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The Long Term Effects of Infection in Early Life (Long View II)

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Twelve years ago it was my privilege to give the presidential address before the Society for Pediatric Research. The title of that report was "The Long View" and in it I discussed the problem of the long interval between certain events and their eventual consequences (14). I illustrated my point mostly from the field of infectious diseases, but I had few concrete examples to cite in man. Indeed, the 2–3-month-long incubation period of serum hepatitis, now referred to as hepatitis B, was regarded as unusual. However, the "slow virus diseases" such as scrapie of sheep with incubation periods of 2–4 years were beginning to stir people's interest and similarities were being noted between the histologic findings in scrapie and certain diseases of man such as kuru. Furthermore, virus-induced malignancies in animals also were known to have long incubation periods. Such data permitted speculation that infections in early life, especially virus infections, might play a much more important role in affecting the health or functional capacity of a person many years later than had been appreciated.

My remarks today are intended to update and extend my address of 12 years ago, hence the title "Long View II."

There are a number of ways in which an infectious agent may have a delayed or long term effect.

ACUTE INFECTION MAY CAUSE CELL OR TISSUE DAMAGE WHICH AT SOME LATER TIME WILL BECOME MANIFEST AS DISEASE OR DISABILITY

This mode of action has been well delineated. It has been known for some time that infection with certain organisms such as *Spirochaeta pallida*, toxoplasma, rubella virus, cytomegalovirus (CMV), Coxsackie B virus, and herpes hominis virus can cause *in utero* or neonatal infections resulting in a variety of relatively severe disabilities. Later in life examples of this process are the bacterial meningitides, various encephalitides which can produce long term central nervous system effects and streptococcal infections leading to rheumatic fever.

The agents cited above as causing congenital or perinatal disease in man remain the only ones for which there is good evidence; they still account for but a small fraction of all congenital defects, most of which remain unexplained. We have learned, however, that pre- or perinatal infection with these agents is more common than had been suspected and that persistent infection lasting months or years often can be demonstrated. It is not difficult to recognize the seriously damaged infant but the implications of infection in the absence of gross abnormalities is not easy to determine, as will be illustrated when we discuss CMV in more detail.

In animals a number of viruses have been shown to produce *in utero* infections which result in abnormalities that morphologically resemble some of the more common congenital defects seen in mar (12). The viruses include influenza A, Newcastle disease virus, mumps, parvoviruses, lymphocytic choriomeningitis, and bovine virus diarrhea. Attenuated vaccine strains of blue tongue and hog cholera viruses produce congenital abnormalities, whereas the wild viruses do not. Mumps virus and certain other myxoviruses can produce aqueductal stenosis and obstructive hydrocephalus in rodents. This is of particular interest since three cases have now been reported in which children have developed obstructive hydrocephalus following a documented mumps infection.

It is noteworthy that in many of the congenital defects produced by viruses in experimental animals there is no inflammatory response, nor can the virus always be identified in the tissues. These observations have obvious pertinence to the effort to identify an infectious etiology in congenital defects of man.

ORGANISM MAY PERSIST INDEFINITELY IN BODY CAUSING LITTLE DAMAGE IN ITSELF BUT EVOKING IMMUNE RESPONSE WHICH ACCOUNTS FOR PATHOLOGY OBSERVED

There are two reasonably clear-cut examples in which this mechanism accounts for the disease observed.

The first example is lymphocytic choriomeningitis virus infection of mice. If infection occurs with this agent in the fetal or neonatal period, a persistent infection with no evidence of disease is produced. Only if the animals are observed over their entire lifespan can any deleterious effects be noted, and this apparently is only true with certain strains of the virus and some stocks of mice. The affected animals have shortened lifespans and show evidence of chronic renal disease. The basis of the pathologic process is a deposition of antigen-antibody complexes, particularly in the kidneys (13).

Schistosomiasis exemplifies a different mechanism possibly

more relevant to man. It has been shown that in animals, at least, the worms and their eggs are quite benign. However, the immune response to them results in granuloma formation, particularly in the liver, which in time produces the characteristic cirrhosis to which the principal pathology can be attributed (19).

