VIRUSES AS PARASITES OF WILD MAMMALS

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Viruses are best known to us as agents causing specific diseases in domesticated species of animals; they have been intensely studied in this respect, almost to the exclusion of other aspects. It is the intention of this paper to describe and assess some of our knowledge of the behaviour of viruses as parasites of mammals in a natural environment.

Virus infection in a domesticated species gives rise, with few exceptions, to a short-lived and often explosive period of viral multiplication, after which the host's defensive mechanisms overcome the infection, with recovery of the host and apparent elimination of the parasite. Very few of the many hundreds of animal viruses at present known to us cause death of their host, other than in experimental conditions. From the virus's point of view there are two kinds of animal, those which are susceptible to infection and those which are not. The latter possess what is described as a species immunity which is an innate, inheritable insusceptibility to certain viruses. There are two defence mechanisms possessed by those animals which are susceptible to infection especially, though not solely, designed for overcoming viral invasion. Firstly, cells being attacked by virus secrete a virus inhibiting substance, "interferon" (Isaacs 1962), which is responsible for controlling initial viral multiplication—at least to some extent—until the second mechanism comes into operation. The introduction into the mammalian body of a strange or foreign protein or other antigenic substance elicits the synthesis of potent and very specific antibodies which neutralise, by combination, any such substance should it remain in the circulation or be subsequently introduced. Viruses are amongst the most potent stimulators of antibody formation and animals which have recovered from viral infection may possess sufficient antibody in every ml. of serum to neutralise as much as 10^4 or more of infectious doses of virus. The immunity of a host to a virus gained in this way is lifelong. Not all viruses in all circumstances are equally antigenic, as with many parasites there is variation in the host response (Dineen 1963), and prolonged association of host and parasite may produce some degree of mutual tolerance, though there is little evidence that this occurs, immunologically speaking, with viruses.

Thus, infection by a virus can only occur in an animal that is firstly of a susceptible species, and secondly has not previously suffered infection in its lifetime. There are only two exceptions to this rule amongst mammals, known to the writer, the phenomenon of immune tolerance, to be described later, and the special case of African swine fever.

The presence of antibody in a host's serum, derived from previous infection, can nowadays be detected and measured with relative ease and enables us to plot the areas of activity and the degree of invasion achieved by a virus in a mammal population. It has also given us the only specific method of establishing, with certainty, the identity of a virus.

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ADAPTATION

Though their mode of existence may appear to be very different, there is no reason to suppose that the principles applying to the survival of viruses are any different from those governing the survival of any other kind of parasite, and mutual adaptation between host and parasite in a natural environment is a first essential to survival. It is obvious that any impairment of the host's ability to feed, to keep up with the herd, to evade predators or of any one of the multitude of other factors necessary for its survival, would confer an equal disadvantage on the survival of the virus. It is imperative therefore that no single member of the normal load of parasites carried by a wild mammal shall tip the balance which is maintained during the usual life span of the host. It is thus necessary to deduce that infection by a successful virus must confer no measurable disadvantage on the host; that is, in contrast to the situation where domesticated species are infected, no detectable pathological reaction may result. We thus cannot recognise the presence of a virus adapted to a herd of wild animals by the presence of disease. Conversely, the presence of obvious signs of disease in a normally healthy population (which they all are) indicates the presence of a new or strange virus which is essentially not adapted to its host. Two obvious examples of this in Africa are foot-and-mouth disease and rinderpest, which cause severe disease in many wild ungulates. Both viruses may have become adapted to peaceful survival in certain species but those in which disease is the response to infection are clearly not the adapted or natural hosts. The natural hosts of viruses can only be found, firstly by their possession of antibody, secondly by their complete lack of pathological response to infection and thirdly by the detection in them and preferably by their excretion of active virus. The concept of viruses being associated solely with pathological reactions has given rise to many frustrations, especially in the medical field, such as are expressed in the phrase "viruses in search of a disease". No virus is searching for a disease, but for a quiet and comfortable habitat. Many viruses are now recognised which are not known to produce disease and have been found as apparently harmless parasites of cattle (Muscovici and La Placa 1962), pigs (Betts, Kelly, Lamont and Sheffy 1961) and humans (Melnick, Dalldorf, Enders *et al.* 1962, Ginsberg 1962, Stanley 1961). These viruses, not belonging to any disease, have been called "orphans", but are in fact well adapted to their hosts. The word adaptation is used in this connection by virologists in the opposite sense, to describe an artificial virus-host association in which the virus produces severe disease.

SURVIVAL

In comparison with our knowledge of other aspects of virology, our knowledge of the natural history and mechanisms of survival of viruses is little more than fragmentary. In the knowledge that all viruses are obligatory intracellular parasites, the obstacles to their survival and transmission to new hosts would seem formidable. Most of our observations have perforce been made in situations where disease has been the axis of the problem, where host and parasite have not been adapted. This has, understandably, been regarded as the only "important"

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aspect of the existence of viruses, as of many other mammalian parasites.

