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NEWER CONCEPTS OF VIRUSES AND VIRAL DISEASES

D. G. McKercher, D.V.M., Ph.D.

OVER THE PAST 15 OR 20 YEARS our ideas concerning viruses and virus diseases have undergone some rather fundamental changes. In the past the term “virus disease” immediately implied an infection manifested by distinctive clinical signs and, in the more extreme interpretation, one characterized by an acute, and frequently fatal course. However, in the light of recent knowledge concerning latency and subclinical infection and the growing evidence that the host-parasite relationship is not static but an ever-changing complex, the old definition of a virus disease is true only in part.

This broader concept of the nature and activities of viruses in no way denies or minimizes the importance of those causing diseases such as hog cholera, rabies, and rinderpest; rather, it simply acknowledges the fact that in addition to these viruses there are others whose relationship with the host animal is, by contrast, so subtle as to make it at times difficult, if not impossible, to determine the nature of the role they play in disease and in disease production.

In keeping with this realization, there is a growing awareness that in virus infection clinical manifestation of disease is probably the exception rather than the rule, and that greater losses are inflicted by viruses that produce mild and insidious infections than by those responsible for diseases of a highly dramatic and spectacular nature.

The theme of this article can probably be best illustrated by reference to the viruses of cattle. Some of these viruses have been proven to be the cause of the infections from which they have been isolated; others have been isolated from animals displaying clinical signs of disease which, however, cannot be reproduced by inoculation of the viruses isolated therefrom; while still others have been isolated from animals regarded as being normal. I should like also to indulge in speculation as to the possible origin of some of the newly recognized viruses, and to suggest a means whereby their identification can be placed on a workable basis.

The first indication of the existence of viruses producing mild and subclinical infection in the bovine was provided by Olafson and his colleagues who recognized a disease which they called virus diarrhea (VD). This disease was followed in fairly rapid succession by the recognition of other syndromes with the result that at the present time there are a number of ill-defined clinical conditions of cattle, most of which were unheard of a dozen years ago. In addition to VD, mucosal disease, and infectious bovine rhinotracheitis (IBR) these include such conditions as “muzzle disease” which has been described in Pennsylvania, an infectious ulcerative stomatitis of cattle in Indiana and possibly in Pennsylvania and New York, and X disease in Saskatchewan. In addition, a number of conditions have been reported from Europe which appear to be closely related to, if not identical with, conditions described in this country.

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It has been established that some of these newly recognized conditions are caused by viruses whereas, in the case of others, evidence for viral etiology is of a circumstantial nature entirely.

As observed by Olafson, VD was manifested in a rather severe form characterized by fever, leukopenia, diarrhea, and by ulceration of the mucosa of the digestive tract, quite suggestive of rinderpest. At first the condition could be reproduced with a fair degree of regularity. However, later transmission attempts resulted in a high percentage of failures, suggesting that many of the experimental cattle had been previously exposed to the virus. Since the clinical entity had been recognized only a short time previously—and then to a rather limited extent—it was concluded that the disease must occur in many instances as a subclinical infection. Lately, it has been noted in New York state that few clinical cases of VD are seen but those which occur are very severe. It is possible that such cases involve animals that escaped infection at the age when the virus produces a relatively mild reaction and, as a result, lacked the immunity necessary to protect them against later exposure.

We recognized several cases of VD in California in 1953, and confirmed that the virus isolated was antigenically identical with the New York strain. Although we rarely, if ever, encounter the clinical infection in California, we have been almost uniformly unsuccessful in infecting cattle with the virus. In fact, wherever the disease has been studied, the great difficulty has been in obtaining susceptible cattle for experimental purposes. Unless subsequent study will reveal some other cause for the resistance of cattle to experimental infection, it can only be assumed that it is due to a widespread immunity, resulting from subclinical infection on a large scale.

Mucosal disease, while much less thoroughly understood than VD, would appear to fit into much the same infectious and epizootiological pattern. Here too, it has been demonstrated that subclinical cases of the disease occur. It is possible that in areas where mucosal disease has been indigeneous for some time, failure to transmit the infection might reflect the existence of a widespread immunity among the cattle population, resulting, as in the case of VD, from subclinical infection with the virus.

While IBR is generally manifested as a distinct clinical entity and little difficulty is experienced in reproducing the syndrome by inoculation, there is increasing evidence that subclinical infection with the virus of this disease does occur. In addition to the detection of IBR antibody in the serum of cattle with no previous history of IBR infection, it has been found experimentally that when the virus is inoculated intraocularly, or if the infection is transmitted by contact, the clinical response is frequently so mild as to be undetectable under field conditions.