Some evidence is beginning to accumulate suggesting that fetal or neonatal infection with hepatitis B virus leads to a persistent infection and later cirrhosis of the liver. It is possible that here, too, the immune response is involved, and it has even been suggested that polyarteritis nodosa may be immune complex disease associated with hepatitis B infection (9). Another situation where this mechanism may obtain is lactic dehydrogenase virus infection of mice.

INFECTIOUS AGENT MAY PERSIST IN LATENT FORM, CAUSING DISEASE ONLY WHEN EQUILIBRIUM IS DISTURBED ALLOWING AGENT TO MULTIPLY AGAIN

To the classic trio of agents long known to establish latent infections in man, namely, herpes hominis, varicella-zoster viruses, and *Rickettsia prowazekii* (the cause of Brill's disease or recrudescent epidemic typhus fever) have now been added the CMV, adenoviruses, certain papovaviruses, and even the virus of measles. Tissue culture studies on a variety of animal tissues have revealed a large assortment of viruses that presumably are latent in the tissues and only proliferate when the conditions are radically altered. This phenomenon has been troublesome to those who prepare vaccines in tissue cultures of animal cells. For instance, it is almost impossible to find flocks of chickens with eggs free of leukosis virus and the kidneys of certain monkeys almost invariably yield SV40 or some other contaminating virus. Gajdusek and associates (6) have made 150 isolations of 11 different virus types from the brains and other organs of apparently healthy chimpanzees. Indeed, it was the rare animal from which they failed to isolate a virus.

The recent discovery that progressive multifocal leukoencephalopathy (PML) is due to a papovavirus (JC) has excited much interest. PML is a subacute demyelinating disease that is almost invariably associated with underlying conditions of the reticuloendothetical system that compromise immunologic competency. The JC virus apparently causes widespread infection in man, since it has been reported that approximately 75% of adults possess antibodies to it. Like its close relatives, SV40 and polyoma viruses, it is oncogenic and produces malignant gliomas when inoculated into newborn hamsters (18). On the basis of the evidence to date, the most appealing hypothesis to explain PML is that it is due to reactivation of a latent JC virus infection of the brain and that the principal provoking factor is impairment of the patient's immune capacity.

GENOME OF VIRUS CAN BECOME INTIMATELY ASSOCIATED WITH GENETIC APPARATUS OF CELL CONFERRING UPON CELL NEW ATTRIBUTES TRANSMITTED TO ITS PROGENY: COMPLETE VIRUS IS NOT FORMED AND DISEASE RESULTS FROM ABNORMAL BEHAVIOR OF ALTERED CELLS OR IMMUNOLOGIC REACTION TO THEM

The distinction between this type of relationship of virus and cell and latency is not always easy to make, but the degree of integration between the genetic material of the virus and that of the cell is more intimate and there is a recognized introduction of new cell characteristics. This mechanism has been shown to be operative *in vitro* with a number of oncogenic viruses and it is assumed that it functions *in vivo* as well. The intricacies of the theories concerning the possible role of viruses as causes of cancer are too much to deal with here. However, we do know that many viruses are causally related to cancer in animals. From our point of view it is important to stress that often cancer does not occur unless the virus infection is established in fetal or neonatal life even though the malignancy may not become apparent until the animal is an adult.

The capacity of viruses to alter the antigenicity of cells in the body could result in a situation where antibodies would be formed to these new antigens, resulting in a disease process that might have the characteristics of so-called autoimmune diseases.

AFTER INFECTION THERE IS EITHER LONG INTERVAL REQUIRED FOR MULTIPLICATION OF INFECTIOUS AGENT TO CONCENTRATION SUFFICIENT TO CAUSE DISEASE OR REACH TARGET ORGAN, OR PATHOLOGIC PROCESS MAY BE A SLOWLY PROGRESSING ONE IRRESPECTIVE OF CONCENTRATION OF AGENT (4, 8, 17)

Within this category we can include rabies since it has been reported occasionally to have an incubation period as long as 1 year. This is now presumed to be because the virus progresses slowly from cell to cell in the nerve sheath, and thus the incubation period is dependent upon the distance of the site of the bite from the CNS as well as the size of the inoculum. Multiple sclerosis (MS) as we will discuss later, may also belong here.

