, the surviving embryos
and hatched chicks remain free from infection. If these chicks are reared in a pro­
tected environment (see below), they remain free from MD. Therefore, vertical
transmission, if it does occur, is exceptional.

**The essential mode of transmission is therefore horizontal**, that is to say infected
birds excrete and disseminate the infective virus to other, uninfected members of the
group. Mention has been made already of the excretion of virus by epithelial cells
of the skin. The enveloped viral particle not associated with cells, which is very resis­
tant to environmental factors, is present in scale debris from feathers which is part
of the dust present in poultry houses. This dust is light and is easily dispersed into
the air. Infection takes place in the upper respiratory tract by inhalation, as has been
proved experimentally. The dust is deposited on the ground, the walls, feedstuffs,
and on the covers and vents of ventilation equipment of rearing houses. It may also
settle on clothes and shoes, as well as on the hands and face of attendants. More
important, it is deposited on eggs the moment they are laid, and when the external
cuticle of the shell is not yet dry, which offers conditions for firm adhesion.

Persons working on or visiting the premises can become carriers of infective dust.

Young and adult fowls are the most important carriers. From the age of 3 weeks
it can be assumed that all are excreting the virus, remaining permanent carriers for
the rest of their lives: Transmission becomes inevitable when young breeders are in-
troduced, when birds are moved to roomier accommodation as they grow, when they
are sorted into new groups, or when birds are brought in from outside to make up
the numbers.

Eggs having shells contaminated by dust may be a source of transmission of in-
fection. Throughout incubation, but particularly just before hatching, the shell
becomes thinner and more fragile, and it breaks up after hatching. The fragments
may come into contact with the chicks.

The epidemiology of MD should always be evaluated on two of its aspects: firstly
the prevalence of the disease, and secondly the prevalence of horizontal transmission
of the herpesvirus.

DIAGNOSIS

DIAGNOSIS IN THE FIELD

This is based on the clinical features and post-mortem findings. Clinical diagnosis
is easy when there are numerous cases of paralysis, particularly of the feet. Unilateral
lameness gets worse rapidly, there are unusual cases of wasting, and mortality mounts
as time passes. It is easier when the birds are kept in floor pens than when they are
kept in collective cages. Clinical diagnosis becomes more difficult when the disease
is acute, without many cases of the paralytic form. The non-specificity of the signs
and the rapid worsening towards death rule out a positive diagnosis. Sometimes there
is no sign of the disease at all, and the disease is discovered only at the abattoir. MD
should always be suspected when there is poorly defined mortality among young
adults.

Differential diagnosis is easy in the case of arthritis, traumatic injury, bony defor­
mity and abscesses. It is more difficult in the acute forms of outbreaks of bacterial
diseases (pasteurellosis and salmonellosis) and viral diseases.

On premises where there is poor supervision of health, clinical diagnosis is rarely
established, and it is necessary to conduct a detailed post-mortem examination.

Post-mortem diagnosis and the examination of lesions is very important because of
the paucity of clinical signs, and also because of the limitations of laboratory
diagnosis. It consists principally of a systematic search for tumours which, as mentioned above, may occur in a wide range of organs and tissues. Any modification in the size, shape or colour of an organ should be noted. In view of the specificity of nerve tumours, all accessible nerves should be examined: sciatic nerves of the limbs, the sciatic plexus (through a small incision of the middle lobe of the kidney); brachial, pneumogastric and intercostal nerves. A comparison of left and right nerves may reveal asymmetry due to tumorous deformation. In the absence of nerve lesions, the main organs to examine are gonads, liver, spleen, kidneys and lungs. In birds which have been slaughtered and plucked, look for nodular tumours around feather follicles. These are characteristic of the cutaneous form (skin leukosis) and are almost always associated with hypertrophy of the liver and spleen. In young adults, premature atrophy of lobes of the thymus and the cloacal bursa provide a good confirmation of tumorous lesions.

For differential diagnosis, the finding of tumours is nearly always definite. However, general hypertrophy of peripheral nerves can occur in riboflavin deficiency. Tumours of organs have to be distinguished from abscesses and necrotic lesions. The most difficult problem is to differentiate the tumours from those of lymphoid leukosis (caused by the retrovirus of the avian leukosis-sarcoma group), which are located principally in the liver, spleen and kidneys. They do not differ much from the tumours of MD, but the more advanced age of the birds and the absence of nerve tumours indicate lymphoid leukosis.

