Chapter 1
Newcastle Disease - An Overview
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Newcastle Disease is the most important viral disease of poultry in the world. It occurs in most countries and has a devastating effect on commercial poultry production. No accurate estimate is available of the cost of Newcastle Disease to the commercial industry but the cost would include deaths and loss of production due to clinical disease, the total cost of purchasing and applying vaccines, the costs of eradication and quarantine programs and loss of trade. In many parts of the world commercial poultry production is possible only because Newcastle Disease vaccines are available that are cheap and fairly effective.

However, this publication is not concerned with the commercial poultry industry. It is concerned with the village poultry industry that is present in most tropical and subtropical countries and that is often larger than the commercial industry. The village poultry owner keeps small numbers of scavenging chickens of indigenous breeds and outlays little capital or labour inputs. The chickens are usually supplied with some form of shelter at night but range freely during the day and receive little supplementary food apart from household scraps. The chickens are poor producers and one great source of loss is Newcastle Disease. As will be seen in this review, we have some knowledge of the interaction between Newcastle Disease virus and the commercial poultry industry, and that veterinary authorities are able to contain the disease. Sadly, we know very little about Newcastle Disease in the traditional rural poultry industries, and until recently there has been no vaccine strategy that was suitable and appropriate for use with village poultry. As an introduction to this volume, it is useful to review our knowledge of the virus and the disease.

The Virus

Classification and Physicochemical Properties

Newcastle Disease Virus is a paramyxovirus, and was for a long time the only known avian paramyxovirus. However it is now recognised as a member of a family of related avian paramyxoviruses. Some of the basic properties of paramyxoviruses should be considered for they have some bearing on the biology of Newcastle Disease virus. An outline of the classification of paramyxoviruses is given here. The common name is ambiguous and may be applied to a member of the genus Paramyxovirus or of the family Paramyxoviridae.

Paramyxoviruses have a genome of single-stranded, negative-sense ribonucleic acid. The viral
particle is enveloped and contains at least six virus-specified proteins. The important proteins in a practical sense are the two associated with the lipid envelope of the virus. These are both glycoproteins and in Newcastle Disease they are termed the haemagglutinin protein and the fusion protein. These proteins are concerned with the reaction of the virus with target cells and with neutralising antibody. The other proteins are internal and have, as yet, no accurately assigned functions. The virion, when first formed, contains large precursors of the haemagglutinin and fusion proteins and is inactive. These proteins gain their biological function after cleavage by cellular proteases. The virus is not able to code for these proteases.

The surface antigens of Newcastle Disease virus are remarkably constant. It is extremely difficult to distinguish strains by serological tests when polyclonal antiserum is used. Monoclonal antibodies do distinguish subtle differences between strains, but these differences are not sufficient to prevent vaccination. The surface antigens do not change with time nor when the virus is present in an immune population.

**Pathotypes**

Although strains of Newcastle Disease virus are antigenically very stable, they vary remarkably in pathogenicity. They vary from strains that cause peracute disease with 100% mortality to strains that cause no disease at all when they spread naturally. It is traditional to recognise three pathotypes of Newcastle Disease virus. Velogenic strains causing severe disease with high mortality are termed *velogenic*. These strains produce high mortalities, even in adult birds, and are further subdivided into *neurotropic* and *viscerotropic* strains according to their predilection for the central nervous system or for organs of the thorax and abdomen. It is the viscerotropic velogenic strains that are the scourge of the poultry industry in Asia. *Mesogenic* strains are of moderate virulence, causing mortalities of up to 50% and seriously reducing egg production. Strains of low virulence are termed *lentogenic*. They can seriously affect egg production but cause little mortality except in young chicks or when other pathogenic microorganisms are present. The divisions between pathotypes are, of course, arbitrary—a human attempt to draw boundary lines in a natural continuum. To these three conventional pathotypes we could add another class, the *avirulent* strains of Newcastle Disease virus. These cause no disease at all when they spread between chickens by natural routes. Strain V4 which will feature in this volume is such a virus.

