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Vertical Transmission of Viruses

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INTRODUCTION

The expression "vertical transmission" refers to the direction of transmission when family trees are drawn on paper. They are represented as lines beginning from a trunk (the ancestors) at the top of the page, the descendants occupying the proliferating branches further down the page. It was because such diagrams looked like the branching digits of a bird that the word pedigree (pied de grue = foot of the crane) came into our language. Relationships that are in this sense vertical have been the classical concern of the geneticist, and the hereditary elements are transmitted down the page, and down from generation to generation. The vertical axis is time, and a given hereditary unit (gene) can in this way be charted over the course of many generations. This is in contrast to the transmission of materials between individuals who are living at the same time, this being represented as a more or less horizontal line on the diagram. Horizontal transmission can take place between related or between unrelated individuals.

Many infectious agents are transmitted vertically, down from generation to generation, whereas others are transmitted horizontally between contemporaries. This article surveys present knowledge about the vertical transmission of viruses. It provides an opportunity to bring together under one heading a great diversity of interesting virological phenomena.

Viruses have been one of the most successful vertically transmitted infectious agents. One reason for this is that certain viruses are uniquely

endowed to persist inside cells, often throughout the life span, without seriously disturbing function or otherwise interfering with host viability and without inducing the immune responses that would eliminate them from the host.

Perinatal and Postnatal Transmission

Having broadly defined vertical transmission, it is necessary to further narrow the concept. In mammals virus infections are often transmitted from parent to offspring at some time after birth. Examples are shown in Table 1. Viruses shed into the milk are obviously transmitted in infancy. Other viruses such as herpes simplex in man can be transmitted to a child whenever the parent develops a cold sore. In the case of varicella-zoster virus, a grandparent suffering from shingles (zoster) transmits the infection directly to a grandchild who then develops chicken pox (varicella).

If an infection is to be delivered to the infant shortly after birth, it is necessary that the parent experiences one of the following. (i) The parent experiences a primary infection at this time, an event that is unlikely to occur very frequently. (ii) The parent experiences a reactivation of a latent infection. Certain persistent viruses are activated during pregnancy (BK and JC viruses in humans), and this may give the opportunity for transmission in the immediate postnatal period. In various parasitic infections, both protozoan and metazoan, the parasite is activated in late pregnancy and lactation so that it appears in milk or saliva and infects the young. (iii) The parent is continuously shedding virus in the course of a persistent infection. An example of this would be a mother who carried hepatitis B virus in the blood, especially when HBe antigen is present (67), with high titers of infectious virus (Dane particles). She may infect her child during or shortly after birth.

Sometimes a virus infection is transmitted to the offspring during the actual process of birth. If a mother is suffering from a herpes simplex type 2 infection of the cervix, the infant can acquire this infection while passing through the infected birth canal. This is referred to as perinatal transmission.

Although perinatal transmission and transmission after birth are strictly examples of vertical transmission, I shall not discuss them further. Instead I will restrict myself, at least as far as mammals are concerned, to antenatal transmission.

TABLE 1. *Postnatal vertical transmission of viruses*

Vehicle	Virus group	Virus	Specimen	Comments
Milk[a]	Retrovirus	Murine leukemia (Friend strain)	Mouse	Transmission via gametes is probably the more natural route
		Mammary tumor virus	Mouse	
		Equine infectious anemia	Horse	Significance not known
	Flavivirus	Tickborne encephalitis	Sheep, goat, cow	Probably not of epidemiological significance in the maintenance of infection in the host species
	Paramyxovirus	Mumps	Human[b]	
	Herpesvirus	CMV	Human	
	Parvovirus	Rat virus	Rat	Possibly important
	Togavirus	LDH[c]	Mouse	
Feces	Togavirus	LDH	Mouse	Little known about vertical transmission of viruses in feces
Urine	Papovavirus	Polyoma	Mouse	
		BK, JC	Human	Significance not known
	Herpesvirus	CMV	Human	
Saliva	Paramyxovirus	Mumps	Human[b]	
	Herpesvirus	CMV	Human	Significance not known
			Mouse	Virus shed in saliva for long periods
		EB	Human	
	Togavirus	LDH	Mouse	
Skin/mucosae	Herpesvirus	Herpes simplex Varicella-zoster	Human	See text
Blood		Hepatitis B	Human	

[a] Various other viruses may be present in milk, but when enough virus is also shed into saliva, urine, etc., milk transmission is unlikely to be important.

[b] Human infection and salivary excretion of virus generally takes place during childhood, so that parents rarely infect children.

[c] LDH, Lactic dehydrogenase virus.

TRANSMISSION DURING FETAL DEVELOPMENT IN MAMMALS

There are many examples of viruses that are transmitted to the mammalian fetus during embryological development (Table 2). The table is not intended to be comprehensive, and numerous other viruses are very occasionally transmitted transplacentally. The pathogenesis of this type of infection has been surveyed (60). Long ago Burnet and Fenner (14) predicted that antigens presented to the fetus before the development of immune responsiveness would be regarded as self rather than nonself, and that immune responses to these particular antigens would therefore be minimal. This might enable an infectious agent to persist indefinitely in the individual after infecting the fetus, as seen in the case of mice that carry lymphocytic choriomeningitis (LCM) virus (see below). As it happens, mice congenitally infected with LCM virus do in fact produce antibodies, albeit of low avidity and not capable of neutralizing the virus. In any case, we know that many viruses such as the human viruses of the herpes group persist in the body in spite of the presence of antibodies, even when these are neutralizing antibodies. Also, children with congenital rubella (see below) produce rubella antibodies in spite of transplacental infection early in embryological development. Immune tolerance, however, refers to cell-mediated as well as humoral immunity, and a defective cell-mediated immune response may allow a virus to persist in spite of the presence of neutralizing antibodies.

But viruses often cause major damage with death of the fetus, as with smallpox or vaccinia in humans and equine abortion virus (equid herpes virus I) infections in horses. With some virus infections the fetus is less severely affected and may survive and be born, often with malformations (16). Such infections are generally less cytopathic in the fetus, and the mother experiences at most a mild illness. Rubella is a classical example.

Rubella

Fetal involvement follows primary infection of the mother during the first 3 months of pregnancy. She experiences little or no illness, so that the pregnancy is not disturbed, and the virus spreads in the bloodstream to reach the placenta. Infection is established here, and the virus is then discharged into the fetal circulation and causes foci of infection in the heart and other tissues (96). By this time antibodies are present in the maternal blood, and those of the immunoglobulin G class pass into the fetus and help control the extent of infection. The fetus itself makes anti-rubella antibody of the immunoglobulin M class, and probably the infected fetal cells are sources of interferon which protect uninfected cells and further prevent the spread of the virus. In addition, the fetus has considerable ability to repair and reconstitute damaged tissues. As often as not the pregnancy proceeds, and birth takes place. But the infant is small, perhaps as a result of growth-inhibiting substances produced from infected cells, and characteristic malformations may be seen in the heart, brain, eyes, and ears. These are a consequence of focal infection in the heart and in the blood vessels of key organs that were being laid down during the first 3 months of development. Maternal and fetal antibodies have failed to terminate the infection, and virus is still present in the infants throat and urine and sometimes in affected organs such as the lens. It is likely that the originally infected cells, and without much spread to uninfected cells, have given rise to clones of infected cells during the course of cell division. An effective cell-mediated immune response is needed to eliminate these infected cells, and this is missing in the fetus and in the infected infant. The congenitally infected infant sheds virus from the throat in the neonatal period and can infect susceptible nurses in the hospital. Only a third of these infants remain positive at 6 months of age and about 5% are positive at 1 year, and the amounts of virus shed are probably small, no longer providing a source of infection for others. Thus, although mothers sometimes infect their fetus with rubella virus, this is far from being an important route of virus transmission. In any case, many females are infected in childhood and the virus is eliminated from the body during recovery and the development of immunity. There is then no question of infecting a fetus later in life because immunity is lasting and the rubella virus does not persist in the body to remain a source of infection. The primary infections that occur during pregnancy and lead to fetal infection and malformation are important human events. But they are inevitably uncommon and unimportant as a method of virus transmission.

