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Impact of Avian Viruses

MICHAEL L. PERDUE and BRUCE S. SEAL

Southeast Poultry Research Laboratory
Agriculture Research Service
United States Department of Agriculture
Athens, Georgia 30605

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References
I. THE AVIAN HOST

A. Comparison of Class Aves with Other Vertebrates

In considering the ecology of the avian viruses and their impact on life on earth, it may be useful to first consider the host itself. The class Aves first diverged from the reptiles between 150 and 300 million years ago, depending on which current paleontological interpretations one accepts. Of the vertebrate classes, they are most often compared with the reptiles from which they evolved and with mammals because of their common warm-blooded nature. This shared feature with mammals is probably the most influential with respect to ecology, since a virus adapted to warm-blooded physiology would not fare well in the cold-blooded world, and vice versa. Along these lines, our recent experience is that some virologists think that a bird is a bird, and that if a given virus replicates in one, it will replicate in them all. This is, of course, far from the truth and perhaps should be a starting point for discussing avian virus ecology.

According to fossil records, the class Aves emerged from the extinctions of the Late Cretaceous period 65,000,000 years ago, somewhat bottlenecked, as did the class Mammalia, but since that time they have undergone parallel evolution with mammals and are equally diverse in their own right. Certainly some viruses, such as avian paramyxovirus 1 (of which Newcastle disease virus is the prototype), are infectious for numerous orders of birds. There are also other important avian virus strains such as the gallid herpesvirus 1 (infectious laryngotracheitis) and the Avihepadnaviridae, which appear to be exclusively confined to a single bird family or even genus. It is clear that birds, because of their close association with powered flight, do present a more homogeneous anatomy and physiology than do the class Mammalia (Feduccia, 1996). Whether this affects or specifies the molecular nature of viruses that infect birds is not really known. This feature, however, almost certainly uniquely impacts the natural distribution and ecology of the viruses that inhabit the flying birds. A virus infecting or persisting in an arctic tern could potentially be translocated up to 12,000 miles in a few weeks. Viruses such as some avian orthomyxovirus or avian paramyxovirus strains, which may exhibit subclinical infections, might be shared among a migrating flock of waterfowl and persist for indefinite periods as the flocks move from lake to lake. Along the way the virus might be shared with other birds crossing flight paths. So birds do present unique environments for transmission of viruses.

The commercial practices of humans have further provided unique opportunities for transmission not normally seen for birds. The order Galliformes in particular, which includes domestic and wild fowl; pheasants, quail, and turkeys, has been unquestionably affected. It would be quite safe to say that humans have both determined and upset the ecological balance among members of this order and the
viruses that affect them. Due to continuous breeding practices, live-virus vaccination regimes, and by housing tens of thousands of birds in a single enclosure, situations never encountered in natural settings are created. Whether this has affected the virus–host ecological balance in other orders of undomesticated birds as well is not known; but it would seem highly likely.

One of the most important features of a host–parasite relationship, of course, is the host’s immune defense. While there are similarities shared with respect to the immune system, particularly the dual (humoral and cell-mediated) nature, there are marked differences between cold- and warm-blooded vertebrates and additional significant differences between birds and mammals (Eerola et al., 1987). The discovery of processing and maturation of immunoglobulin-producing lymphocytes was made as a result of characterization of an avian-specific organ, the Bursa of Fabricius (Ratcliffe, 1989). Although functional equivalents exist in mammals, the bursa is a distinct and wholly avian-specific organ. Since several viruses are known to affect this organ specifically, it should be considered a unique ecological niche.

A second significant difference in the immune system of birds is in the apparent genetic content responsible for specifying the avian major histocompatibility complex (MHC). The chicken MHC appears considerably more simple (providing the oxymoron: a simpler complex) than the mammalian MHC (Kaufman and Wallny, 1996). Several alleles have arisen and considerable recombination documented in the mammalian MHCs that thus far have been studied. These are responsible for producing a great variety of class I-, II-, and III-type proteins used in recognition and presentation of antigen. In the chicken, some MHC haplotypes produce only one type of class I protein and there is no evidence for recombination at all (Kaufman and Wallny, 1996). This has led to speculation that the relationship with the avian pathogens has evolved significantly differently from the mammals. One result of this difference may be the occurrence and frequency of either resistance or sensitivity to specific viral infections encountered in chickens (see below). Thus, the class Aves presents several unique features that might ultimately affect the ecology of viruses that infect them.

B. Elements of Avian Systematics

The classification of birds has presented a significant challenge to systematists. The number of species has actually decreased over the years because of the clearer genetic relationships that have emerged. Conversely, additional species have been defined as recognition of convergent evolution has become clearer. Currently, new species are identified at a rate of about two per year. While there remains some disagreement among specialists, most accept the current classification of 30
orders, 174 families, 2044 genera, and 9020+ species (Gill, 1990). Molecular analysis of avian genes for phylogenetic studies is still in its early stages. Restriction fragment length polymorphism (RFLP) analysis and sequence analysis of 12S mitochondria DNA has yielded some molecular phylogenetic information but not enough to gain any insight regarding the viruses of birds (Hedges et al., 1996; Cooper and Penny, 1997; Mindell et al., 1997). Roughly speaking, the flightless orders represented by ostriches, rheas, cassowaries, and kiwis are thought to be the most ancient, while the bewildering array of members of the order Passeriformes (representing 60% of known species and 40% of known families) are thought to be the most recent (Gill, 1990). Trying to determine how long viruses have been associated with various avian groups is of course as impossible as it is with virus–host relationships in any other classes. Orthomyxoviruses, paramyxoviruses, and coronaviruses have recently been isolated from ostriches, rheas, and emus, indicating no absolute barriers in these more ancient birds.

C. Geographic Distribution of the Avian Host

The class Aves is of course distributed worldwide. In addition, there are several hundred species that migrate, sometimes in spectacular fashion. Biogeographers have divided the earth into six distinct faunal regions, which correspond somewhat with the major continental areas (Welty, 1982). These include the Nearctic (North America and Greenland), Palearctic (Asia, Europe, and North Africa), Ethiopian (Central and Southern Africa), Oriental (India, Southeast Asia), Australasian (Australia, New Guinea), and Neotropical (South and Central America). Each area contains its own characteristic birds. In the Northern Hemisphere (Nearctic and Palearctic), most species are migratory, which is not the case in the other areas. The Neotropical has the richest and most abundant bird life, and the Southern Hemisphere has by far the most families represented, as well as the most families peculiar to a given region.

Each year, billions of land birds and waterfowl in North America and Asia head south to South America and Africa, respectively, carrying their viruses with them. The size and scale of these geographic relocations are unmatched by any other land vertebrates. The sea mammals are the only other comparable migrating vertebrates, and they surely cross paths with the birds. In the most interesting putative contacts, purely avian-origin type A orthomyxovirus of at least two different subtypes were isolated from dead and dying seals off the coast of New England in 1980 and 1982–1983 (Webster et al., 1981b; Hinshaw et al., 1984). This represents viral ecology at its most forceful, being effected between two warm-blooded vertebrate orders during their natural migration and geographic interaction.
II. REPLICATION AND PERSISTENCE OF VIRUSES IN THE AVIAN HOST

A. The Embryonated Egg

If one takes a broad look at the virus families associated with avian hosts (Table I), it is actually easier to list the families of viruses that infect vertebrates but that do not yet have a clear avian member. These are the Iridoviridae, Arenoviridae, African swine fever-like viruses, and Filoviridae. A similar comparison of families that do not contain a mammalian member yields only the Birnaviridae. So, in one sense, the mammalian host might be considered more virus-friendly, rather than the alternative. Still, many investigators think of bird tissues, in particular the embryo, as being an ideal medium for identifying new viruses. Just from an experimental and practical, rather than a natural, point of view, the avian host has played a tremendous role in our understanding of viral ecology. Many of the most important findings in virology have been made utilizing the chicken embryo and in chicken cell cultures. The egg also continues to provide an abundant and important substrate for the production of veterinary and human vaccines.

If we think of ecology as the study of organisms and their relationship with their environment to include all other organisms, we most certainly encounter a unique relationship with viruses. Unlike higher pathogens, viruses really do not mate, communicate, or colonize (except in the very broadest stretches of the imagination); they simply parasitize and replicate. We try and make them more familiar by defining higher organism-type genetic alterations as "evolution," when in truth the viruses may simply be adapting to the evolutionary pressures encountered by, or within, its host. Obviously, the host is central to the viruses' lifestyle and must be considered a major part of virus ecology. In this sense, information gathered on various viruses as they replicate in embryos or embryo cells, in the absence of immune pressure, should only be considered "natural" for those viruses that are transmitted vertically. The embryo or cell culture then can only provide a window on the natural ecology of the organism in which the immune system is not a factor. In ecological terms, only the natural state of the virus-host relationship becomes important. Viruses being parasites, these relationships more often than not eventually result in a disease state.