Among the classic slow virus diseases are visna and maedi of sheep. Both are due to viruses with some similarity to the RNA tumor viruses and are slowly progressing illnesses lasting months or years. The principal lesion in visna is a demyelinating encephalitis and in maedi is pulmonary fibrosis.

The most interesting diseases within this group are the spongioform encephalopathies: scrapie of sheep, transmissible mink encephalopathy, kuru, and Creutzfeldt-Jacob (CJ) disease. Kuru is the chronic degenerative disease of the CNS that is limited to the Fore peoples in the highlands of New Guinea. CJ disease is a sporadic disease of worldwide distribution that mimics premature senility. These maladies are grouped together because of pathologic features in common and because they are caused by transmissible agents that are at this time indistinguishable. The outstanding common features are these. (*1*) They are all slowly progressing degenerative diseases of the nervous system with very long incubation periods, *e.g.*, 2–4 years for scrapie in sheep. (*2*) The pathologic changes in the CNS are those of cell vacuolization, death of neurons, and proliferation of glial cells with no inflammatory response. (*3*) They are caused by transmissible agents, all of which have characteristics that set them apart from conventional viruses: (*a*) no formed structures that in any way resemble virions have been identified; (*b*) no convincing evidence has been obtained of the presence of a nucleic acid component; (*c*) they are unusually resistant to heat and certain chemicals but are inactivated by fat solvents such as ether; (*d*) so far no one has been able to detect antibody to these agents, nor have antigen-antibody complexes been identified; (*e*) no means of laboratory propagation or identification has been developed other than passage in animals.

Thus we are dealing with agents, or an agent, that fulfill the criteria for a filterable virus that were used before the advent of the electron microscope and other modern methods of biophysically characterizing viruses. It will be a fascinating and difficult problem to elucidate the structure and function of these agents.

I should now like to address myself in more detail to two specific agents: CMV and measles virus.

CMV

The CMV virus belongs to the herpes virus group. It was first recognized as a pathogen for man when it was identified as the cause of the uncommon but dramatic syndrome of neonates characterized by hepatitis, thrombocytopenia, and destructive CNS lesions. The infection is usually acquired *in utero* and the severity of the disease appears to be related to the stage of development at which infection occurs (21). I will not attempt a complete review of the subject of CMV infection but rather will emphasize what has been required to get a reasonable estimate of the true long term consequences of congenital or perinatal CMV infection. Several prospective studies have been conducted enrolling women as early in pregnancy as possible and testing for CMV antibodies and virus excretion (10, 15, 16). Their infants have been evaluated at regular intervals for CMV infection and examined for any abnormalities that might be ascribed to the infection. Thousands of women and their infants have been followed for more that 4 years. These studies have revealed that 1.0–2.0% of all infants are excreting CMV in their urine or respiratory secretions at or within a day or two of birth. It is presumed that in most instances infection occurs *in utero,* but it is possible for the infant to become infected during or shortly after delivery since virus has been isolated with considerable frequency from the uterine cervix of pregnant mothers and from breast milk. Infection is more frequent in the offspring of young primipara of lower socioeconomic status. The most remarkable discovery however, is that only the very rare infected infant shows any evidence of disease even though the majority of them continue to excrete virus for 4 years or more. As larger groups of infected infants are carefully observed for longer periods of time we are beginning to get some idea of the long term consequences of fetal or neonatal infection. The report of Reynolds *et al.* (16) is not conclusive but does suggest that infection may result in some retardation of mental development and/or auditory loss. They estimate that the frequency of some impairment may be as high as 1 in every 1,000 live births. Other studies suggest that these estimates may be high, but it will be some time before the data are definitive. The potential importance of these observations is obvious, but I am not sure that you all realize how difficult it is to do such studies. Until we have a clear picture of the consequences of CMV infections, the need to pursue these studies cannot be emphasized enough. However, it is equally important to elucidate the epidemiologic features of the infection in hopes of finding a weak link in the chain that might be exploited in order to prevent infection.