There are probably as many routes of transmission to new hosts and mechanisms of survival from season to season as there are species of virus. Few, if any, are completely understood, but some knowledge has been gathered over the last few years of intense activity in virology, which indicates some of the ways in which viruses might survive from season to season and through succeeding generations of hosts.

Long developmental cycles

Most viruses, at least in a domesticated environment, multiply rapidly in their hosts, viraemia lasting at most a fortnight, usually a few days; in addition, incubation periods are generally short. Such behaviour in a contagious infection, giving rise to rapid serial transmission or to an explosive panzootic in a natural situation, would result in the rapid sterilisation of the host community due to its resulting acquired immunity and thus to the limitation of the spread of virus. Some viruses however, have long and irregular incubation periods, release of active virus into the system taking place at long and irregular periods after initial infection. Rabies exhibits this type of behaviour, incubation periods of many months having been recorded, thus resulting in longer host to host cycles in a given community and in greater geographical dissemination. This virus, thought to have been introduced into southern Africa at about the turn of the century (Henning 1956), has not, as far as can be seen, become truly adapted to a wild host, apparently always causing sickness and death of all its hosts excepting possibly certain species of bats. The recently reported eradication of this disease from Southern Rhodesia, with its relatively high population of susceptible wild mammals (Shone 1962), indicates that this virus is able to survive sporadically but successfully in domesticated species.

Reservoir situations

Apart from the two exceptions mentioned earlier, no virus-host relationship amongst mammals is known to exist in which virus is occasionally or continually present in the blood of a host. Though considerable contention exists in certain quarters, the supposition that virus can circulate in the presence of antibody is untenable.

Dynamic reservoir systems must of course exist, surrounding every animal community to which a virus has become adapted, and passage from host to host must occur, but such systems, as detected by the occurrence of disease in contact domestic stock, are very poorly defined and have been very little studied. Plowright (1963) has recently demonstrated the existence of a reservoir system of malignant catarrhal fever ("snotsiekte") virus in wildebeest in East Africa, and du Toit (1962) has considerably elucidated the part played by cattle in maintaining bluetongue virus which is innocuous in cattle but pathogenic in sheep. There must be many other virus reservoir systems but few, if any, have been defined. Many isolations of pathogenic organisms from sick or dead wild animals have been reported (McDiarmid 1960), and conclusions have been too readily drawn, often on single isolations in abnormal conditions, to incriminate species and genera on evidence which does not withstand even superficial examination. The supposed "wild animal reservoirs" of disease in Africa are too often of this

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type, the enthusiasm to incriminate wild species as reservoirs of disease of domestic stock having reached the stage where, for example, the quagga has been cited as a reservoir of the virus of African horsesickness (Hagan 1943).

In any assessment of the part played by wild mammals as reservoirs of virus infection, susceptibility to clinically observable disease indicates clearly in the light of the foregoing that such an animal does not, in its natural state, normally come into contact with the causative virus. Insusceptibility to observable disease, coupled with the demonstration of antibody in a reasonably high proportion of adult animals, would, on the other hand, indicate close or frequent contact with the virus. Whilst ultimate proof would depend upon detection of active virus in apparently healthy individuals, experience of a viral infection in a community of animals can be detected by its indelible fingerprint in the hosts' sera. The response of many species of wild animals to rabies, rinderpest and foot-and-mouth disease indicates the absence of resistance, tolerance or mutual adaptation, and the nature of the true reservoir, if any, must be sought elsewhere.

There has been considerable effort over the last 50 years to incriminate the bushpig and the warthog as reservoirs of African swine fever virus, much of it based solely on the apparent similarity of these with the domestic species. In spite of many thousands of these animals having been shot, especially in Kenya where a bounty has been in force since about 1920, virus has only been detected in warthog at a time when the disease was active also in domestic pigs (Steyn 1928, 1932). It was not detected in either species in Kenya until 1954 (Hammond and de Tray 1955), and has not, as far as is known, been detected since. No serological surveys have yet been carried out. The virus has never been detected in *Potamochoerus*; on one occasion it maintained itself in domestic pigs, in spite of stringent quarantine measures, for a period of five years (de Kock, Robinson and Keppel 1940) in an area where neither warthog nor bushpig occur (Thomas and Kolbe 1942). The observation that African swine fever virus was not pathogenic in fifteen experimental bushpig, but partly so in two experimental warthog, suggests that the former is a more likely natural host of the virus than the latter. These are the only recorded experiments with wild African pigs and were carried out by Montgomery in 1912, to whose remarkable work on this disease the writer wishes to pay special tribute. No experimental work approaching the calibre of Montgomery's has been done until very recently (Malmquist and Hay 1960).

