GILBERT DALLDORF*

Sloan-Kettering Institute for Cancer Research, New York

A GREAT EXPERIMENT

"It is good thus to try in imagination to give any one species an advantage over another. Probably in no single instance should we know what to do. This ought to convince us of our ignorance on the mutual relations of all organic beings: a conviction as necessary, as it is difficult to acquire."

—*Charles Darwin.*

It may be characteristic of our age that so tremendous an experiment as the infection of seventy-seven million Russians with three avirulent strains of poliomyelitis virus was undertaken as with the sweep of a hand. Perhaps only a commissar's hand could do it. But much may be due to the arrogant confidence of twentieth century man and his habitual disregard of the limitations of his knowledge.

Mass use of the oral vaccine followed careful small trials which firmly established that the viruses used did not of themselves cause disease. And the result of the mass application seems to have been an outstanding success. Poliomyelitis dwindled to a fraction of the number of cases reported in the preceding years. Indeed, these trials have emboldened some experts to confidently predict the *eradication* of the poliomyelitis viruses. Time alone can tell whether that is feasible or even possible. Meanwhile it seems of some interest to consider certain biological phenomena that will presumably affect the final result and that characterize the undertaking as a great experiment.

The prevailing view seems to be that truly comprehensive immunization of a population with the vaccine viruses, feasible because of the ease of administration and economy, may provide a degree of active immunization and refractoriness to reinfection that will eliminate all possible hosts of the epidemic virus strains. Such an undertaking can doubtless be more easily carried out in a rigidly managed society but it is, of course, quite likely that universal immunization would not be required, that a threshold would earlier be reached at which the propagation of the field strains of viruses would cease. The extent of immunization necessary for control is an important value still to be determined.

A greater effect would follow if the vaccine virus strains were capable of suppressing, of successfully competing with, the field strains. Under such

*Chief of the Division of Experimental Pathology of the S.K.I.

conditions it would be necessary only to seed the attenuated strains into a population and await their spread. This seems unlikely with the present strains which appear less capable of spread and prolonged excretion than the field strains. Doubtless other characteristics may play a part. Nevertheless, we have no reason at present to expect that control will be possible through the mere introduction of the modified viruses. Moreover there is considerable evidence that the attenuated viruses, if they were propagated through a susceptible population, might eventually acquire virulence and change toward their original form.

It therefore seems much more likely that complete control or eradication would be accomplished, if at all, through universal immunization much as smallpox has been eradicated. In practice, repeated doses may be required, since a present disadvantage of the poliomyelitis vaccines, in comparison with vaccinia, is our inability to recognize successful vaccination short of laboratory tests while the immune status to vaccinia may be easily established by inspection.

Other differences between these two live virus vaccines and the diseases they prevent are still more significant. The most conspicuous difference that makes the Russian trials an important experiment and introduces endless biological complexities is that there are three polioviruses and some fifty cousins of them showing various degrees of likeness. The mass use of the vaccine strains, therefore, provides an opportunity to observe the ecological effects of a drastic change in the intestinal virus flora, a feature wholly lacking in the case of vaccinia.

Ecological problems have been neglected in the animal virus field, despite much suggestive evidence that they may eventually prove of considerable importance. Animal virologists somewhat belatedly (plant virologists were already fully familiar with these phenomena) recognized that certain viruses interfere with others. Attention was drawn to such reactions twenty-five years ago by two independent studies in one of which yellow fever[1] and in the other experimental poliomyelitis[2] were shown to be influenced by particular concurrent infections. Initially, attention was attracted to the sparing effect which one infection had on the disease caused by the second. This was quickly extended to susceptibility to infection as well as resistance to the disease. The phenomenon is now generally known as *interference*. It has been studied chiefly in terms of experimental diseases or cultivated cells. Its epidemiologic significance has been only superficially explored.

The recognition of three distinct types of poliovirus was followed by the discovery of other enteric viruses having similar properties. The list of these now numbers nearly sixty small, ether resistant human pathogens (or potential pathogens) and many additional ones that are native to lower animals. Many of the former are known to be quite similar to the polioviruses including when and where they may be found. They cohabit. A number of them interfere with or are interfered with by the polioviruses. Others may infect simultaneously with the polioviruses and may possibly contribute to the severity of the resultant disease. It is in terms of this complex ecological relationship that the wholesale use of vaccine viruses may profitably be considered.

Antagonisms between the polioviruses themselves are well known. Presumably the common tendency of one type to predominate during epidemics is an expression of that antagonism. It became evident during the early trials of the vaccine viruses when it was observed that simultaneous ingestion of all three types sometimes led to infection with merely one. It is therefore recommended that the three types be given independently at intervals of several weeks. This routine has been somewhat modified in Russia but not in principle. The Russian practice is to combine two types in the second dose and three in the third in the expectation of benefiting individuals who may have escaped infection with the repeated type during the first exposure.