Catarrhal vaginitis of cattle is another disease which appears to be characterized in many cases by a mild or subclinical course. It has been found that apparently healthy cattle carry antibodies to the agent without there having been any record of a previous attack of the disease. Even newborn calves were found to possess neutralizing antibody to the virus. The fact that the virus has been isolated from the brain of a bovine fetus obtained at a slaughter plant indicates that prenatal infection with the virus can occur.

Losses from these diseases are, to some extent, of a direct and obvious nature resulting from lowered milk production, and possibly abortion in the case of VD. Reproductive failures of various types appear to be associated with vaginitis infection while all are accompanied, to a certain extent, by loss of condition. However, it is undoubtedly the inapparent losses exacted by subclinical infection that represent the greater economic loss. These losses are difficult to ascertain because of the absence of the normal standard to which reference can be made. What is considered normal is undoubtedly substandard from the point of view of the hypothetical ideal.

I should now like to mention another group of viruses, much less well defined as to clinical disease production but which are quite distinctive in their biological properties as viral entities per se. These
viruses, all of which have been isolated by tissue culture methods, present a problem because they have been isolated only from animals displaying symptoms of disease. On the other hand, they sometimes cause only a mild infection, but most frequently they produce no response on experimental inoculation. Reference to several of these viruses with which we have dealt over the past two years will illustrate the nature of the situation regarding these agents.

We have isolated two different viral agents from cattle affected with shipping fever. Both were recovered with some difficulty from the nasal secretions of acutely ill animals, suggesting that the amount of virus was minimal when the isolation attempts were made. The first isolate, which is apparently a member of the Myxo group of viruses, since it gives a positive hemadsorption test, produced a mild reaction, which was manifested as a slight fever, in only one of several calves inoculated. However, virus was recovered for several days from the nasal secretions of all the animals inoculated. This finding suggested that multiplication of the agent occurred. The second isolate, which was also recovered from cases of shipping fever, produced no reaction in calves on inoculation. Unfortunately, no serology has as yet been done with this isolate. However, in the case of the first isolate, the animal from which it was recovered demonstrated a rise in antibody titer and other cattle in the outbreak were found to possess high titers to this virus several weeks following the attack. Low titers to the virus were found also in the serum of animals which, insofar as is known, had not experienced an attack of shipping fever.

Despite such evidence, it seems difficult to avoid the impression that the first isolate at least is involved etiologically in some manner, in the condition from which it was recovered. During the course of our studies on respiratory infections of cattle we have cultured the nasal secretions of hundreds of animals, yet we have recovered this virus only from cases of shipping fever. Thus, we have a virus which according to its serological classification and clinical associations appears to be at least a potential pathogen. It has, moreover, produced mild infection in a small proportion of the animals inoculated. On the other hand, antibodies to this agent have been found in normal cattle.

The picture which emerges is that of a virus, widespread in cattle but existing normally at the minimal survival level only. This might account for the failure to recover it from normal cattle. However, the presence of antibody in such animals would indicate that, at this level of activity, the virus can exert a mild antigenic stimulus. This, in turn, might explain the difficulty that has been experienced in producing infection with the virus. It is visualized that when the state of equilibrium, which presumably exists between the host and the virus, is disrupted by stress and possibly by other factors, the virus multiplies rapidly and paves the way for other agents, probably of a bacterial nature in most cases, which give rise to the clinical syndrome which is known as shipping fever.

Another problem with which we are confronted in California is an epizootic form of bovine abortion. Intensive studies of the condition over the past six years have failed to incriminate any of the
recognized bacterial causes of abortion except in the minority of cases. It was concluded, therefore, that a virus or viruses might possibly be involved. Efforts to isolate such an agent from aborting cows and aborted fetuses proved to be uniformly negative when egg and mouse inoculation techniques were employed. However, with the application of tissue culture techniques to the problem, two viral isolations have been made. These were recovered from the uterine contents of cattle collected within several hours of the abortions.

These agents are highly cytopathogenic in cultures of beef embryo kidney cells, producing complete destruction of the cells in from 24 to 36 hours. Neither gives a positive hemadsorption test. No clinical or thermal responses were produced when nonpregnant heifers were inoculated, and pregnant guinea pigs remained clinically normal and gave birth to normal young at the term following parenteral inoculation with these agents. Their effects on pregnant cattle have yet to be determined. Thus far, no serological studies have been carried out so that the distribution of these viruses among cattle is not known.