Pathotyping ultimately depends on the response of chickens to natural infection. However, certain laboratory procedures may be used to indicate pathotypes. Velogenic viruses kill embryos very quickly, are pathogenic for 8-week-old and 1-day-old chickens under standard conditions and are readily cytopathic in cell cultures. Lentogenic strains kill embryos slowly, are poorly pathogenic in chickens and are cytopathic to cell cultures only in the presence of certain additives. Mesogenic strains have intermediate properties while avirulent strains rarely kill embryos and are not pathogenic in chickens or cytopathogenic in cell cultures.

Variations in pathogenicity can be explained in part by the biochemistry of the two surface proteins. The precursor proteins of velogenic viruses are susceptible to proteases in many types of cells, so that many types of cells are able to release active virus. With less virulent viruses only one of the surface glycoproteins is readily cleaved to active form. Both glycoproteins of avirulent viruses apparently have very specific requirements for proteases and very few cell types are able to produce active virus. Variations in pathogenicity, target organ specificity and age susceptibility could all be a function of interactions between viral glycoproteins and cellular proteases. It is well recognised that strains of Newcastle Disease virus differ in organ specificity. Some, for example, colonise the intestinal tract very poorly. Some have organ specificities that vary with age of chicken and this may reflect variation in protease production with age. Avirulent strains of Newcastle Disease virus are apparently limited to the allantoic cavity of the developing embryo because only the cells lining the cavity possess suitable proteases. More virulent strains have a less restricted range of host cells.

There are, of course, other aspects to pathogenicity. Ease of spread and rapidity of spread are very important. Control by slaughter is more difficult with strains of virus that spread rapidly.
Rapid spread is usually associated with respiratory infection.

There has been little detailed study of the ability of various pathotypes of Newcastle Disease virus to cause latent infections. Carrier states are fairly easily established in mammalian cell cultures and in avian organ cultures. It is sometimes possible to isolate Newcastle Disease virus from birds only by cocultivation of infected cells with indicator cells. This suggests some form of defective replication, a feature of the replication of many paramyxoviruses.

**Haemagglutinin**

The haemagglutinin glycoprotein of the virus finds receptors on the red blood cells of many species and will agglutinate these cells. It also has neuraminidase activity which allows its eventual release from the cell surface and the separation of the agglutinated cells. Red blood cells are not a target for the virus in the chicken, but many laboratory procedures with Newcastle Disease virus employ the haemagglutination reaction. In particular, the haemagglutination-inhibition reaction is the most commonly used serological test for detecting antibody. The replication of non-cytopathic strains of Newcastle Disease virus in cell culture is detected by observing the attachment of erythrocytes to the infected cells, which express haemagglutinin on their cell membranes. Additional characterisation of strains of Newcastle Disease virus is possible by studying the species of red blood cells that are agglutinated, the time required for elution and the heat stability of the haemagglutinin. Differences in these characters appear to express fine differences in the chemical structure of the haemagglutinin.

**Laboratory Procedures**

All strains of Newcastle Disease virus grow readily in the allantoic cavity of embryonated eggs and all except the avirulent strains kill the embryo. The presence of virus in the allantoic cavity is detected by a simple haemagglutination test. Embryos are preferred to cell cultures for vaccine production because of the higher viral titres achieved in embryos and many laboratories prefer embryos to cell cultures for the detection of virus.

Anti-Newcastle Disease virus antibody is most conveniently detected by the haemagglutination-inhibition test (HI-test). This is a very simple test, using chicken erythrocytes and simple buffers. When avian serum is used there are only a few problems with natural agglutinins, and adsorption of the serum is seldom required. Simple dilutions of allantoic fluid serve as haemagglutinin. Microtitre adaptations of the test save the need for large volumes of reagents. It is probable that this will remain the standard laboratory test, although other tests have been investigated. ELISA tests could eventually be used for rapid diagnosis in the field and for detecting virus, the possibility of automation being their greatest potential advantage. Neutralisation tests and complement fixation tests have special but limited uses.

Laboratory tests are used in the diagnosis of Newcastle Disease and to test the response to vaccines. Serological tests are not of absolute use as indicators of immunity. Certain levels of haemagglutination-inhibition antibody can be equated with protection against fatal disease or protection against loss of egg production. Chickens with low levels of antibody and even chickens without antibody following vaccination are not necessarily susceptible. Antibody titres are most useful when a standard test is used and standard control sera are used to validate the test. It is possible that complement-fixation or neutralisation tests would give results that more clearly indicate immunity, but these tests are cumbersome and they have not been widely used.

