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PRESENT STATUS OF WORK ON IMMUNIZATION OF HUMAN BEINGS WITH LIVING ATTENUATED POLIOMYELITIS VIRUSES

The two basic facts which form the foundation of experiments on the immunization of human beings with living, attenuated poliomyelitis virus are:

(1) that neurotropic activity and capacity for multiplication in the alimentary tract are determined by distinct genetic complexes in the virus, and

(2) that primates occupy an inverse position with regard to susceptibility of the nervous system and the alimentary tract -- the nervous system being more resistant and the alimentary tract more susceptible in the higher primates.

| INVERSE POSITION OF PRIMATES WITH REGARD TO SUSCEPTIBILITY OF NERVOUS SYSTEM AND ALIMENTARY TRACT |
|-----------------------------------------------|-----------------------------------------------|
| CELLS                              | MOST SUSCEPTIBLE | MOST RESISTANT |
| NEURONES...MONKEY (Lower motor), MONKEY (Brainstem), CHIMPANZEE (Lower motor), [MAN] |
| ALIMENTARY TRACT...MAN, CHIMPANZEE, CYNOMOLGUS, RHEAS |

The results of tests on many strains indicate that neurotropic activity is not an "all or none" character of poliomyelitis virus but rather that a great multiplicity of so-called "virulence genes"
provide strains with a wide spectrum of activity that has been measured quantitatively in monkeys and chimpanzees. Strains of the three immunologic types exhibiting varying degrees of low neurotropic activity have been segregated experimentally either by passage in rodents or by selective propagation in tissue culture, and have also been found in nature among healthy children who had no contact with clinically recognized cases during non-epidemic periods. Despite many experimental manoeuvres and the screening of a total of 69 strains from healthy children from different parts of the world in two different laboratories (49 in Cincinnati and 20 in New Haven) no strain that is completely devoid of neurotropic activity on the most sensitive lower motor neurones of the monkey has been found. However, strains of each of the 3 types which are not paralytogenic for chimpanzees after spinal inoculation of $10^6$ to $10^7.5^{TCD50}$ and possess only minimal activity after the inoculation of very large amounts of virus intraspinally in monkeys have been found.

Approximately 100 tests on 60 adult volunteers have been carried out with strains of each of the three types. The properties of the available strains are such that only the oral route provided susceptible tissue for multiplication of virus. The activity of four type 1, two type 2, two type 3, naturally occurring or experimentally segregated strains was compared and certain variations were encountered in the amount of virus excretion, detection of traces of virus in the blood, time and
level of antibody formation, and appearance of a certain proportion of virus particles which exhibit increased intracerebral activity in monkeys but are still innocuous intraspinally in chimpanzees.

There appears to be no immediate prospect of developing or finding strains completely devoid of neurotropic activity in the monkey. However, from among the strains that have been tested in human volunteers it has been possible to select one of each type that possesses only minimal activity in the spinal cord of monkeys and at the same time the greatest stability on multiplication in the alimentary tract.

The importance of the potential appearance of virulent variants during multiplication in the alimentary tract and the spread of the virus must be considered. The fact that extensive dissemination of endemic strains of poliomyelitis virus of relatively low virulence can continue in certain populations for many years without evidence of the appearance of highly virulent variants, indicates that reversion to high virulence is an uncommon phenomenon under natural conditions where the majority of strains are much more neurotropic for the monkey than the attenuated strains used in the human volunteers.

No spread of virus from person to person was observed in our studies on adult volunteers either at the reformatory or on two occasions under the conditions of intimate family life.
The spread of virus from vaccinated to unvaccinated persons by faecal contamination may, however, be expected to occur, although under ordinary hygienic conditions particularly during the winter this might be expected to be limited. Where poorer hygienic conditions might favor dissemination it would only substitute the spread of highly attenuated strains for the more neurotropic viruses that are already being disseminated under natural conditions.

The results of further studies carried out in 1956 will also be summarized.

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