At least two other members of the *Togaviridae* are capable of causing intrauterine infection, but here again it is not an important feature in the transmission of these viruses in nature. Avirulent strains of hog cholera virus cause multiple malformations and death in the fetus when given to pregnant sows (38), and offspring of naturally infected mothers die in utero or are born showing congenital tremor and neurological lesions. Bovine diarrhea-mucosal disease virus causes

transplacental infection, often with extensive damage and death of the fetus. Live-born fetuses generally show growth retardation and malformation and clinical nervous disease (20).

Lactic dehydrogenase virus causes a persistent infection in mice, with a constant viremia. This virus shows an almost unique growth restriction, in that the sole cell type infected appears to be

TABLE 2. *Intrauterine transmission of virus infections*

Virus group	Virus	Species	Comments on transplacental transmission
Togaviridae	Rubella	Human	Congenital malformations
	Hog cholera (vaccine strain)	Pig	Probably important ecologically; leads to stillbirth or malformations in offspring (97)
	Lactic dehydrogenase virus	Mouse	Inapparent fetal infection; significance unknown
	Bovine diarrhea—mucosal disease virus	Cow	Fetal damage (cerebellar hypoplasia, etc.) with virulent or attenuated virus strain (40)
	Akabane	Sheep	Congenital malformations (71)
	Equine infectious arteritis	Horse	Fetal death
Herpetoviridae	CMV	Human	Fetal damage (cerebral hypoplasia, etc.)
		Pig	Fetal death or fatal disease in newborn
		Guinea pig	Fetal death; infected survivors occur?
	Varicella-zoster	Human	Rarely in late pregnancy; lesions usually present
	Virus of malignant catarrh	Wildebeest cattle	Fetal death in cattle; inapparent infection in wildebeest fetus
	Feline herpesvirus	Cat	Fetal death (35)
	Equine rhinopneumonitis virus	Horse	Abortion in mare (and experimentally in guinea pigs)
	Infectious bovine pneumonitis virus	Cattle	Fetal abortion
Poxviridae	Variola, vaccinia	Human	Fetal death
Reoviridae	Reovirus types 1 and 2	Mouse	Fetal or neonatal death (33)
	Colorado tick fever	Mouse	Fetal or neonatal death
	Blue tongue (vaccine strain)	Sheep	Malformations of central nervous system (69)
Arenaviridae	LCM	Mice	Fetal death
Parvoviridae	Feline panleucopenia	Cat	Kittens become chronic carriers; may have brain lesions (45)
	Porcine parvovirus	Pig	Fetal damage
	Bovine parvovirus	Cattle	Virus detected in fetal calf serum
	Kilhams rat virus	Rat	Fetal damage
	Aleutian disease virus	Mink	Inapparent fetal infection; significance unknown
	Minute virus	Mouse	Infected fetuses stay healthy?
Papovaviridae	Polyoma virus	Mouse	Fetus infected experimentally (55)
	Stump-tailed monkey virus	Stump-tailed monkey	Fetal infection occurs naturally (87)
Retroviridae	Equine infectious anemia	Horse	Fetal damage
Orthomyxoviridae	Influenza	Human Mouse	Evidence generally against transplacental transmission (52)
Miscellaneous	Hepatitis B	Human	Occurs in HBe antigen-positive mothers; peri- and postnatal transmission common

the macrophage. Infection is probably transmitted to the fetus across the placenta without serious effects on the offspring (18), but the importance of this route is not clear because the virus is also present for long periods in feces, and is shed in saliva, urine, semen, and milk, providing alternative sources of infection.

Cytomegaloviruses

Cytomegalovirus (CMV) is a medically important cause of fetal damage in humans. This nearly always follows primary infection of the mother during pregnancy rather than reactivation of a persistent infection. This virus is a supremely effective parasite, causing little or no harm, yet persisting for many years in the infected host and maintaining itself in the smallest and most isolated human communities. It seems likely that throughout human history most people were infected during childhood. Nowadays increased cleanliness and other changes in living have made transmission among children via saliva and urine less effective, so that up to 30% of young adults have no antibodies. There are therefore significant opportunities for primary infection during pregnancy.

Maternal infection with CMV is unnoticed, and as with rubella foci of infection are established in the placenta which lead to infection of the fetus. The newborn may suffer from hepatosplenomegaly, hepatitis, and/or thrombocytopenic purpura, but in most instances there are no signs of infection. Malformations are less obvious than in the case of rubella. The virus sometimes induces abnormalities in cerebral development that cause mental retardation, and defects in hearing are also seen. The vulnerable stage of gestation has not been clearly defined. Congenitally infected infants excrete virus in the throat and urine.

Pig and guinea pig CMVs also cause fetal infection and damage (23, 47), but in each case primary infection must take place during pregnancy. As with CMV in humans, this is not common under natural circumstances. Piglets are most likely to be infected postnatally from persistently infected sows. The infection is mild because it takes place under the cover of antibodies acquired from maternal colostrum and milk. Mouse CMV, although widely studied as a model for human infection, differs markedly in many of its features. Unlike human CMV it is not shed into the urine, and the striking involvement of the salivary glands of the mouse presumably reflects the importance of saliva in the transmission of infection in this species. More importantly, it is not transmitted to the fetus. A limited involvement of the placenta is seen after primary infection during pregnancy, and there have been confirmed reports of CMV deoxyribonucleic acid (DNA) in fetal tissues, but there is no acceptable evidence that this virus reaches the fetus. In spite of heroic attempts to produce fetal infection, including intravenous infection of the mother at all stages of pregnancy and blocking the reticuloendothelial clearance of injected virus by thorotrast treatment (C. A. Mims and J. J. Gould, unpublished data), all such manuevers have merely served to confirm and strengthen the original finds of Medearis (57). The mouse placenta is not established until about day 10 of pregnancy, and three cell layers separate maternal from fetal blood. Virus must become established in the placenta and grow through these layers, but since CMV has a leisurely cycle time in cells, the young have generally been born before there has been time for virus transfer to the fetus. This is a possible explanation of the failure of mouse CMV to infect the fetus.

Other Herpesviruses

The virus of malignant catarrh is particularly interesting because it illustrates the importance of the host species in vertical transmission. Infection is nearly always fatal in cattle, but there is a report (75) of a cow that became persistently infected during pregnancy and subsequently produced infected calves. These did not survive for long. The wildebeest is the natural host for this virus, and in this species the infection is completely subclinical and infected calves show a viremia which persists for up to 8 months. There is reason to suppose that the virus reactivates and reappears in the blood during pregnancy, and transplacental transmission is thought to occur in 25 to 30% of pregnancies. This leads to an inapparent infection in the fetus and no illness in infected calves. Intrauterine infection appears to be important in the natural maintenance of malignant catarrhal fever virus in wildebeest populations (74).

With Aujeszky's disease (pseudorabies), transplacental transmission is demonstrable experimentally and also occurs in infected herds (3). It results in abortion or stillbirth and is therefore not an important mechanism of virus transmission. There are many opportunities for postnatal transmission because immune sows continue to excrete the virus from the respiratory tract and in milk.

