without success. It has been contended that it is the same kind of experiment as the Foucault pendulum, owing its result, in some manner not made clear, to the influence of "all the matter in the universe." "All the matter in the universe" thus becomes a new fixed framework, which is going far afield, for questionable gain, from the luminiferous ether which so directly and accurately explains the experiment. At any rate it can not be gainsaid, I think, that all the experiments in this field, from the aberration of light, through the Michelson-Morley and Kennedy-Thorndyke experiments, the recently demonstrated variation of atomic clock rate and the Sagnac and Michelson-Gale experiments, are consistently and satisfactorily described in terms of a luminiferous ether.

In conclusion, let me summarize the point of view I have adopted in these remarks, and the chief points I have tried to make. I have endeavored to present the subject from the standpoint of the experimental physicist, to whom the properties of his apparatus must be constantly under scrutiny, so that he may not ascribe to the phenomena he is observing what are in fact peculiarities of his instruments. I have taken the variation of atomic clock rate with velocity as indicated by experiment, and investigated the influence such variation will have on the measurement of one of the fundamental factors in physical theory, namely, velocity. It develops that a variety of "velocities" can be measured with such clocks, no one of which has any *a priori* claim to be chosen as "correct." They are all deviations from the simple Newtonian concept of velocity, which is in terms of rods and clocks which are unaffected by motion. I urge the merit of the Newtonian framework as the only unambiguous basis for the idea of velocity. I have further pointed out that one of the conventions for measuring velocity when using variant clocks is equivalent to the Lorentz transformations and the Second Postulate of the Restricted Theory of Relativity. Conversely, this postulate is nothing more than a specification of a method of measurement to be used to the exclusion of others. Conclusions drawn from it are consequently of limited applicability and significance. They constitute no ground for revolutionizing the Newtonian ideas of space and time. I have considered the popular claim that the ether has been "abolished," and pointed out that the essence of this claim is that for the ether it is proposed to substitute a particular prescribed measuring procedure, which has no justification except as derived from considerations involving the ether.

Reverting to experimental findings I have reviewed the experiment of Sagnac, having in mind the claim that the ether can not be detected experimentally. I have asserted that, in the light of the experimentally found variation of clock rate with motion, this experiment does detect the ether, and that it and others in this field are all in complete agreement with the existence of a fixed framework. These views will be recognized as those of the earlier students of the subject—Fitzgerald, Larmor, Lorentz—but not of those who would shift the burden from variant measuring instruments to the nature of space and time. If you remember my opening paragraph, you see that I stand with Professor Morley.

CONSTITUTIONAL BARRIERS TO INVOLVEMENT OF THE NERVOUS SYSTEM BY CERTAIN VIRUSES[1]

By ALBERT B. SABIN, M.D.

ASSOCIATE PROFESSOR OF PEDIATRICS, UNIVERSITY OF CINCINNATI, COLLEGE OF MEDICINE, AND FELLOW OF THE CHILDREN'S HOSPITAL RESEARCH FOUNDATION, CINCINNATI, OHIO

IT has been realized for some time that in nature not all who are infected with certain neurotropic viruses exhibit signs of central nervous system disease; indeed, the number of those who develop paralysis or encephalitis may constitute a very small proportion of the total number of the animal or human population which is infected. The hypothesis that exposure to small doses of an unmodified, virulent, neurotropic virus can immunize without producing infection is still without experimental basis, because in the laboratory one usually finds that the dose is either large enough to initiate multiplication and infection or is too small to give rise to an immune response. Why, then, is infection apparent in some and inapparent in others? Instead of assuming that the major portion of a population is resistant because it has somehow acquired a specific immunity, we may inquire whether it might not be the other way around, *i.e.*, that immunity develops without disease because of some preexisting constitutional resistance. In the investigations which I shall now summarize an attempt

[1] Address delivered on December 28, 1939, to the Section on Medical Sciences upon receipt of the Theobald Smith Award of the American Association for the Advancement of Science. The work which forms the basis of this communication was carried out at the Rockefeller Institute for Medical Research in association with Dr. Peter K. Olitsky.

was made to define some of the ways in which such constitutional resistance may operate.[2]

Studies with the viruses of vesicular stomatitis and equine encephalomyelitis have revealed a type of resistance which depends neither upon specific immunity resulting from prior exposure to infection nor upon the presence of antibodies against the virus in the blood, but rather upon the condition of some of the tissues which the virus must pass before the nervous system can become sufficiently involved to give rise to clinically apparent and fatal disease.

