The Newcastle virus may attack man; evidence of this is unequivocal. Yet such important considerations as incidence and severity of human Newcastle disease are vague and unreckoned. First reports described the human infection as a benign process, characterized by transitory conjunctivitis. Subsequent contributions have, however, presented findings suggestive that Newcastle disease of man is frequently more than a localized conjunctival reaction, and that it is encountered as an infection of the central nervous system, often confused clinically with poliomyelitis. Human respiratory and gastrointestinal disorders have also been ascribed to the agent of Newcastle disease.

The Newcastle virus is widespread in nature. The disease in the apparent natural host—the domestic fowl—is, for all practical purposes, worldwide in distribution. Evidence of its economic importance in the United States is shown by the fact that livestock sanitary officials of 21 states recently listed Newcastle disease as their foremost problem in poultry production. The avian disease is an even greater cause of loss in many other parts of the globe. Considering this wide diffusion in poultry and the relatively close association between man and the domestic fowl, the opportunities for human exposure to the Newcastle virus are abundant.

Evidence that the Newcastle virus may give rise to a general infection in the human body has never been completely convincing. Recent reports have served to further weaken that evidence. This survey of the developments in the knowledge of Newcastle disease is made in an attempt to reveal the most serious omissions in that knowledge and, in turn, suggest experimental approaches for supplying the missing information.

Knowledge concerning human Newcastle disease is so meager that much of this discussion focuses upon the disease in fowls. The epidemiology and epizootiology of the disease are, however, so connatural that their joint consideration is probably desirable under any circumstance.

**NOMENCLATURE**

This disease has received wide disposition with regard to nomenclature. In the United States, the term "avian pneumoencephalitis" is preferred by some authors. However, "Newcastle disease," as originally proposed by Doyle appears to be the expression of choice in this country as well as abroad.
**NEWCASTLE DISEASE**

**HISTORY AND DISTRIBUTION**

Kraneveld, in the Netherlands East Indies, was the first to describe an outbreak of Newcastle disease, although he failed in attempts to isolate the causative agent. In the same year (1926) an outbreak of a disease of chickens at Newcastle upon Tyne, England, was studied by Doyle. He identified the agent as a filterable virus. Soon thereafter, investigators in various parts of the world described epizootics of a poultry disease under a variety of names, but with many features in common. Viruses exchanged for purposes of cross-immunity studies, between England, Dutch East Indies, Philippine Islands, India, Korea, and Japan, showed the agents to be immunologically identical. In the early reports, Newcastle disease was described as a devastating plague, extremely infectious, with a high mortality rate usually approaching 100 per cent, and, in the main, affecting domestic fowls, although field observations suggested the possibility that other species of birds might be susceptible.

Within the space of a few years, new outbreaks occurred in Australia (1930); Kenya (1935), spreading to the Congo (1939); Palestine, Syria, Italy, Sicily; Roumania, Hungary and Switzerland (1940); Germany (1941); South Africa (1945); Mexico (1946); Russia and China (1947); Tunisia, Hawaii and Canada (1948). Information on the existence of the disease in South America is not available, but reports have been made of its occurrence in Panama.

Newcastle disease is prevalent throughout all of Southeast Asia. The virus has been isolated in Peiping, Shanghai, Nanking, Canton and Chungking, and the disease is considered to be present in all parts of China. The virus has been isolated also in Siam where the disease is widespread, especially in the south. Reports of large losses from a disease resembling Newcastle disease have emanated from Indo-China, Malaya and Burma.

In the United States, Beach, of California, applied the name avian pneumoencephalitis to what had previously been termed "a respiratory-nervous disorder of chicks," and that had been observed in mature chickens in California since 1935 as "9-day pneumonia." This disease, ultimately identified by Beach as Newcastle disease, may have existed in California as early as 1931. Despite its apparent localization in California, the virus was isolated in New Jersey in 1945. Within 2 years Newcastle disease virus was demonstrated in 41 states and the District of Columbia, and is now considered to exist in all states. Beaudette is of the opinion that, rather than this seemingly rapid spread in a relatively short period of time, the disease actually extended itself across the country unnoticed or without being correctly diagnosed.

The delay in identification of the Newcastle virus in the United States is readily explained by the unusually mild and atypical characteristics
assumed by the avian disease upon its initial appearance in this country, as contrasted with the typical fulminating and highly fatal Newcastle infection described from other parts of the world.

The most accurate estimate of the occurrence of Newcastle disease in American poultry is the result of a survey conducted in the Middle Atlantic region, an area of intense poultry farming, by the U.S. Bureau of Animal Industry in 1947. The incidence in that region was placed at about 30%, the country-wide incidence is, however, probably somewhat lower.

**Etiology**

Attempts to isolate the causative agent of the first reported outbreak of what was later found to be Newcastle disease were unsuccessful. Although failure marked the efforts to demonstrate the agent in the Dutch East Indies outbreak of 1926, Doyle, working with the disease in England in the same year, was more fortunate. He found that mouth exudate from both dead and moribund birds, passed through Chamberland L3 or Berkefeld filters, produced infection and death. Mouth exudate from the dead birds, passed through the same types of filters and injected intravenously or intramuscularly, also produced the disease and death. Using Berkefeld filtrates, the virus was passed serially through seven chickens. This work was soon confirmed by others, and it was found that the Newcastle disease virus was also filterable through Chamberland L5 filters and Seitz pads, as well as through Berkefeld V, N and W candles. Similarity of the clinical disease of poultry as was described in widely scattered parts of the world led to the exchange of viruses for comparative studies. As mentioned previously, the viruses were found to be immunologically indistinguishable. Beach and others later recognized the immunological identity of the virus of avian pneumoencephalitis in the United States with that of Newcastle disease.