CMV can cause a primary infection in susceptible persons at any age, usually without recognized symptoms, although it may cause a syndrome like infectious mononucleosis. Like its relatives of the herpes virus family, zoster-varicella, herpes simplex, and Epstein-Barr, CMV establishes a latent infection that is probably permanent. Active infection is provoked by a variety of stimuli including pregnancy and treatment with immunosuppressive drugs. Activation of latent infections with CMV, varicella-zoster, papova, herpes simplex viruses, and other organisms is becoming a more important problem as more treatment modalities such as organ transplantation are employed. Admittedly, under these conditions it is not always possible to distinguish between a primary infection and a recrudescent one, but there is no doubt that many of them, particularly virus infections, do indeed represent activation.

MEASLES

Until recently measles was a disease universally prevalent throughout the world, and it was the rare individual who escaped infection. The consequences of infection were considered to be highly predictable, the disease was of limited duration and never recurred. Pulmonary and CNS complications were recognized as being acute episodes with only the latter having any long term effects. The encephalitis associated with measles was estimated to occur in 1 in 1,000 cases of measles and its pathogenesis was and still is unknown. The most popular theory has been that measles encephalitis, along with certain other postinfectious encephalitides, is due to an immunologic reaction analagous to experimental allergic encephalitis. However, this theory does not provide any explanation of how the virus is involved in the process. Direct evidence for viral invasion of brain during measles was meager and inconclusive, although transient EEG changes had been described in association with the acute illness in approximately 50% of cases. There had been some efforts to implicate measles virus in MS, but the evidence was unconvincing and generally ignored.

The situation today is entirely different. We now recognize that measles virus establishes a chronic or latent infection and that it is the cause of that distressing CNS illness described many years ago by Dawson as inclusion body encephalitis and now referred to as subacute sclerosing panencephalitis (SSPE). Furthermore, there is mounting evidence that the majority of cases of multiple sclerosis may be associated with measles virus in the CNS. Thus, this common garden variety virus infection which was classified by many as an unavoidable nuisance has assumed a totally new and important role as one of the agents capable of producing a "slow virus disease."

SSPE

I will make no attempt to review SSPE in any detail; most of you are familiar with it already. For the purposes of this presentation I wish to emphasize the following points.

A. There is now no question that measles virus is the cause of SSPE although some investigators have presented evidence that another virus also may be involved. The evidence in support of this unequivocal statement concerning the role of the measles virus is that: (*1*) the presence of measles virus in the brains of patients has been repeatedly demonstrated both morphologically and by virus isolation; (*2*) patients, with a few exceptions, have abnormally high titers of measles antibody in both serum and cerebral spinal fluid (CSF); (*3*) a disease resembling SSPE can be produced in hamsters by inoculation of measles virus (17).

B. Most patients with SSPE are known to have had measles as long as 20 years before. Epidemiologic evidence suggests that SSPE is more likely to occur if the original measles infection was experienced before 2 years of age. Likewise, Johnson and Byington (17) have found that the chronic infection can only be produced in the hamster if it is inoculated as a weanling. Younger animals experience an acute, usually fatal, infection whereas older ones develop antibodies but no evidence of disease.

C. The virus infection of the CNS is unusual in SSPE in that there is no detectable extracellular virus and it requires extraordinary measures to isolate the agent from the brain. The virus that is isolated has some of the characteristics of a modified virus and differs biologically from the wild virus that presumably caused the original infection.

D. SSPE runs a prolonged course of months or even years from the first symptom until death (the usual outcome) or recovery. Surviving patients display permanent CNS impairment.