**The Disease**

**Clinical Signs**

The incubation period in experimental Newcastle Disease, and probably in natural Newcastle Disease, is usually less than one week. Velogenic strains often produce a rapidly developing weakness and birds may die without showing any other clinical signs. In birds that survive for a longer time there may be gasping breathing due to involvement of the respiratory organs, or muscular tremors and spasms, torticollis and even paralysis. A green diarrhoea is sometimes noted. Mortality is very high.

With strains of lower pathogenicity, respiratory signs dominate the early clinical phase. There is severe respiratory distress with gasping and sometimes coughing. Egg production falls dramatically and in surviving birds signs of nervous involvement may develop. These include paralysis and torticollis. Mortality is variable.

Lentogenic strains tend to infect adult birds without causing severe disease and to produce mortalities in young chickens when other disease agents are present. The respiratory organs are usually affected. Bacterial infections (**Mycoplasma, Pasteurella, E. coli**) and other viral infections (infectious bronchitis, infectious laryngotracheitis) will all complicate the response to infection with Newcastle Disease virus or to vaccination with live Newcastle Disease vaccines.

Clinical signs are modified in immune birds. The chicks of immune hens are protected for some time...
by antibodies that are transmitted through the Yolk. Vaccination is usually protective, although it is easier to protect against fatal disease than against loss of production. Birds whose immunity is sufficient to suppress clinical signs completely may still excrete virulent virus. Many factors have been identified that decrease the immunity of chickens to viral infections and probably all of these apply for Newcastle Disease. Chickens with impaired immunity are more susceptible to virulent virus, excrete greater quantities of virus if they survive, and are less responsive to vaccination. Infectious bursal disease virus is probably the most important of the infectious immunosuppressive influences. In Asia aflatoxins are important environmental factors that impair immunity. They are probably more important for intensive and semi-intensive poultry that may receive contaminated feed than for scavenging poultry. Hypovitaminosis A also increases the susceptibility of chickens to the respiratory lesions of Newcastle Disease. This latter effect is more likely to have a basis in damage to epithelial cells rather than damage to immune cells.

Pathology

The pathological changes in chickens infected with Newcastle Disease virus vary with the pathotype and tropism of the virus and with the immune status of the host. Surprisingly for a disease with such a high mortality rate, the actual pathological changes are usually relatively slight. A haemorrhagic enteritis with necrosis of the intestinal wall is often detected in severe cases. These changes are seen most commonly in the small intestine but haemorrhages in the proventriculus and in the caecal tonsils are also indicative of Newcastle Disease. The lymphoid tissue in Peyer’s patches is swollen early in the disease but later may ulcerate. Respiratory changes predominate in less severe forms of the disease. The nasal passages and the upper respiratory tract contain serous or catarrhal exudates and there may be tracheal haemorrhages. The histological changes in organs with gross lesions are hyperaemia, oedema and haemorrhage. Lymphoid tissue is reduced late in the disease. Necrotic lesions are found in many visceral organs and intense infiltration with mononuclear cells occurs in the respiratory mucous membranes. Encephalitis is found in chickens that had neurological signs during life. None of the lesions found in Newcastle Disease is distinctive to Newcastle Disease. The pathogenesis of Newcastle Disease has yet to be adequately explained. Virulent strains of Newcastle Disease virus are lymphocidal, so that there is necrosis of normal accumulations of lymphoid cells and of the abnormal accumulations that gather during infection. Epithelial cells and endothelial cells seem to be targets for necrotic changes induced by the virus. It is difficult to find explanations at the cellular level for the respiratory distress, nervous signs or loss of egg production encountered in Newcastle Disease.

Human susceptibility to the virulent strains of Newcastle Disease virus must be remembered. The virus causes conjunctivitis, sometimes severe conjunctivitis, in poultry farmers, abattoir staff, vaccinators and laboratory workers.