**Chick Embryo Propagation.** The virus of Newcastle disease can be propagated with relative ease in chicken embryos, as was first demonstrated by Burnet and Ferry in 1934. Infected chicken spleen, in 1–1000 dilution, instilled upon chorio-allantoic membrane usually killed 10-day-old embryos in 30 to 48 hours. The virus was found in the liver and brain of the embryo in high concentration.

**Human Newcastle Virus Infections**

Burnet, in 1943, recorded the first known case of human Newcastle virus infection. It occurred in a worker in his laboratory and was due to the accidental splashing of infectious chick-embryo fluids into the eye. Within 24 hours there was acute unilateral conjunctivitis with preauricular lymphadenitis, headache, chills and general discomfort. Symptoms soon subsided with complete recovery within two weeks. Newcastle virus
was recovered from the conjunctival fluid, and neutralizing antibodies were demonstrated in the patient's serum. Later, Anderson reported two similar cases from the same laboratory. One of these was a mild bilateral conjunctivitis with no other clinical symptoms, the other a mild conjunctivitis with slight regional lymph node involvement. The Newcastle virus was isolated from the tears in both of these cases.

In Palestine, Shimkin reported a case of conjunctival hemorrhage involving a worker in a poultry disease laboratory. Although the Newcastle virus was believed to be the cause, virus isolation and serological determinations were not attempted. Yatom described an epidemic of 17 cases of unilateral conjunctivitis which occurred in women who had helped in preparing fowl infected with Newcastle disease for table use. After a 3-day incubation period, an acute conjunctivitis with mucopurulent discharge was evident. There was full recovery in all cases within 14 days. The epidemic stopped as soon as the affected fowl were slaughtered; no person to person spread could be detected. There was no attempt to isolate the causative agent or perform serological tests. The author could, however, differentiate these infections from the type of conjunctivitis endemic in Palestine on the basis that they were confined to one eye and did not involve the cornea.

The only report of recovery of Newcastle virus from human infections in the United States is the recent announcement of Ingalls and Mahoney. Their series consisted of two cases of conjunctivitis: one involving a broiler-plant operator on whose premises Newcastle disease was in progress, the second in a veterinary student who had autopsied chickens affected with acute cases of Newcastle disease. Virus, recovered from the conjunctival exudate in each of the cases, was identified as the Newcastle virus.

Howitt, Bishop and Kissling, in 1948, produced evidence that the Newcastle virus may possess systemic pathogenicity for man. The cases in their study all occurred in Tennessee and Alabama where for several years a poliomyelitis-like, mild central nervous system infection, especially in children, and an influenza-like disease in adults, had been observed. Symptoms of the disorder in children included headache, fever, malaise and chilly sensations. In some of the more severe cases there was evidence of meningeal irritation, with stiff neck and back, and occasionally nausea and vomiting; there was no residual paralysis. These manifestations were termed the "Newcastle disease syndrome" and were distinguished from cases showing a definite encephalitis. Sera from 20 of 25 patients exhibiting this mild central nervous system involvement showed the presence of neutralizing antibodies for the Newcastle virus, but not for the viruses of eastern or western encephalomyelitis, or St. Louis encephalitis. Fecal specimens and throat washings from several of the cases were tested and found negative for poliomyelitis virus. Several
of the cases were known to have been associated with chickens afflicted with Newcastle disease. No virus was recovered from any of these cases.

This same report reveals that, after studies with the Newcastle virus were begun, an acute influenza-like disease developed in six laboratory employees. Antibodies in high titer against Newcastle virus were found in the sera of these workers, as well as in several employees who did not become visibly ill. Hemagglutination inhibition tests were positive for the Newcastle virus, but negative for the viruses of influenza A and B. Attempts to isolate a virus from these cases were also without success.

Despite the fact that the causative agent was not isolated, Howitt and associates suggest airborne spread of the Newcastle virus from fowl to man, and then from man to man. They visualize the probability that Newcastle virus of fowls is the agent responsible for many of the atypical central nervous system infections that have been reported in man during

### TABLE I

**HUMAN NEWCASTLE DISEASE**

*Tabulation of Reported Cases*

<table>
<thead>
<tr>
<th>Observer</th>
<th>Number of Cases</th>
<th>Type of Exposure</th>
<th>Primary Symptoms</th>
<th>Epidemiological</th>
<th>Serological</th>
<th>Virus Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burnet (Australia)...</td>
<td>1</td>
<td>Laboratory</td>
<td>Conjunctival</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Anderson (Australia)...</td>
<td>2</td>
<td>Laboratory</td>
<td>Conjunctival</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Ingalls and Mahoney</td>
<td>2</td>
<td>Contact with Infected Chickens</td>
<td>Conjunctival</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Shimkin (Palestine)...</td>
<td>1</td>
<td>Laboratory</td>
<td>Conjunctival</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yatom (Palestine)...</td>
<td>17</td>
<td>Contact with Infected Chickens</td>
<td>Conjunctival</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McGough (Ohio)...</td>
<td>10</td>
<td>Ingestion of Infected Chicken (?)</td>
<td>Gastro-intestinal</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Howitt et al. (Tennessee)</td>
<td>12</td>
<td>Contact with Infected Chicken (?)</td>
<td>Mild CNS</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>(Alabama)</td>
<td>8</td>
<td>Contact with Infected Chicken (?)</td>
<td>Mild CNS</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>(Alabama)</td>
<td>6</td>
<td>Laboratory</td>
<td>&quot;Influenza-like&quot;</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>
the past few years, and that, as in fowls, the manifestations are neurological in young individuals and respiratory in adults.