E. SSPE is not a common disease, but approximately 200 cases are now reported in the United States/year. There are areas in the world of unusually high incidence; *e.g.*, in the United States it is more frequent in the Southeast (11). In spite of the millions of doses of measles vaccine that have been administered, very few cases of SSPE have occurred in children who received vaccine and had no history of natural infection.

MS

The evidence supporting the involvement of measles, or any other virus, in the etiology of MS is still incomplete. However, it is sufficiently compelling to give me the strong conviction that it is only a matter of time until the causative relationship is established. The evidence to date can be summarized briefly as follows.

A. Epidemiologic data (1) reveal marked variation in incidence in various parts of the world. In general, the disease is more frequent in the more northerly and southerly regions and infrequent near the equator. Scandanavia, Scotland, and adjacent islands have unusually high rates. However, perhaps the most significant observation has been that after the age of puberty moving from a high to a low incidence area or vice versa does not alter the individual's chances of developing the disease. Thus, it would appear that something happens in early life that determines whether or not a person will develop MS. The data also suggest that the incubation period is a minimum of several years and may be as long as 20+ years. These observations have been interpreted as being compatible with an infectious etiology but certainly do not prove it.

B. Although there has been much controversy on this point, there would now appear to be enough agreement among the data of different investigators to support the earlier suggestions that the average concentration of measles antibody is higher in the sera of MS patients than in the general population. Henson and associates (7), however, made the intriguing observation that siblings of MS patients display a comparable difference from normal.

C. Abnormal levels of γG-globulin, which are reactive with measles virus antigen in the majority of instances are found in the CSF of MS patients (2, 20); antibodies to other common viruses such as herpes hominis, rubella, mumps and parainfluenza are also found. The globulins in the CSF have been found to be oligoclonal on electrophoresis, indicating that only a limited number of molecular species are present. Also, there is a reduced ratio of antibody concentration in the blood to that in the CSF. These findings are strong evidence that the CSF antibody is elaborated locally in the brain and has not leaked from the vascular compartment. This in turn suggests that viral antigen is also available in the CNS.

D. In spite of the CSF antibody data, only rarely have viruses been isolated from the tissue of MS patients or been seen morphologically. Parainfluenza has been isolated on one occasion, measles once, and myxovirus-like nucleocapsides seen by electron microscopy in fresh lesions of a third case.

Clearly we are not in a position to implicate any virus as the cause of MS, but evidence is accumulating that strongly points to the involvement in its pathogenesis of measles virus and perhaps a limited number of other prevalent viruses.

I should now like to emphasize a few general points that are important to our basic theme.

It has become increasingly evident that the age at which the infection or insult occurs is a critical determinant of the consequences. This may relate to interference with specific developmental events as one sees with rubella and many other teratogens, or it may be related to the immunologic competency of the host at the time of infection, as is possibly the case in SSPE and is clearly important in many experimentally induced malignancies. Then, too, it is obvious that if the incubation period is very long only an infection occurring early in life will be able to produce disease within the person's normal lifespan.

Another variable of great importance is heredity. There are many experimental models that illustrate this. For instance, only mink with the Aleutian gene develop Aleutian mink disease even though other strains become infected. Scrapie occurs only in certain breeds of sheep, and before it was recognized to be caused by a transmissible agent it was considered to be a hereditary disease.

A clear demonstration of genetic influences, in both the host and the virus, affecting the disease outcome is provided by encephalomyocarditis virus (EMC) infection in mice (3). This virus may produce in mice a diabetes-like disease due to damage to pancreatic islet cells. However, this effect is only caused by a specific variant of the EMC virus. Furthermore, only some strains of mice are susceptible, whereas others are almost totally resistant, the outcome depending upon the severity of the pancreatic lesion. Although the precise mechanism underlying the differing susceptibility has not been worked out, it is apparent that in this example the genotype of the host and the virus are independent and critical variables in determining the outcome of infection. Such situations are less clear-cut in man, but there is no reason to believe that he differs in this regard from other animal species.