In ungulates, herpesvirus infections are generally lethal for the fetus, and it has been suggested (W. Plowright, personal communication) that this is partly because maternal antibodies are not transmitted across the placenta in these mammals. Various other herpesviruses are occasionally or experimentally transmissible

across the placenta (Table 2), but in no case is this a significant method of virus transmission.

Parvoviruses

Experimental infection of pregnant rats with Kilham rat virus leads to fetal infection (44). Some fetuses die, but others are born, and these may suffer from hepatitis or show cerebellar hypoplasia. The cerebellar lesions result from infection and destruction of the external germinal layer cells in the developing cerebellum. These cells are actively dividing and about to migrate and take up their position below the Purkinje cells, and their loss leads to severe hypoplasia of the cerebellum. Intrauterine infection has been recorded under natural circumstances among wild rats.

Feline panleucopenia virus passes the placenta during primary infection of pregnant cats and infects the fetus (45). The kittens may appear normal at birth but become chronic carriers and later develop ataxia due to cerebellar hypoplasia. This virus is excreted from intestinal epithelial cells into the feces and also into various other secretions and excretions. In this way it spreads with facility among young cats. There might be a theoretical role for vertical transmission of this virus in isolated communities of animals.

When pregnant mice are infected with minute virus of mice, a few fetuses are infected and contain large amounts of virus but appear healthy (43). Further studies are needed to assess the role of transplacental infection in the maintenance of this particular parvovirus in the host species.

Porcine parvovirus has been recovered from occasional batches of fetal pig kidneys (58, 78), so that intrauterine infection certainly occurs on occasions. When pigs are infected during pregnancy, the virus spreads across the placenta and infects the fetus, but fetal damage is the rule. Fetal death and mummification is known to be a cause of sterility in female pigs.

Bovine parvovirus infection is widespread in cattle, and antibodies to the virus have been detected in commercial batches of fetal calf serum (88). If this signifies fetal infection, the virus can be presumed to have spread transplacentally without seriously harming the fetus, but the importance of intrauterine infection is unknown.

Aleutian disease virus causes a persistent infection and viremia in mink, and this virus, like lactic dehydrogenase virus in mice, infects macrophages exclusively. Transplacental transmission has been demonstrated and would seem likely to be important because virus was present in 32 of 53 live fetuses tested (70), but horizontal transmission also occurs.

There is no information about intrauterine infection with dog parvovirus, nor for the various adeno-associated viruses. However, transplacental infection seems fairly frequent in the parvoviruses as a group. The fact that infected fetuses generally suffer damage would make transplacental infection for most of them, as studied, an inefficient mode of transmission. On the other hand, it is possible that the named host is not always the original natural host, and some of these viruses may well be transferred more effectively via the placenta in other host species.

Arenaviruses

When adult mice undergo primary infection with LCM virus they generate a vigorous cell-mediated immune response which, if the infection had been initiated intracerebrally, leads to meningeal inflammation, cerebral edema, and death. The infection itself is noncytopathic, and this is the classic example of an immune-mediated disease. If a pregnant mouse is infected intravenously the placentas are infected, the details depending on the virus dose and on the stage of pregnancy (61). The infection then spreads to the fetuses which die and are resorbed. Infection of placenta and fetus causes no histologically detectable damage, and at the time of fetal death the mother appears well. But her liver is infected, showing fatty change and necrosis, and 2 days later she becomes sick. Maternal sickness and fetal death are prevented by immunosuppression and this allows the fetus, which is heavily infected, to develop normally until birth. For unknown reasons the newborn die soon after birth.

Thus, transplacental transmission of LCM virus during primary infection of mice is complicated by maternal infection and immunopathology. Even with heavy immunosuppression, infected offspring fail to survive for long after birth. With LCM virus, all results must be critically scrutinized because of the immense differences in response that are seen according to the strains of virus and mouse that are used. Nevertheless, it seems probable that after primary infection, the transplacental route of transmission is far from being a natural or a successful one.

In contrast to this, mice persistently infected with LCM virus show immune tolerance, and infection of the placenta would then cause less damage. A smoother infection of the fetus by this route would be conceivable. Infection of the egg with LCM virus is referred to below. The other arenaviruses all have highly specific rodent hosts to which they are closely adapted. Persistent nonpathogenic infection is the rule, and when it has been tested, neonatal infection

leads to persistent and harmless carriage of virus. Although little work has been done on the transplacental transmission of these viruses, it would seem to be a possible mechanism for the maintenance of the infection in the natural host. These comments apply to Lassa fever virus in *Mastomys natalensis*, to Machupo virus in *Calomys callosus*, and probably to the other arenaviruses.

Papovaviruses

Most papovaviruses cause little primary pathology or damage in the infected host. They also persist for long periods in the body, so that reactivation during pregnancy might provide a source of virus for fetal infection. Polyoma virus persists in mice, often in noninfectious form, after infection in the newborn period. In such mice the virus reactivates during pregnancy, in the sense that titers are increased in infected tissues (56). It is not known whether this acts as a source of virus for infection of the fetus, but it has been shown that primary infection during pregnancy leads to fetal infection (55). Polyoma virus, therefore, could theoretically infect the fetus under natural conditions.

The stump-tailed monkey carries its own papovavirus, and this virus has been shown to be present under natural circumstances in all fetuses tested (83). Evidently some of the papovaviruses establish infection in the fetus, but whether this is transplacental or via the germ cells has not been elucidated.

Miscellaneous Persistent Viruses

Equine infectious anemia, a retrovirus, causes chronic infection and viremia in horses, and has been isolated from a naturally aborted fetus (42). Evidently this virus can infect and damage the fetus. It is also present in milk so that the transplacental route of infection, even if the infected fetus sometimes survives, is of unknown status.

Scrapie

Scrapie is not a conventional virus. It is referred to here because there have been suggestions that it is transmitted vertically in sheep, the natural host species. Facts about scrapie are discovered only when the research worker has shown great patience, care, and caution. This is particularly so with sheep scrapie, where tests for the presence of the agent must be made by inoculation of susceptible uninfected sheep and then observing these animals for about 3 years. The scrapie agent appears to replicate especially in the brain and spleen of sheep, and there is one report (72) that the agent was also detected in a placental cotyledon of an infected pregnant sheep. From the incubation period of the disease in inoculated test animals, it was concluded that fairly large amounts of the agent were present. Infection of the placenta could lead to fetal infection, but so far there is no conclusive evidence for this. Scrapie in the mouse has been more fully investigated, and in this species there is clearly no maternal transmission of the infection. The mouse, however, is not a naturally infected host.

Conclusions

In summary, transmission of infection to the fetus during pregnancy, although theoretically it might lead to immune tolerance and persistent virus carriage in the affected offspring, is nearly always an unimportant matter from the epidemiological point of view. With most viruses and in most species, primary infections during pregnancy are uncommon under natural circumstances. Persistent viruses are sometimes reactivated during pregnancy (e.g., malignant catarrhal fever virus in the wildebeest, see above), but for most viruses this does not appear to be an important source of fetal infection. The virus must be present in the blood of the pregnant animal at the right stage of gestation, and it must reach the placenta and be either carried across, leak across, or grow across this barrier to reach the fetus. The placenta is the obvious route for passage of an infectious agent from mother to offspring, but infection directly from oviduct or uterine wall would also be possible. In any case, the fetus must not be unduly damaged, and throughout this process the virus must contend with both maternal and fetal immune responses. Infection of the fetus, moreover, is generally inefficient, and fetal mortality or congenital abnormalities are the rule, arguing against the significance of this phenomenon in the maintenance of the infection in the species. Infection by natural routes (milk, blood, saliva, feces, urine) in the early postnatal period and under cover of passively aquired maternal antibodies would be a less demanding method of transfer of viruses to offspring (see above).