McGough, in Ohio, has reported the presence of neutralizing antibodies for the Newcastle virus in the sera of ten persons who became ill following the ingestion of cooked chicken. Three of the cases were studied clinically; symptoms included sudden onset of nausea, vomiting, fever (about 101°F), malaise, anorexia, headache, and abdominal and lumbar pain. All of the cases gave a history of having consumed chicken purchased, in the frozen state, from the same vendor.

Reported cases of human Newcastle infection are analyzed in Table No. 1.

**PATHOGENESIS**

With the scant number of proved human cases of Newcastle disease reported, there has been little opportunity to gain an understanding of the pathogenesis of the disease in man and one must, therefore, turn to studies of the disease as it occurs naturally or experimentally in lower animals. Beaudette states that workers in India, on the basis of nervous symptoms, believed the virus to be neurotropic in fowls. Histopathologic examinations, conducted by Jungherr and associates on a large series of experimental cases in chickens, showed European strains (English and Italian) to be endowed with remarkable enterotropic potentialities, as expressed by necrosis of spleen and intestine, but with limited affinity for the respiratory tract and virtually none for the central nervous system. By way of contrast, the American strains showed predominance of neurotropism or pneumotropism depending upon parenteral or intratracheal infection, respectively, while enterotropism was evidenced by occasional spleen involvement. Newcastle virus is usually widely distributed in the bodies of infected fowls; it has been isolated from the saliva, crop content, intestinal content, feces, liver, spleen, pancreas, liver, bile, blood, bone marrow, kidney, testes, ovaries, brain and spinal cord. On the basis of these findings, the virus of Newcastle disease might be considered as being pantropic in character, yet there is good evidence that, in fowls, it is primarily pneumotropic, secondarily neurotropic. This is supported by the fact that respiratory symptoms are the first clinical signs of the disease, regardless of age. In North American experience, a large proportion of the younger birds surviving this initial phase develop nervous symptoms; mature and semi-mature fowls, however, are much less likely to progress from the respiratory to the nervous stage. Foreign reports, dealing generally with a more severe form of the disease with less age differentiation, describe nasal discharge, dyspnea and cyanosis as usual symptoms, whereas nervous symptoms are expected only in the more protracted cases. These late occurring nervous manifestations may be accounted for, at least in part, by the delayed protection of the central nervous system, resulting from slow penetration of the blood-brain barrier by circulating antibodies. With the appearance of
Newcastle disease in new and virgin territory, the septicemic form with short incubation period and course has been observed almost exclusively, while after recurrent attacks the nervous form has been found to predominate\textsuperscript{20}. It has been noted, also\textsuperscript{20}, that evidence of central nervous system injury may appear late after exposure in fowls with known low circulating antibody titers and without present or prior evidence of the lesions characteristic of the typical peracute or acute form.

Pigeons, ducks and geese are comparatively resistant to Newcastle disease; when it does occur in them the symptoms are predominantly of the paralytic type and rarely of the respiratory form\textsuperscript{14}. This would seem to provide added evidence that the nature of the pathogenesis of the disease depends, in large part, upon host resistance.

While much concerning the pathogenesis of Newcastle disease can be learned from the disease in poultry, the mammalian pathogenesis should provide an even better understanding of its possible nature in human beings. Studies with monkeys should prove to be particularly enlightening, yet such experiments have been few in number and were designed primarily to pursue other aspects of the disease. Reagan and co-workers\textsuperscript{71}, using hamster-adapted virus, succeeded in producing the disease in monkeys by intracerebral inoculation, but were unsuccessful in a few attempts at using the intranasal route. Wenner and Lash\textsuperscript{77} produced a choreo-meningoencephalitis in rhesus monkeys by intracerebral inoculation with egg-propagated virus. After a 2 to 5 day incubation period, the animals became restless and tremulous, with awkward locomotion and fever which lasted 2 to 7 days. Convalescence was slow, with nervous symptoms persisting for 7 to 10 days after abatement of the fever. Upon histopathological examination, the central nervous system showed encephalitis, focal meningitis, perivascular cuffing, neuronecrosis and neuronophagia. The virus was found in the blood and central nervous system tissues, suggesting widespread proliferation.

Thus, experimental Newcastle disease in monkeys, produced by intracerebral inoculation, is characterized by neurological manifestations. However, it is not reasonable to assume that such an artificial route of infection is comparable to natural exposure. It has been pointed out that respiratory symptoms are infrequently seen in fowls after experimental parenteral infection, but are common following exposure by contact or by respiratory tract instillation\textsuperscript{61}. This suggests that the portal of entry has a determining influence upon the disease process. Newcastle disease in nature is an airborne infection. Studies of the disease in monkeys, utilizing respiratory instillation of the virus or contact with infected fowls as modes of transmission, might be expected to provide useful results in terms of possible human infections.

The pathologic expressions of Newcastle disease in chickens are modified principally by individual and host factors, the inherent pathogenicity
of the virus strains, quantitative differences in infective dosage, route of infection, and degrees of immunity. These same modifiers may well apply to Newcastle disease as a human infection, although the order of their importance is far from being understood.