B. Unique Tissues and Viral Replication

It is not possible to distinguish the molecular biology of avian viruses from that of non-avian viruses on the basis of features unique to the avian system. However,
### TABLE I

**Families of Viruses Infecting Birds**

| Virus family | Representative member(s) | Primary host(s) isolation | Range of hosts (4) | Pathogenesis (5) | Transmission (6) | Ecological/economic impact (7) |
|--------------|--------------------------|---------------------------|--------------------|------------------|-----------------|-------------------------------|
| **dsDNA**    |                          |                           |                    |                  |                 |                               |
| **Poxviridae** | Fowlpox, Canarypox      | Domestic poultry, turkeys, pigeons | >60 species, and 20 families of birds; distribution worldwide | Mild cutaneous form and more severe diphtheric form; mortality may reach 100% in canaries | Common in domestic poultry; slowly spreading cutaneous form; Respiratory, mechanical — insects | Low to moderate in poultry; can be devastating in avianries |
| **Herpesviridae** | Infectious laryngotracheitis (ILT); Marek's disease virus (MDV) | Domestic poultry: chickens, turkeys, ducks, pigeons | Several strains of herpes in many orders, including falcons, cormorants, psittacines, cranes, quail | ILT: Acute respiratory, & milder enzootic MDV: classical and acute forms — oncogenic; DPV: acute enteric disease in ducks, geese and swans | Lateral — respiratory and ocular; virus may be reactivated from latency and transmitted; MDV can spread from feather follicles | Quite high; MDV and ILT two of the major viral diseases of commercial poultry; virulence increasing in field isolates of MDV |
| **Adenoviridae** | Duck plague virus (DPV) | Ducks | Limited | I. Widespread in fowl; II. Primarily Galliformes; III. Ducks, geese, laying chickens | I. Low: poultry; high: quail. II. Variable in turkeys, chicks. III. Low | Vertical transmission very important mode | Low to moderate in poultry; different in different countries |
| **Papovaviridae** | Fringilla papilloma virus; Budgerigar fledging disease (polyoma-like) | Finches; perhaps African green parrots; Budgerigars | Typical papillomas on legs and feet | Assumed same as mammalian papillomas | None or very low; occasional problems in avianries |

*continued*
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| ssDNA | Paroviridae | Goose parovirus (GPV); Muscovy duck parovirus | Geese, Muscovy ducks | Only Geese and ducks thus far | Derzyn's disease; age dependent; high mortality in young birds; only seroconversion in adults | Vertical transmission to goslings most serious; horizontal also important | Restricted thus far to commercial geese, duck operations |
| Circoviridae | Chick anemia agent virus; Psittacine beak and feather disease virus | Chickens, pigeons, psittacines | Chickens, pigeons, psittacines, doves, canaries, finches | All strains immunosuppressive thus far; low mortality in chickens; high in pigeons and psittacines | Horizontal and vertical; mixing of racing pigeons important mechanism for PCV | Difficult to assess because of immunosuppressive effect and secondary infections |
| Reverse-transcribing DNA/RNA viruses | Hepadnaviridae | Duck hepatitis B virus (DHBV); heron hepatitis B virus | Ducks, herons | Limited to ducks and herons | Very low; no known association with hepatocarcinomas | Primarily vertical | Essentially none |
| | Anatohepadnaviridae | | | | | | |
| | Retroviridae | Lymphoid leukemia virus (LLV)/sarcoma virus group | Chickens, pheasants | Other Galliformes | Lymphoid leukemia; various other neoplasms | Vertical and horizontal; present in large proportion of flocks | Variable; sporadic significant problems yield significant economic loss |
| | Genus: Avian type C retroviruses | Reticuloendotheliosis virus | Turkeys, ducks | Turkeys, ducks, chickens, quail, pheasants | | | |
| dsRNA | Reoviridae | Avian orthoreoviruses, avian rotaviruses, avian-associated orbirviruses | Chickens, turkeys | Numerous strains isolated from turkeys and chickens; numerous isolations — other orders | Variable, generally low in commercial birds; predominantly arthritis/enosynovitis | Vertical transmission important as "seed" to promote horizontal transmission | Significant although usually low-performance rather than high-mortality |
| | Birnaviridae | Infectious bursal disease virus (IBDV) | Chickens, turkeys | Antibody and other surveillance suggest widespread distribution | Variable; inapparent to acute; highly pathogenic strains in Europe; immunosuppressive | Horizontal, highly contagious; "natural" hosts unknown because of widespread vaccine use | Worldwide distribution; significant poultry pathogen |

continued
|                    | sRNA (-)                                                                 |                    |                    | sRNA (+)                                                                 |                    |                    |                    |
|--------------------|--------------------------------------------------------------------------|--------------------|--------------------|--------------------------------------------------------------------------|--------------------|--------------------|--------------------|
| **Orthomyxoviridae** | Avian influenza virus (AIV) subtypes H1-H15; N1-N9                       | Ducks, shorebirds, | Strain dependent;  | Subclinical to highly     | Horizontal only, highly       | Low path form varies |                    |
|                    |                                                                          | turkeys, chickens  | can include diverse | lethal; apparently subtype  | contagious, oral and         | from insignificant to  |                    |
|                    |                                                                          |                    | array, e.g., rats,  | dependent; HP = systemic   | respiratory; documented      | mildly significant,   |                    |
|                    |                                                                          |                    | but not unlimited   | infection                  | transmission to mammals      | HP form: high impact  |                    |
|                    |                                                                          |                    |                    |                            | and humans                   | and potential as OIE list A|                    |
| **Paramyxoviridae** | Newcastle disease virus; avian paramyxoviruses (PMV) 2 and 3             | Waterfowl; chickens; pigeons; exotic birds, turkeys | Very widespread, many orders of birds susceptible | Three broadly defined pathotypes of NDV: mild to highly lethal | Horizontal only, highly contagious, oral/respiratory; documented transmission to humans | Very significant worldwide; sporadic in nature; vaccination has influenced isolates; lethal form: high impact, OIE list A disease |
| **Rhabdoviridae**   | Turkey rhinotracheitis virus, avian pneumovirus                          | Antibodies in a few species including wild turkeys, chickens | Pathogens of mammals that may be transmitted to birds | None except under experimental conditions | None, appears to only be acquired from infected mammals during heavy outbreaks | None |
| **Bunyaviridae**    | Too numerous to list                                                     | Several            | Over 50 members of the family isolated from more than 20 bird species | No characteristic pathogenesis; many infections detected by Ab | All arthropod-borne viruses; various invertebrate vectors | Not well understood if any impact at all |
| **Coronaviridae**   | Infectious bronchitis virus (IBV); Turkey coronavirus                    | Chicken            | Very limited; some evidence in other Galliformes; worldwide | Variable; some can yield 10-20% mortality; respiratory symptoms predominant Enteric disease | One of the most rapidly transmitted poultry respiratory viruses | Very significant; vaccination has generated new strains; new antigenic variants continue to arise Virulence increasing? |
|    |    |    |    |    |    |    |    |
|----|----|----|----|----|----|----|----|
| 1  | 2  | 3  | 4  | 5  | 6  | 7  |    |
| Togaviridae | Eastern equine encephalitis virus (EEEV) | Horse; pheasants, turkeys, ducks, pigeons, passerine birds | Arbovirus; *Culiseta melanura* mosquito main vector; wild Passeriformes | Neuropathic; high mortality in pheasants and young poultry | Arbovirus vector; birds appear to only transmit to insects, except EEE, which can transmit bird to bird | Minor, except in affected game-bird operations |
|   | Western EEE and 10 others, from naturally infected wild birds | Various wild birds | Wide | Insignificant |
| Flaviviridae | Turkey meningoencephalitis | Turkeys | Unknown but limited | Neuropathic; variable mortality; egg production drop returns to normal following disease | No known arthropod vector | Minor |
|   | 16 or more isolated from naturally infected wild birds | | | |
| Astroviridae | None isolated | None isolated | Unknown but seen by EM only in turkey pouls | Moderate enteric disease associated with weight loss | Unknown; detectable only by EM thus far | Unknown but minor |
| Picornaviridae | Avian encephalomyelitis virus (AEV) | Chickens, pheasants, quail, turkeys | Limited, not found in wild birds | Encephalomyelitis | Oral, horizontal; vertical also important; natural isolate enteric | Significant in commercial chickens, only in chicks of unvaccinated stocks |
|   | Avian nephritis virus (ANV) | Chickens, turkeys | | Enteric disease and nephritis | Oral, not completely understood | Insufficient |
|   | Duck hepatitis virus (DHV) | Chickens, turkeys | Other hosts; experimentally no natural | Gross hepatitis and opisthotonos; high mortality in young birds | Respiratory; contagious; becomes endemic in affected flocks | Only significant in commercial duck populations |
|   | Domestic ducks | | | | | |
| Caliciviridae | Chicken calicivirus | Chickens | Unknown | Enteric disease shown using purified virus preparation | Unknown | As member of enteric disease complex, holds some importance |
| (tentative assignment) | | | | | | |

*Information collected primarily from three sources: Calnek et al. (1997), McFerran and McNulty (1993), and ICTV (1995).*
there are some important distinctions with which viruses must deal. One dramatic difference between birds and mammals is body temperature. On average, birds operate at 3–4°C higher than mammals, and most can readily regulate their temperature, some dropping body temperature as much as 10°C during the night (Gill, 1990). While this certainly could influence such things as rates of viral enzyme activity, polymerase fidelity, or protein stability, there are no situations documented in which a particular virus group is restricted to class Aves solely on the basis of body temperature.

It is possible to distinguish some important receptor-specific distinctions unique to avian systems. One example is found in the influenza type A viruses. The glycosidic linkages associated with sialic acid residues on the avian versus mammalian cell surface serves to restrict the strains of viruses able to replicate. Influenza virus hemagglutinin (HA) proteins bind to sialic acid residues on the surface of the host cell. Although there is no absolute barrier, those viruses that replicate well in avian cells have a receptor binding pocket on the surface of the HA that has a preference for the α-2,3 sialyl–sugar linkages abundant in bird tissues. Those viruses that replicate well in mammalian cells have a preference for α-2,6 linkages more prevalent in mammalian cells (Rogers and Paulson, 1983; Murphy and Webster, 1996). There are probably many more receptor specificities associated with other avian virus infections, particularly among the herpesviruses, where host range is narrowly dictated.

Another example of virus-specified tissue tropism unique to birds would be infectious bursal disease virus (IBDV; genus Avibirnavirus), which has “evolved” an affinity for the bursa, a bird-specific organ. The other two known genera of Birnaviridae infect fish and invertebrates. Since there are as yet no mammalian members, it is tempting to speculate that IBDV is bird specific because of its evolved affinity for the bursa.