TRANSMISSION VIA THE GERM LINE—VERTEBRATES

If the ova or sperms are infected without being damaged, the virus can then be transmitted to the zygote and the developing embryo. This is by far the most logical and powerful method of vertical transmission. But it requires that the virus is not merely noncytopathic in the infected cells, but also that it does not interfere with the complex events of fertilization and embryologi-

cal development. The virus must also maintain itself in the rapidly dividing cells of the embryo. It must be shielded from immune responses which could inactivate it or damage infected host cells. The ultimate way of avoiding immune elimination is by inducing immune tolerance, and this must be complete enough for the infection to be maintained throughout postnatal life until the individual comes of reproductive age, at which time the virus must be present in a large proportion of the eggs or sperms. In spite of the demands of this mode of transmission it has been achieved by a number of fascinating viruses.

Retroviruses

Oncoviruses. Historically these were distinguished on morphological (electron microscopic) grounds, and types A, B, C, and D viruses are recognized. Type A particles are always intracellular and are precursors of B and C type particles. At least 20 strains of leukemia virus (type C viruses) are known which cause leukemia or lymphosarcoma in mice alone. In mice there are also various strains of mammary tumor virus (type B viruses) causing mammary carcinoma. Closely related to mammary tumor virus of mice are certain oncoviruses isolated from Old World monkeys, and these are called type D viruses. They include the Mason-Pfizer monkey virus, isolated from a rhesus monkey mammary carcinoma. The mouse oncoviruses infect and sometimes transform mouse embryo fibroblasts, and the development of sarcomas or leukemias in infected animals depends on the virus strain and on host genotype. Many of the tumors and some of the viruses are laboratory artifacts in the sense that virus strains have been artifically passaged and cause leukemia or lymphosarcoma in certain strains of laboratory mice. Similar viruses infect and cause leukemia in cats, cattle, and other mammals. Reptiles and birds also carry viruses of this type. Leukemia viruses have been isolated from primates, but so far, although oncovirus nucleic acid sequences have been detected in human cells, there is no generally accepted leukemia or mammary tumor virus of man (1).

In recent years most of the interest in these viruses has been in their molecular biology and their oncogenic potential. We now know a great deal about the viral polypeptides expressed on the cell surface, about their unique method of replication, and the part played by the viral ribonucleic acid (RNA)-dependent DNA polymerase (reverse transcriptase). The viral polypeptide involved in transformation has been identified for many of these viruses, but we still have little understanding of the precise mechanisms by which normal cells are transformed into malignant cells.

Some of the oncoviruses are excreted in infectious form and can be transmitted (horizontally) to other individuals. Feline leukemia virus for instance is present in large amounts (10^6 50% infective doses per ml) in the saliva of infected cats. When such a virus is present in the blood of the mother, intrauterine (transplacental) infection would be possible. But the importance of oncoviruses in vertical transmission stems from their ability to synthesize in the infected cells a DNA copy of the virus RNA genome. This is an essential step in viral replication, and indeed these viruses can be looked upon as DNA viruses with an intermediate RNA form. The virus-specific DNA sequences become permanently associated with the genome of the infected cell and are then transferred down to progeny cells during division. The infection, moreover, is never cytocidal, and when the germ cells are involved, the viral genome is transmitted to all embryo cells and is thus maintained in all of the offspring. Virus functions may or may not be expressed so that viral antigens and infectious virus may or may not be detected.

Although certain mouse leukemia viruses can be transmitted experimentally to mice or to mouse cells in vitro, there are other oncoviruses already present in normal mice. Specific DNA sequences of these endogenous oncoviruses are detectable by hybridization in all embryonic tissues of all strains of mice, and virus-specific antigens are sometimes expressed on the cell surface. The full viral genome is contained in the cell because infectious virus particles are synthesized when normal mouse embryo cells are exposed, for instance, to iododeoxyuridine. Endogenous C-type viruses are also present in the genome of cats, chickens, and presumably many other vertebrates. For this reason each experimental transmission of a leukemia virus to a cell or an animal is in fact a superinfection. The endogenous oncoviruses are inherited as nucleic acid sequences. Unlike the experimentally transmissible ones, they often do not replicate when inoculated into cells of the species of origin. Also, although the transmissible oncoviruses induce leukemias and transform cells, the endogenous viruses generally do not do so in the species of origin.

Numerous tests for endogenous viral nucleic acid sequences in the tissues of normal animals have now been made. Often it is known that more than one virus is present, and there may be multiple copies of a given virus. In mice, for instance, these sequences account for 0.04% of

the entire host genome (92). Oncovirus genomes have become fixed in the germ line during evolution and since then have been transmitted as cellular genes. The picture has become complicated, not only because more than one inherited virus may be present in a species, but also because genetic recombination between the inherited viruses and the horizontally transmitted viruses can take place to give viruses of intermediate character. The expression of the inherited viral genes is under tight control in the host cell, and the production of the group-specific antigen of murine leukemia virus in mouse embryo fibroblasts for instance is determined by a single dominant autosomal host cell gene.

Very similar findings have been made for chicken oncoviruses. Certain strains of chickens contain infectious virus in embryo cells, but the cells from "virus-free" embryos contain viral nucleic acid sequences and will synthesise their own endogenous infectious virus when exposed to iododeoxyuridine. Here too, the expression of the endogenous virus in cells is regulated by host cell genes.

All of these oncoviruses can be transmitted via the egg, and direct evidence was obtained many years ago when Fekete and Otis (25) transferred fertilized ova from high leukemia (AKR) mouse strains into the uterus of low leukemia (C_3H) mouse strains and found that the offspring carried the high leukemia virus. More recently, C-type particles have been seen by electron microscopy, for instance, in ova from baboons (41). Infection of the hen egg with oncoviruses can be automatic because the virus is present in host chromosomes, or it may take place in the oviduct from viruliferous albumen-secreting cells (87).

Since these viruses are present in chromosomes, male transmission via sperm should also occur. This is a known method of transmission of certain strains of mammary tumor virus in certain strains of mice (4). It is not often that we have firm information about the transmission of mammalian viruses via sperm. This powerful fluid has been neglected by virologists. As often as not (Table 3), there is merely a recovery of virus from semen and it is not known whether the virus is present in secretions from accessory glands or present in the sperm cells themselves. But viruses present in semen are likely to be of

TABLE 3. *Viruses present in semen*

Virus group	Virus	Species	Comments
Herpesviridae	Herpes simplex	Human	Presumed present; virus isolated from prostatic fluid, prostate, vas deferens (17)
	CMV	Human	High titers (10^7 $TCID_{50}$[a]/ml); virus fluid rather than sperm; persists for >1 year (48)
		Mouse	Viral DNA reported in sperm by in situ hybridization (22); no infectious virus in semen (Mims and Gould, unpublished data)
	Infectious bovine rhinotracheitis	Cattle	Persists for years in genital tract of bulls
Retroviridae	Mouse mammary tumor virus	Mouse	Virus transmitted via sperm in some strains of mice
	Enzootic bovine leukosis virus	Cattle	Semen is infectious
	Equine infectious anemia	Horse	Probably not significant for transmission
Reoviridae	Bluetongue	Cattle	Not known whether virus is in fluid or in sperm
Picornaviridae	Foot and mouth disease	Cattle	$10^{6.2}$ ID_{50}[b]/ml present in ejaculate of bull (82)
Togaviradae	Border disease	Sheep	Sperm probably infected (also oocytes)[c]
	Bovine virus diarrhea	Cattle	
	LDH	Mouse (17)	
Miscellaneous	Marburg and Ebola	Human	Sexual transmission recorded (Marburg) and virus present in semen (Ebola)
	Hepatitis B	Human	Virus probably present in semen

[a] $TCID_{50}$, 50% tissue culture infective dose.
[b] ID_{50}, 50% infective dose.
[c] A. C. Gardiner, J. Comp. Pathol., in press.

significance for venereal transmission of infection to the female rather than germ line transmission to the offspring.

