Developments in Biological Standardization Vol. 52

17th INTERNATIONAL CONGRESS ON

HERPES VIRUS OF MAN AND ANIMAL: STANDARDIZATION OF IMMUNOLOGICAL PROCEDURES

XVIIth INTERNATIONAL CONGRESS
ON

HERPES VIRUS OF MAN AND ANIMAL: STANDARDIZATION OF IMMUNOLOGICAL PROCEDURES

Proceedings of a Symposium
organized by the
International Association of Biological Standardization
and held at the
Palais des Congrès, Lyon, France

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130 figures and 149 tables

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	Chairman :	P.M. Biggs	(U.K.)
	Secretary :	U. Krech	(Switzerland)
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Contributors: Mérieux Foundation — Lyon (France)

Attention is drawn to the first Regamey Memorial lecture which was delivered by Dr G.C. Schild, of the National Institute for Biological Standards and Control, London, on the subject: «New approaches to the standardization of viral vaccines». This lecture is to be published in its complete form in the Journal of Biological Standardization.

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Vol. 52

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"PROGRESS in Immunobiological Standardization, Vols 1-5"
and
"SYMPOSIA SERIES in Immunobiological Standardization, Vols 1-22".

OPENING ADDRESS

Our Association is celebrating its 25th anniversary. We can proudly say that during those twenty-five years we have always been in the forefront of standardization in biotechnology. We have organized more than sixty symposia and congresses in this field and our publications are meeting with growing success worldwide.

Preventive medicine has made tremendous progress during the last twenty-five years both in the human and in the veterinary field. More than ever before, the emphasis is shifting towards prophylaxis and this phenomenon is justified by medical, ethical and economic reasons. The eradication of smallpox through vaccination has been one of the greatest victories of medicine. Other scourges of mankind, such as polio, measles, tetanus, diphtheria, whooping-cough, yellow fever, rubella and others can now be kept under control by immunization. This also applies to many diseases in several animal species. Our Association has maintained its interest in the veterinary field as well as in human biologicals. Recently we organized our first symposium on Fish biologicals, which proved to be a great success. Very often we have been able to bring together representatives of the human and veterinary fields and generally these contacts have been very fruitful.

Vaccines and immunodiagnostics are essential tools in preventive medicine and here the role of our Association is of primary importance, because, without standardization, it is impossible to guarantee the supply and use of safe and effective biologicals.

Our Association brings together representatives from the industry, from the regulatory authorities, from research and from public health and our aim is to make sure that we continue in the future to be a forum and a meeting point where results and information can be exchanged and solutions proposed. With the development of new products and more complex technologies, these contacts between producers, controllers and users will become even more necessary than in the past.

I would like to thank all those who during the last twenty-five years contributed to the growth of our Association and we are glad to have several of our founder members with us today.

We are also happy to be back in Lyon, and I wish to thank the Mayor for his hospitality. This city is a rather exceptional combination of an artistic and scientific centre, an important industrial town and, as most of you know, a gastronomic paradise.

C. Huygelen
President

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SESSION I

EPIDEMIOLOGY OF HERPES VIRUSES

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THE EPIDEMIOLOGY OF AVIAN HERPESVIRUSES IN VETERINARY MEDICINE

P.M. Biggs

ABSTRACT

There are ten avian herpesviruses which have been isolated from eight orders. Six of these are of veterinary importance: Pacheco's parrot disease virus, pigeon herpesvirus, duck plague virus, infectious laryngotracheitis virus, herpesvirus of turkeys and Marek's disease virus. The knowledge on the epidemiology of each virus and the disease it causes is discussed. Features in common to infections with most avian herpesviruses are: infection is persistent in individuals and ubiquitous in populations; virus is shed for long periods of time after infection although in some cases erratically; infection does not necessarily result in disease and at least in some of the avian herpesvirus infections the incidence of disease is affected by the pathogenicity of the virus; the genetic constitution of the host and stress factors affecting the host. It is concluded that man's interference with the natural history of host species often increases the threat and incidence of disease unless preventive action is taken.

Herpesviruses have been isolated from many species of the class Aves belonging to eight orders. Marek's disease virus (MDV) and infectious laryngotracheitis virus (ILTV) are natural infections of the domestic fowl causing well recognised diseases. The herpesvirus of turkeys (HVT) is a natural infection of domestic turkeys and serologically closely related to MDV. Duck plague virus (DPV) causes disease in domestic ducks, and also in wild ducks, geese and swans. The pigeon herpesvirus (PHV) has been described as causing disease mainly in domestic (table and racing) pigeons, but also budgerigars (9, 17, 42) and is serologically closely related to herpesviruses isolated from several diseased species of owl (owl herpesvirus) (8) and of falcon (falcon herpesvirus) (33). Pacheco's parrot disease virus (40) is unrelated to other known avian herpesviruses and causes disease in Amazonian parrots and possibly other psittacines (34, 41). Finally, there are two further avian herpesviruses which appear to be serologically distinct. These were isolated from a little pied cormorant (*Phalacrocorax melanoleucos*) and two black storks (*Ciconia nigra*) (19, 28).