Intracellular survival in the presence of antibody

Survival of virus within an infected host requires finding a niche where humoral antibody cannot penetrate. Antibodies do not, in general, penetrate within living cells and viruses adapted to existence within living cells without causing their destruction can thus avoid the host's antibodies. In the last few years a great many viruses have been discovered surviving in this way. The use of primary cultures of monkey kidney cells for the production of commercial quantities of poliomyelitis and other vaccines has exposed the site of survival of more than forty different viruses in wild *Macacus rhesus* monkeys caught in India and the Philippines (Scherp 1963). Some of these have been found in as many as 70 per cent of animals; they are

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not pathogenic and survive in the kidneys when effective amounts of antibody are present in the blood of their hosts (Meyer *et al.* 1962). They remain "latent" within the host's cells and only become evident when these cells are removed from their normal environment and are cultured *in vitro*. The best known of these—S.V.40—when inoculated into young Syrian hamsters gives rise to malignant tumours (Borman, Grubbs and Young 1962). This, apart from raising philosophical eyebrows, demonstrates another type of host reaction to infection by strange viruses. A similar reaction has been demonstrated by Adenovirus-12, an innocuous inhabitant of the human respiratory tract (Trentin, Yabe and Taylor 1962). Sixteen viruses have been detected in *Cercopithecus aethiops* in southern Africa (Malherbe, Harwin and Ulrich 1963) in the same way as those in rhesus monkeys and though we have no reliable knowledge of the degree of immunity present in the host, no detectable disease has been associated with these viruses. Foot-and-mouth disease virus has similarly been shown to be present in the kidneys of cattle for periods of up to 90 days after infection (Hess, Bachrach and Callis 1960), and van Bekkum has demonstrated the excretion of small quantities of this virus, sufficient to infect mice but not cattle, in the saliva of infected cattle up to five months after apparent recovery from the disease (van Bekkum, Frenkel, Frederiks and Frenkel 1959). Others have indicated how convalescent animals can spread the disease (Dzhupina and Sviridov 1963). A further example of this type of survival mechanism has been shown in the persistence of sub-viral particles (these being genetic material only) of S.V.40 virus within cells (Gerber 1963) in a manner reminiscent of the behaviour of some bacteriophages.

The history of smallpox—a virus of which the human is the only known host—and of many other viruses with their long periods of apparent inactivity, strongly suggests that similar methods of survival are utilised. Rabies virus, thought to have been introduced into North America from Europe in about 1830, has recently been found lodging in the brown adipose tissue of bats (Sulkin 1962), having thus apparently found a means of peaceful adaptation in a new environment, as it may also have done in the spotted skunk of North America (Johnson 1959).

TRANSMISSION

The transmission of a virus from such situations as have just been described similarly requires avoidance of contact with host antibody, in addition to the hazards of other physical factors which rapidly destroy most viruses once outside the host. Very few viruses are sufficiently hardy to withstand desiccation, sunlight or radio-active fallout without special protection. The discovery of viruses in kidneys, salivary glands and respiratory tracts leads at once to an obvious means of liberation to the exterior and to new susceptible hosts without coming into contact with antibody. S.V.40 virus has indeed been obtained from the urine of infected monkeys and it is well known that poliomyelitis virus, the attenuated strains of which are innocuous inhabitants of the cell wall of the human gut, can be excreted in the faeces of infected individuals for long periods after infection, and after the development of antibodies. The salivary glands offer a similar escape route for foot-and-mouth disease virus.

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Release of virus from antibody

In normal circumstances, admixture of serum antibody with virus results in an irreversible neutralisation of virus. Recent work has shown however, that experimentally it is possible to dissociate this complex and to recover active virus from the mixture (Mandel 1960, Brown and Cartwright 1960). One method makes use of trypsin and it is thus possible that virus escaping into the bloodstream and neutralised by antibody might subsequently be liberated by, for example, the digestive processes of ectoparasites. It has long been supposed that intermittent escape of small quantities of virus into the circulation is necessary to maintain the lifelong immunity that infection confers. Another, little-studied phenomenon of great interest in this context is the presence in suspensions of some viruses, notably that of African horsesickness, of small numbers of particles which, *in vitro*, are not neutralised by antibody (Polson 1956).

Immune tolerance

The phenomenon of immunological tolerance, whereby an antigen introduced into the system before or very soon after birth, is treated by the host as if it was a natural part of the system, and no immune response is elicited, would be perhaps the most admirable method for a virus to evade a host's antibodies. There are indeed some examples known of the use of this pathway for survival. Lymphocytic choriomeningitis virus (LCM) has adapted itself to certain strains of laboratory mice in this way and has become a serious nuisance in some laboratories, for the presence of one virus in the system interferes with others that are introduced. Mice born with this virus in their systems do not develop immunity and are true carriers of infective virus, which is adapted to the stage where it is not pathogenic. The same virus, when inoculated into intolerant mice, is pathogenic and immunogenic (Medawar 1961, Hotchin, Benson and Seamer 1962, Volkert 1962). Similar situations have been demonstrated in birds (Rubin, Fanshier, Cornelius and Hughes 1962) and the phenomenon of immune tolerance has been demonstrated experimentally for some other viruses in mammals (Niven *et al.* 1952, Law and Moloney 1961).