Distribution

Newcastle Disease is sometimes described as worldwide in distribution, but this is not strictly true. Some countries, and many of the island states of Oceania and the Americas, have no records of infection with Newcastle Disease. A few countries (Australia, New Zealand, Papua New Guinea) recognise only avirulent strains of the V4 type. However, the poultry industries of most countries of the world have problems with Newcastle Disease virus or control the disease by using vaccines. Newcastle Disease is particularly serious in the countries of Asia. Official FAO returns indicate the Newcastle Disease virus is present in all the countries of Asia. In about half the countries of Asia, the presence of velogenic strains of virus is acknowledged. On a world scale, about 20% of countries have velogenic virus. Newcastle Disease, and especially velogenic Newcastle Disease, is an extremely important problem to the countries of Asia.

Records of the distribution of Newcastle Disease are probably not entirely accurate. There is no agreed description of Newcastle Disease virus or of the various forms of the virus and diagnostic and reporting facilities vary greatly between countries. Some reports of freedom from infection may be based on inadequate diagnosis. The use of vaccine also influences reporting. Some countries report only strains of indigenous virus that are more virulent than the vaccines in current use.

There can be few doubts that Newcastle Disease, especially in its velogenic form, is spreading. Legal and illegal trade in domestic poultry or aviary birds seems to account for much of the spread. Very few countries are in the fortunate position of being able to eradicate outbreaks of virulent disease. This requires a well organised veterinary service, a developed and well-controlled commercial poultry industry and a great deal of expense. The virulent virus sets up a permanent home in most newly infected countries. The burden is heaviest in developing countries, where large village poultry industries preclude any attempt at eradication. Vaccination is the only answer in these countries and
as a result Newcastle Disease vaccine is probably the most widely used viral vaccine in the world.

The Immune Response

Haemagglutination-Inhibition Antibodies

Almost all serological studies on Newcastle Disease have involved the haemagglutination-inhibition test and standards for vaccine testing usually specify this test. The test detects antibodies directed against surface antigens but it should not be assumed that the test is directly measuring neutralising antibody. Antibody usually appears during the first week after infection or vaccination. In infected chickens clinical signs may still be apparent when antibody becomes detectable. With standard tests, levels of haemagglutination-inhibition antibody that correlate with protection can be determined. Chickens with these levels of antibody will usually be refractory to infection. No statement can be made about chickens with lower levels of antibody. Some, even if they have no detectable antibody, will resist infection. This is so especially in chickens recently vaccinated but such resistance is also observed after vaccine-induced antibodies have waned. Chickens that are antibody-free and that have had no exposure to virus are not protected.

Most studies on maternally-derived antibody also use the haemagglutination-inhibition test. Antibodies are present in the yolk and are transmitted to the chick, where they have a half life of about 5 days. Maternally-derived antibodies can confer protection and seriously interfere with living vaccines and efficacy tests of Newcastle Disease virus vaccines. An important contribution to the decline of levels of maternal antibody is dilution in the increasing bulk of body fluid in the chicken. Antibodies would be expected to remain longer in the slowly growing progeny of village hens than in commercial chickens.

Uneven levels of maternal antibody are of great epidemiological importance in commercial chickens. Uniform levels of antibody ensure that the entire batch of chickens becomes susceptible to Newcastle Disease and responsive to vaccination over a short period. Variations in levels of antibody produce populations that are not uniformly responsive to vaccination. Repeated, expensive applications of vaccine must then be made.

Other Types of Antibody

Neutralising antibody would probably correlate well with protection, but its presence is seldom measured. Antibody directed against internal antigens of the virus is unlikely to be protective. However, the internal antigens of some viruses reach the plasma membranes of infected cells and may render these cells susceptible to cell-mediated immune responses. Excretory antibody is probably important in Newcastle Disease and more studies of this aspect of the immune system are being made. Secretory IgA is present in lachrymal fluid, saliva, tracheal exudate and bile and probably protects at portals of entry. IgA is produced in response to live vaccines but there may not be a secondary response on revaccination. In the absence of IgA, transudates containing antibody from plasma may also afford effective protection at sites of entry.