Air sacs are also uniquely avian structures. The bird lung is a fixed tissue incapable of expansion like mammalian lungs. The air sacs are a series of extensions of the respiratory system that expand with the musculature of the body cavity and allow the large-scale rapid oxygen transfer needed for powered flight. The air sac system is extensive throughout the bird, even encroaching into bone tissue; some birds have as many as nine distinct air sacs. Many viruses replicate and cause disease in this unique organ system, and there are examples of apparent preferences by some viruses for air sac tissue over other respiratory tissue. Finally, feathers, the most notable and prominent distinguishing feature of the class Aves, provide a unique niche for at least two three viruses — avipox, Marek’s disease, and psittacine beak-and-feather disease virus — which can replicate in and are spread from feather follicles (Biggs, 1985; Tripathy and Reed, 1997).
C. Effects of the Immune System on Virus Replication and Spread in Birds

As mentioned previously, the immune system of the intact bird is a critical feature in the establishment of ecological relationships between many viruses and hosts. As the immune system plays a major role in the relationships, they will be covered, but there are some extraordinary examples that deserve their own mention. Marek's disease, caused by an alphaherpesvirus, is most commonly associated with lymphomas developing relatively early in the life of a chicken. The initial infection in MD is a respiratory infection probably initiated in macrophages. A typical field infection would then progress through the following phases in a bird:

Initial lytic infection $\Rightarrow$ Latency $\Rightarrow$ 2nd lytic infection $\Rightarrow$ Oncogenesis

Latency is established primarily in lymphoid cells, and mostly in activated T lymphocytes. In susceptible birds, the latent state progresses to a second round of lytic infections at multiple sites in the bird. Interestingly, at this point the feather follicle epithelium is the only site where complete virus replication occurs and becomes a significant source of environmental infectious virus (Calnek and Witter, 1997). Concomitant and permanent immunosuppression occurs in the affected bird. The disease then progresses into a lymphoproliferative phase in susceptible birds that can range in severity depending on the virus strain and breed of chickens. Some breeds have shown natural resistance to this progression, and, although the mechanism of resistance is not completely understood, it involves primarily lymphoid tissue and is dictated mostly by genes involved in the immune response (Venugopal and Payne, 1995). It should be clear from this scenario that the immune system in this host–parasite relationship plays a critical role in the ecology of Marek's disease virus.

Infectious bursal disease virus, as mentioned earlier, is a virus that replicates exclusively in lymphoid tissue. The virus can be detected replicating in the bursa of Fabricius and within circulating lymphocytes as early as 4 hours after infection of a chicken. It causes acute degeneration of various lymphoid tissues within the first day of infection and results in a severe, albeit age-dependent, depression in the humoral immune response, being most dramatic in very young birds. Interestingly, the infection does not suppress B-cell responses to the viral antigens themselves; in fact, there is stimulation of proliferation of B cells committed to anti-IBDV antibody production (McFerran, 1993). One may only speculate as to what role, if any, this may play in the viral ecology or replicative cycle, but the immune system is once again a major participant in this host–parasite relationship.
Finally, the effects of vaccination programs on the ecology of avian viruses cannot be overemphasized. In one sense, we have an ongoing experiment where humans control the type of viruses to which certain species of birds are exposed. Since live viruses generally yield much better immune responses, they are employed most often. In the case of the single-stranded RNA viruses, noted for their ability to rapidly mutate and avoid the immune system, this has the effect of artificially challenging the immune system, creating selection pressure between host and parasite that would not normally occur. This may be effective in the short run, protecting against disease, but the long-term effects are unknown.

III. THE MAJOR GROUPS OF VIRUSES THAT INFECT BIRDS

Summarized in Table I are some of the most important features of relationships of various viruses with their avian hosts as well as the wide variety of relationships that exist. It is not feasible to list all the interesting attributes for each virus–host relationship, but the table presents a variety of relationships that will be covered in more detail in the following sections. As such, the table should not be taken as the final word on each member virus. For example, in the case of turkey meningoencephalitis virus, a Flavivirus, reduced egg production is listed under pathogenesis. Reduction in egg production is a common feature in many virus infections of poultry, and while listing it under pathogenesis somewhat stretches the meaning of that word, this clinical sign is one of the most important aspects of that disease in turkeys.

Although there is variation in the economic or ecological impact of various viral groups from year to year and among geographic sites, the “Top Ten” list of virus groups exhibiting routine significant impact on commercial poultry worldwide (not necessarily in order of impact) are paramyxoviruses (Newcastle disease); coronaviruses (infectious bronchitis); herpesviruses (infectious laryngotracheitis; Marek’s disease; duck enteritis); reoviruses (viral arthritis); picornaviruses (avian encephalomyelitis); adenoviruses (egg drop syndrome); retroviruses (lymphoid leukosis); orthomyxoviruses (avian influenza); poxviruses (fowlpox); and birnaviruses (infectious bursal disease). The circoviruses (chick anemia) could likely be included in the above list, except it is not yet known to what extent the viral infection alone influences morbidity and mortality (see below).

What may not be obvious from Table I is that if one searches for viruses in a given avian species one will likely find them. In some of the virus families listed, investigators were forced to clearly separate the disease-causing virus in question from accompanying “contaminant” viruses, which may or may not have influenced the original disease manifestation. There appear to be many viruses of birds
that in certain ecological conditions and in certain species may be considered "normal flora" and are not associated with disease. These, obviously, are less interesting to any funding agencies and consequently do not receive much research attention. No one really knows to what extent their transmission and persistence in avian populations affect their own ecology or that of their hosts.

The Office International des Epizooties (OIE), the principal world organization for animal health, provides listings of the most serious infectious diseases of animals (OIE, 1996) and divides them into two groups: list A diseases, which "includes those diseases that spread rapidly, the scope of which extends beyond national borders" and "have particularly serious socioeconomic or public health consequences"; and list B diseases, which include those "that are considered to be of socioeconomic and/or public health importance within countries." Of the avian viral diseases listed above, only highly pathogenic avian influenza and velogenic Newcastle disease are in list A; Marek's disease, infectious bursal disease, infectious bronchitis, duck enteritis, and infectious laryngotracheitis are in list B. The only avian disease in OIE's list and not on our top 10 list is duck hepatitis, which is a complex of diseases caused by at least three virus families, and generally limited to country-specific origins.

IV. IMPACT OF VIRAL TRANSMISSION AMONG MEMBERS OF THE CLASS AVES

A. Commercial Poultry Production

The ecological impact of viruses of birds ultimately interests us as Homo sapiens, perhaps only to the extent that we are affected. In this respect, there is no question that the major impact thus far has been on raising birds as a food source for our species. Ecologically speaking, this impact could have very significant consequences when one considers that poultry provide the most widely used protein source in the world. Thus, we will consider for the most part how viruses affect this food source. The most significant and widespread infections of wild birds will be discussed as they are encountered relative to commercial and domestic birds.

The most imminent and significant human public health concerns with regard to bird viruses appear to be twofold:

1. The potential relationships with type A orthomyxoviruses that have become at least partially adapted in a totally nonpathogenic state to some avian orders. There is compelling evidence that these viruses may also replicate in pigs and re-assort with pig and/or human strains of influ-
enza, yielding new variants capable of replicating and causing disease in humans. They also find their way into commercial poultry, sometimes with devastating consequences. With the recent documented transmission of a lethal avian influenza virus from commercial poultry to humans, these ecological relationships take on new significance.

2. The presence of a large reservoir of arboviruses in wild birds, some of which, when transmitted by invertebrate vectors to mammals, cause disease.

Beyond these two examples, other relationships are less directly important to human public health. Other avian-origin viruses are capable of replicating in and sometimes causing mild disease in humans, but there is obviously not room in one chapter to cover each in detail.

B. Infectious Laryngotracheitis and Other Nononcogenic Herpesvirus Infections

1. Infectious Laryngotracheitis

Infectious laryngotracheitis (ILT) is a respiratory disease almost exclusively of chickens. Infections in turkeys and pheasants have been reported, but surveys have yielded no wild bird reservoir or other domestic poultry reservoir (Cranshaw and Boycott, 1982). Based on this and the knowledge that ILT apparently exhibits little antigenic heterogeneity, it has been proposed that through proper husbandry practices and appropriate vaccination techniques the disease could be eliminated from commercial poultry (Bagust and Johnson, 1998). The virus is a member of the Alphaherpesvirinae subfamily and is identified taxonomically as gallid herpesvirus I. The disease is almost exclusively respiratory, with no systemic involvement. The severity of disease can vary from significant mortality (70%) in young birds to an inapparent infection of adult birds. There are age-dependent effects on the pathognomonic signs, and there do appear to be strain-specific virulence differences. However, different isolates do not exhibit sufficient genetic heterogeneity thus far to identify specific virulence factors (Bagust and Guy, 1997). The most interesting aspect of ILT is its capacity for persistence in infected birds and flocks showing no disease signs. This persistence is most likely due to establishment of the latent state and recrudescence. Numerous studies have demonstrated re-isolation of virus many months after initial infection, and one more recent study demonstrated reactivation of latent virus due to stress factors (Hughes et al., 1989). This latency achieved by herpesviruses could certainly be considered a unique ecological state, and most herpesvirus infections in birds are associated with its establishment.
2. Duck Viral Enteritis

Duck plague, also known as duck viral enteritis (DVE), is caused by an alpha-herpesvirus classified as anatid herpesvirus-1, which infects free-living and domestic ducks, geese, and swans (Sandhu and Leibovitz, 1997). The disease is acute and often associated with high morbidity and mortality. The virus has a worldwide distribution and has caused numerous documented outbreaks in free-living anatids. The first documented North American outbreak was in commercial ducks on Long Island, New York in 1967 (Leibovitz and Hwang, 1968), and since that time sporadic reappearance of the virus in commercial and wild populations has occurred. Major outbreaks in free-living birds along the Mississippi flyway and a large epornitic in South Dakota in 1973 killed tens of thousands of wild ducks and geese (Brand, 1987). Vertical transmission and recrudescence of latent virus has been established experimentally in mallard ducks but has not been demonstrated in wild waterfowl. Species susceptibility may vary among various waterfowl, although more than 30 species have been shown to be naturally or experimentally infected and virulence differences among DVE strains have been demonstrated.