A finding of the customary diversity of lesions of MD in a number of carcasses is reliable for differential diagnosis.

LABORATORY DIAGNOSIS

This is resorted to when the disease is suspected but not confirmed by clinical and post-mortem examination, and particularly to identify the tumours by histological and cytological techniques.

Histological examination distinguishes neoplastic process from lesions due to abscess, inflammation, necrosis and leukocytic proliferation. Samples should be taken from a large number of tissues, whether they appear normal or abnormal upon post-mortem examination. In any event the sciatic and brachialplexuses are removed and so positioned that longitudinal sections (not transverse) can be prepared. A search is made for the presence of mononucleated cells in a sufficient number of sections cut at different levels. Because of the uneven distribution of tumours, the result may be negative if only one section is examined. When a focus is found, an attempt should be made to identify the different types of lymphoid cells (lymphocytes, lymphoblasts, hyperbasophil cells, plasma cells) in order to correlate their identity with macroscopic lesions and clinical signs. The presence of such lymphoid foci provides reliable confirmation of MD. The small lymphoid foci present in normal birds or birds with other diseases may be the microscopic lesions of infection with a specific herpesvirus. In MD-resistant birds they may be interpreted as latent forms of the neoplastic process.

Differential diagnosis of tumours by histology is necessary when lymphoid leukosis is suspected because of simultaneous hypertrophy of liver, spleen and kidneys. Homogeneous tumours composed of lymphoblasts can be confused with acute MD, hence the importance of examining nerve plexuses, which are seldom involved in spontaneous forms of lymphoid leukosis. Other leukotic tumours (myeloblastosis, erythroblastosis) and sarcomas are easily identified and distinguished from those of
MD. Reticulo-endothelial tumours closely resemble those of MD under experimental conditions, but they are confined to young birds and are identifiable by the presence of large foci of polyhedral reticular cells.

Nevertheless, histological differentiation from lymphoid leukoses can be difficult. New methods of identifying the line of neoplastic lymphoid cells are now ready for introduction into laboratory practice. Starting with fresh samples of tumorous tissues, it is quite easy to separate lymphocytic cells by light scraping of the sample in an isotonic solution. The cells are washed and then treated with specific antibodies directed against T and B specificity. In tumours attributable to MD, most of the cells are type T, while in lymphoid leukosis all cells are type B. It is also possible to detect special MD tumour antigens on the cell surface (Marek-associated tumour-specific antigen, MATSA) (15, 18). We await progress in the adaptation of this cell testing to routine laboratory work.

Experimental laboratory diagnosis by detecting MD virus raises some questions of principle. If every flock of fowls is infected, field strains of the virus will be present all the time. Moreover certain live vaccines derived from avian herpesvirus can be transmitted horizontally. Thus the detection of the virus by means of standard virological techniques may not provide proof of the presence of the disease (10). In order to furnish a specific diagnosis it would be necessary to demonstrate a high pathogenicity of the strains isolated, and to verify that the usual vaccination does not confer protection against them. Such demonstration is slow, difficult and costly, which restricts its use. Current research on the viral genome may make it possible to use molecular probes capable of identifying dangerous strains (11, 13, 16, 30, 32).

Testing for antibodies in birds is just as deceptive as virological testing. Every bird may possess antibodies induced by field strains or vaccine strains of the virus. It is possible to classify certain strains into antigenic serotypes I, II and III. Progress in immunobiochemistry may make it possible to identify the specific antibodies of highly pathogenic strains (21, 28, 36, 37, 38).

Much work has been done to find specific alterations in whole blood, serum or plasma from fowls infected or ill with MD, including erythrocyte count, leukocyte count, enzymes, proteins and globulins (17). So far, the results have been too variable or inconstant to confirm a diagnosis.

A comparison of all the procedures described above shows that the best diagnostic results are obtained by a detailed examination of the lesions, supplemented by histology and cytology (33).