Oncoviruses as parasites. The mammalian oncovirus genome consists of more than 10,000 nucleotides divided into five genetic regions. Four of these regions are distinct for the viruses from different species. Recently a nucleic acid sequence at the 3′ terminus of the genome has been shown to be common for rat, mouse, baboon, and other oncoviruses (46). It is possible that these common sequences are of host origin, perhaps carrying out an important function in the life cycle of the virus. Indeed, it has been suggested that the oncoviruses themselves originally arose from the genome of eucaryotic cells. For the purposes of this review, however, I prefer to think of them all, including the endogenous nucleic acid sequences, as parasites.

The relatedness of different oncoviruses can be determined from nucleic acid hybridization studies, and from the sequences present in the cells of different species it has proven possible to study their evolutionary origin. For instance, the endogenous virus of the domestic cat (distinct from feline leukemia virus, see above) shares DNA sequences with the endogenous virus of the baboon. The findings suggest that this virus was present in an ancestor of the present Old World monkeys, and infected the domestic cat and related cats 5 to 10 million years ago after they had evolved away from other feline species (6). Hybridization studies have led to the suggestion that the nonendogenous feline leukemia virus was acquired by cats from rodents several million years ago (5). It has also proven possible to reach conclusions about the evolutionary relationships of the primates. Four distinct classes of primate oncovirus have been defined (8), three of them endogenous and one, the gibbon virus group, infectious among primates. From an analysis of the virus sequences present in man and the hominids (his closest relatives), it was concluded that most human evolution since divergence from the Pongid ancestors had taken place outside Africa (7).

Parasitic deoxyribonucleic acid. Thus, during the hundreds of millions of years of evolution, oncoviruses have diversified and infected many species. Some of them have become firmly established in the genome of the host species (endogenous), whereas others are still regularly produced in infectious form, still transmitted horizontally, and are perhaps in an early stage of evolution after having infected a new species. The fact that these viruses also produce tumors is irrelevant and not in any sense necessary for the maintenance of the infection in the species. It is not easy to account for the presence of the virus genes that transform cells (*onc* in mice or *src* in chickens) because these genes are not needed in virus replication, but conceivably they arose as an unfortunate consequence of the operation of the virus genes that mediate integration into the host genome. Throughout evolution presumably there have been numerous opportunities for oncoviruses to become established in the host genome. Insertion of parasite DNA into host DNA is the ultimate in parasitism, since it ensures continuous carriage in the host species without the need for the production of virus particles, and without the need for the spread of infectious virus from cell to cell or from individual to individual. Furthermore, a short length of virus-specific nucleic acid, even if it can no longer code for the production of virus particles, represents a supremely successful parasite if it is conserved by the host and transmitted in this way.

On general principles, as argued elsewhere (62), it seems likely that this type of parasite has become established in a given host on more than one occasion during evolution, and many oncovirus sequences, from exceedingly ancient to comparatively recent, might be expected to be present. For their survival in the host, it is not enough that their nucleic acid sequences should be entirely free of harmful effects on the host. Ideally they would need to have come to terms with host genes and enzymes that control DNA expression and replication and to have insinuated themselves in such a fashion that they were watched over and conserved by the host. If this were at all possible, we can assume that some of the oncoviruses, as they diversified and evolved, would have reached this stage of balance with the host genome.

On the other hand, there have been suggestions that oncovirus genomes are actually useful to the host, and this would certainly help ensure their conservation. Three possibilities have been raised. First, the expression of virus-coded surface antigens on cells could conceivably be important during embryological differentiation. Second, they could have a function in the immune control of tumors. If, for instance, a tumor arose due to the action of a chemical carcinogen in the environment, this might lead to a disturbance in the control of a carried oncovirus genome so that virus antigens were now expressed on the surface of the tumor cell. Immune responses directed at these viral antigens might help in the elimination of tumor cells. Third, the viruses that are still transmissible between different species or subspecies could carry with them useful genetic information. This would

help provide fresh combinations of genes in the recipient, which might be useful.

Theoretically it should be possible to remove the endogenous virus genes and see whether the host is any the worse for it. White Leghorn chickens carry endogenous viral genes in 10 genetic loci, and recently a fertile rooster has been produced lacking nearly all of these sequences (2). So far no abnormalities have been detected, but the obvious difficulty is that, on an evolutionary time scale, even exceedingly small changes could have a selective effect.

This is a difficult field, at the borderline of infection and heredity. Interpretations are made more difficult because of the possibility that nucleic acid sequences can be transferred in the opposite directions if retroviruses pick up sequences (e.g., oncogenes) from the infected cell. If many oncoviruses have trodden the pathway into genetic integration, it might account for some of the redundant, nonfunctional DNA which is characteristic of most species. But there is no reason why such parasitic DNA sequences should be related to past or present oncoviruses. For instance, there are repeated DNA sequences in man that are fairly complex, consisting of two tandem repeats of 171 nucleotides each. They have been quite well conserved from lower primates (53). The repeated 300-nucleotide sequences studied by Rubin et al. (81) are interspersed in the DNA of man and other primates, and represent 3% of the entire human genome.

I have been looking at things largely from the point of view of viral parasites that invade the host cell, establish themselves in the genome, and later become defective. If the parasite occurs in all individuals of the host species, it is a perfect parasite, and at first sight it is of no consequence whether it is present in the form of a full viral genome or a mere fragment of nucleic acid (62). But parasitic DNA would be vulnerable to losses and deletions. Like other parasites it would need at times to spread from cell to cell or from individual to individual. There might be great advantages in retaining the capacity to code for infectious virus, so that there would be opportunities for bursts of horizontal transmission between individuals (64). In procaryotes these requirements have been met when parasitic sequences exist as self-transmissible plasmids. Once the parasitic DNA can no longer arrange for its own transfer, its days are perhaps numbered.

A similar approach to nonspecific, nonfunctional DNA in eucaryotes has been taken by molecular biologists (21, 68). If most of this DNA is "junk," at least some of it can be regarded as parasitic or selfish (19) DNA that has bypassed gene duplication controls and turned them to its own advantage. Whatever its origin, its only "function" is survival. Its movement within the genome has been considered and to a lesser extent its movement between individuals of the host species. The many interesting implications of this point of view cannot be considered here. There would be a limit to the proportion of parasitic DNA that an organism could carry without being disadvantaged in comparison with competitors. In evolutionary terms, higher organisms with a longer generation time would probably take a longer time than rapidly multiplying procaryocytes to eliminate disadvantageous DNA. Thus, if parasitic DNA is constantly emerging, higher organisms at any given time will have the most, whereas procaryocytes will be able to maintain a smaller, more "streamlined" genome.

Spumaviruses. Spumaviruses have a reverse transcriptase and comprise the foamy viruses. Foamy viruses of cats, monkeys, and cattle have been described, but so far there is no generally acepted human representative. Cytopathic effects in cells are minimal, with vacuolation of the cytoplasm as a distinctive feature, and DNA copies of viral RNA are in principle capable of being inserted into host DNA, as shown by the ability of these viruses to transform cells. Much less work has been done on these than on oncoviruses, although theoretically they too would be capable of vertical transmission via the host gametes. The only evidence about vertical transmission concerns the bovine foamy virus. This has been recovered from calf embryo cells, and antibodies have been detected in fetal calf serum (30); calves do not receive maternal antibodies by the transplacental route. Virus has also been isolated from fetal blood, showing that the fetus is infected (93), but it does not tell us whether infection was via parental gametes or via the placenta.