Little can be said regarding the large group of viruses that have been recovered from normal cattle. Keeping in mind the fact that viruses are obligatory, intracellular parasites, it is difficult to visualize how a large percentage of any cell population can be infected without some adverse effect being produced, either directly or indirectly, on the host animal. Nevertheless, there is no clinical evidence to indicate that a direct effect, at least, is produced. It is known that certain viruses multiply in cultures of the host’s cells in vitro without causing visible changes in the cells. From this it might be inferred that virus multiplication can occur in cells in vivo without any harm to the host. This would, of course, represent the ultimate in parasitism — a goal which appears to be the aim of every virus. The progenitors of these viruses might have caused disease in the distant past. However, through a reciprocating process of adjustment between the host and the parasite — a process which might have required centuries to perfect — the ideal relationship was ultimately attained. The viruses that today cause clinical disease might, in reality, represent those that are still in the process of attaining this acme of parasitism. Obviously, much has yet to be learned about the host-parasite relationship at the cellular level. It would now appear that until further light is shed on the various responses of the cell to virus invasion, the true significance of these viruses will remain largely a matter of conjecture.

It is tempting to speculate as to the origin of these newly recognized disease producing agents, and those recently isolated but which have not, as yet, been incriminated as the cause of the conditions from which they were isolated. Several possibilities present themselves. The first is that these are not new viruses in the strict sense of the word in that they existed previously and their presence was not detected until suitable media (tissue culture) became available for their detection.

This theory, although rather plausible, of necessity concedes that the diseases caused by these viruses existed in the past. It is very difficult, however, to believe that such distinctive clinical syndromes asVD, mucosal disease, and IBR could have existed earlier without their having been recognized. While some claim to have observed clinical entities characteristic of these infections years before they became generally recognized, such claims have always arisen when a new disease appears and few, if any, have ever been authenticated.

It is more likely that, rather than being viruses which existed per se in the past, these are mutants of either highly virulent viruses that existed previously or exist at the present time in other parts of the world, or of nonpathogenic viruses existing currently. In this event, the mutational process must have resulted in decreased virulence in the cases of some viruses and of enhanced virulence in the case of others. As a consequence, mild forms of deadly virus diseases appear whereas in other cases entirely new clinical syndromes are observed.

We might examine the first possibility to determine how it fits the observed facts.
We know, for example, that rapid passage of a virus through the natural host species does not always result in enhancement of virulence. This fact has been strikingly demonstrated in the case of the myxoma virus in Australia. A short time after its introduction among the rabbit population of that continent as a biological control weapon, the virus began to lose virulence, accompanied by a dramatic drop in its killing power and in the severity of the infection it produced. Is it not possible that a virus, even such as the highly virulent rinderpest agent, might have undergone a similar change and, instead of producing highly fatal rinderpest, it produces a disease bearing many of the clinical and pathological earmarks of rinderpest but characterized by a low mortality? In fact, even in Africa and Asia where rinderpest is enzootic, the disease is not nearly as severe at the present time as it has been in the past. When we consider the clinical and pathological manifestations of rinderpest, VD, and mucosal disease, one is impressed by the similarities of all three conditions. In essence, the difference between rinderpest on one hand, and VD and mucosal disease on the other, is largely a matter of degree. Therefore, might it not be possible that VD and mucosal disease are actually manifestations of infection with a markedly altered strain of rinderpest virus? The immediate objection to this postulation is that no antigenic relationship has been demonstrated between the virus of VD and rinderpest. However, we must keep in mind that a virus can exist in multiplicity of distinct antigenic types. In the case of bluetongue, for example, the virus exists as several immunological types, and immunity to one type provides little or no protection against a heterologous antigenic type. It would be surprising, in view of the great versatility of viruses in being able to alter their biological behavior, if the characteristics of field attenuation and alterations in antigenic behavior were confined to a few viruses only.

There is possibly less evidence for the likelihood of nonpathogenic viruses acquiring, through the process of mutation, the ability to produce disease. While the existence of a nonpathogenic bacterial flora in the animal body has long been recognized, only recently has the presence of analogous forms of viruses been detected. While the digestive tract has yielded the greatest number of isolates, isolations have been made also from the genital tract of cattle and from their respiratory passages. Inasmuch as many of these isolations have been made from clinically normal animals, it would not be any more presumptuous to consider them as being related to disease than are the bacteria which are also present and which, under normal conditions, are considered to be nonpathogenic. The nature of the stimulus inducing these nonpathogenic viruses to acquire hypothetical virulence is strictly a matter of conjecture. It would appear in this connection that the various microbial flora of the body are in a relatively fine state of biological balance. This has been demonstrated by the effect exerted on certain bacteria, normally regarded as being nonpathogenic, by the continued administration of antibiotics which kill off, or suppress, the normal bacterial flora. Is it not possible that an imbalance between the various bacterial populations would affect, indirectly, other forms of microbial life, including the viruses, with the result that certain of the latter which, under normal conditions are nonpathogenic, acquire the ability to invade and cause disease?