**Spread of the Virus**

**Host Range.**—Investigators are agreed that Newcastle disease is primarily an infection of chickens, and most reports deal with the spontaneous disease in that species. Other avian categories reported to have been affected during natural outbreaks include turkeys, guinea fowl, ducks, geese, pigeons, swans, pheasants, partridges, crows, sparrows, martins, parrots, and several unidentified species of free-flying birds. The evidence for susceptibility of several of these species is, however, largely circumstantial and lacks verification by isolation of the virus. Of the common domestic poultry types, chickens and turkeys are regarded as most susceptible; ducks, geese, guinea fowls and pigeons are comparatively resistant. No naturally occurring case of Newcastle disease has been reported in household cage birds.

Among mammalian species, man is the only one in which Newcastle virus infection is known to have occurred naturally. Attempts to produce the disease experimentally in horses, cattle and swine have failed. The disease has, however, been successfully produced by intracerebral inoculation in Syrian hamsters, mice, and monkeys. The hamster-adapted virus has been used to infect sheep, monkeys, guinea pigs, mice, also by the intracerebral method. Burnet produced influenza-like pulmonary consolidation in mice using massive doses of the virus intratracheally, but failed to establish the virus by serial passage.

**Reservoir.**—Wild birds have been suspected by numerous observers as being susceptible to Newcastle disease and as being an important reservoir of infection. Insufficient data is available to evaluate this possibility. As previously noted, the evidence with regard to wild free-flying birds dying during epizootics of Newcastle disease in domestic poultry has been largely circumstantial. That certain species of wild fowl are at least susceptible to the Newcastle virus was shown by experiments conducted with upland game birds in Minnesota. Hungarian partridges and Ring doves, inoculated either intratracheally or intramuscularly, developed clinical infections. Chinese pheasants, Chukar partridges, quail and racing pigeons all developed significant hemagglutination-inhibition power, but remained asymptomatic. There is no record of attempts to recover the virus from this group of birds in order to pursue the possibility of their having become carriers. It might be anticipated that the observed irregularity with which epizootic infection spreads among chickens of different ages may be magnified in the case of other less susceptible genera and species of birds. The possibility of wild birds undergoing latent, or
inapparent, Newcastle infection and then remaining as carriers of the
disease for a considerable period of time cannot be discounted on the
basis of existing information.

Judged from the standpoint of possible human infection, domestic
poultry constitute a widespread and potent reservoir of Newcastle dis-
ease. The infection is now virtually global in its enzooticity, and oppor-
tunities for human contact are patent. Arguments to the contrary
notwithstanding, Newcastle disease in chickens is a well-balanced infec-
tion—i.e., a state of ecological relationship between agent and host in
which neither is in danger of extinction because of that relationship.

Carriers.—Carriers are generally not believed to be an important factor
in the spread of the disease in domestic poultry. The longest period of
time, after actual infection, for recovery of the virus from chickens is
three months. This was the isolation of virus from the lungs of chickens
which had had respiratory symptoms only.

Mode of Transmission.—The relatively high tenacity of the Newcastle
virus favors indirect, as well as direct, transmission of the disease. This
is true whether one considers it in terms of world spread or local exten-
sion. Traffic in live fowls or infective fowl carcasses in the form of
dressed poultry are considered to be major factors in introducing the
disease into areas previously free from the infection, as well as in dis-
semination of the disease once it gains the initial foothold. Doyle has
reported experiments showing that the Newcastle virus remains viable
for at least six months in the bone marrow and muscle tissue of fowl
carcasses stored under “trade chilling conditions.” Wartime and postwar
conditions, especially as they have allowed for the relaxation of inter-
national and local animal disease control measures, are undoubtedly an
important underlying factor in the recent rapid spread of Newcastle dis-
ease in the world’s poultry population.

The virus has been demonstrated in eggs laid by a flock in the active
clinical stages, and as long as two months following an active out-
break, of Newcastle disease. The fact that about a third of the eggs
laid during the acute stages of a natural infection contain the virus
raises the question of transovarian infection. That such parent-to-off-
spring transmission does occur was shown by DeLay, who succeeded
in finding the virus in four-day-old chicks hatched from eggs laid during
an acute attack.

The mode of transmission to human beings is by direct contact with
infected fowl tissue or with diseased fowls, the infective material
gaining entrance into the eye. Whether the infection may be spread to
man by contact with infected or contaminated material by other than
the ophthalmic route rests on no certain evidence, although inhalation
of the virus is a reasonable possibility.

Ingestion of the meat of fowls infected with Newcastle virus is also
suspected, but the evidence is not conclusive. In this regard, a report
that the virus was recovered from the feces of a cat that had been fed upon chicks infected with Newcastle virus is of interest. Whether the virus actually invaded the tissues of the cat's alimentary tract, or whether the process was purely mechanical, are matters for speculation. Investigations regarding the possible hazard to humans of ingesting tissues of infected poultry, as well as eggs, would seem to be indicated.

Person to person spread, although suspected, is entirely without proof. As a rule, the infection chain of virus diseases conveyed from warm blooded animals to man are broken following the first transmission to the human host. A change of host, such as the transfer to man, usually leads to a blind ending of the chain. There is no reason to believe that Newcastle disease is an exception to this principle.

Portals of Entry.—Confirmed human cases of Newcastle infection have all been introduced via the conjunctival route. This portal of entry has been proved experimentally in fowls, but is not considered to be the agent's usual portal of entry for naturally occurring avian Newcastle disease.