Work with foamy viruses poses numerous technical difficulties, but more representatives of this group will undoubtedly be discovered, and we will obtain further information about the mechanism of vertical transmission.

Lentiviruses. Visna virus, or progressive pneumonia virus of sheep, is the classic representative of this group of retroviruses. Bovine and monkey visna viruses have also been described. In culture, sheep visna virus undergoes a complete cycle of replication in fibroblasts derived from choroid plexus tissue, with production of fully infectious particles. The classical strain of virus does not replicate in other cells of the sheep, although recent isolates from sheep in the United States replicate in sheep macro-

phages (O. Narayan, personal communication). In the infected animal, a disease of great interest, involving the brain or lung, is produced after a very long incubation period, but our understanding of the pathogenesis of this disease is poor compared with our understanding of virus replication at the in vitro level. Tissues contain very low titers of infectious virus, and viral antigens are rarely detectable in the infected animal by fluorescent antibody staining. Occasional choroid plexus or white blood cells can be persuaded to release virus after explantation and subculture in vitro. In situ hybridization shows that visna virus nucleic acid sequences are present in a larger number of cells (31).

Visna virus does not appear to be transmitted vertically in sheep, either transplacentally or via the gametes. Infected ewes give birth to uninfected lambs which remain uninfected as long as they are separated from the mother shortly after birth. The longer they remain with the mother the more likely they are to acquire infection from maternal saliva or milk. Intrauterine infection was accomplished experimentally when the virus was inoculated (64) into fetal lambs at day 60 to 70 of pregnancy (gestation period 150 days). There was little or no virus replication and no pathological consequences, but virus could be recovered from explanted tissues up to 9 weeks after infection and from one of two animals 1 year after birth. On the other hand, a retrovirus assumed to be bovine visna virus is a fairly common contaminant of fetal calf serum (29), so this particular virus is certainly transmitted transplacentally or via the gametes. Thus, visna virus possesses the requirements for successful vertical transmission, and this apparently occurs with the bovine visna virus. Vertical transmission seems unlikely with sheep visna virus, and there is no information about monkey or other visna viruses.

Equine infectious anemia. Equine infectious anemia has now been shown to have a reverse transcriptase, so that it has the machinery for integration into the host cell genome. It is one of the oldest known virus diseases, the filtrable nature of the infectious agent having been established in 1904 (36). But because the host is a large and expensive animal and perhaps also because the story of the virus and its pathogenesis in the host is not a simple one, there are still many gaps in our understanding. The virus is known to be transmitted from infected mares to foals (42). Twelve of 52 foals from infected mothers were infected, and virus was isolated from 1 fetus that aborted at 8 months' gestation. The virus is known to be present in milk, and some of the foals became infected after nursing, but clearly the fetus is infected occasionally. The mechanism of spread to the fetus is unknown.

Parvoviruses

The single-stranded DNA viruses called parvoviruses are divided into two groups. First the adeno-associated viruses which can only replicate in cells concurrently infected with an adenovirus. They have been shown to establish latent infection in cultured cells, each cell containing three to five virus genome equivalents (10). Most of the virus DNA is incorporated into the host cell genome (32). They also persist in the body, particularly in lymphoid tissues, and there have been reports in man of the isolation of adeno-associated virus from spinal cord and muscle in amyotrophic lateral sclerosis (15). However, they are not known to produce disease and are difficult to study. There is no information about their mode of transmission, but the fetus is occasionally infected because virus is said to be present in approximately 1% of human embryo kidney cultures (34).

The second group of parvoviruses, although their replication too may be "helped" by other viruses, produce more conventional infections and disease in their host, and several of them are capable of infecting the fetus. When the fetus is infected transplacentally, congenital malformations or lesions are generally seen if the young survive until birth, as discussed earlier (feline panleucopenia, porcine parvovirus, Kilham rat virus). For most of these viruses it seems unlikely that this is a significant method of transmission under natural circumstances. However, bovine parvovirus has been recovered from batches of serum from presumably normal calf fetuses (88), and there is a possibility that infected young may be born normally without lesions or malformation. It is not known whether transmission is via the gametes or via the placenta. Parvoviruses appear to be capable of close association with the host cell genome, and if integration is possible they will have had the opportunity to be transmitted vertically via the gamete.

Adenoviruses

Adenoviruses are mentioned because experimentally virus DNA can be incorporated into host cell DNA to cause stable transformation. As has been argued elsewhere (63), this facility is of immense significance for the establishment of persistent infection in the host (see below) and thus for the maintenance of these viruses in nature. Although much of the interest has focused on their associated ability to transform

cells and induce malignant change, I consider this to be an irrelevant side effect. Some of the tissue culture cell lines transformed by adenoviruses do not contain a complete copy of the viral genome, and they therefore cannot be induced to reactivate and produce infectious virus. Most cell lines transformed by adenovirus 12, however, contain multiple copies of the entire genome (86). Recent work shows that normal placenta contains RNA sequences that hybridize with DNA from adenovirus 2, 5, 7, and 12 (39; K. W. Jones, personal communication). Early adenovirus antigens were also detected, but it is not known whether complete copies of the virus genome are present. In situ hybridization studies were carried out, but the placental cells containing the sequences could not be identified. Perhaps they were lymphocytes, so that the placental site has no particular relevance for transplacental transmission. It would predict that such cells, being the site of persistent infection in the intact host, would contain the complete virus genome, so that reactivation and reshedding of virus was possible. In principle it is conceivable that complete adenovirus genomes could be incorporated into the genome of the host gametes and vertical transmission would thus be achieved. There is no evidence for this possibility.

Papovaviruses

The papovaviruses, like the adenoviruses, are referred to here because they can insert their DNA into host cell DNA. Once again, this facility is probably important for persistent infection and transmission rather than because it sometimes leads to cell transformation and malignancy. In any case, papovaviruses are not known to cause malignant tumors in the host species under natural circumstances. Integration into the DNA of the host gamete would produce the ideal type of vertical transmission which could be the source of virus in the stump-tailed monkey fetuses (see above), but we have no information about this.

Arenaviruses

The arenaviruses consist of 8 to 10 viruses that establish persistent tolerated infection, each restricted to one or two species of rodent. Pathological effects are minimal in the naturally infected host species, and virus is shed into various bodily secretions and excretions, giving ample opportunities for postnatal and horizontal transmission. Infection at an early stage in development is more likely to give immune tolerance and freedom from immunopathological effects. Transplacental infection has been referred to earlier, and their is evidence that at least one of these viruses can be transmitted via the host gamete. In colonies of mice carrying LCM virus, adult animals have been shown to have infected cells in all organs and tissues (59). Ovaries are infected, and infected ova have been clearly seen by fluorescent antibody staining (59). In early embryos all cells were infected. Vertical transmission via the ovum is therefore possible, and as long as infection of embryo cells does not interfere with embryological development, this would be a most effective method of transmission. It must be remembered that different strains of laboratory mice differ in their response to LCM virus. The most relevant information about vertical transmission would be obtained from naturally infected colonies of wild mice.

Fluorescent antibody studies of mice carrying LCM virus showed that not all cells contain virus antigen, and the infectious virus content of tissues is low when compared with that in primary infection of normal noncarrier mice. Cells that are free of viral antigen nevertheless resist superinfection (66), and it was therefore suggested that there was infection of all cells in the body, but that at a given time some of them were "non-producers." Arenaviruses are single-stranded RNA viruses which do not possess a reverse transcriptase. The virological basis for persistent nonproductive infection is not known.

