The Influence of Host and Intermediate Reservoir Host in Determining the Epidemiologic Pattern of Bovine Pseudorabies and Swine Influenza.* **

By

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With 1 figure.

Introduction.

Very little is known concerning the preservation of infective agents from one outbreak of disease to the next. As a rule, a lapse of many months or even years takes place between epidemics, and similar long periods of time may separate sporadically occurring cases of disease from one another. Thus, some infectious diseases are of annual occurrence; others, such as measles and whooping cough, tend to appear in epidemic form at roughly two-year intervals; while as much as two decades or more may separate one outbreak of pandemic influenza from the next. No satisfactory explanation of the periodicity of infectious diseases has ever been furnished, nor has the whereabouts of the causative agents between epidemics been satisfactorily explained. The origin and source of infectious agents responsible for the starting of fresh outbreaks of disease have largely remained obscure, so far as most human diseases are concerned.

In the realm of animal diseases, however, the above statement is not so strictly true, because for several of these an explanation, at least tentatively considered correct, is at hand. I propose this afternoon to discuss two of these diseases, bovine pseudorabies and swine influenza, and to compare the ways in which their epidemiologic patterns are influenced by the three factors involved in each case; namely, the causative virus, the host, and the intermediate reservoir host. But before

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making this comparison it will be necessary to describe some of the clinical and epidemiologic characteristics of the two diseases which are of importance to the later discussion.

Epidemiology of Bovine Pseudorabies.

Bovine pseudorabies may be defined as an acute, highly fatal, infectious disease of cattle, caused by the pseudorabies virus. It is known popularly throughout the Middle West, where it is most prevalent, as "mad itch" from its cardinal clinical feature, an extreme pruritus in which the animals mutilate an area of skin somewhere on their bodies by persistently licking and biting at the affected area. Death always ensues, usually within 36 to 48 hours of the time the animal is first noticed to be affected. As a rule, only a small portion of a herd is involved, and it is not uncommon to have single cases observed in rather large groups of animals. More commonly, however, the incidence in an affected herd ranges in the neighborhood of 10 to 20 per cent. Bovine pseudorabies never reaches epizoötic proportions, and long periods of time may elapse between the appearance of individual cases in a community. The disease has no recognized seasonal incidence and many farms, even in areas where it is known to be enzoötic, escape infection entirely.

These epidemiologic facts suggested that pseudorabies was not contagious in cattle and that a secondary host of some sort must be responsible for its spread from animal to animal. In the early days, rats were suspected of being the intermediate host, and the basis for this suspicion was the observation that not infrequently, on farms where pseudorabies was occurring in cattle, rats showing evidence of having died of an itching disease were sometimes found (1—3). In several instances pseudorabies virus was actually demonstrated in the central nervous systems of these dead rats. Investigators who maintained that the rat might be the intermediate host responsible for the infection of cattle, however, never clearly visualized in just what manner infected rats might transmit the virus to cattle. The absence of virus in the salivary glands of infected rats excluded rather well the possibility that transmission might be by biting.

Subsequently it was found that swine were susceptible to infection with pseudorabies virus,[3–8] and this observation furnished the key to our present understanding of the epidemiology of bovine pseudorabies. The disease in pigs was found to be quite different from that in any of the other animal species studied. Instead of regularly killing, as it did in cattle and all of the small experimental laboratory animals, pseudorabies virus caused an extremely mild and almost "silent" infection in swine. Aside from a temperature elevation for two to six days, swine showed few other clinical manifestations of illness. Despite the mild

character of porcine pseudorabies, however, infected swine regularly developed specific virus-neutralizing antibodies in their blood sera after recovery.[4, 8–10] Furthermore, pseudorabies in swine proved to be highly contagious in contrast to its non-contagiousness in cattle and other experimental animals.[8, 11, 12] Its mild but highly contagious character thus fitted it, potentially at least, as an ideal reservoir infection. It was found that transmission from swine to swine was by way of the nasal passages, and in some instances virus could be detected in or on the noses of infected swine for as long as 10 days.[12] Pseudorabies could be transmitted from swine to rabbits merely by bringing the noses of infected swine into contact with abraded areas of skin on rabbits. The disease produced in rabbits in this way was typical, fatal pseudorabies. To one familiar with the behavior of swine when they are with cattle, it seemed likely that a virus present in and on the nose of a hog could be readily transferred to the skin of a cow, because cattle lying about a barnlot in which hogs are also kept come frequently into contact with the pigs' noses.