Howitt and associates, in discussing their series of suspected cases of human Newcastle infection, imply that dissemination of the virus from fowl to man is by air-borne transmission. This mode of spread of the Newcastle virus has been emphasized by the recovery of the causative agent from air contaminated as a result of natural infection. DeLay and collaborators, in 1948, using special apparatus, drew air from poultry houses which contained infected chickens through allantoic fluids from normal 10-day chick embryos, whereupon the liquid was injected into chick embryos and later into chicks. All died of Newcastle infection. In further experiments by these same workers, healthy chickens were placed inside the contaminated house (suspended 4½ feet above the floor) so that the only source of infection might be the air. The birds developed clinical Newcastle disease within six days.

With the air-borne nature of the spread of Newcastle disease established, the question as to the exact portal of entry arises. The disease in chickens is readily reproduced by mixing the virus in the feed or drinking water, and the report of McGough suggests the digestive tract as a portal of entry in man. However, in the case of contaminated material taken into the mouth, there can be no degree of certainty as to whether actual invasion of the virus takes place through the digestive or the respiratory systems. Further, one must consider the relative ease of experimental transmission to chickens by intratracheal inoculation.

It seems worth noting that respiratory distress, a major characteristic in many outbreaks of natural avian infection, is not present when the disease is induced artificially by parenteral injection. However, experimental infections brought about by respiratory-tract instillation, as well as by contact, produce the respiratory symptoms.
The conjunctival portal of entry has been proved both in the avian and human infections. The evidence in favor of the digestive and respiratory routes, at least in the case of fowls, is almost as conclusive; it is quite conceivable that either or both avenues are involved.

**Diagnosis**

Consideration of the importance of Newcastle disease as a human infection may well be reduced to an evaluation of the diagnostic criteria on which determinations of such human infections are based. Analysis of cases diagnosed as, or considered to have been, Newcastle disease is revealing. These cases may be classified into three categories.

Five cases of human Newcastle infection, each of them a relatively mild ailment with conjunctivitis as the principal symptom, have been confirmed by diagnostic criteria agreed upon by virologists as conclusive. These cases include the three Australian laboratory infections\(^{36,37}\) and the two recently reported Ohio cases\(^ {48}\).

A second, and larger, group of cases, also with conjunctivitis as the major manifestation, have had a diagnosis arrived at entirely on the basis of history of recent exposure to infectious material, followed shortly thereafter by appearance of the clinical symptoms. Included in the category are the 18 cases reported in Palestine\(^ {74,78}\). The cases comprising this series, even though the diagnosis is disputable, fall readily into the clinical and epidemiological pattern of the proven ones.

The third and largest series consists of a number of cases suggested, on the basis of serological tests, as being Newcastle virus infections. Some of these cases were known to have been associated directly with the Newcastle virus or with chickens infected with Newcastle disease; however, epidemiological evidence is indefinite in several instances. These cases differ also, from those included in the first two categories, in their clinical manifestations. Whereas conjunctivitis has been the primary symptom of the proven cases, the symptoms of patients in this group have been neurological in children and influenza-like in adults; a few have shown evidence of gastro-intestinal involvement. It is this group of cases, including those of Howitt et al\(^ {46}\) and McGough\(^ {59}\), that has given cause for suspecting Newcastle disease in man as being more than just a mild eye infection. Since the syndrome described for the patients in this group is commonly encountered, particularly in certain areas\(^ {47,46}\), demonstration of the causative agent is highly desirable. The methods used for determining its probable cause as being the Newcastle virus must, however, be critically examined.

Newcastle disease in poultry is diagnosed by several methods: clinical examination, gross and histological observations, serum-virus neutralization tests, hemagglutination and hemagglutination-inhibition tests, and
isolation of the virus. Unfortunately clinical and pathological symptoms are not a reliable basis for judging the presence of the avian disease since it bears close resemblance to several other infectious chicken maladies. Clinical diagnosis of human Newcastle disease is certainly no more reliable. The only exact means of diagnosis are, therefore, by laboratory procedures. The three recognized laboratory methods have been well described by numerous writers. Reliability of Serological Diagnosis.—The serological tests, hemagglutination-inhibition and serum neutralization, have been widely used as diagnostic aids in virus diseases. The hemagglutination-inhibition test, which measures either the level of neutralizing antibodies themselves or some other factor in serum, the level of which closely parallels such antibodies, is a relatively simple and rapid procedure. The serum-neutralization technique, although somewhat more involved and protracted, is usually considered to be the more reliable. These tests, often done concurrently, are routinely performed as aids in the diagnosis of Newcastle disease in poultry flocks in areas where the disease is known to exist. Another example of their application is in human influenza, but in that disease also they are considered only as supplements to virus isolation. Once the virus has been isolated during a given outbreak, cases that exhibit a significant (i.e., fourfold or greater) rise in antibody titer are diagnosed with reasonable certainty. Even at best, then, serological tests cannot be substituted for isolation and identification of the virus. If this is true for clinical entities with known etiology, it is all the more applicable to a syndrome, the causative agent of which has never been demonstrated. Recent reports of Kilham and associates serve to emphasize the questionability of a serological diagnosis of Newcastle disease in man. Paired sera from 18 of 22 proven mumps patients showed significant serological response when tested against the Newcastle virus. Thirteen of these showed significant antibody levels by the neutralization test, and 11 by the inhibition of hemagglutination. In a further study of the relationship between the Newcastle and mumps viruses, these same investigators produced evidence that serum from Newcastle-immune guinea pigs will neutralize the mumps virus. Pooled sera from guinea pigs that had been housed near chickens infected with Newcastle disease showed very definite antibody responses to both the Newcastle and mumps viruses by the neutralization test. A single guinea pig, exposed to the Newcastle virus by intranasal instillation, showed a substantial rise in antibodies (both neutralizing and anti-hemagglutinating) against the Newcastle virus, 3½ weeks later. At the same time it showed a 100-fold rise in the amount of mumps virus it could neutralize. Although additional experimentation is necessary in order to evaluate the relationship between the mumps and Newcastle viruses, the evidence just presented
is sufficient to cast serious doubt upon a diagnosis of human Newcastle infection when based solely upon antibody determinations.