I have mentioned all the avian herpesviruses by way of introduction to this paper reviewing the epidemiology of avian herpesviruses in veterinary medicine. I interpret veterinary in the context of this paper as applying to domestic avian species. This restricts the discussion to MDV, HVT, ILTV, DPV and PHV. I should also include the Pacheco's parrot disease virus because there are great numbers of domesticated parrots in the households of the world. However, as far as I am aware there is little information available on the epidemiology of this infection.

It has been suggested that there are symptomless carriers of the infection (16). It was noted disease often followed movement or delays in transit of birds, actions which presumably stress the birds.

Pigeon herpesvirus (PHV)

The isolation of a herpesvirus was first described (17) from diseased racing pigeons in the United Kingdom. The virus causes a systemic disease with necrotic lesions in many organs. Similarly diseased domestic table and homing racing pigeons associated with evidence of infection with a herpesvirus have been reported in North America, Europe and the Antipodes (6, 9, 27, 30). The virus is serologically closely related to the owl and falcon herpesviruses (33, 38). However, there is no evidence that this is epidemiologically significant. The owl and falcon viruses produce disease in owls, falcons and ring necked turtle doves but not pigeons, whereas the pigeon virus does not produce disease in raptors (33). Knowledge of their evolutionary relationship would be interesting, but there is no evidence to suggest that these viruses are the same or that they spread naturally from species to species. It is more likely that this serological relatedness is due to a small genetic homology as has been shown in the case of HVT and MDV.

Little is known of the epidemiology of pigeon herpesvirus, but the infection appears to be widespread and endemic in an affected loft which is probably maintained by healthy adult carriers (17). The disease affects pigeons of all ages although it is more frequently seen in young pigeons.

How infection is introduced to a group of pigeons is unknown. The occasional appearance of an exotic racing pigeon in a loft could introduce the infection. However, this does not explain why some infected individuals and groups suffer from disease while others do not.

Duck plague virus (DPV) (31)

Duck plague is an acute disease of domestic and wild ducks, geese and swans. It is interesting epidemiologically because there is an interrelationship between wild and domestic birds. The disease has been described in domestic ducks, particularly in areas of high density duck production, zoological gardens, private waterfowl collections and in free flying waterfowl, and it affects birds of all ages. It can have a devastating economic effect on commercial duck production, particularly if the management system uses ponds. This allows free access to wild waterfowl and ready spread of the causal virus.

The disease has been described in several breeds of domestic ducks including Muscovies and many species of wild duck, some of which have been reported to be more resistant to the effects of the infection than others. It has been suggested that the more resistant species such as the Mallard may act as natural reservoirs of infection (7).

All virus isolates studied have been serologically identical, but differences in virulence have been noted (31).

Spread of the virus can be by direct or indirect contact and, when present, water appears to be the natural medium of transmission of the virus from infected to susceptible individuals. The course and duration of infection is determined by the population density and population movements in both domestic and wild waterfowl. The higher the density of birds the more readily infection is transmitted. However, the disease is self-limiting provided there is no continuous introduction of susceptible uninfected individuals. In the commercial production of ducks this is not always possible and control of the disease once infection is present requires vaccination. The natural routes of shedding the virus of infection are not known, but experimentally the disease can be transmitted by the oral and intrasanal route. There is no evidence for congenital infection via the egg. Laboratory studies suggest the virus is not very hardy and it is probable that survival outside the body is limited to days or a few weeks at most.

From these observations it can be postulated that wild waterfowl act as a repository for the virus and that outbreaks of disease in wild or domestic waterfowl are the result of the introduction of the infection by free flying wild waterfowl. This hypothesis is supported by observation (7, 31). Control of the disease in commercial domestic duck farms has been more effective since their management has been designed to reduce contact with wild waterfowl by the elimination of ponds and the enclosure of such ducks in small runs and/or houses. Once infection has been introduced its spread is encouraged by high population densities and the presence of water. Such infection is self-limiting, because recovered birds are immune to reinfection, unless susceptible uninfected birds are continuously introduced.

Infectious laryngotracheitis virus (ILTV) (21, 23, 25)

Infectious laryngotracheitis is a respiratory disease primarily of the domestic chicken which varies from an extremely acute to a mild disease. The disease is seen in most countries of the world and it affects all ages, but mainly adults. It can be endemic in focal regions, but is more commonly epidemic or sporadic in nature. There is no experimental information on the effects of the genetic constitution and the age of the fowl on infection, but anecdotal information suggests these factors are unimportant. All isolates of ILTV that have been examined except one have been serologically closely related, although some minor antigenic variation has been noted using the neutralisation test. It is not believed that these variations are epidemiologically significant. Variation in the pathogenicity of isolates of ILTV is well documented.