In nature, the immunologically distinct New Jersey and Indiana strains of vesicular stomatitis virus are responsible for a mild disease of cattle and horses without apparent involvement of the nervous system, but, experimentally, in mice these viruses can give rise to fatal encephalitis or ascending paralysis. The starting point of these investigations was the observation that as mice grow older they acquire a resistance to inoculation by intraperitoneal, intramuscular, subcutaneous, intraocular and intranasal routes, while the nervous system as a whole, as evidenced by the effect of inoculation directly into the brain, remains equally susceptible in young and old. It seemed, therefore, that certain changes associated with or the result of the process of normal growth could either modify or completely suppress the effects of peripherally inoculated virus.

It was clear that in order to obtain some idea of the nature of this resistance it was necessary to determine in considerable detail the pathways by which the virus spread after inoculation in different parts of the body. Experimental and histological studies revealed that when virus was injected directly into the brain it spread through the open ventricular system and quickly involved the entire brain and cord in both young and old mice, while after peripheral inoculation the evidence pointed to progression in a closed system of neurons and their processes, at least in the stage preceding neuronal necrosis, the distribution of virus and lesions depending upon the central associations of the primary neurons connected with the inoculated site. Thus after nasal instillation of virus in young mice fatal encephalitis follows invasion of the entire central nervous system through the olfactory neurons and their connections, progression of the virus occurring from cell station to cell station along specific tracts, as is evident from the distribution of neuronal lesions. In resistant mice the virus also invades the central nervous system, but its spread is held up in a silent area somewhere in the anterior olfactory regions, and the animals show no signs of disease. The very fact that virus could multiply and remain localized in this limited area for a period of at least 4 days without involving the rest of the brain, suggested that it had spread in a closed system, for after direct intracerebral injection of even a minimal dose there are large amounts of it throughout the central nervous system within one day; it also suggested that some barrier must have been encountered which was capable of arresting the infection. The question then came up whether this hypothetical barrier exists in the animal before it is exposed to the virus, or whether it represents a rapid acquisition of specific tissue immunity. In other words, does the virus fail to progress because the remainder of the brain has become immune by the time it is reached, or is the remainder of the brain still susceptible, the spread of the virus being inhibited by a preexisting, localized insusceptible zone? In the experiments undertaken to answer this question, an attempt was made to circumvent such a zone, if one existed, by direct intracerebral injection of minute amounts of virus in old mice at intervals of 2, 3, 4 and 5 days after nasal instillation, when the anterior olfactory regions could be expected to contain virus. For if the brain had acquired an immunity in that short time one would expect these mice to remain well, whereas if the brain as a whole were still susceptible, these animals would die, while the uninoculated controls which received virus only by nasal instillation would survive. Actually, the mice injected intracerebrally at the stated intervals after nasal instillation died and the evidence was against a rapidly acquired immunity and in favor of some preexisting barrier. Whether this barrier is an insusceptible group of neurons or an impenetrable synapse somewhere in the chain, or something else, it is clear that the halting of virus progression must also depend on the failure of the neurons, which are affected, to disintegrate and liberate virus into the open system.

The course of events after intraocular injection was investigated because the special anatomical conditions in the eye appeared to supply a good opportunity for studying further the nature of virus spread along other pathways and the modifications which develop with age. It was possible to obtain satisfactory evidence by experimental and histological techniques that after injection into the vitreous of the eye, vesicular stomatitis virus attacks the nerve cells of the retina and pursues the decussating optic pathway into the brain. [In mice the proportion of optic nerve fibers which do not decussate is apparently very small.] It could be demonstrated that after injection into the right eye, virus first appeared in the left diencephalon, mesencephalon and occipital cortex, and it was possible to produce lesions in either the right or the left lateral geniculate body and superior colliculus, depending on whether the left or the right eye was injected. It was thus apparent that the primary pro-

[2] A. B. Sabin and P. K. Olitsky, *J. Exp. Med.*, 66: 15, 1937; *ibid.*, 66: 35, 1937; *ibid.*, 67: 201, 1938; *ibid.*, 67: 229, 1938; *Am. J. Path.*, 13: 615, 1937; *Proc. Soc. Exp. Biol. and Med.*, 38: 595, 1938; *ibid.*, 38: 597, 1938.

gression of the virus after intraocular injection was also in a closed system. Since the retina and the optic nerves are actually extracranial portions of the central nervous system it is interesting to note that minimal amounts of virus produced encephalitis in 15-day-old mice as readily by the intraocular as by the intracerebral route, while at least 90 per cent. of old mice which remain just as susceptible to intracerebral injection are completely resistant to virus introduced into the vitreous. In the resistant mice the virus failed to invade the brain and the barrier appeared to be within the eye, if not actually in the nerve cells of the retina.