**Isolation of the Virus.**—The unequivocal method of diagnosing any infectious disease is to recover and identify the causative agent. Such procedure is, of course, the preferred method for Newcastle disease. Although serological diagnosis of avian Newcastle disease in the United States are permitted in areas where infection is known to be enzootic, new foci or extensions of the disease are recognized only by isolation and identification of the virus.

While the serological evidence for incriminating the virus of Newcastle disease as a neurotropic and pneumotropic pathogen of man is highly inconclusive, it cannot be ignored. Continued attempts to isolate the causative agent from naturally occurring cases exhibiting the so-called Newcastle disease syndrome are fully warranted. There are three plausible explanations as to why such attempts have thus far been unsuccessful; either, (1) the syndrome is not indicative of Newcastle infection, and therefore the virus is not present; (2) appropriate specimens for culture have not been employed; or (3) inadequate virus-recovery techniques have been used. Assuming, for discussion purposes that the cases actually are Newcastle disease, an examination of the other two explanations of failure is in order.

**Specimens for Virus Isolation.**—Returning to the avian disease, it is evident that specimens for isolation of the virus should be selected from cases in the early stages, that the virus is more readily recovered from individuals in the younger age groups, and that certain types of specimens are more likely to yield the agent than are others. The rapid disappearance from, or masking of the virus in, the tissues of the host has been evidenced by the development of a demonstrable refractivity to inoculation infection. Early clinical cases or, preferably, preclinical cases if the time of exposure may be estimated should, therefore, be used in attempts to recover the virus. Beaudette et al. confirm the observations of others that the virus is recovered less frequently as the age of the host increases. Finally, with regard to selection of specimens, foreign reports suggest that respiratory exudates of fowls affected with Newcastle disease are usually higher in virus concentration than body excretions or the tissues. The spleen, lung, bone marrow, brain and spinal cord, crop and intestinal content, and feces were found infectious quite regularly, the liver and blood less so. North American experience has shown respiratory exudates to be an excellent source of the virus, second only to spleen tissue. Since post mortem specimens from cases of suspected human Newcastle infection are not available, the choice of material for virus recovery work is limited. Respiratory exudates are the obvious choice. The fact that Wenner and Lash were able to demonstrate virus in the blood of experimentally infected monkeys is sugges-
tive, even though the route of inoculation did not simulate natural exposure.

On the basis of these findings it might be predicted that attempts to isolate the agent from general infections, suspected of being Newcastle disease, in man would have the best chance of success if specimens from the respiratory tract of children in the early or preclinical stages were used; blood and feces should also be considered as potential virus sources.

**Virus-recovery Technic.**—Although there are reports of difficulty in establishing the infection in chick embryos\(^8, \text{24}\), it would appear that successful virus recovery is dependent largely upon the suitability of the specimens utilized\(^66\). Several excellent descriptions of technic for recovering the Newcastle virus have been published \(^88, \text{10}, \text{24}, \text{16}, \text{44}\), a review of which is beyond the scope of this paper. It is of interest to note, however, the suggestion that some degree of virus adaptation from the original host to the embryonated egg is necessary, at least when the virus content of the inoculum is extremely low. The desirability of inoculating susceptible young chickens, as a supplemental procedure to egg inoculation, is stressed\(^24\).

**Immunity**

Infection with the Newcastle virus results in a very definite antibody response. This is true of both natural and experimental infections, and has been observed in a wide variety of hosts—both avian and mammalian. The high level of neutralizing antibodies developed in fowls which were presumably uninfected\(^69, \text{12}\) is taken as an indication of latent infection. Significant antibody rises with absence of clinical manifestations have followed experimental inoculation in mice\(^25\) and monkeys\(^89\). Guinea pigs housed near chickens affected with Newcastle disease have shown no clinical symptoms but have developed a high level of neutralizing antibodies for the virus\(^55\). The presence of antibodies in the sera of asymptomatic laboratory personnel\(^46\) exposed to the virus is also indicative of latent infection.

Congenital passive immunity during the first month of life has been observed in chicks hatched from eggs laid by Newcastle immune hens\(^3\). Both living and inactivated vaccines are used for immunization of fowls. Although the immunity engendered by the inactivated vaccine is short-lived\(^78\), the product is successfully used and is preferred on premises where the infection is not known to exist\(^78\). The active vaccines are biologically modified by serial passage in eggs, either hen\(^49, \text{65}, \text{64}, \text{1}\) or other eggs; or, they may be modified by passage in some animal host such as the hamster\(^70, \text{72}, \text{67}, \text{68}\) or duck\(^56\). Immunity from these active vaccines seems to be for life\(^15\). Beaudette\(^16\) has warned vaccinators of the danger of contaminating the fingers in the process of mixing and administering the vaccine and then carrying the live agent into the eyes.
BIOLOGICAL CONSIDERATIONS OF THE NEWCASTLE VIRUS

The Newcastle virus is of more than ordinary interest from the biological standpoint for several reasons. Among these are its multiplicity of strains, and its relationship with the viral agents of other diseases.