Our information about vertical transmission in other arenaviruses is less complete. The natural host for Machupo virus is the South American rodent *Calomys callosus*, and persistent infection is established in this species. The ovary and occasional ova are infected as well as the uterus and placenta (95). Fetuses are heavily infected, and, although most die, about 5% survive. Milkborne transmission is probably important, but the role of germ line as opposed to in utero infection is not clear. The natural host for Lassa fever virus is the African rodent *Mastomys natalensis*. Here, too, animals are persistently infected, and transmission resembles LCM rather than Machupo virus in that the infected fetuses are born live and healthy (K. Johnson, personal communication). It is thought that LCM and Lassa viruses are maintained in the host species by antenatal transmission, whereas Machupo virus is maintained largely by postnatal transmission because of the severe effects of the developing fetus.

Conclusions and Comments

Germ line transmission, although not the "easiest" for a virus to achieve, is nevertheless the most logical and effective route of transmission. The well established examples are seen

among the oncoviruses, whose reverse transcriptase permits integration into the host gametes, but it is not known whether germ line transmission also occurs with the other retroviruses.

Several groups of DNA viruses have the capacity to insert their DNA into that of the host, and as long as the cell is not damaged and can divide, virus DNA can be transmitted to the resulting clone of cells. If this happens in somatic cells, it might facilitate persistent infection but it would not otherwise be of any significance for transmission from host to host. Unless gametes were infected, there would be no opportunity for direct germ line transmission into subsequent generations. So far there is no evidence for gamete infection and germ line transmission of adenoviruses, herpesviruses, or papovaviruses.

Why then, if such things have a meaning, do these non-retroviruses have the capacity to integrate? It might conceivably be because at one stage in their evolution in certain species they infected germ cells, but no longer do so. A much more plausible explanation is in relation to viral persistence. Many persistent viruses infect lymphoreticular or epithelial cells (63). When the viral genome is incorporated into host DNA, no antigens or extracellular products need be produced and the infection in these cells is sheltered from immune and other host defenses. Persistence is therefore favored.

If the virus is reactivated later in the life of the host and shed once more from the body, it can then infect other individuals. Such a capacity is of great importance in the maintenance of certain virus infections in nature, especially when the host species lives in small groups (63). The complete virus genome must persist in host cells, and under natural circumstances reactivation and virus shedding occurs during pregnancy (JC and BK virus in humans) or in old age (varicella-zoster in humans). Although varicella-zoster, a herpesvirus, is mentioned here, less is known about the form in which herpes-viruses persist in cells. They generally remain in the body throughout life, especially in lymphocytes and in neurones (EB virus, herpes simplex) which contain viral DNA sequences. Reactivation with shedding is often associated with a weakening of antiviral immune responses. It involves a complete cycle of replication, and in at least some of these viruses this leads to death of the infected cell.

Of course, integration is not the only way in which viruses can persist in the body. A continuous low-grade productive infection in isolated groups of cells, under partial control by host defenses, could act either as a constant source of small quantities of virus, or as a site for a flare-up of infection. Hepatitis B virus, for instance, persists for as long as 20 years in an individual and could behave in this way. It has been shown that certain human hepatoma cell lines contain integrated hepatitis B virus DNA sequences. Complete sequences were detected in some cell lines (24) and sequences were found in the actual tumor tissue from three patients with liver cancer (12).

TRANSMISSION VIA THE GERM LINE—ARTHROPODS

There are several examples of egg transmission of viruses in arthropods. The viruses are present inside the egg cell, but there is no information as to the form in which they are carried.

Sigmavirus

Sigmavirus provides a good example of vertical transmission in an insect host (50, 51). Since about 1910 the fruit fly (*Drosophila*) has been a classic object of study for the geneticist, and we know more about the genetics of *Drosophila* than of any other multicellular animal. About 30 years ago it was noticed that certain flies were abnormal in that they failed to recover from CO_2 narcosis, or else recovered and then died the same day. Flies can normally be kept under narcosis in pure CO_2 for hours without injury. This CO_2 sensitivity was shown to be due to a transmissible agent, which in recent years has been identified ultrastructurally as a rhabdovirus. The literature on sigmavirus is complicated and mostly in French, but transmission is by the vertical route from infected female fly to offspring. The fly contains about 10^5 infective units of virus, and there are about 50 infective units per egg, but not all offspring are necessarily infected. There is no information as to whether sigmavirus is associated with the host genome, but the geneticists who discovered the infection concluded that it was not transmitted in a Mendelian fashion. Infected males do not generally transmit to their offspring. The infection is quite common in wild populations of *Drosophila*. It appears to be completely harmless except that the insect becomes sensitive to CO_2 at concentrations that would never be encountered under natural circumstances. Certain laboratory strains of sigmavirus lower the fertility of infected females, but these strains are not found in naturally infected flies. Evidently the association of the virus with *Drosophila* is an ancient one, perhaps extending back to the origin of the genus. Interestingly, *Drosophila* can be infected in the laboratory with vesicular stomatitis virus, another rhabdovirus (77). *Drosophila* is not a

natural host, and the infection is more damaging, leading to decreased egg laying and a shorter life span, as well as CO_2 sensitivity. CO_2 sensitivity is perhaps a result of virus replication in nerve ganglia, and it has recently been shown that sigma-virus also replicates certain species of mosquitoes, who develop CO_2 sensitivity when infected either with sigmavirus or with other rhabdoviruses (79).

Mosquitoes

For many years arboviruses were not thought to be transmitted transovarially in arthropods. In was an important question because vertical transmission in the arthropod host would help explain the "overwintering" problem, that is to say the maintenance of the infection in a given locality in the absence of detectable vertebrate infections. Also, the fact that arboviruses only seldom (65) cause any damage in the arthropod host suggested that the arthropod cycle was the most ancient one, the vertebrate host having been involved at a later stage in evolution. As long ago as 1906 there was a report that yellow fever virus was very occasionally transmitted to human volunteers transovarially in *Aedes aegypti* (54). Attempts to confirm this finding failed (73), and later there were similar failures to demonstrate transovarial transmission or to isolate arboviruses from eggs and larvae of infected mosquitoes. Recently, using more sensitive methods such as direct injection of test material into mosquitoes or inoculation of cultured mosquito cells, transovarial transmission has been shown to occur with a number of arboviruses. Examples include LaCrosse (94), Keystone, dengue, yellow fever, and Japanese encephalitis virus (80). Virus is present in the egg, and although the transmission rate is often low and sometimes regarded as a purely laboratory phenomenon, at times it probably plays a part in overwintering. In the case of LaCrosse virus, infected male mosquitoes had virus in semen, but fluorescent antibody studies indicated that this was in seminal fluid rather than in the sperm cells (91). Venereal transmission to the female mosquito is thus possible, but the offspring are not directly infected.

Ticks and Sandflies

Transovarial infection in ticks is established for some of the tickborne flaviviruses and was surveyed by Burgdorfer and Varmer (13), but it does not appear to play an important part in the maintenance of the infection in nature. It has also been demonstrated with African swine fever virus (76) and is thought to make a significant contribution to the maintenance of the virus in nature (W. Plowright, personal communication). Sandflies infected with vesicular stomatitis virus have been shown to transmit the infection to offspring via eggs (90), but the transmission rates were only 20 to 30%, so that this would not be enough by itself to maintain the infection in sandflies.