3. Herpesvirus Infections of Pigeons and Wild Birds

The other notable avian herpesvirus infection occurs in pigeons. The virus is taxonomically designated as columbid herpesvirus I and is antigenically indistinguishable from natural isolates taken from wild falcons and owls (Vindevogel and Duchatel, 1997). The causative virus is antigenically distinct from ILT, MDV, herpesvirus of turkeys (HVT), and the anatid herpesvirus I. The disease associated with infection by columbid herpesvirus I is a major cause of growth retardation and bad performance in homing pigeons, though mortality is generally low. This virus, like ILT, becomes latent, reappears, and is shed in asymptomatic birds and flocks. Other antigenically distinct herpesviruses have also been isolated from cormorants, quail, and storks. Kaleta (1990) has proposed the division of these various herpesviruses into eight antigenic groups. The host specificity for each group varies, but in general they appear to be strictly adapted to the host of origin (as exemplified by the gallid herpesvirus I). Gallid herpesvirus II and HVT will be discussed in the following section.

C. Avian Tumor Viruses

1. Herpesviruses

The impact of transmissible neoplastic diseases of poultry has been quite variable over the years. Prior to vaccination, losses to Marek's disease were often
devastating, and even in marketable flocks condemnations due to lymphomas at processing plants could reach 2%. Lymphomas caused by MDV and retroviruses are still the most common viral neoplastic diseases of poultry, and a recent increase in mortality and evolution of more virulent MDV strains indicates that the impact of these viruses will continue to be felt (Witter, 1996). Marek's disease is caused by a herpesvirus that has two very similar relatives: a second nononcogenic serotype and the herpesvirus of turkeys (HVT). These are sometimes classified as serotypes 1–3, respectively, of the gallid herpesvirus II strain. They share common antigens that distinguish them from the nononcogenic herpesviruses but can be distinguished on the basis of antigenic differences (Calnek and Witter, 1997). Only the oncogenic MDVs (serotype 1) cause significant problems in commercial poultry. The herpesvirus of turkeys is ubiquitous among commercial flocks and quite prevalent in wild turkeys but has not been directly associated with disease. The serotype 2 strains were originally thought to be nononcogenic apathogenic MDV isolates until they were serologically distinguished from the original isolates. The type 2 serotypes are associated with subclinical infections in chickens, although not as prevalent as turkey strains.

The HVT isolate is a very interesting and important isolate, as it was used (and is still used) in vaccine formulations against Marek's disease in chicken flocks. It has been very effective at protecting flocks against lymphomas and thus correctly billed as the first anticancer vaccine. Marek's disease is relatively well controlled by using mixtures of primarily serotype 2 and 3 isolates in vaccine formulations. However, this vaccination program may ultimately extract a price. Shown in Figure 1 is a diagrammatic representation of the evolution of virulence in MDV strains associated with changing vaccine formulations. The extent to which these formulations have influenced the evolution of virulence is not proven, but certainly the association is undeniable. The 1990s have brought an increase in incidence of Marek's disease cases, and the presence of these acutely virulent strains raises concerns for the future. What is clear is the role of humans in the generation of these strains. There is evidence that the commercial housing practices developed in the 1950s and 1960s resulted in generation of strains that were oncogenic and that this rapid evolution of virulence in the last 40 years is probably due to human control of commercial bird populations.

2. Retroviruses

The avian retroviruses have one of the most interesting histories of all of the avian viruses. The first transmissible lymphomas were demonstrated in 1908 by Ellermann and Bang (1908) and the first cell-free transmissible solid tumor by Peyton Rous three years later (Rous, 1911). The etiologic agents of both of these diseases were later shown to be members of what is now known as the avian leukosis virus–avian sarcoma virus complex (ALV–ASV) of related retroviruses.
Fig. 1. Representation of field and laboratory observations in the United States on the development of virulence in Marek's disease (MD) isolates. The turkey herpesvirus (HVT) vaccine was first introduced in 1970 to protect against MD. Then in 1983 a bivalent vaccine was introduced, followed in 1995 by the Rispens strain vaccine. There is an apparent relationship between introduction of these vaccines and development of virulent phenotypes among recovered field outbreak isolates. M = moderate, V = virulent, VV = very virulent, VV+ = very virulent plus. Graciously provided by Dr. Robert Silva, Avian Disease and Oncology Laboratory, USDA, East Lansing, Michigan.

Scientists investigating this interesting group of viruses have garnered more Nobel Prizes (six) than with any other group. Because of their relative simplicity in genetic content and their close association with the genetic character of their host, they have provided a bountiful model for the study of oncogenesis. These are RNA-containing viruses that replicate via an intermediate DNA stage that is most often incorporated into the host genome. The integrated viral genomes serve as templates for production of new progeny genomic RNA molecules and the mRNAs needed to make new viral proteins (Coffin, 1996). In the process, these viruses transform the host cell into a tumor cell. There is a significant array of viral subtypes and relationships that exist between the host and avian retroviruses and numerous reviews that may be consulted (Crittenden, 1981; Swanstrom and Vogt, 1990). There are several viral subgroups, based on antigenic differences alone, in the surface envelope glycoproteins. Viral subtypes have also been grouped on the basis of whether the viruses rapidly induce neoplasia because of the presence of a viral oncogene, or whether they induce slow development of tumors due to their integration into the host genome and subsequent activation of cellular oncogenes.
In commercial poultry, the predominant problems are caused by the latter, the slow-inducing lymphoid leukosis viruses (LLVs). The sarcoma-, myeloblastosis-, and erythroblastosis-inducing strains cause only sporadic problems. Additionally, it has been calculated that losses due to LLV because of poultry performance decreases are actually greater than those due to the lymphomas. Still, these viruses continue to cause condemnations at slaughter and must be distinguished from the more rapidly forming MDV-induced lymphomas.

Two other oncogenic avian retroviruses pose significant problems and possess much wider host ranges than the LLV–sarcoma complex. The relatively new subgroup “J” has been characterized in Europe as causing significant myelocytoma and endothelioma. In contrast to the LLVs, subgroup J viruses have a high tropism for cells of the myelomonocytic series but a very low tropism for bursal cells (Arshad et al., 1997). A related subgroup J virus has been identified in broiler-breeder flocks in the United States as well (Smith et al., 1997). Additionally, of note are those retroviruses of the reticuloendotheliosis virus (REV) group. Infection with members of this group only rarely results in disease, and then disease most commonly occurs only in the hosts from which REV was first isolated: turkeys. Still the REV group is predicted to have significant potential for causing problems in poultry (Witter and Johnson, 1985), and the wide host range of the virus group has prompted speculation regarding potential as a public health risk. There are, in fact, data demonstrating antibodies to the virus in human and other mammalian sera (Johnson et al., 1998).

D. Coronavirus Infections

1. Chickens

Coronaviruses contain a large positive-sense RNA genome of approximately 30 kb. Members of this virus family infect both mammals and birds (Cavanagh et al., 1994). Infectious bronchitis, caused by a *Coronavirus*, infectious bronchitis virus (IBV), is one of the major poultry viral diseases of worldwide economic importance. It is also one of the most rapidly spreading avian respiratory diseases known (McMartin, 1993). The virus is antigenically variable owing to a high mutation rate in the surface glycoprotein S gene. New antigenic variants of IBV continue to be isolated from various geographic regions. Thus far, it has not been possible to determine the number of distinct IBV subtypes, but there are at least six (Siddell, 1995). Strains can differ in their virulence and tissue tropism, but in general the disease is a rapid-onset respiratory distress that can cause significant mortality in young birds. In established flocks, the infection is often associated with growth retardation and reduction in egg production that may be exacerbated by other
respiratory pathogens. Estimates of a 10 to 20% loss in market value have been made for a typical outbreak in a flock. Vaccination is employed to control the disease, and an interesting related feature is the demonstration that vaccine strains can undergo recombination with wild-type strains. Consequently, new IBV antigenic variants of the S1 gene emerge with characteristics of both viruses (Cavanagh et al., 1992; Wang et al., 1993). IBV is also an excellent example of a virus exquisitely adapted to its host, as it is not found naturally in any other reservoir. Chickens seem to be the only reservoir, and the virus is capable of persisting in some manner within populations and later being transmitted to naive flocks. Evidence suggests the mode is primarily airborne transmission. In controlled studies, birds in houses 115 feet away from an experimentally “seeded” house were infected via aerosol transmission (McMartin, 1993), and circumstantial data from natural outbreaks suggest transmission over distances of several hundred yards (Cumming, 1970).

2. Turkeys

Coronaviral enteritis of turkeys, also known as bluecomb disease, may also be species specific since chickens, pheasants, and quail do not exhibit any disease following inoculation with a strain of virus that is virulent for turkeys (Hofstad et al., 1970; Larsen, 1979). Coronaviruses have been isolated from ratites with enteric disease in zoological collections, but the relationship of these isolates with the turkey coronavirus (TCV) has not been investigated (Frank and Carpenter, 1992; Kennedy and Brenneman, 1995). Transmission of TCV appears to be restricted to the fecal-oral route, although cell-free lysates of the bursa from infected birds can be used to transmit the agent orally. Among turkey flocks, the primary mode of transmission of coronaviral enteritis is via contaminated personnel and equipment. However, since TCV is excreted in fecal material and is very stable, it is conceivable that wild birds may serve as vectors for the agent. Morbidity is usually as high as 100%, with mortality becoming as high as 50% in an infected turkey flock. Mortality among pouls may be much higher with increased numbers of secondary bacterial gastrointestinal infections contributing to severity of disease.