In observing natural outbreaks of bovine pseudorabies on Middle Western farms, it had been noted that all cases occurred on farms where swine and cattle were kept together in the same pens. This practice of allowing swine to "follow" cattle is a very common one in the Middle West. In two outbreaks where the matter was studied, it was found that pseudorabies virus-neutralizing antibodies were present in the sera of swine associated with the infected cattle, thus indicating clearly that the swine had undergone a previous infection with pseudorabies virus.[12] The possibility that the swine on these farms may have been infected with pseudorabies before the cattle, and may have been responsible for the spread of the virus to cattle with which they were associated was strongly suggested by the findings. A point of some interest in this regard was that no observable illness had been noted in the swine by the owners; that is, the porcine pseudorabies infections had apparently been completely "silent".

Pseudorabies has never been recognized clinically as a naturally occurring disease in swine in this country. However, the finding that in the two herds referred to above, infection had occurred among the swine without the owners' knowledge suggested that it might even be a widespread infection, though undetected because of its mildness. To obtain some conception as to its possible incidence, pooled serum samples from large groups of Middle Western swine were studied for their content of pseudorabies virus-neutralizing antibodies. The results obtained were surprising in that they indicated an incidence of pseudorabies infection of 5 to 50 per cent among the various groups of swine studied. While it was realized that these data at best were only approximate, they

indicated that porcine pseudorabies was indeed a very prevalent disease. Similar tests of relatively large numbers of sera from Eastern-reared swine of comparable age failed to reveal the presence of neutralizing antibodies, indicating that although pseudorabies infection in Middle Western swine was high, the disease was lacking in Eastern swine.[13] On further study it was found that the rat, whose suspected role in bovine pseudorabies had never been clearly envisaged by earlier workers, might be of importance in the epidemiology of porcine pseudorabies. It was observed that the wild brown rat developed a fatal pseudorabies after eating tissues from animals dead of pseudorabies. The carcasses of these rats, when fed to swine, induced a typical mild type of pseudorabies in the pigs, and these pigs in turn transmitted pseudorabies to experimental animals when their noses were brought into contact with abraded areas of skin or to other swine by pen contact.[13] The rat, thus, while possibly playing a direct role in porcine pseudorabies, seems to play at most only an indirect role in the epidemiology of the bovine disease.

The final epidemiologic set-up of bovine pseudorabies may be visualized approximately as follows.

Pseudorabies is an ever present infection among swine in our Middle Western states. It spreads from swine to swine within a herd as a contagious disease. It is transmitted to swine herds on other farms, either by direct contact of infected swine with normal swine, or by the migration of infected rats. With two such efficient modes of dissemination of the virus among swine, one would expect the disease to be very prevalent in this species. However, because of the extremely mild nature of porcine pseudorabies, its existence is not suspected. Only when the virus breaks away from its swine reservoir and spreads to cattle is its presence on Midwestern farms made known. The transmission of the virus from swine to cattle is thought to take place when the noses of infected hogs come into contact with abraded areas of skin on cattle. Carcasses of cattle dead of the disease, if gnawed by rats, serve as a fresh source of virus from which a rat population can become infected. A cycle of rat to swine to cow and back to rat is thus possible.

Epidemiology of Swine Influenza.

The other animal disease whose epidemiology is to be discussed this afternoon is swine influenza. Swine influenza may be defined as an acute, highly contagious respiratory disease of hogs caused by *H. influenzae suis* and the swine influenza virus.[14] Its onset is sudden and the morbidity rate in an infected herd approximates 100 per cent. Fever, anorexia, prostration of an extreme type, cough, and a rapid, peculiar, abdominal type of respiration are salient features of the disease. Leucopenia is

usually to be observed. The period of illness is short, varying from two to six days, and, in uncomplicated cases, recovery is almost as sudden as the onset.

The disease occurs annually among hogs in the Middle Western states and is rather strictly seasonal in its incidence. Epizoötics seldom begin before October and have usually run their course before Christmas time. The disease apparently completely disappears during the eight or nine months intervening between its annual outbreaks. The bacterial component of the etiological complex, *H. influenzae suis*, can persist indefinitely in the upper respiratory tracts of some recovered swine. However, similar persistence of the virus cannot be demonstrated. The whereabouts of the virus during the interepizoötic periods and the origin of that infecting the first cases in the succeeding epizoötic have only recently been exposed.[15] It has developed that a rather complicated process is required. This involves an intermediate host, and in addition the intermediate host has a required intermediate host of its own. The swine lungworm is the actual carrier of the virus, but, since the lungworm must pass its first three developmental stages in an earthworm, the latter becomes of great importance as an innocent but essential bystander in the epidemiology of swine influenza.