Considerable evidence for the use of this mechanism of survival by the virus of malignant catarrhal fever in wildebeest has been found in East Africa (Plowright, Ferris and Scott 1960, Plowright 1963). Virus has been recovered from the blood of gravid adults, from foetal spleen and from the blood of very young calves and the presence of a continuous viraemia for as long as eight months has been shown. The virus is not pathogenic in wildebeest calves, it is not contagious and considerable evidence exists for trans-placental passage.

Immune tolerance is one exception to the rules of immunology, African swine fever (and possibly equine infectious anaemia (Dreguss and Lombard 1955)) is another. This virus is of great interest in that almost 100 per cent of infected domestic pigs die and the few survivors suffer a continuous viraemia with no apparent antibody formation. In bushpig it is apparently innocuous (Montgomery 1921) and transmission is very difficult to achieve (de Tray 1957). In cell cultures *in vitro*, this virus has a predilection for the cells of the reticulo-endothelial system; the cells of bone-marrow and macrophages (Malmquist and Hay 1960, Malmquist 1962). The hypothesis for the exceptional behaviour of this virus in domestic pigs is offered

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here, that the virus infects and destroys those very cells that are responsible for the antibody formation thus stripping the animal of its ability to respond immunologically to infection.

The vector-borne viruses

Apart from the virus of North American hog cholera which has an extremely complex life cycle, making use of a number of hosts (Shope 1959), the great majority of viruses coming under this heading are obligate arthropod-borne parasites.

Where a vector is a necessary vehicle for virus transmission this opens the way to channels of survival other than in mammalian hosts. It is necessary firstly for the virus to pass in a blood meal to a vector during the period of viraemia in the host, which is, in experimental animals, brief. These viruses undergo an innocuous cycle of multiplication in the vector (lasting one to three weeks) before being passed on to another susceptible host. That this is a purposeful path of survival however, is demonstrated not only by the biological success of viruses such as yellow fever, bluetongue, Rift Valley fever, and many others in this category, but by the concentration of the virus in the salivary glands of the vector after multiplication. The arthropod-borne viruses are therefore markedly seasonal in their cycles of activity and their apparent inter-seasonal eclipse is of great interest. The problems in Africa in this respect are not different from those elsewhere and have been thoroughly analysed by Reeves (1961) amongst others. There is now some evidence that trans-oval passage can take place with the tick-borne viruses (Singh, Pavri and Anderson 1963) and survival of virus through metamorphosis in the tick has been established for some viruses, including that of Nairobi sheep disease (Burgdorfer and Eklund 1959, Lewis 1946) thus demonstrating one means of survival in a vector through two or three seasons. In spite of much elaborate, careful and painstaking investigation, no uncontroversial evidence has been found in support of the supposition that the mosquito-borne viruses make similar use of their vector's life cycle for their over-winter survival. Some evidence has been found for the survival of certain arthropod-borne viruses in hibernating mammalian and non-mammalian hosts (Gerbhardt and Hill 1960) but this has not yet provided an answer for the great majority of these viruses. Much attention has been paid to the part that might be played by migratory birds, both as carriers of virus infection and as vehicles for hitch-hiking vectors. The world-wide distribution of histoplasmosis for example, a birds transmitted infection, indicates what could have been achieved by viruses using this mean- of dissemination, and yet the arboviruses remain markedly restricted geographically. The part played by birds as virus hosts is being investigated for the reason that their immune reaction is certainly different from that of mammals and prolonged or intermittent viraemia can occur (Reeves, Hutson, Bellamy and Scrivani 1958).

The release of virus from antibody-virus complex by tryptic digestion, referred to earlier, or by other means (Fenner 1962), could apply to cycles of arbovirus transmission as a means of avoidance of host antibody. However, this mechanism, one would expect, if popularly used, should result in a much greater incidence of arbovirus infection than exists, whereas these viruses, even in what is believed to be their natural habitat, occur in peculiarly random and irregular cycles. In short, the use of alternative non-mammalian hosts, as could occur,

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especially with vector-borne viruses has not, so far, yielded evidence bringing us near to an understanding of their methods of inter-seasonal survival.

The solution of this and of many of the survival and transmission problems of viruses would seem therefore to depend upon the study of these sub-cellular creatures in circumstances which must essentially be divorced from those in which they are associated with the diseases which have given many of them their names.

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