PROPHYLAXIS

PROPHYLAXIS BY HYGIENIC PRECAUTIONS

The ideal prophylaxis prevents transmission of the virus. This method can be applied only in experimental, breeding or SPF flocks, because the sources of infection are ubiquitous, virus is continuously excreted by carriers, and the free virus present in dust is very resistant. It must be stressed that when the procedure is applied successfully against MD, it also provides protection against a large number of other contagious bacterial and viral diseases. It can also be adopted once highly pathogenic strains have been identified on a premises.
The procedure will not work in buildings provided with large openings, and can be used solely in buildings having controlled artificial ventilation operating by positive interior pressure. The buildings must have provision for the personnel to change their clothing, suitable arrangements for feeding and egg collection, and appropriate disinfection procedures (formaldehyde or ultraviolet light). Eggs destined for incubation are disinfected as soon as possible after being laid, and placed in a sterile incubator inside a room supplied with air under positive pressure. The chicks are highly susceptible during the first weeks of life, so they should be reared apart from the adult birds.

The above conditions are not applied in full in practice, because of the high cost of the buildings and the restrictions placed on personnel. However, certain of the procedures will diminish the intensity of natural infection, and postpone the infection of chicks.

A discussion of prevention should include the principles for trade in birds and in products capable of transmitting the herpesvirus. It is impossible to propose logical restrictions for young adults and breeding stock, because all the birds will be infected, excreting the virus and possessing antibodies common to various strains of viruses. Protracted testing would have to be done to guarantee the absence of a given virus, such as a highly pathogenic strain.

Fertile eggs from infected breeding stock are probably contaminated by deposition of infective dust on the shell surface. The usual disinfection cannot guarantee complete elimination of the virus, although it can considerably reduce the risk of infection. Progress in disinfection techniques might bring better prospects for this method in the near future. The fact that the breeding stock has not experienced mortality from MD does not mean that it is necessarily free from the virus.

There is no good way of preventing the development of tumours in infected birds. Numerous environmental factors resulting in stress are sometimes correlated with the appearance of tumours. Prevention of stress can be improved, particularly by reducing the amount of transporting and transfer from building to building or from cage to cage, and by careful attention to the environment. Any improvement aimed at preventing other diseases may also enhance the resistance of the birds to tumour development.

MEDICAL PROPHYLAXIS. VACCINATION

Vaccination against the tumours of MD was the first vaccination against cancer in the history of biology (9). Because of the difficulty in implementing other preventive measures, it is the best way of controlling the disease, and is practised throughout the world. It consists of the injection of a live apathogenic virus (herpesvirus of turkeys – HVT) or a strain of low pathogenicity (SBI, CVI 988, etc.) into newly-hatched chicks. It is important that the vaccine virus is able to multiply early, preferably before infection with field virus from an infected premises. The dose and mode of injection are specified by the manufacturer of the vaccine, and should be observed scrupulously. The degree of protection of experimental flocks against a strain of ordinary pathogenicity can be greater than 80%, but it is not as high against very virulent strains. Experiments are under way to produce more active bivalent or trivalent vaccines against such highly virulent strains.
The vaccines provide protection against the development of tumours, but they do not prevent the active multiplication and excretion of field strains of virus. This explains why it is impossible to guarantee freedom from infection in vaccinated birds which are also carrying the virus. Effective vaccination does not reduce the risk of horizontal transmission, and consequently should not be interrupted.

There are some accounts of vaccination failure resulting in severe outbreaks of MD. Some of these are explained by errors in vaccination, by early infection, or by infection with highly pathogenic virus, but the remainder cannot be explained.

*There is room for progress in vaccine immunogenicity, vaccination of the embryonated egg (34) and the stimulation of immunity in vaccinated birds.*

**GENETIC PROPHYLAXIS**

Resistance to the tumours of MD can be exploited to create resistant lines, or to eliminate susceptible lines. Most of the current research is aimed at detecting markers associated with resistance to tumours, in order to avoid prolonged and costly experimentation (2, 12, 20). While certain lines are classed as "resistant", they still harbour, multiply and excrete field strains of virus in the same way as susceptible lines. The establishment of lines resistant to the multiplication of virus would be a considerable advantage in limiting virus excretion.

None of these special lines is commercially available because it is difficult to fix the gene (or genes) coding for resistance. Many special conditions have to be met: existence of a marker gene firmly associated with the resistance genome, absence of genetic correlation which diminishes performance, and heritability to a high degree for rapid selection. Attempts are being made to isolate the genes associated with immune responses, and to transfer them directly or indirectly (by the intermediary of a viral vector) into the genome of the fowl.

**REFERENCES**

(see p. 1022)