The lungworm cycle, as determined by the *Hobmaiers*[16] and by *Schwartz* and *Alicata*,[17] may be briefly summarized as follows. The fully embryonated eggs are laid by the adult female lungworm in the bronchi of the swine she infests. These are coughed up, are swallowed, and reach the outer world in the feces. Their further development then is dependent upon the ova being ingested by earthworms. Once within the earthworm, the lungworm eggs hatch and the larvae develop to the third or infective larval stage. They persist in this stage within the earthworm until it is ingested by a hog. In the hog, the lungworms undergo two further developmental stages, finally reaching the swine respiratory tract and becoming adults. The whole of this cycle can occupy a space of several years for its completion, or under the most favorable conditions can be completed in slightly more than one month. Lungworms constitute a very common parasite in swine reared under the usual farm conditions.

In the transmission of swine influenza virus, the cycle, as far as the lungworms in their earthworm intermediate hosts are concerned, is the same as that just described. Lungworms in the respiratory tracts of swine during the acute stage of influenza lay eggs just as do those in normal swine respiratory tracts. However, the larvae and adult lungworms developing from such ova are carriers of swine influenza virus. A very interesting and puzzling feature of the transmission of swine influenza virus by the lungworm is that virus cannot be detected by direct means either in the larvae in their earthworm intermediate hosts

or in the adult lungworm after its transmission to its definitive host. It appears to be present in an occult or masked form, and knowledge of its presence in the intermediate host is furnished only by its subsequent behavior under very specialized conditions in the swine respiratory tract. Swine infested with lungworms that are carriers of this masked swine influenza virus remain normal to all appearances and there is no way of detecting directly that they are actually carrying swine influenza virus. However, such swine are in a very precarious situation as far as their eventual well-being is concerned, because all that is required to bring them down with a severe or perhaps even fatal attack of swine influenza is the application of some stimulus, of itself relatively harmless. Several such provocative stimuli have been used, but the one that has proved most regularly effective consists in the administration of multiple intramuscular injections of the bacterium *H. influenzae suis*.

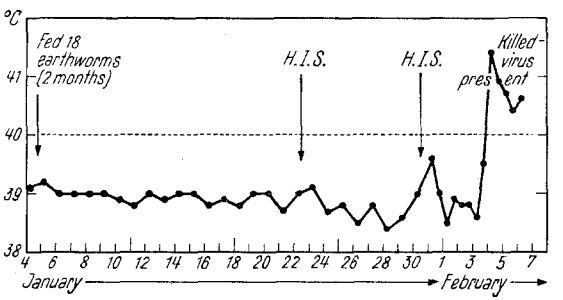

Fig. 1. Swine 2200. Fed 18 earthworms that two months previously had ingested embryonated lungworm ova from a pig with swine influenza. Swine 2200 developed clinically characteristic swine influenza after the second intramuscular injection of a suspension of *H. influenzae suis* (H. I. S.).

A typical experiment shown in Figure 1 will illustrate the usual sequence of events. In this particular experiment Swine 2200 was fed earthworms which two months previously had ingested lungworm ova from a pig with swine influenza. The pig remained normal after the earthworm feeding. Subsequently it was given two intramuscular injections of a suspension of live *H. influenzae suis* and on the fourth day after the second injection came down with clinically characteristic swine influenza. The findings at autopsy on the third day of illness were characteristic of an acute swine influenza, and swine influenza virus was demonstrated in its respiratory tract by mouse inoculation.

A very large series of such experiments have been conducted, and while only little is known about the mechanism involved, a number of facts indicating its importance in the epidemiology of swine influenza are at hand. It is known that swine influenza virus in its masked form can persist for at least as long as 16 months in third stage lungworm larvae in their intermediate earthworm hosts. Furthermore, it can persist for at least an additional three months in association with adult lungworms in the respiratory tracts of their swine hosts without giving any evidence of its presence. This constitutes a total elapsed time of

19 months between the case of swine influenza supplying the virus and the hog eventually becoming infected with it. It is apparent that this is over twice the time which must be accounted for to explain the survival of the virus from one outbreak of swine influenza to the next.

The sequence just outlined, whereby swine influenza virus can be transmitted from swine to swine through a complicated intermediate host arrangement, is rather strictly seasonal. The experiments take place as described if they are conducted between September and April, that is, during the fall, winter, and spring months. However, experiments carried out from May to September have as yet, during two summers, yielded only negative results. The failure of the virus to cause infection by way of its intermediate host during the summer has no explanation, but all the evidence at hand indicates that this failure is due, not to the inability of the worm intermediate host to transmit virus in its masked form, but to failure of the provocative stimuli that are applied to render the masked virus infective. An endocrinological basis for this state of refractoriness is suspected, and, although its explanation is not clear, it does fit very well with the known seasonal incidence of swine influenza under field conditions.