Other Forms of Immunity

Immunity to Newcastle Disease is not solely a function of antibody, because immunity is sometimes demonstrable within a short period after vaccination, before antibodies are detectable. Cell-mediated immunity appears to be part of the protective mechanism that evolves in chickens. There also appears to be an immune barrier at mucosal surfaces, probably involving cellular components of the immune system and secretory antibody. There have been reports of resistance developing within hours of vaccination with live vaccine. This is unlikely to result from mechanisms responding to specific antigens. Probably this protection is nonspecific and interferons may be involved.

The Vaccines

Types of Vaccines

Most of the commonly used vaccines are cultures of Newcastle Disease virus containing either lentogenic or mesogenic strains of virus. These are introduced into chickens by some suitable route and they multiply, provoking the production of antibody and probably also of cell-mediated immunity. Even lentogenic vaccines can cause some clinical reaction in vaccinated chickens, especially if other disease agents are present. Mesogenic viruses produce better immune responses but, because of their higher pathogenicity, their use is restricted to mature birds that have already received a course of lentogenic vaccine. The more invasive mesogenic viruses produce a better secondary response, as well as a better primary response, and they are widely used in Asia as booster vaccines.

Strains F and Bl are examples of lentogenic vaccines and Komarov and Mukteswar (or Standard) are mesogenic vaccines. Strain V4 is an example of an avirulent virus that has been used as a conventional vaccine in commercial chickens. The special use of the V4 strain in village chickens is the subject of this volume.

The practice of using killed vaccines to give long-
term protection in laying birds is increasing. These vaccines are chemically inactivated and are often included with an oil adjuvant or some other adjuvant to increase the immune response. They appear to be most effective in birds that have already some degree of immunity because of vaccination with a living vaccine. Killed vaccines are also subject to interference by maternally-derived antibodies. Controls for the production of killed vaccines are often less strict than those for living vaccines.

In most countries vaccines are subject to official controls. Ideally they should be made in specific-pathogen-free eggs from specific-pathogen-free seed material. This assures their freedom from other pathogenic viruses and bacteria. Specific-pathogen-free vaccines require expensive laboratories and stringent methods of production and testing and not all countries have access to them. They are warranted because of the risk of dispersing viruses such as avian leucosis virus or reticuloendotheliosis virus in contaminated vaccines and major pathogens to poultry. Vaccine standards usually impose a seed-lot system to ensure genetic stability of the vaccine. Strict potency requirements ensure that each chicken receives a protective dose of vaccine. A problem in tropical countries is the heat sensitivity of vaccine viruses. Unless a cold chain is maintained from vaccine laboratory to user, the chickens may receive vaccine that is heat inactivated and no longer potent. This problem is greater for wet vaccines than for freeze-dried vaccines.

Routes of Vaccination

Newcastle Disease vaccines are often administered individually to chickens. Catching and handling chickens is an expensive business and vaccination is often done when chickens are being handled for some other reason. Lentogenic vaccines are often given by nasal drop or eye drop to young chicks and mesogenic vaccines may be given by injection to older birds. Methods of mass vaccination are gaining favour. These include the use of aerosol generators or coarse sprays, or the addition of vaccine with suitable additives to drinking water. A problem with many living Newcastle Disease vaccines is that of residual virulence. Most seem capable of causing some disease or slowing growth rates. This is particularly important for virus delivered by spray or aerosol. It is generally considered unwise to use these routes for the primary vaccination if the chickens are not of mycoplasma-free stock. Respiratory disease and even deaths may result.

Some strains of vaccine virus spread naturally between chickens. In some circumstances this is an advantage and vaccinated chickens are used to vaccinate chickens in direct contact. Strain V4 spreads readily by direct contact.

In areas where Newcastle Disease is endemic, it is necessary to vaccinate young chickens. This is difficult. The immune system is not fully developed until some weeks after hatching and the presence of maternally-derived antibodies interferes with vaccination. A particular problem in large flocks is uneven levels of passive antibody, so that the chickens are not uniformly susceptible to disease or receptive to vaccination. Newcastle Disease vaccines are relatively ineffective when compared with other paramyxovirus vaccines (for example, rinderpest or distemper). Newcastle Disease vaccines must be administered on several occasions in high doses and it is difficult to prolong immunity for even the short productive life of a chicken.