The effects of this postulated disruption of balance might be reflected in one or more of three possible ways: It might simply enable disease producing or potential disease-producing viruses, now released from the inhibiting influence of various other microbial populations, to cause disease in a manner comparable to that of certain bacterial species which, under ordinary circumstances, do not produce infection. Another possibility is that disruption of the biological balance results in alterations in the susceptibility of the body cells to viral invasion. Finally, there is the possibility that qualitative changes in the microbial flora of the body result in changes being produced in normally nonpathogenic viruses which endow them with the ability to produce pathogenic mu-
tants. Mutants arising in this manner would, obviously, produce new clinical manifestations of disease. It is possible that the viruses of VD and mucosal disease are actually mutants of viruses that were, at one time, nonpathogenic but which, either under the influence of the process described above, or through processes as yet unknown, they reverted — possibly but temporarily — to the virulent form.

Another possibility that would tend to account for the appearance of new clinical syndromes is based on the fact that viruses tend to alter their tissue and, frequently, their host specificities. This can be shown quite readily under experimental conditions while there is at least one example of this having occurred in the natural state. It was found recently that the IBR virus invades the vaginal mucosa of cattle, giving rise to a clinical condition which is entirely different to the infection produced when the virus localizes in the respiratory passages. The vaginal infection with the IBR virus, which is known as infectious pustular vulvovaginitis (IPV), is similar to, if not identical with, coital vesicular exanthema. If, as some believe, the IBR virus is responsible for coital vesicular exanthema as it occurs in Europe, then it is obvious that the virus must have remained localized in the genital tract of cattle for 75 years or more. However, when introduced under favorable conditions into the respiratory passages of cattle, it produced an entirely different clinical entity. Might it not be possible, therefore, that some of these supposedly new viruses are viruses which existed previously but, through some unknown circumstance, have altered their tissue and, in some cases, their host specificity with the result that new manifestations of disease become apparent?

Regardless of the origin of these viruses and the possibility that many more might be revealed by future investigations, the question of most immediate concern is the matter of their identity and relationship with each other. We do not know how many of these isolates are one and the same virus. With the isolation of “new” viruses being reported in almost every issue of scientific journals, we are in a situation analogous to that of the early bacteriologists when bacteria were being isolated almost at will. Unfortunately, we cannot adopt the form of taxonomy which the bacteriologists devised because of the failure of viruses to lend themselves to this type of classification. At this time the only solution appears to be the development of serological methods so that each new isolate can be typed and catalogued on the basis of its antigenic structure. However, this undertaking is fraught with problems. In the first place, use of the natural host species is not satisfactory for the production of antiserum because of the possible presence of multiple antibody in the same animal used for the production of the antiserum. In other words, the serum of an animal immunized to one particular virus, might contain antibodies to other viruses to which it was exposed during its lifetime, and which might be isolated from time to time from other members of the same species of animal. Therefore, each virus would react with the same antiserum, and the erroneous conclusion that they were identical agents would be drawn.

The use of birds for the production of antibody to the mammalian viruses, other than to those which can be propagated in chicken embryos, has proven most disappointing in our hands in that roosters did not produce detectable neutralizing antibody to the viruses inoculated. There are objections to the use of rabbits for the reason that the serum of many contain nonspecific neutralizing substances for certain of the cattle viruses. The same problem has been encountered in connection with some of the viruses of human origin but it has been circumvented by using a number of different species to produce antibody. In this way, typing sera have been developed against most of the so-called “orphan group” of viruses of man.

There appears to be no reason why the same procedure cannot be followed in the case of the viruses of cattle and of other domestic animals. It might be well to centralize such an activity where, ideally, viral isolates could be submitted for serological identification, much as cultures of
Salmonella are submitted to typing centers. Until such time as a coordinated effort of this nature and scope is accomplished, the problem presented by the "orphan viruses" as well as by the newer viruses of pathogenic disease producing potential, will continue to grow.

Summary

It appears that the main challenge to the virologist today is not the conquest of viruses that produced the plagues of old as these viruses have long been recognized and measures developed against them. It appears that the day is gone when new pandemic-producing viruses are likely to make their appearance. The challenge is, instead, the elucidation of virus infections of an incipient nature — infections which are manifested possibly in many instances under the guise of complexes; infections in which multiple etiology, and the interplay of environmental, meteorological, and biological factors are all involved in a process which, in some cases rarely, and in others never, manifests itself as a clinical syndrome.

Interprofessional Relations

(Continued from page 14)

highlighted the various activities of each profession and we in veterinary medicine feel that we have been able to disseminate much information on veterinary medicine to other health professions by this means.

8. Educational requirements and professional status — Educational requirements of each of the professions, to obtain their respective degrees, has been discussed at length by the council and the results of this discussion, as far as veterinary medicine has been concerned, have been very gratifying in that our professional status has been recognized and appreciated by the other professions.

Although our interprofessional relations in Illinois should be improved, we feel that through the interprofessional council, we have taken a big step in the right direction and it is encouraging to note that each of the professions is now placing more emphasis on their relations with the other professions.

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