After intramuscular injection a different type of barrier appeared to be responsible. In young susceptible mice the virus multiplies in the muscle cells, invades the nervous system along the spinal nerves of the region and the animals die with an ascending paralysis. In old mice, however, there is no evidence of local multiplication or involvement of the muscle cells, and in spite of the injection of as much as 10 million minimal cerebral lethal doses and the local persistence for days of much of the virus, there is invasion neither of the regional nerves nor of the central nervous system, and the animals remain well. That the barrier is not in the spinal nerves is evident from the fact that the majority of old mice develop fatal ascending myelitis when the virus is injected directly into the sciatic nerve. That the virus was not forced into the central nervous system during the course of the intraneural injection was suggested by the observation that it took at least three days for virus localized in the nerve to become demonstrable in the spinal cord. To identify the nature and precise location of the barrier at the site of intramuscular injection one must have a clearer and better-founded conception than is now available of the mechanism by which a peripheral nerve, like the sciatic, is invaded by virus deposited in the muscle. If, as is probable, the virus can progress to the central nervous system only along the axons, it might first have to penetrate certain specialized nerve endings, which perhaps may not be accessible except through the cells that they supply. If this were the case, one could understand how the mere presence of a large amount of virus without the simultaneous capacity to attack the cells might fail to involve the nerve endings. And yet there is evidence to suggest that the nerve endings themselves may perhaps constitute the barrier, as will be pointed out when the behavior of this virus in guinea-pigs is discussed. Before ending our consideration of the behavior of this virus in mice it may be interesting to note that just as different structures apparently function as barriers along different pathways, so is resistance demonstrable at different ages, depending upon the route of virus inoculation. With the intraperitoneal route it is found as early as the fifteenth day of life, with the intramuscular and intraocular routes it appears sometimes during the fourth week, while for nasal instillation it becomes apparent after the fourth week and affects between 50 and 90 per cent. of the animals in different groups of mice.

Although the central nervous system of guinea-pigs is about as susceptible to vesicular stomatitis virus as that of mice, nasal instillation of the virus produces encephalitis only occasionally in very young guinea-pigs and not at all in old ones. When the nasally instilled virus was traced in young guinea-pigs it was found that it always invaded the central nervous system along the olfactory pathways but that it never got beyond the rhinencephalon or diencephalon; in old guinea-pigs it was possible to demonstrate a transitory multiplication in the nasal mucosa but in at least 90 per cent. of them there was no invasion of the brain. Injection of the virus into the skin of the pads or into the muscles of very young and old guinea-pigs is followed by local multiplication, but the nervous system is not invaded, and the animals remain well. The fact that direct intrasciatic inoculation frequently led to a fatal ascending myelitis tends to eliminate the peripheral nerves themselves as the barriers to invasion of the central nervous system and suggest a consideration of the myoneural junctions and other specialized nerve endings, through which is effected the intimate relationship between the axis cylinders and the inoculated tissues. The striking difference between guinea-pigs and mice in relation to this virus is that the guinea-pigs, at a very early age, possess the barriers which mice acquire considerably later in life.

There are a number of other instances in nature where a virus may be highly neuroinvasive in one species and either not at all or very rarely in another. As a classical example, one may cite the virus which causes only herpes simplex in man, but when transferred to the skin, cornea or mucous membrane of the rabbit gives rise not only to local lesions like those in man, but also clinically apparent and fatal disease of the central nervous system.

It is well established that not all neurotropic viruses invade the nervous system in the same manner, and the barriers which may come into play with one virus may be entirely without influence on another. In the course of investigations on the mode of spread of the equine encephalomyelitis viruses still another type of resistance that develops with age was encountered. The change appears to be in the blood vessels which the equine encephalomyelitis viruses must traverse or grow through in most instances in order to invade the central nervous system.