Turkey coronavirus also shares features reported for mammalian hemagglutinating coronaviruses and is closely related by sequence and antigenic crossreactivity to bovine coronavirus and a human coronavirus isolate (Verbeek and Tijssen, 1991). This close relationship suggests recent interspecies transmission of the coronaviruses. While no etiologic agent has been pinpointed, a bovine origin coronavirus has been implicated in an emerging enteric disease of turkeys called poult enteritis mortality syndrome (PEMS) (Barnes and Guy, 1997).
E. Arbovirus Infections

The arthropod-borne viruses (arboviruses) present a unique challenge to evaluating ecological virus–host relationships. This grouping includes members from several virus families, six of which have members isolated from birds: Togaviridae, Flaviviridae, Reoviridae, Arenaviridae, Bunyaviridae, and Rhabdoviridae. Of these, only the Togaviridae and Flaviviridae have strains that have caused documented disease in commercial poultry and game birds. Although difficult to assess in feral populations, isolates from the remaining virus families as well as several isolates from the Togaviridae and Flaviviridae are not associated with any pathology in birds.

Of the Togaviridae, the genus *Alphavirus* contains the encephalitic strains causing eastern equine encephalitis (EEE), western equine encephalitis (WEE), and a closely related wild bird isolate — the Highlands J virus (HJV). Pheasants have been the primary targets of significant outbreaks of EEE. Signs of infection are primarily but not exclusively neural, and mortality rates have reached 80% in some natural outbreaks (Ficken *et al.*, 1993; Eleazer and Hill, 1994). Economically significant outbreaks of disease due to EEE virus in turkeys have occurred in Wisconsin, with severity of the disease decreasing with increasing bird age. Significant outbreaks have also been recorded in chukar partridges, ducks, and chickens. WEE has been only rarely associated with disease in avian species, and the closely related HJ virus appears to be the Eastern United States equivalent to WEE. HJV has caused severe neuropathogenic outbreaks in chukar partridges and has been associated with infections in turkey flocks resulting in acute reduction in egg production (Wages *et al.*, 1993). Of course, these encephalitic viruses also cause disease in humans and horses.

Another interesting alphavirus, Ockelbo virus, related to Sindbis virus, has been implicated in causing arthralgia and rash in humans following its isolation from mosquitoes collected during the outbreak. These viruses are transmitted by mosquitoes among bird populations, which may act as the vector for transmission between humans and avian species. Ockelbo virus, therefore, is apparently maintained in an enzootic cycle involving birds and mosquitoes with transmission to other hosts such as humans. Antibodies to Ockelbo virus, either experimentally or naturally infected, have been detected in Passeriformes, Galliformes, and Anseriformes (Lundstrom *et al.*, 1992; Lundstrom and Niklasson, 1996). Viremia in the absence of disease resulting from infection with Ockelbo has also been demonstrated in these bird groups. Given the widespread occurrence of antibodies to these encephalitic alphaviruses, it seems logical to conclude that birds in many cases act as “natural” and reservoir hosts.
The only flavivirus thus far associated with disease in birds is the Israel turkey meningoencephalitis virus. Infected birds exhibit neurological dysfunction and occasional significant mortality. This virus has also been identified in turkeys in South Africa.

F. Infections with Double-Stranded RNA Viruses

1. Reoviruses

Double-stranded segmented RNA viruses are unique and intriguing. The distinguished virologist Dr. Wolfgang K. Joklik, when asked what in the world he thought they meant in the grand scheme of biology, replied (and I paraphrase), “they represent an evolutionary step forward in the establishment of the ideal genetic material.” The reoviruses have fascinated virologists for some time. They have an unusual and complex replication strategy, are able to undergo reassortment of their genes, and are curious in that they retain their infecting subviral cores as their RNA replication template. Reoviruses are also quite stable outside the host, remaining viable for up to a year at room temperature (Nibert et al., 1996). The mammalian strains have a wide host range but are found without any associated clinical signs, the origin of the name REO (respiratory and enteric orphan) telling most of the story. In poultry, several antigenic subtypes have been identified, and the virus can be classified based on serotyping and virulence, but there is no unified typing scheme as yet (Kawamura and Tsubahara, 1960; Robertson and Wilcox, 1986). The most severe and common pathology associated with reoviruses is arthritis–tenosynovitis, although associations with other clinical syndromes including respiratory and enteric disorders have been described (Rosenberger and Olson, 1997). Often, the clinical states are influenced by the presence of other pathogens. Arthritis is a significant problem in birds but primarily only in young chicks and turkey poult. Other Reoviridae in birds include several members of the genera Orbivirus (arboviruses; see below) and Rotavirus, which have been associated with a runting–stunting syndrome in chickens.

2. Infectious Bursal Disease Virus

The Birnaviridae are a relatively recently characterized family of viruses that contain two double-stranded segments of RNA and have no mammalian members thus far (ICTV, 1995). They were difficult to classify for many years because of their cell-associated nature and slow replication in cell culture systems. Currently, two serotypes (1 and 2) are accepted, with significant antigenic variation and
numerous proposed subtypes within each serotype (McFerran et al., 1980; Jackwood and Saif, 1987). Chickens are the only animals known to develop disease and lesions when naturally infected by avibirnaviruses. Both serotypes are distributed worldwide, but serotype 1 strains are the only ones associated with pathogenicity and immunosuppression. The bursa is the primary target organ, and strains of differing virulence have been identified. The disease is most significantly manifested when young birds are infected and permanent immunosuppression results. This sets the stage for subsequent severe viral and bacterial infections later in life. Interestingly, IBD is an example where maternal antibodies derived by either vaccinations or natural infections provide significant immune protection. Highly virulent strains of these viruses exist in various countries worldwide, and there are indications that new virulent variants do arise in the face of immune pressure (Chettle et al., 1989b).

G. Adenovirus Infections

Avian adenoviruses are double-stranded DNA viruses containing 30–40 genes. These viruses can be loosely divided into three groups based on antigenic relationships of internal proteins (McFerran, 1997), although the three groups have not been officially recognized by the ICTV. The avian group I adenoviruses include at least 12 serologically distinct types, all of which have been isolated from mildly or asymptomatic poultry. The type species is known as the CELO (chick embryo lethal orphan), or Phelps strain, or F1 (fowl) strain. There are also numerous isolates from other avian species plus electron microscopy and immunological evidence that the type I aviadenoviruses are widely distributed in birds. By themselves, these viruses present no particular clinical problems in commercial poultry, but they are thought to cause significant problems in mixed infections with immunosuppressive viruses such as IBDV and chick infectious anemia virus (CIAV). A virus virtually indistinguishable from the CELO strain known as quail bronchitis virus (QBV) can be devastating in commercial quail operations, causing as high as 80% mortality (DuBose and Grumbles, 1959; Montreal, 1992). Virus isolations and significant antibody levels in wild quail suggest that the virus may present disease problems in nature (King et al., 1981), although there are no documented cases or epizootics.

The group II aviadenoviruses include turkey hemorrhagic enteritis virus (HEV), pheasant marble spleen disease virus (MSDV), and the avian adenovirus splenomegaly (AAS) of chickens. These three agents are serologically indistinguishable but induce differing clinical manifestations in the different species. Infections caused by this virus group appear to target lymphoid tissue, often resulting in
Immunosuppression, and there are strain-specific differences in virulence among the various group II isolates (Pierson and Domermuth, 1997). HEV reached epidemic proportions in the 1960s and still causes significant problems in turkey-producing states in the United States and elsewhere. MSDV is a significant pathogen in confinement pheasant operations, causing significant economic losses. AAS is virtually ubiquitous among chicken flocks in the United States, in which case mild respiratory signs and splenomegaly are occasionally associated. The syndrome is similar to the disease state observed in pheasants, but in general AAS virus causes no significant problems among chickens. Evidence indicates that these group II avian adenoviruses are limited to the order Galliformes, and that wild bird populations (even wild turkeys) are unaffected.

The more interesting group III adenoviruses first appeared in 1976 associated with a distinct clinical manifestation called egg drop syndrome (EDS), in which egg production decreases and thin-shelled or shell-less eggs are produced. The disease has caused significant egg production losses mostly in the Eurasian and Australian-Pacific poultry markets. A virus named EDS76, which has been found associated with this syndrome, may have been originally introduced via a contaminated vaccine, but it seems clear now that sporadic cases are initiated by introduction of the causative virus from domestic and wild waterfowl, mostly ducks and geese. When endemic in flocks, the virus is transmitted vertically and exhibits a latent phase, which is reactivated in laying hens, usually after egg production begins. The virus initially appears to replicate in lymphoid tissues but rapidly moves to the oviduct, where replication causes inflammation and production of aberrant eggs. Unlike other avian adenoviruses, the group III strains do not replicate in the intestinal mucosa. It is likely that EDS76 virus or very similar strains are present ubiquitously in wild ducks and geese, but rarely appear to be associated with disease (McFerran, 1997).

H. Poxvirus Infections

The avipoxviruses are widely distributed throughout the class Aves, having been isolated from some 60 species representing 20 avian taxonomic families. The avipoxviruses are responsible for economically important disease problems in commercial poultry and aviaries (Tripathy, 1993). They may cause a slowly developing cutaneous disease with low mortality or, conversely, significant mortality, and generalized infections when in the diphtheritic form on mucosal surfaces of the respiratory tract and associated areas. These large DNA viruses replicate in the cytoplasm of the cell, where they form characteristic inclusion
bodies within rapidly proliferating nodular lesions. The poxviruses may be transmitted by mechanical means such as introduction from poultry workers into abrasions in the skin of uninfected poultry. There is also real evidence for transmission of the disease by mosquitos and other vectors such as mites in close conditions, where the number of diseased birds is high. The avipoxviruses can also apparently establish a latent state and be naturally or chemically induced to reactivate (Kirmse, 1967b). Cutaneous lesions containing infectious virus persistent for more than a year have also been documented in wild birds (Kirmse, 1967a). Variant strains of avipoxviruses have since been isolated from previously vaccinated flocks that were experiencing significant mortality from the diphtheritic form of the disease (Tripathy and Reed, 1997). This suggests that, similar to Marek’s disease, vaccination against poxviruses may ultimately lead to escape of more virulent forms of the viruses. The avipoxviruses are also considered one of the most promising DNA virus vectors for delivery of recombinant poultry vaccines, and poxvirus-vectored vaccines against Newcastle disease and avian influenza have been licensed.