The probability that the mechanism described is the one which actually accounts for the interepizoötic persistence of swine influenza virus was considerably strengthened by the observation that, in some instances at least, earthworms dug on Middle Western farms, where swine influenza is of annual occurrence, contained lungworms that were harboring masked swine influenza virus. Swine fed these naturally infected lungworms came down with characteristic swine influenza after an appropriate provocative stimulus had been applied.

The role played by lungworms in the epidemiology of swine influenza may be briefly summarized as follows. Lungworm larvae from pigs with swine influenza harbor swine influenza virus throughout their development both in their intermediate host, the earthworm, and in their definitive host, the swine. The virus apparently lies latent within the lungworm after the parasite has finally migrated to the swine respiratory tract, and is only liberated or activated to cause infection when a provocative stimulus is applied.

Furthermore, such stimuli to be effective must be employed during the late fall, winter, or early spring months. During the summer, potentially infected swine are refractory to provocation. The observation that earthworms containing naturally infected lungworms can be demonstrated on Middle Western farms suggests strongly the probability that swine influenza virus actually carries over between epizoötics in this host under natural conditions.

Discussion.

It is apparent that in bovine pseudorabies and swine influenza we have two diseases whose epidemiologic patterns are very different. I should like for the rest of the time available to relate these contrasting epidemiologic patterns with contrasts in the behavior of the two viruses in their hosts and intermediate hosts.

Bovine pseudorabies is a sporadic disease occurring frequently as isolated cases, while swine influenza is an epizoötic disease infecting all susceptible animals in swine herds that it involves, and almost annually spreading over large areas of our Middle Western hog-raising states. The sporadicity of bovine pseudorabies is quite obviously associated with its non-contagiousness, while the widespread nature of swine influenza outbreaks quite as obviously results from the highly contagious character of the disease. It is apparent that the varied characters of both make them self-limited diseases, so far as their definitive hosts are concerned, and that an intermediate reservoir host is required to perpetuate the infections. Were it not for such a host, bovine pseudorabies, being non-contagious and uniformly fatal, could never progress from cow to cow, and swine influenza should also cease after it had spread widely through swine herds and had either killed or immunized the entire swine population.

The reservoir intermediate host for bovine pseudorabies must of necessity be one with which each individual case comes into direct contact. Because each bovine case constitutes in reality a blind alley infection, the virus in the intermediate reservoir host should be capable of propagation sufficiently to maintain an ever-present nidus of infection. It can be seen, thus, that because pseudorabies is contagious in swine this animal is admirably fitted to serve as a reservoir source of infection for cattle.

The reservoir intermediate host for swine influenza, on the other hand, need not directly come in contact with more than one member of a susceptible population. The establishment of a single case of swine influenza is sufficient to ensure its spread to other susceptible swine by contact. Furthermore, the extreme contagiousness of the disease in swine renders less essential any widespread distribution of virus in an intermediate host. Only a relatively limited nidus of infection in an intermediate host is requisite for the establishment of widespread infection during the next epizoötic period. There is, therefore, no necessity for the virus to be capable of spreading in the intermediate host: the only function that need be fulfilled is simple preservation of the infective agent from one outbreak of disease to the next. The swine lungworm possesses the requisite specifications, fitting it well to serve as the intermediate host for a disease of the character of swine influenza.

Bovine pseudorabies does not have a seasonal prevalence, while

swine influenza, occurring as a barnyard infection, has a rather strict seasonal incidence. The reason for this difference is quite clearly evident from consideration of the character of the respective viruses in their intermediate hosts. Pseudorabies virus in swine is at all times fully infective, both for swine and cattle, and its transmission to cattle is dependent therefore only upon opportunity. Swine influenza virus, on the other hand, is not infective *per se* in its lungworm intermediate host. Although it can probably be transmitted in its masked form to swine at any time of the year, it can be made to elicit infection only during a fairly definite season. Swine influenza must thus of necessity be a disease limited largely to the autumn and early winter months. Its epizoötics cease after a large proportion of the swine population has become refractory by virtue of immunization, and, although a new crop of susceptible swine are born in the spring, and a few may acquire masked swine influenza virus during the summer and early fall from lungworms they pick up during the ingestion of earthworms, a new epizoötic will not get under way until the seasonal refractory state of summer is past.

In retrospect, it seems quite evident that it would be impossible for bovine pseudorabies and swine influenza to have epidemiologic patterns other than the ones they are believed to have. The behavior of their causative viruses both in the intermediate and definitive hosts is such as to make only one epidemiologic pattern possible for each disease; that is, bovine pseudorabies could in no possible way be anything but a rarely occurring sporadic disease, while swine influenza must of necessity occur in widespread outbreaks at roughly yearly intervals. The characters of the two diseases as determined by their causative viruses, their hosts, and their reservoir intermediate hosts, are fixed in such a manner as to ensure the persistence of both for long years to come.

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