With the eastern strain of equine encephalomyelitis virus young and old mice are equally susceptible to

infection by the intracerebral or intranasal routes. After intramuscular or intraperitoneal inoculation, however, 15-day-old mice are all susceptible while at one month of age 40 to 50 per cent. are already resistant, and beyond the age of three months this resistance rises to 95 per cent. After intramuscular injection in young mice this virus was found to invade the central nervous system along the local peripheral nerves in only about 5 per cent. of the animals, while in most of the others it appears to be eliminated from the blood onto the olfactory mucosa from where it invades the brain along the olfactory pathways. Studies on the nature of the resistance in older mice revealed that it is bound up with a failure of the virus to traverse the blood vessels, for the systemic phase of the disease, with virus circulating in the blood, occurs in both young and old animals. In guinea-pigs there is an indication that virus in the blood may pass or grow across the vessels directly into the brain and it is interesting that here too old animals were found to be resistant except when overwhelming doses were injected. That similar factors may play a role in human beings is suggested by the fact that in the first epidemic of this disease in man the majority of cases occurred in children, and also by the observation that adult laboratory workers may develop antibodies against the virus without having exhibited any signs of disease of the nervous system.

With the western strain of the mouse-passage virus, the first evidence that age has produced some change in the animal is found in the fact that after injection into the muscles of a hind leg, 80 to 90 per cent. of 15-day-old mice develop signs of encephalitis and the rest, signs of flaccid paralysis, while at 21 days the ratio is reversed, the majority developing flaccid paralysis, and about 20 per cent. resisting altogether. At one month of age and beyond, 90 per cent. or more are resistant to intramuscular inoculation, although injection directly into the sciatic nerve results in the paralytic disease in a large proportion of the animals. There are thus at least three phases during the maturation of the mouse, at which the neuroinvasiveness of the western virus is differently affected: first, at 15 days of age when certain vessels still permit the virus to traverse and spread in the central nervous system by some definite pathway; second, at the age of 21 days when the virus can no longer do this in the majority of mice, but now progresses along the nerves supplying the inoculated muscle; and third, between the 21st and 30th days of life when the appearance of some change in the muscles or specialized nerve endings in the great majority of mice now prevents invasion of the nervous system altogether.

Finally it should be noted that practically all the animals in whom constitutional resistance operated in one form or another to arrest and render inapparent, infection with the vesicular stomatitis or equine encephalomyelitis viruses ultimately developed specific immunity of the entire body, including humoral antibodies. This, at least as regards these neurotropic viruses, is an excellent illustration for the hypothesis that specific immunity without apparent disease is the result of preexisting resistance rather than the reverse.

In summary, it may be said, therefore, that as a result of the special mode of spread of certain viruses from the periphery into the central nervous system and also within it, the insusceptibility or inavailability of certain isolated tissues or structures, rather than resistance or immunity of the whole animal can act as a barrier to virus progression and prevent the development of apparent disease of the nervous system. While this mechanism may be only one among a number of others which operate in protecting the major portion of the animal and human population from disabling or fatal disease of the nervous system, it is especially interesting because it lends itself to the kind of experimental manipulation by which one may attempt to change susceptible individuals into resistant ones.

OBITUARY

ROY GRAHAM

DR. ROY GRAHAM, geologist at the Britannia Mines, British Columbia, was fatally crushed by a fall of rock in the mines on August 10, 1939. Thus tragically a life of unusual promise was brought to a close. Graham received his undergraduate education at the University of British Columbia, graduating in 1930 and receiving the master's degree in 1931. From 1931 to 1933 he held a fellowship in geology at the University of Chicago, where, under Dr. A. C. Noé, he became interested in the field of paleobotany, writing his doctor's dissertation (1933) on the Pennsylvania flora of Illinois as revealed in coal balls.

His excellent record at Chicago brought him the award of a National Research Fellowship in the fall of 1933 and enabled him to spend a year at Cambridge, England, studying under the distinguished English paleobotanist, Professor A. C. Seward. Returning to America in the fall of 1934, Graham soon thereafter was appointed to an assistantship at the University of British Columbia, serving in that capacity until May, 1937, and spending his summers in field work in Saskatchewan under the auspices of the Geological Survey of Canada.

His greatest talents and keenest desires lay in the field of paleobotanical research, but while awaiting