I. Avian Encephalomyelitis and Other Avian Picornavirus Infections

Avian encephalomyelitis is primarily a disease of young chicks caused by a picornavirus. The disease was quite economically important prior to initiation of live-virus vaccination. The host range is very limited (order Galliformes), and there is only one virus serotype. The natural isolate is enterotropic and is transmitted horizontally (orally) and vertically. There is a gradient of pathology dependent on the age of infection of young chicks. Pre-immune chicks from non-immune parents will generally die if infected within 1 to 2 days of hatch. If infected between 2 and 8 days of age, they may live but exhibit significant nervous involvement (encephalomyelitis). If infected beyond that age, they may exhibit enteric pathology but not neural signs. At adulthood or full immunocompetence, they may be infected but refractory to any clinical signs. So the immune status of the host in this case is very important in affecting the course of the viral replication (Calnek, 1997).

Another avian picornavirus, distinct from AEV, is the avian nephritis virus (Shirai et al., 1991). This virus is similar to AEV in that it is primarily a problem in very young birds and has a very limited host range. As the name implies, a distinct clinical syndrome is associated with the agents, but it is has not yet been determined how extensive infections are in commercial poultry. Finally, another picornavirus, duck hepatitis 1 (DHV-1), has caused significant problems in com-
commercial duck operations. There are still unknowns with regard to the overall importance of DHV-1, and there are additional virus-induced types of hepatitis disease with at least two others often encountered.

J. Other Avian Enteric Infections

The most significant cost involved in raising birds for food sources is feeding them. Consequently, diseases that affect the feed–protein conversion ratio will directly affect the cost of marketable birds. As such, enteric disease, even when nonlethal or mild in nature, can affect the performance of food-source birds. In recent years, investigators have identified rotaviruses in chickens, astroviruses in turkeys, and enterovirus-like particles in several avian species associated with enteric diseases. Many of these have been associated with significant pathogenesis, particularly in mixed infections where immunosuppression occurs, with subsequent decrease in marketability due to weight loss (Barnes, 1997).

K. Chicken Infectious Anemia

The virus designated chicken infectious anemia virus (CIAV) is a single-stranded circular DNA-containing virus, tentatively classified with two similar agents in a new family: Circoviridae. The agent has only recently been recognized, purified, and characterized, and its unequivocal role in economically important disease is not yet fully established. Purified virus inoculated into young chicks results in severe anemia and immunosuppression, but inoculation of 2- to 3-week old birds results in little if any pathology (Yuasa and Imai, 1986). The virus has been associated with adult anemic conditions, however, in conjunction with other viral and bacterial infections and may thus play a significant role. The agent is widespread in commercial poultry flocks worldwide, and infection with the virus has been statistically related to a decrease in overall growth and performance (Chettle et al., 1989a). The extent to which two other tentative members of the family Circoviridae — psittacine beak-and-feather disease virus (BFDV) and porcine circovirus — are related to CIAV is under question, and these stated taxonomic relationships may differ in the future. BFDV has proven to be a significant pathogen in aviaries and commercial in psittacine birds to the extent that vaccines are now routinely administered. Recent evidence also suggests that Circovirus particles can be detected by EM and isolated from several other wild and captive bird species. Consequently, the Circoviridae may emerge as a more significant disease-causing agent in the near future.
L. Caliciviruses

The Caliciviridae is a family of small single-strand positive-sense RNA viruses with a polyadenylated genome. Virus-like particles resembling caliciviruses have been isolated from a variety of wild-bird and captive-raised species. A chicken calicivirus has been replicated in cell culture and caused apparent gastrointestinal disease in specific pathogen-free day-old chicks (Cubitt and Barrett, 1985). Intestinal contents of goldfinches with hemorrhagic enteritis have been found to contain calicivirus-like particles and gastrointestinal disease associated with caliciviruses has been reported in guinea fowl and pheasants (Gough et al., 1985). Caliciviruses were originally isolated from marine mammals and have caused disease in both domestic and feral swine due to consumption of uncooked garbage containing seafood. Interestingly, caliciviruses have been detected in pelagic birds, such as the white tern (Poet et al., 1994). Calicivirus isolations such as these lead to the speculation that wild sea birds may be important in the transmission of these agents across large areas or to other animals.

M. Parvoviruses

Parvoviruses are the smallest of the DNA-containing viruses, carrying a single-stranded genome of about 5000 nucleotides. They cause or are associated with three infections in birds (Kisary, 1993). In wild and domestic geese and Muscovy ducks, Derzy's disease refers to a syndrome that had been variously called goose influenza, goose hepatitis, gosling enteritis, and infectious myocarditis in different countries. This collection of names gives some indication of the variety of signs associated with Derzy's disease. The virus, which can be transmitted horizontally and vertically, induces differing pathologies depending on the age of the bird and, in the case of hatchlings, the level of maternal antibodies. An interesting pathology often associated with infection of older birds is the virtually complete loss of feathers. The extreme stability of the parvoviruses makes control of this disease difficult in commercial operations worldwide, and the disease can result in 100% mortality in young hatchlings.

In chickens and young turkeys, parvoviruses have been associated with runting stunting syndrome (RSS), as have other agents. Experimental inoculations have indicated that the associated viruses, which are distinct from the goose viruses, can cause significant pathology, but the extent to which these viruses participate in the RSS is not yet established (Trampel et al., 1983; Decaesstecker et al., 1986). Another parvovirus, the avian adeno-associated virus is almost always found associated with adenovirus infections in poultry. The avian adeno-associated viruses are grouped with their mammalian counterparts in the Dependovirus genus, although they are serologically unrelated. The avian dependovirus appears
to contribute to disease only in the sense that it can affect multiplication of the associated adenoviruses (Yates and Piela, 1993).

N. Newcastle Disease and Other Paramyxovirus Infections

Newcastle disease virus (NDV), classified as avian paramyxovirus-1, contains a single-strand negative-sense RNA genome of 15 kb containing coding sequences for six genes. The virus infects all bird species tested to date, including free-living and domestic species. One panzootic outbreak of the disease is thought to have originated in Asia, with subsequent spread to Europe, with outbreaks of disease first reported in poultry during the 1920s in Java, Indonesia, and Newcastle-upon-Tyne, England. Worldwide dissemination of the disease, particularly during the 1960s and 1970s, has been attributed to increased international trade of both commercial poultry and pet birds. This led to development of inactivated and live-virus vaccines for commercial poultry. The transmission of infectious NDV may occur by either ingestion or inhalation, and this knowledge is the basis for mass-application vaccination procedures during poultry production.

Isolates of NDV are grouped into three main pathotypes depending on the severity of disease that they cause (Alexander and Parsons, 1974). Mildly virulent "lentogenic" viruses may cause unnoticeable infections in adult chickens or a mild respiratory distress and are used extensively as live-virus vaccines. "Mesogenic" NDVs are of intermediate virulence and cause respiratory distress, with mild infections of various organs detectable only by histopathology. Highly virulent viruses that cause severe morbidity and mortality are termed "velogenic." Velogenic viruses can manifest themselves as neurotropic or viscerotropic forms of Newcastle disease with extensive systemic replication throughout a bird. Virulent forms of NDV can replicate within cultures of most avian and mammalian cell types without the addition of trypsin, while lentogens require added proteases for replication in cell culture. The presence of dibasic amino acids at the proteolytic cleavage site (PCS) of the viral fusion protein and the ability of cellular proteases to cleave the fusion protein of various pathotypes specify the molecular basis for NDV virulence. Fewer basic amino acids are present in the fusion protein cleavage site of lentogenic NDV than is the case for mesogenic or velogenic isolates. The presence of the increased number of dibasic amino acids in the fusion protein PCS sequence of NDV allows for systemic replication of these more pathogenic viruses in the host (Nagai et al., 1976).

Although the principal concern with NDV is its effect on poultry production, it may have severe consequences in other free-living avian species. Major outbreaks of Newcastle disease have occurred in North American cormorants during the summers of 1990 and 1992, and again in 1997. Outbreaks during 1990 and 1992 occurred in the north central United States and south central Canada, while in 1997
Newcastle disease occurred among cormorants of the western United States and Canada. Mortality in young nestlings in some areas was as high as 80 to 90%, and the affected birds had characteristic neurotropic lesions (Heckert et al., 1996). During the 1992 outbreak in cormorants, an unvaccinated North Dakota turkey flock became infected with NDV, resulting in high mortality. Using nucleotide sequence analysis, the virus causing disease in turkeys was proven to be the same virus isolated from afflicted cormorants in the central United States and Canada. The cormorant virus was also phylogenetically related to other known NDV isolates of psittacine origin (Seal et al., 1995) that had caused a major outbreak in Southern California poultry during the early 1970s that resulted in a depopulation of two million chickens (Utterback and Schwartz, 1973).

Illegal importation of pet bird species into the United States continues to be a source of highly virulent NDV and certainly may play a role in spread of viruses that threaten commercial poultry worldwide (Panigrahy et al., 1993). What role free-living birds play in spread of NDV is unclear. Although persistent infections of chickens by NDV do not appear to occur, the virus’ persistence in poultry flocks may result from virus reintroduced from wild populations. Also, different bird species vary in their level of susceptibility to NDV. Ducks, geese, and certain psittacine birds do not exhibit signs of disease when infected with highly virulent NDV, while other psittacine species may have high mortality. Persistent infections have been demonstrated in various psittacine birds, with virus isolations noted up to a year following experimental infection of parrots with velogenic NDV chicken isolates (Erickson et al., 1978). Although psittacine birds have been directly linked as a source of NDV highly virulent for gallinaceous birds, such as chickens and pheasants, no studies have shown direct isolation of NDV from feral psittacines.

Newcastle disease occurred in racing and show pigeons during the 1980s in both western Europe and North America. The outbreaks in western Europe were linked to contaminated feed, and disease was controlled in both areas via vaccination with mildly virulent NDV commonly used for poultry. The virus isolated from these birds varied somewhat from traditionally virulent NDV in having only one set of dibasic amino acids in the fusion protein cleavage site. Increased virulence for poultry subsequently occurred only after passage in chickens (Collins et al., 1994). These examples demonstrate the fact that variant forms of NDV may arise in different bird species and that free-living birds may be a constant source of viruses that affect both domestic and wild birds.