Strain Variation.—Variations in the infectiousness and pathogenicity of the Newcastle virus are, perhaps, best exemplified by the marked contrast between its behavior in the United States and abroad. The North American disease is relatively innocuous when considered in the light of foreign experience, a difference which is generally agreed to result from a character of the virus, rather than from a host factor31, 32.

Wartime research conducted at the Huntington Laboratory, in which English, Italian and American strains of the Newcastle virus were studied, showed that subacute or chronic cases of experimental avian Newcastle disease were more common with strains isolated in the United States than with those from Europe31. It was also noted that neurological symptoms, the incidence of which correlated with the length of the disease course, predominated the infection produced by American strains, as contrasted with the early septicemic or toxic reactions induced by the European strains of the virus. Variations in the severity of Newcastle disease are such that a strain of virus isolated during an outbreak in one part of the world may be used as live vaccine in other areas. Such a vaccine, used in India, produces a disease that is comparable to the American disease and would therefore serve no purpose in the United States. Yet it is of use in India, where the mortality is 100%, or approximately that15.

Differences in strains of the Newcastle virus are quite apparent in the clinical and pathological results produced in the avian host. In addition, differences in antigenic structure and efficiency have been suggested21, but the evidence in this regard is incomplete. Considering these wide differences in the behavior of the Newcastle virus strains in fowls, it is to be expected that similar strain conduct obtains, presumably on a lower plane, with respect to other hosts, e.g. man.

Whether Newcastle disease is actually a new disease, considering that there is no record of its existence prior to 1926, is a point that can never be fully settled. There are those who have doubts that new diseases arise through sudden permanent modifications or variations of a disease agent instead of through a slow, orderly, evolutionary adaptation to the new hosts81. Others are of the opinion that mutants or variants offer the most logical explanation of the appearance of what seemingly are new diseases. The genesis of the Newcastle virus is a subject upon which there has been considerable speculation. Manning has regarded that agent as an attenuated strain of the fowl plague virus, with differential features limited to certain characteristics of the clinical syndrome they produce; evidence in support of this view is scant.

The Newcastle virus has been considered in its relation to the viral agents of several human infections:
Influenza.—Burnetz\textsuperscript{25, 28, 27, 26} has observed sufficient points of similarity in the viruses of human influenza A and B, swine influenza and Newcastle disease to conclude that they are related and derived eventually from a common ancestral form. He considers the possibility of a mutant of the Newcastle virus undergoing selective survival, finding opportunity for human passage, and giving rise to a new antigenic type of influenza. In this regard, the influenza-like syndrome of adults, believed by some\textsuperscript{40} to result from Newcastle virus infection, is perhaps significant.

Mumps.—The virus of mumps behaves in the same way as the Newcastle virus in that they form a linear series with the influenza viruses, in their capacity to be eluted from susceptible fowl erythrocytes. This has been interpreted by Burnet\textsuperscript{27} on the hypothesis that all viruses become attached to a single series of receptors, but that these receptors vary in their accessibility and in the ease with which they can be removed by virus action. He suggests that the mumps virus is also derived from an ancestral form common to the influenza and Newcastle viruses. Kilham and associates\textsuperscript{55} suggest a close relationship between the Newcastle and mumps viruses on the basis of another kind of evidence: their findings of neutralizing and anti-hemagglutinating antibodies against the Newcastle virus in convalescent mumps sera. In addition to serological cross-reaction between the two viruses, Kilham has provided evidence of close biological relationship in his discovery\textsuperscript{64} that Newcastle virus possesses a hemolysin with properties similar to that previously described for the mumps virus\textsuperscript{65}.

Poliomyelitis.—Reagan and co-workers\textsuperscript{65} have observed that monkeys injected with the Newcastle virus later evidenced some degree of resistance to active poliomyelitis virus. Their observations, although interesting, are not statistically significant. Wenner and Lash\textsuperscript{77}, after using Newcastle virus to produce central nervous system infections in monkeys, suggested further studies to determine whether Newcastle disease resembles experimental poliomyelitis.

Lymphocytic Chorea meningitis.—It has been suggested that the pathogenesis of experimental lymphocytic chorea meningitis and Newcastle disease in monkeys be studied for comparative purposes\textsuperscript{77}.

Infectious Mononucleosis.—Numerous investigators\textsuperscript{39, 37, 41} have shown that sera of patients recovering from infectious mononucleosis will agglutinate erythrocytes that have been sensitized by adsorption and elution of Newcastle virus. No satisfactory explanation of this finding has been offered.

\textbf{NEWCASTLE VIRUS AND THE HUMAN HOST}

Determination of the importance of the Newcastle virus as a human pathogen is a problem in ecology. Newcastle disease is undoubtedly a disease primarily of avian species, and there are good indications that the
relation between the agent and its normal host is a well balanced one. The persistence of the disease in nature is thus explained. Overflow from this reservoir into the human population is known to occur, yet whether it is a rare accident or a relatively frequent occurrence is undetermined. Similarly unknown is whether the morbid process resulting from the virus invasion of the human host is a mild localized reaction or a general systemic affliction. Suspicion that it is more than a rare and inconsequential accident is cause for further investigation. Several interesting and, perhaps, productive approaches for exploring human Newcastle disease become evident.

**Reservoir.**—The fact that several species of game birds have shown serological evidence of experience with Newcastle virus, without having shown the clinical disease, raises the question of latent infection—with the possibility of carriers—in wild birds. Surveys of avian wild life to determine its true status with regard to Newcastle disease are indicated.