Epidemiology

Hosts

Domestic chickens are the important host of Newcastle Disease virus and the one most likely to develop disease. Other domestic birds become infected but, except for turkeys, disease is rare. A variant of Newcastle Disease virus that causes disease in domestic and feral pigeons has recently been recognised. Recovered domestic chickens appear not to become long-term carriers of Newcastle Disease virus.

Very many species of wild birds become infected with Newcastle Disease virus. Again this is a common finding in Asia. Infection is sometimes associated with disease but more commonly Newcastle Disease virus is isolated from clinically normal birds. Some psittacine birds appear to be long-term carriers of the virus.

Human infection with the more virulent strains of Newcastle Disease virus is frequently recorded. The result is an intense conjunctivitis, but transmission from person to person or from person to birds appears not to be recorded.

Methods of Spread

Three situations need to be considered: the spread of Newcastle Disease from infected to non-infected countries, the spread from farm to farm within infected countries, and the spread within an infected flock. Fortunately Newcastle Disease virus appears not to be egg-transmitted, so that this complication of the epidemiological chain need not be considered.

Spread between countries is often mediated by birds-migrating birds, caged birds, racing pigeons or domestic chickens. Quarantine authorities try to guard against such introductions which are often made illegally. Mechanical transfer on fomites is also possible.

Spread within a country is often also attributed
to movement of birds, either domestic poultry or wild birds. The pigeon variant of the virus has been spread with poultry feed contaminated with pigeon faeces. During an outbreak inadvertent transmission by human movement becomes important and transmission of the virus over short distances with the wind occurs.

Aerosols appear to be the chief means of transmission within a flock and strains with tropisms for the respiratory organs spread very rapidly. The respiratory tract acts as a source of virus and as a portal of entry. Birds infected with virulent virus excrete large quantities of virus in the faeces. Infection by ingestion is possible but it requires large amounts of virus and spread by the oral-faecal route is probably slow.

**Village Chickens**

Although Newcastle Disease is enzootic in Asian countries, the situation in individual villages seems to be one of an epizootic disease. The relatively small chicken population of the village is uninfected and unprotected. When virulent virus is introduced, very high mortalities occur and it is often necessary to reintroduce a poultry population. The trade in chickens is probably the source of infection, with affected flocks being salvaged through the markets. The role of wild birds in transmission of Newcastle Disease virus is not known and there has been no explanation for the seasonal prevalence of Newcastle Disease in village poultry that has been observed in some countries.

Village chickens are apparently a source of Newcastle Disease virus for commercial poultry. The free-range chickens gain contact with birds in large commercial farms and especially with the smaller, semi-intensive commercial units that are found in rural areas.

**Eradication**

Velogenic Newcastle Disease outbreaks, even large ones, have been contained and eradicated under favourable circumstances. The techniques used are usually (1) the identification of infected properties, with the destruction of the entire chicken population and disinfection before restocking; (2) enforcement of strict quarantine to limit spread of the disease; and (3) use of vaccines to produce buffer areas with protected birds. There are enormous difficulties involved in slaughtering and burying large numbers of birds, in disinfecting large poultry farms and in vaccinating large numbers of chickens rapidly. Most of the common viricidal chemicals seem to be active against Newcastle Disease virus, and it is common practice to allow disinfected premises to stand idle for several weeks before sentinel birds are introduced.

Veterinary considerations are not the only ones in an eradication campaign. The destruction of birds that are still healthy can be difficult to justify. Surviving birds protected by vaccination are sometimes processed, at a financial loss, to keep processing plants in action. Carcasses from these salvage operations could be a source of further outbreaks. Vaccination alone does not achieve eradication.

**The ACIAR Project**

There would be immense benefit in many countries if Newcastle Disease could be controlled in village chickens. Conventional vaccines, conventionally applied, have not been effective. The Australian Centre for International Agricultural Research has, for the past 3 years, supported a joint project to investigate this problem. Those concerned have been a team at the Universiti Pertanian Malaysia under Professor A. Latif Ibrahim, the Dean of the Faculty of Veterinary Medicine and Animal Science, and researchers from the Department of Veterinary Pathology and Public Health, University of Queensland. The results of this joint project form the basis of this volume.

**Suggested Reading**