Vaccination programs against NDV for the most part have been effective at controlling the virus in commercial poultry. However, all of the vaccine strains available today, while effective against lethal disease, share less sequence identity with currently circulating disease strains. This is effectively illustrated in Figure 2, which may also be considered a useful example for other RNA-containing viruses. The phylogenetic tree demonstrates the relationship between current
strains and the vaccine strains based on the sequence of the fusion protein. It shows that vaccine strains are relatively far removed from the recent isolates coming from wild birds. The future consequences of such heterologous vaccination approaches are unknown. The same scenario might unfold for NDV, as has occurred in the attempt to control Marek’s disease where the immune status of vaccinated flocks promotes generation of novel antigenic variants with new virulence characteristics.
O. Avian Influenza

Avian influenza (AI) presents one of the most interesting ecological relationships between birds and their viruses. Its ecology has been reviewed in depth (Webster et al., 1992; Hinshaw et al., 1980), but AI presents such a complete picture of a virus with multiple impacts on several species that it must be included in this chapter. The type A orthomyxoviruses are essentially bird viruses. The infections in birds can range from clinically inapparent with minimal serologic response, to a devastating systemic disease that can result in 100% mortality within a matter of days. There are 15 identified subtypes of AI viruses based on the hemagglutinin (HA) protein antigenic structure and nine subtypes based on the neuraminidase (NA) structure. These two genes code for the predominant surface glycoproteins, which are embedded in the lipid bilayer of the viral envelope. These are only 2 of 10 genes coded for by the virus. The virus' genetic material is contained on eight separate negative-sensed single-stranded RNA segments ranging from 890 to 2450 nucleotides in length.

All of the HA and NA viral subtypes have been identified in feral waterbirds, and it has been proposed that these birds act as a "natural" reservoir for the virus (Webster et al., 1992; Slemons and Easterday, 1977). Determination of the phylogenetic relationships of several genes from several subtypes of AIV collected from wild birds indicated that the general rate of evolution in the avian reservoir is low compared to the rate of evolution observed in human and other mammalian strains of type A orthomyxoviruses (Gorman et al., 1992). Other recent studies, however, have shown that the mutation rate of the HA gene and the NS gene even in wild birds approaches that seen in human strains (Garcia et al., 1997; Suarez and Perdue et al., 1998). Measurement of clinical signs among infected migrating waterbirds is, of course, a difficult task. Thus far, only a single instance of severe clinical signs has been associated with free-living birds — a lethal outbreak in terns in South Africa in 1961 caused by an H5N1 strain (Becker, 1966). Given the recently measured mutation rates, and the appearance of this severe lethality in a wild bird population, it must be considered that AIVs do continue to evolve in feral birds (indeed 15 subtypes have arisen already!). There is no reason to believe that the present count of 15 subtypes will be the final tally.

While some have proposed that the AIV strain in wild birds causes no disease problems as a result of "evolutionary stasis," without question the virus has dramatic effects when it leaves this proposed reservoir. In addition to the fixed influenza populations in pigs and horses, avian strains can directly infect mammals and have been identified in whales, seals, and mink (Lang et al., 1981; Berg et al., 1990). The dramatic association with seals in 1980 and 1982 mentioned earlier clearly points out the potential impact of AIVs. This avian reservoir then serves as a sort of base for the viral "biological invasions" that are a part of interspecies
transmission. Ecologically and economically, the transmission of these AIV subtypes to commercial poultry has perhaps yielded the most important impact. The situation is most clearly played out in Minnesota each year. Due to the large number of lakes in the state, migratory waterfowl, primarily Anseriformes (ducks, geese), frequent the area in large numbers seasonably. Nearby commercial turkey operations suffer infections nearly every year, particularly in the cooler fall months, caused by different influenza subtypes of different virulence (Halvorson et al., 1985). In severe years, the associated costs due to turkey mortality, as well as performance and egg production losses, can reach several millions of dollars (Poss and Halvorson, 1986).

In chickens, introduction of influenza viruses from waterfowl has been more devastating. In the northeastern United States, the H5 subtype caused the first large-scale outbreak of highly pathogenic AI in numerous flocks in 1983. Twenty-three million birds were destroyed at a cost of more than $65,000,000 in order to contain the infection. Clinically, the disease was indistinguishable from the disease originally described as “fowl plague” in 1927 in Europe (Eckroade and Silverman, 1986). Today we know that all of the classical “fowl plague”-type outbreaks have been associated exclusively with only two subtypes: H5 and H7. Evolution to virulence in these subtypes has been closely associated with accumulation of basic amino acids at the proteolytic cleavage site of the hemagglutinin protein (Bosch et al., 1981; Webster and Rott, 1987). In order for AIV strains to be infectious, the HA protein must be cleaved into HA1 and HA2 subunits, which subsequently allows structural rearrangement and exposure of a protein sequence needed to fuse the viral envelope with the plasma membrane of the target cell (Klenk et al., 1975; Skehel et al., 1995). Isolates of low pathogenicity lack multiple basic amino acids and are only cleaved by trypsin-like extracellular proteases. These proteases are abundant on the mucosal surfaces of the respiratory tract and gut, so the viruses replicate unrestricted at these sites. The highly pathogenic (HP) forms, however, have additional basic amino acids, which are recognized by the intracellular furin-like proteases ubiquitous in bird tissues (Rott et al., 1995). Thus, in birds, these viruses are able to escape the respiratory tract and infect a wider variety of internal tissues and organs. This is one of the most important of the virulence factors (Webster and Rott, 1987). Only two subtypes have been shown to accumulate these basic amino acids: H7 and H5. These subtypes appear to do so by either base substitution or by insertion events (Wood et al., 1993; Perdue et al., 1997). Nucleotide insertion events appear to be the most common mechanism, and Table II and Figure 3 illustrate what is presently known about occurrence of these HP virus isolates in commercial poultry. The HP isolates, with only two exceptions, have additional inserted basic amino acids within the well-conserved region surrounding the cleavage site. From the data in Table II and Figure 3, it may be easily surmised that both the number of HP isolates and the number of basic amino acids at the cleavage site are increasing.
TABLE II
Cleavage-Site Sequence Conservation among Type A Influenza Hemagglutinin Proteins and Insertions in HP Strains

| Subtype | HA1              | HA2              |
|---------|------------------|------------------|
| 1       | GLRNVPSIQSR      | GLFGAIAGFIE      |
| 2       | GLRNVPQIESR      | GLFGAIAGFIE      |
| 3       | GMRNVPEKQTR      | GLFGAIAGFIE      |
| 4       | GMRNIPEKATR      | GLFGAIAGFIE      |
| 5       | GMRNVQRETR       | GLFGAIAGFIE      |
| 6       | GLRNVPQIETR      | GLFGAIAGFIE      |
| 7       | GMRNVPENPKTR     | GLFGAIAGFIE      |
| 8       | GLRNTPSVEPR      | GLFGAIAGFIE      |
| 9       | GLRNVPAVSSR      | GLFGAIAGFIE      |
| 10      | GMRNVPEVQGR      | GLFGAIAGFIE      |
| 11      | GPRNVPAIASR      | GLFGAIAGFIE      |
| 12      | GLRNVPQVQDR      | GLFGAIAGFIE      |
| 13      | GLRNVPASNR       | GLFGAIAGFIE      |
| 14      | GMRNPGKQAK       | GLFGAIAGFIE      |
| 15      | GMKNVPEKIRTR     | GLFGAIAGFIE      |

Selected HP Isolates

| Subtype            | Selected HP Isolates |
|--------------------|----------------------|
| H5                 |                      |
| A/Tk/Ireland/83:   | PQRRKRKQR \(\downarrow\) GLF... |
| A/Ck/Puebla/94:    | PQRRKTR \(\downarrow\) GLF... |
| A/Ck/Queretaro-20/95: | PQRRKRKTR \(\downarrow\) GLF... |
| A/Hong Kong/157/97: | PQRERRRKKR \(\downarrow\) GLF... |
| H7                 |                      |
| A/Tk/England/199/79: | PEIPKKREKR \(\downarrow\) GLF... |
| A/Ck/Queensland/95: | PEIPRKRRKR \(\downarrow\) GLF... |
| A/Ck/Pakistan/95:  | PEIPKRRKRR \(\downarrow\) GLF... |

The amino acids surrounding the hemagglutinin protein cleavage sites of a representative member of each of the 15 subtypes of avian influenza viruses are shown above. Subtypes 7, 10, and 15, which cluster together in a phylogenetic tree, all have five amino acids between the conserved proline and arginine; the remaining subtypes have four. Highly pathogenic isolates (subtypes H5 and H7) more often than not, have insertions of arginines and lysines, increasing the length of the cleavage site and making the hemagglutinin accessible to ubiquitous proteases. This has the effect of greatly increasing the tissue distribution and virulence of the virus.
The avian influenza viruses are distributed worldwide. In addition to the United States, outbreaks of highly pathogenic AI have occurred in Mexico, Canada, Europe, Asia, and Australia. In most cases, there is some sort of connection between the affected flocks and nearby waterfowl. The extent to which the reservoir of viruses exists in waterfowl is not really known. Surveys have shown that, in addition to the viruses being widespread, the various subtypes increase and decrease in prevalence over successive years. The order Charadriiformes (shorebirds and allies), in addition to Anseriformes, has been shown to carry AIV strains (Kawaoka et al., 1988), and the extent to which AIVs are carried in other orders has really only been superficially explored. Molecular and phylogenetic evidence have clearly shown that these segmented viruses share various genes back and forth within the populations of circulating virus strains (Garcia et al., 1997). They are also capable of donating genes through genetic reassortment to viruses in swine and those genes ultimately end up in humans (Webster et al., 1993). Add this capacity to the known (albeit rare) transmission of purely avian influenza strains directly into mammals and one creates a potential ecological bonanza for the virus, and potential nightmares for new hosts.
VI. IMPACT OF TRANSMISSION OF AVIAN VIRUSES OUTSIDE THE CLASS AVES

A. The Variety of Unknowns

As advanced as our study of viruses has become, there are still a variety of unknowns with regard to the extent to which avian viruses infect other vertebrates. It would not be unreasonable to suggest that, because of their mobility and longevity of existence, that the class Aves may have played a critical role in distribution of viruses to other classes. In the case of the avian orthomyxoviruses, phylogenetic evidence points to recent introduction of these viruses from birds to mammals. Following introduction, the natural mutation and evolution of the virus produced strains that now appear to be adapted to their new hosts. There are swine, equine, and human strains of type A influenza viruses that do not replicate well outside their respective host species. If birds are indeed responsible for us coming down with the flu today, we know of no reason why they might not have participated over the eons in the establishment of other purely mammalian diseases. Of course, one could easily argue the opposite relationship, but, intuitively, birds do present an ideal mobile vector, particularly for the enterically transmitted viruses.