Plant Viruses

Transovarial transmission of plant viruses is well documented in aphids and in leafhopper and planthopper vectors. Tongue-twisting viruses, such as rice stripe, rugose leaf curl, oat dwarf tillering, and clover club leaf (11), are transmitted with fairly high efficiency (up to 90%). Other viruses such as sow thistle yellow vein virus (89) are transmitted with low efficiency, giving overall congenital transmission rates of about 1%. On the whole there has been little assessment of the epidemiological importance of transovarial transmission.

It is assumed that eggs are infected, and in the case of wound tumor virus in leafhoppers this has been demonstrated by immunofluorescence (84). Plant viruses are not found in sperm of vector males.

TRANSMISSION VIA THE GERM LINE—PLANTS

Seed Transmission

Seed transmission has been thoroughly surveyed by Bennett (9), and my treatment of the subject will be brief. As with mammalian embryos, the embryos of seeds are for the most part well protected against direct invasion by viruses present in the mother. But the embryos can also be infected through the female gamete (ovule) or the male gamete (pollen), and seed transmission has been recorded with nearly 50 plant viruses in more than 60 species of plants. At one time seed transmission would have been responsible for local spread in crops, but nowadays the transfer of viruses through commercial seed lots can lead to widespread dissemination.

Usually only a small proportion of seeds from affected plants are infected, but elm mosaic virus, for instance, can be transmitted to nearly half the seeds. Even when only a small proportion of seeds carry virus, this can be important in virus spread. Lettuce mosaic virus is present in about 5% of seeds from diseased plants, but seed transmission to new crops is a major factor in the spread of infection. Ovules and pollen seem to be of about equal importance in conveying infection to the embryo. It is interesting to note that infected pollen sometimes infects the mother plant, as with necrotic ringspot virus of

cherry, but such "venereal" transmission is uncommon.

The factors determining seed transmission are poorly understood. In a few instances, even when gametes are infected, they are rendered sterile. Tomato aspermy virus, for instance, interferes with the behavior of pollen and ovules and prevents seed formation. Seed transmission is characteristic of viruses transmitted by nematodes, for example, tomato black ring and raspberry ringspot viruses. The reason for this is not clear, but such viruses are widespread because they are disseminated over greater distances by seeds than by nematodes. Seed transmission is also relatively common in the case of viruses that are invasive for parenchymatous tissues or meristem, invasion enabling viruses to enter gametes at an early stage in development. It is less common in viruses that are restricted to vascular tissues presumably because there are no vascular connections between mother plant and embryo.

Integration of Plant Viruses into Host Cell Genome

At first sight this might seem an attractive method for transmission of plant viruses. A recent attempt to detect cauliflower mosaic virus DNA sequences in host chromosomal DNA was unsuccessful (R. Hull, *in* Proceedings of the International Workshop on Plant Cell Cultures, Elsevier/North Holland, Amsterdam, in press).

VERTICAL TRANSMISSION IN SINGLE-CELLED ORGANISMS

In single-celled organisms the somatic cells are also the germ line cells. Under these circumstances any infectious agent will be vertically transmitted if it multiplies without decreasing host survival or interfering with host cell division. Certain protozoa carry bacteria that behave in this fashion, and the development of a symbiotic relationship over the course of years has been followed in the laboratory (37). If multiplication of the infectious agent does not keep pace with host cell division, and especially if it is located in the cytoplasm, it is likely to be segregated out in the host progeny.

The ideal state of parasitism is seen in vitro when viruses are carried in transformed (persistently infected) mammalian cells. Nonintegrated viruses can also be carried effectively provided infectious virus is liberated to infect any virus-free progeny. Such infections might be less likely to persist in naturally occurring protozoa, whether free-living or parasitic, because the maintenance of the protozoan species depends on adequate dissemination of its offspring throughout the environment. Under these circumstances losses of the infecting virus would be more likely to be irreversible.

There are many viruses that infect eucaryotic microorganisms, including fungi, algae, and protozoa such as *Entamoeba histolytica* and *Plasmodium* sp. (49). Probably most of them are persistent and latent in the host species. Many, especially the double-stranded RNA viruses of fungi, are transmitted vertically, and also by direct cytoplasmic exchange between susceptible hosts rather than by the release of infectious particles. Certain strains of fungi also contain double-stranded RNA components that are inherited cytoplasmically and encode for the production of a killer factor acting on other strains. In the larger fungi, virus transmission is often vertical, via the spores. It has been suggested that some of these viruses, for instance the one infecting the wheat "take-all" fungus, can be transmitted as a DNA provirus, but so far there is no evidence for this. Many races of *Paramecium aurelia* contain particles referred to as kappa particles. These are responsible for the release into the culture medium of particles that kill other strains of paramecium (85). Individuals carrying kappa are resistant to the lethal effects. Kappa multiplies by transverse division, and several thousand may be present in a single paramecium. Kappa particles are now known to be bacteria (*Caedobacter taeniospiralis*), and these carry a phage that is somehow responsible for the killer effect, probably producing a toxin. When an appropriate stock of paramecium is maintained at 27°C, kappa fails to multiply fast enough to keep up with the rate of cell division (3.5 fissions per day), and kappa-free cells emerge. But kappa can infect kappa-free paramecia, and this helps maintain the parasite in paramecia throughout the world.

EPIDEMIOLOGICAL CONSIDERATIONS IN VERTICAL TRANSMISSION

Vertical transmission sometimes plays a central role in the epidemiology of infectious diseases, and vertical transmission in this sense can be contrasted with other types of cytoplasmic or extrachromosomal inheritance studied by geneticists. Fine and Sylvester (28) and Fine (26) have developed interesting quantitative theories on vertical transmission of infectious agents. Using these theories the conditions for a stable prevalence rate of a hereditary infection in a population can be defined. Given enough data, one can calculate whether a vertical transmission mechanism of given efficiency could play a significant role in the epidemiology of the infection (27). When the efficiency is too low, predictions can

be made of the amount of horizontal transmission that will be needed if the same prevalence is to be maintained over the generations.

SUMMARY

Vertical transmission is surveyed mostly with reference to mammals. True vertical transmission is contrasted with peri- and postnatal transmission and then subdivided into transplacental and germ line transmission.

Transplacental transmission is important in human (rubella) or veterinary (hog cholera, border disease in lambs) medicine because the infected fetus is often aborted or born with reduced viability. This means that it is generally not significant as a means of maintaining the infection in the host species. For this the infected fetus must develop more or less normally and survive after birth. There is an occasional exception (e.g., malignant catarrhal fever in the wildebeest), but generally opportunites for transmission are greater in the postnatal period.

Germ line transmission is a feature of oncoviruses, and here there is integration of viral nucleic acid sequences into host DNA. It is a possibility but has not yet been demonstrated for other viruses (e.g., spumaviruses) that have a reverse transcriptase.

Integration of viral into host DNA is also seen with adenoviruses, papovaviruses, certain herpesviruses, and parvoviruses. Germ line transmission would theoretically be possible for these viruses, but it is suggested that integration is more likely to be a virological adaptation permitting persistent infection and reactivation in the host.

Viral DNA sequences harmlessly integrated into the host genome represent the ultimate in successful parasitism, and these sequences can be short, incapable of coding for viral antigens or infectivity. Mention is made of parasitic DNA.

Germ line transmission occurs in arthropods infected with their own viruses as well as with certain arthropod-transmitted plant and animal viruses. In plants, seed transmission is quite common and usually follows virus invasion of ovules or pollen.

Incomplete viral nucleic acid sequences can only be maintained in the host species by germ line transmission. In the case of infectious viruses or complete viral nucleic acid sequences, non-germ line transmission is likely to play a part. The epidemiological significance of germ line transmission of virus infections of arthropods and plants is largely unknown.

When single-celled organisms are infected with multiplying non-cytopathic viruses, germ line transmission is almost inevitable.

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