A startling finding has been the frequency with which viruses exist in persistent, latent, or integrated form in apparently normal tissues. Indeed, they are so frequent that one hypothesis of cancer etiology is that the genetic potential for the elaboration of certain types of tumor viruses or that portion of their genome that determines malignancy exists in all cells and only when the gene is derepressed does cancer occur. In any case we have seen that latent viruses may be activated by a wide variety of stimuli; these include alterations in immunologic competency such as occurs with lymphomas, sarcoid, some types of treatment and possibly even aging with resulting overt disease. However, one cannot help but wonder whether or not there is some cumulative damage that accrues as the result of such parasitism. When one considers the extraordinary changes induced by the causative agent of CJ disease that have some similarity to those normally associated with aging but in an exaggerated and accelerated form, it is easy to hypothesize that it or a similar agent might be involved in what would appear to be the natural process of aging (5, 6).

Thus, as we have reviewed the various ways that microbial agents can cause delayed or long term effects, it would seem reasonable that we should look to fetal or early life for the genesis of many of the afflictions of the older child or adult.

On the basis of the kinds of evidence summarized above we have had to reorient our concept of the relationship between the host and microbial agents, particularly viruses. It is an exciting time because one has the feeling that we are on the verge of important discoveries in the field of cancer and a variety of chronic diseases. However, it is well to temper our enthusiasm with a recognition of some of the problems that face investigators in these areas.

When cause and effect are far removed in time, the difficulties inherent in the epidemiologic approach to elucidation of the factors involved in etiology need no elaboration. However, it is probably worth pointing out that longitudinal studies have proved to be less rewarding than some had hoped. Nonetheless, they are the only way that some questions can be answered. The prospective studies on children infected with CMV are good examples of well planned investigations of this sort but also illustrate clearly the problems. In order for such efforts to have any prospect of success the protocol must be carefully constructed with the questions to be answered clearly defined, limited in scope, and capable of being answered. There must be a stable staff and funding committed for an adequate period. Unfortunately, in the scramble for the scarce research dollar such studies have not always fared well in competition with the more glamorous molecularly oriented projects with prospects of quick payoff. A condition of paramount importance is a cooperative and available population. This is often difficult to achieve and is becoming more difficult all the time, in part because of the suspicions with which certain elements in the population now regard any effort to involve them and the increasingly stringent regulations that govern human experimentation. Also, it is not easy always to identify populations that can be followed for

significant periods of time. Groups such as the subscribers to the Kaiser and similar plans are well suited for certain kinds of studies, as Yerushalmy and associates have demonstrated so well. However, in my opinion, the private physician is in a peculiarly favorable position to make accurate longitudinal observations. He has the stable relationship with a group of people about whom ideally he knows a great deal. It would require a degree of standardization of records and organization of follow-up, but not much that a good physician is not doing already. Some practitioners have done important studies: Hope-Simpson, a general practitioner in England has made significant observations on the epidemiology of acute respiratory infections; Burtis Breese in Rochester, New York, and Virgil Howie in Huntsville, Alabama, have done outstanding clinical research on streptococcal infections and otitis media, respectively. Furthermore, it is through the alertness of physicians in practice that important relationships such as that between rubella and congenital abnormalities (first observed by the Australian ophthalmologist Gregg) have been suspected. It has always seemed to me that the physicians of this country, if properly organized and motivated, could provide us with an early warning system for the abnormal frequency of unusual diseases, congenital abnormalities, or reactions to drugs and biologicals. Our system of specializing according to the age of the patient does limit the ability of the physician to make long term observations of an individual and to appreciate fully the significance of the family from the genetic and environmental point of view, and if this sounds like an argument for family practice, so be it.

I should like to reiterate the basic theme of my presentation, namely that the greatest impact upon the quality of life is to be achieved through preventive measures applied at an early age. This applies no matter whether one is concerned with the role of infectious agents, nutrition, or the general environment. Those of us who deal with children must better inform ourselves on the life-long spectrum of human illness. We must have a greater sensitivity for the long term implications of the problems with which we deal and the measures we prescribe with the intent of improving health.

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