In addition to the diseases discussed here, there is a growing group of emerging diseases or diseases of as yet unknown etiology in commercial poultry (Saif, 1997). Many of them have virus particles clearly associated with the syndrome, but only limited research and characterization has been carried out thus far. It is probably safe to assume that the future will continue to bring new avian diseases and bring to light new or undiscovered avian viruses.

B. Birds, Viruses, and Insects

The relationships existing among birds, insects, and viruses is one area that should be explored in more detail by increased research efforts. In free-living birds, the large number of apparently innocuous infections with Bunyaviridae, Togaviridae, and Flaviviridae suggest that birds may act as an ecological reservoir for maintenance of these virus populations. From a virocentric point of view (if there is such a thing), having a potentially highly mobile population of susceptible hosts on which transmission vectors may feed would be advantageous. It would provide a mechanism by which to transfer viruses over large geographical distances where they could then be transmitted by new related or unrelated vectors, thus increasing host range. Of course, one runs the risk here of assuming that the virus would be ecologically improved by extending its replicative capacity in new
hosts. This may not be a valid assumption. For example, if variola virus or human poliovirus type 1 had been exploiting this strategy, they made a bad choice in extending their host range into humans!

From one human vantage point, birds provide a useful monitor for detection of arboviral diseases in a given area. Sentinel chickens are actually in use today along the East Coast of the United States to gauge the extent to which some mosquito populations are carrying eastern equine encephalitis and St. Louis encephalitis viruses. The future is perhaps the most important aspect to consider. What viruses other than the orthomyxoviruses may someday establish a similar relationship where transmission to a mammalian intermediate or even direct transmission may allow introduction into the human population?

C. Transmission to Mammals and Humans

One fundamental unanswered question is whether birds, acting as reservoirs for arboviruses, should be considered an important ecological niche for those viruses. There is no evidence of which we are aware to indicate either yes or no. There have been no documented transmissions of arboviruses from birds to mammals without the insect vector in nature, however, so at this point wild birds could be considered dead-end hosts for the arboviruses. In commercial poultry during outbreaks of the alphavirus EEEV, there is no evidence of infection of workers in close contact with infected birds. If, however, a bird provides the necessary reservoir of EEEV that infected the human, then this bird becomes very important. But there are no data that as yet identify the bird as the required reservoir for disease transmission to human.

Newcastle disease virus provides an interesting new disease problem in humans that has only arisen as a result of increased vaccination of birds. A live-virus vaccine is available for control of NDV that is administered by aerosol spray. In a small number of cases where precautions have not been taken, vaccinators can contract a conjunctivitis caused by the vaccine. This outcome has been seen in the heavy poultry-producing areas of northern Georgia, on a common enough basis now, to be easily recognized by ophthalmologists. There is usually no seroconversion to the virus in these cases, and they are not particularly serious infections. There is also suggestive evidence in the form of measured seroconversion that poultry workers occasionally may be subclinically infected with avian coronaviruses and avian retroviruses.

The evidence for direct infection of humans with avian influenza viruses is growing. Human strains have classically included only three subtypes (H1–3). Until recently, the only other strains shown to cause disease in humans were of the H7 subtype. Conjunctivitis caused by purely avian H7 subtype viruses has
been reported on two occasions (Kurtz et al., 1996; Webster et al., 1981a). The most disturbing set of events, however, was the more recent highly publicized influenza outbreak in Hong Kong. A purely avian H5 subtype virus was isolated from some 18 patients, 6 of whom died, from May through December of 1997. The index case, a 3-year-old child, in May followed a highly pathogenic outbreak of avian influenza that had just previously occurred in chickens in Hong Kong and its environs. The child had been exposed to ill birds at a day care center, and it was clear that the recovered virus was essentially the same as that recovered during the chicken outbreak. Considerable efforts were made to determine whether the virus was a contaminant and whether it was replicating in the child. The evidence strongly suggested that it was indeed replicating (Subbarao et al., 1998). Subsequent to this event, in November–December the remaining confirmed cases were reported and an intense effort was mounted to determine exactly how this virus was transmitted. It is clear now that the H5N1 viruses infecting humans in Hong Kong 1997 were all of avian origin (Suarez et al., 1998). There is limited serologic suggestion of human-to-human transmission but no genetic evidence of adaptation to humans. This case was touted as a premier test run for the next predicted influenza pandemic. Whether this outbreak represents a simple dead-end zoonotic transmission or whether these purely avian influenza viruses can become fixed in the human population is a matter for conjecture. The avian H5 and H7 influenza strains have been the only natural influenza strains thus far to unequivocally cause systemic lethal infection in any species owing to the unique structure of their HA protein (see Fig. 3). A major fear is that by adding such HA subtypes to a population of mammalian viruses a whole new class of virulent strains might be created. Our experience in working with numerous highly pathogenic and nonpathogenic strains has been one of very little or no evidence for human infection in the 25 years that scientists and technicians have spent working with hundreds of different stains. But our experience has also been that, when one attempts to confine influenza viruses by setting biological rules for them, they usually find a way to break them.

VI. CONCLUSIONS AND FUTURE CONSIDERATIONS

If ecology is the study of the relationship of organisms to their environment, for bird viruses, the active, pertinent, environment is always within the bird and its tissues. While one cannot discount the effects of the environment outside the host, there are no positive effects on an avian virus life cycle outside the host of which we are aware. That is, there are no activation events outside the avian host of which we are aware; only events of inactivation. Certainly, avian viruses, as all viruses, have evolved survival strategies to allow passage from host to host, and some are
much more refractory to environmental inactivation than others. But without really knowing which, if any, "evolutionary direction" viruses are taking, it is impossible to determine whether a large herpesvirus of 150 genes is ecologically more fit than the enterovirus with five genes!

The relationship of birds and insects in the transmission and life cycle of the arboviruses is poorly understood. Until this recent transmission of H5N1 influenza strains to humans, this relationship appeared to be the only significant one in which there is interaction among a genetically unaltered virus, an avian host, and a non-avian host. As mentioned earlier, other documented cases of avian-to-mammalian viral transmission are Newcastle disease infections of humans and influenza A infections of mammals and humans. There is also serological evidence for avian retrovirus and avian coronavirus infections. In the case of Newcastle disease, the documented infections are mostly minor conjunctivitis. In the case of influenza, discussed earlier, the avian viruses most often acquire RNA segments from other sources before they are established in a new host. Thus, in general, the impact of avian viruses on public health might currently be considered small, but clearly the potential exists for significant future impact.

A major interesting question arises when evaluating virulence of avian-origin viruses. Conventional wisdom seems to be suggesting that virus entry into naive host populations is more likely to result in a general decrease in virulence as the virus adapts to the new host (Morse, 1994). This may be true under truly "natural" conditions; but what happens under human-dictated conditions such as vaccination and by defining the host population through breeding and housing? In the case of Marek's disease, we see an example of virulence increasing in the face of continued vaccination against the virus (Fig. 1). Whether this is occurring as a result of the vaccination or a combination of factors, the fact is that the population of Marek's disease herpesviruses in nature is becoming more virulent. The vaccination programs for Newcastle disease utilize vaccines whose genetic compositions are becoming farther and farther removed from the virulent strains circulating in wild fowl (Fig. 2). This may not bode well for future control of virulent strains in commercial poultry.

In the case of avian influenza viruses, we have seen the number of highly virulent outbreaks increase in recent years, often following prior circulation of a nonpathogenic precursor, and we have seen concomitant changes in genetic structure related to virulence (Fig. 3). Again there are unknowns in this system, but the fact remains that we are seeing more virulence as the nonpathogenic AIV subtypes replicate in commercial poultry settings. Thus, this naive commercial population, unlike the waterfowl hosts to which the virus has adapted, appears to allow generation of heretofore unencountered virulence phenotypes. Similar scenarios appear to be playing out as more virulent infectious bronchitis strains and infectious bursal disease strains appear worldwide. One must be cautious, then, in working strictly under the previously mentioned virulence-decrease paradigms for
mammalian viruses. These have been suggested mostly by the experiences with artificial introduction of rabbit papilloma viruses in Australia or where new introductions occur as human encroachment ensues (such as in the recent cases of Ebola virus or monkey poxvirus infections). In these cases, it was proposed that virus transmission results first in high virulence for the host followed by subsequent adaptation and attenuation.

Finally, it may be dangerous to attempt to confine avian viruses to some of our more "logical" inferences based on Darwinian evolution. One paraphrased definition of evolution is "moving from a prior more primitive (or less fit) state to a current more advanced (or more fit) state." It is difficult, for us at least, to say that any avian viruses are following such a progression. Additionally, other than use as molecular biological vectors, viruses in general have not been shown to provide anything positive to the ecology of any other organisms. The future may yet reveal such relationships, but, for now, ridding ourselves of these fascinating parasites by continuing such policies as those resulting in the eradication of smallpox and polio still appears to be our most prudent course.

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