The extent to which interferences between the vaccine viruses and their cousins may determine the effectiveness of vaccination has been evident in many trials, especially in areas and at times when the cousins were prevalent. An extreme situation occurred among a Mexican population of low economic status.[3] One of the groups included in that study was known to be excreting non-polioviruses. Only three of the thirty-three who received oral vaccine became infected and only fourteen of the forty-seven studied developed antibodies to the type of vaccine virus administered. In consequence of such observations, vaccination with the attenuated viruses is only undertaken during seasons of low incidence of infection with enteric viruses, although it may be that viruses will be found and dosages established for them that would make it possible to dispossess the interfering agents and successfully immunize under such circumstances. But these are relatively trivial, practical problems implicit in the use of the live virus vaccines. More interesting issues lie beyond them.

The antagonisms between enteric viruses are presumably quite varied. There is a pronounced interference between Group B Coxsackie and type 2 poliovirus infections in mice,[4] and the influence of Group B infections persists for a surprisingly long time.[5] Considerable evidence has been assembled to show that Bornholm disease or epidemic pleurodynia (which is caused by Group B viruses) suppresses paralytic poliomyelitis in man.[6] These two diseases characteristically have a reciprocal relationship when judged by numbers of reported cases; because both are highly characteristic clinically these data seem significant. The Danish records provide the best raw data since both were reportable diseases in Denmark for many years and Danish physicians were expert in their recognition. During the twenty-five years for which records exist, epidemics of paralytic poliomyelitis and epidemic pleurodynia never occurred simultaneously. In seven of the years both were infrequent, in eighteen of the years one or the other was epidemic.[7] Interestingly, it was a Dane who first called attention to the epidemiologic similarities between the two.[8]

Striking interferences have been demonstrated experimentally between Group A Coxsackie viruses.[9] The two most completely studied (A-10 and A-14) are known to be quite similar to the polioviruses. Strains of A-14 may cause, in mice, a disease indistinguishable from poliomyelitis and both have been associated with paralytic disease in man. Relatively few of the Coxsackie viruses and none of the ECHO viruses have been methodically examined to determine the range and degree of whatever interfering effects they may have on the family of enteroviruses. However, enough is known to justify the suspicion that great variations in their interrelationships will be found to exist.

The massive dissemination of vaccine virus strains, in view of these facts, may be of special interest on three counts. It seems evident that the immediate effect of the rapid infection of millions of subjects may differ considerably from the late effect. One would expect that the introduction of live enteric viruses to a large part of the population would interfere not only with the poliovirus, but certain other enteric viruses as well, and that the suppressed viruses might in some cases be displaced or excluded. While the vaccine viruses may be incapable of competitively displacing the native strains of polioviruses, they may exclude other enteric viruses and establish a changed pattern of infection which could conceivably persist.

It is also possible that the elimination of the polioviruses through sustained widespread immunization would be reflected in a greater prevalence of whatever enteric viruses they may have suppressed in the past. The Group B Coxsackie viruses would seem likely candidates and it will be of considerable interest to observe, once the immediate effects of vaccination have subsided, whether epidemic pleurodynia becomes more common in Russia. During a recent discussion with M. P. Chumakov, who has directed the Russian program, I was told of outbreaks of paralytic disease which he had established as being caused by certain Group A Coxsackie viruses including Type A-7 which, when it was first identified in Russia, was considered to be a new type of poliovirus. There are substantial reasons, indeed, for considering several of the Group A strains to be much more like the three accepted types of polioviruses than most of the enteroviruses. The impression I gained from the discussion was that most of the paralytic "poliomyelitis" that occurred in Russia during 1960 following the large scale immunization was due to Coxsackie viruses rather than polioviruses. Whether this is the harbinger of the emergence of certain of these viruses as important epidemic strains is not yet known. Ecologic changes have rarely been predictable. We can expect to do no better than explain whatever changes occur after they take place.

Underlying all these considerations are problems of viral genetics which are so much a part of species competition. Because of the number and variety of the enteric viruses and their frequent coexistence, the possibilities of change are of a high order indeed, and if these prospects be added to what is already recognized as a current feature of enteric virus infections, namely their increasing importance in consequence of changing hygienic practices, we should prepare ourselves for further alterations in the nature and behavior of the numerous, worldwide little viruses.

In all of these ways the massive, abrupt, and nationwide introduction of experimentally modified virus strains may be presumed to be a huge experiment, unique in its size and boldness and rich in opportunities for the study and understanding of the ecologic relationships of human viruses. One would hope that every effort will be made to follow such experiments closely, to observe and record with an open mind. The opportunity is a challenging one.

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