Infection is almost entirely restricted to the respiratory tract and conjunctiva. Shedding of virus and the route of infection under natural conditions is believed to be via the respiratory tract and conjunctiva. There is no evidence for congenital transmission via the egg. Infected birds may remain carriers for periods of up to two years, although it would appear such birds shed the virus erratically. Survival of the virus outside the body can be for several weeks (24) which allows spread by indirect contact via animals, man and fomites.

Surveys have shown that in some countries infection is present in more than 25% of flocks (32, 39), whereas in others it is considered to be absent or only present in endemic areas or where epidemic disease has occurred.

In areas of endemic disease it is easy to accept that the combination of the continuous supply of susceptible uninfected chickens to the area and physical transmission by man or by fomites maintains the infection. It is more difficult to understand how sporadic and epidemic disease occurs. What is the source of the primary infection in these cases and why should disease suddenly occur in an area where infection was already present? These are questions which still require answering.

Herpesvirus of turkeys (HVT)

Infection with the herpesvirus of turkeys occurs naturally in the turkeys, although under experimental conditions spread by the airbone route from turkeys to chickens has been described (46). It is an ubiquitous infection of commercial turkeys which spreads by the airbone route but produces no overt disease. Two commercial flocks of turkeys were studied (45) and it was found that maternally derived antibody was universally present in one-day-old poults. The antibody disappeared by 3 weeks of age virus was first isolated between 5 and 6 weeks of age and thereafter spread rapidly throughout the flocks. Viraemia and antibody persisted in virtually all turkeys for the period the flocks were studied (to 20 weeks of age). Although latent infection of the testis and presence of HVT in semen has been described (1), there is no evidence for vertical transmission of the infection (35, 44).

Marek's disease virus (MDV) (5, 37)

Marek's disease virus infection is ubiquitous amongst domestic and feral fowl. Marek's disease is a lymphoproliferative disease affecting visceral organs, tissues and peripheral nerves which can vary in incidence between 0 and 80% in infected flocks. It primarily affects the young growing chicken prior to sexual maturity. It is one of the most highly contagious diseases of the domestic fowl and the virus spreads from infected to uninfected chickens by direct or indirect contact (3). There is no evidence for vertical transmission of the virus and it is the general view that it spreads only horizontally. Infection is believed to be by the respiratory route.

MDV strains vary greatly in pathogenicity from apathogenic to highly oncogenic and infection with one strain of virus does not necessarily prevent superinfection with another and individual chickens can be infected with two strains of differing pathogenicity (14).

Prior to the widespread use of vaccines chicks in most flocks were infected within the first few weeks of life. Virus is present in an infectious form in the feather follicle epithelium (10) within two to three weeks of infection and therefore an infected chicken is from that time a source of infection to other chickens. Infected chickens remain carriers and a source of infection for other chickens for the remainder of their life (29, 45).

Although faeces and oral and nasal washings of infected birds have been found to be infective the major source of infection is dander and feather debris

(2, 26, 29, 43). Infectivity of this material may persist for as long as 7-8 months (12, 13) which allows ample time for dissemination to other groups of fowl. This material is not only difficult to disinfect in a poultry house between crops of chickens, but is readily discharged by the forced ventilation used in poultry houses and distributed by wind and fomites.

MDV infection is ubiquitous, yet only a proportion of infected birds develop the disease and the incidence varies greatly between flocks, poultry houses and pens within a house. There must therefore be factors which influence the incidence of Marek's disease. These can be grouped under virus, host and environment.

Virus

The strain of virus with which a chicken or group of chickens is infected influences the outcome of infection. The more pathogenic and oncogenic strains are likely to produce disease in an individual and a high incidence of disease in a flock of chickens. However, the position is more complicated. Most, if not all, flocks are infected by strains of MDV of varying pathogenicity. The variable incidence of disease in groups of chickens has been shown to be related to the prevalence of the strain of virus first infecting each group. Higher mortalities were found in groups which were initially infected with viruses of high pathogenicity than in those first infected with viruses of low or no pathogenicity. Subsequent exposure of these latter groups to viruses of high pathogenicity did not alter the prognosis. It has been suggested that when infection with a non-pathogenic strain preceded that by a pathogenic strain, natural vaccination occurred (4, 22).

Host

A number of factors controlled by the host affect the outcome of infection with MDV. These include genotype, age at infection, sex and immune status.

Two loci have a profound effect and probably several others have a minor influence on the susceptibility of chickens to Marek's disease (37). The major histocompatibility locus, B has a major effect with the B^{21} allele providing a strong resistance to the development of disease which is believed to depend on differences in immune competence against virus infected and transformed cells. The second major locus, Ly-4 is believed to control the susceptibility of the presumed target cell, the T-lymphocyte, to infection with MDV.

It has long been recognised that susceptibility to MD declines with the age at infection. Age resistance is not a manifestation of declining susceptibility to infection but is probably due to a developing immune competence. There is probably a relationship between age resistance ad genetic resistance controlled at the B locus because they are both based on immune competence and little age resistance develops in some genetically susceptible strains of chickens (11).

The sex of the bird has an influence on the development of disease. There