**Portals of Entry.**—The respiratory and digestive tracts have been suspected as portals of entry of the Newcastle virus; there is good reason to believe that both routes are possible invasion points in the avian host. Investigations as to the possible hazard to human beings from ingestion of infected fowl or eggs laid by infected hens are suggested. Study of the reaction of monkeys to respiratory-tract instillation of the virus and to contact with infected fowls might also be useful in determining the importance of this possible portal of entry.

**Pathogenesis.**—Study of the disease process in monkeys might well produce information that could be interpreted in terms of human infection. Route of inoculation should simulate natural exposure, and should include the digestive tract, respiratory system and conjunctivae.

**Pathogenicity.**—Studies with primates offer the most reasonable approach for experimental interpretation of the pathogenicity of the Newcastle virus for man. The use of human volunteers for such studies holds interesting possibilities.

**Diagnosis.**—A serological diagnosis of human Newcastle infection is not sufficient. Koch's postulates are as valid to-day as they were when he originally propounded them, and apply in virology just as truly as in bacteriology.

The Newcastle virus cannot be incriminated as the agent of influenza-like, poliomyelitis-like, or gastro-intestinal syndromes until it has been isolated from cases exhibiting the appropriate clinical symptoms. Virus-isolation should be attempted from respiratory exudates obtained preferably from children, as early as possible in the disease course. Fecal specimens should be used for virus-isolation in cases exhibiting gastro-intestinal symptoms. Blood specimens, obtained during the early clinical, or if possible the preclinical, stages of suspected Newcastle infection, should be used in attempts at virus-isolation. The fact that mumps virus
has been demonstrated in the bloodstreams at the onset of clinical symptoms of that disease has been demonstrated in the bloodstreams at the onset of clinical symptoms of that disease seems pertinent, especially since such attempts are usually unsuccessful. Viremia, if present in human Newcastle infection, may be as transitory as it apparently is in mumps.

Serological tests for Newcastle disease are now in need of critical re-evaluation with regard to specificity. The revelation that sera from mumps patients will neutralize the Newcastle virus and, conversely, that sera from Newcastle-infected guinea pigs will neutralize the mumps virus, allows for serious doubt of the value of the serum-neutralization test. The possibility that similar relationships exist between the Newcastle virus and other viruses should be explored.

**Relationship With Other Viruses.**—There are indications that the Newcastle virus has a close biological relationship to other viruses; among these are the agents of influenza, mumps, poliomyelitis, lymphocytic choreomeningitis and infectious mononucleosis. These indications stem from several kinds of evidence: clinical, epidemiological, pathological and serological. Further study of biological relationships between these several agents might well produce information of considerable value to the biological scientist.

**REFERENCES**


54. Kilham, L., A Newcastle disease virus (NDV) hemolysis. (To be published).

64. Nakamura, J., Personal communication, June, 1947.


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**EPIDEMIOLOGIA DE LA ENFERMEDAD DE NEWCASTLE**

*(Resumen)*

Los primeros informes obtenidos sobre la infección humana causada por el virus de Newcastle, la describieron como un proceso benigno, caracterizado por una conjuntivitis transitoria. Las contribuciones subsiguientes han presentado evidencia serológica y epidemiológica que indica que la enfermedad de Newcastle humana es con frecuencia algo más que una mera reacción conjuntiva localizada, y que puede encontrarse como una infección del sistema nervioso central, a menudo confundida clínicamente con poliomielitis. Otros desórdenes respiratorios y gastrointestinales humanos han sido también atribuidos al agente de la enfermedad de Newcastle. Solamente en los casos de conjuntivitis ha sido posible aislar el virus de Newcastle, probándose inequívocamente que es el agente causal.
El virus de Newcastle se halla por naturaleza extensamente diseminado. La enfermedad, en su huésped natural aparente—las aves domésticas—constituye un problema económico de gran importancia para la crianza de aves de corral en Europa, Asia, África, Australia y Norte América. No hay informes disponibles sobre la existencia de la enfermedad en la América del Sur, aunque se ha informado en Panamá. En las aves de corral, el virus es primariamente neumotrópico y secundariamente neurotrópico. Su tenacidad relativamente alta favorece tanto su trasmisión directa como indirecta. Un factor importante para la propagación de la enfermedad es el comercio con aves infectivas vivas, o preparadas para cocinar. El medio de trasmisión al ser humano ocurre mediante el contacto directo con tejido infectado o con aves infectadas, cuando la infección gana acceso al ojo. No se sabe a ciencia cierta si la infección puede afectar al hombre mediante otra ruta que no sea la oftálmica, aunque la inhalación del virus ofrece posibilidades. Se ha sospechado también de la ingestión de carne de aves de corral infectadas. Desde el punto de vista de la posible infección humana, las aves domésticas constituyen un extenso y poderoso reservorio potencial de la enfermedad de Newcastle. Ya se conocen casos en que la infección fue trasmitida de este reservorio a la población humana, aunque se desconoce si este hecho es un accidente raro o una posibilidad frecuente. Para considerar la importancia de la enfermedad de Newcastle como infección humana basta evaluar los datos en los que se basa el diagnóstico. La evidencia serológica por sí sola, no es decisiva, en vista del reciente hallazgo de que el suero de enfermos con parotiditis neutraliza el virus de Newcastle, e inversamente, que el suero de cobayos infectados con la enfermedad de Newcastle neutraliza el virus de la parotiditis. No se pueden atribuir al virus de la enfermedad de Newcastle los síndromes parecidos a la influenza, poliomielitis o afecciones gastrointestinales, hasta tanto no se logre aislarlo en aquellos casos que presentan los síntomas clínicos apropiados. El A. hace varias sugestiones para la investigación de este problema en el laboratorio.