standard of life, security and delight in work, and leisure, it will be through much trouble and opposition, such as men have always encountered in winning political and religious freedom. There is an opportunity to attain this economic freedom in the United States by peaceful means, and this problem offers a challenge to business men, economists and engineers such as no similar group has ever had. Will they have the vision, courage and intelligent statesmanship to accept this challenge?

PREVENTION OF POLIOMYELITIS[1]

By Dr. SIMON FLEXNER

DIRECTOR OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK

THE evidence presented on the mode of infection in poliomyelitis has established two important facts: First, that the disease is a particular form of infection of the upper respiratory tract; and second, that in harmony with other epidemic diseases of respiratory origin, the cases arising during an epidemic cover a wide latitude in degree of symptoms and pathological effects. There is consensus of opinion among clinicians that the number of children suffering some degree of infection, the slight cases expressing themselves as minor illnesses only, is very large, being in comparison with the number that are frankly paralyzed many times as great. The wide occurrence of the slighter forms of infection can be taken as a means, favorable in character, of delimiting the prevalence of the severer affection, since early experimental observations showed Lewis and myself[2] that any degree of actual infection, irrespective of whether muscular paralysis arose or not, protected the inoculated monkeys from the effects of a second administration of the virus.

Hence the investigation of the immunological phenomena in poliomyelitis became at once a rewarding field of experiment. The knowledge of the phenomena has become considerable during the twenty-year period of the experimental study of the disease, and the application of this knowledge to the prevention of epidemic poliomyelitis has met with encouraging results in the severe outbreaks occurring in New York State in 1931 and in Pennsylvania in 1932. I shall endeavor to guide you quickly through the main discoveries which have led to the practical achievements to be described. It is, however, necessary at the outset to explain that I have taken the lecturer's privilege of including in this statement certain later results bearing out the earlier ones presented, which were obviously not available when the lecture was delivered. It is sometimes advantageous to defer writing a lecture until the time of publication arrives, especially when, as in this instance, a new method has been under trial. During the intervening period, the method may have been given a wider test, with results sometimes favorable, and of course sometimes unfavorable to its employment. We appear in this instance to be in the happier situation, and while it is still too early to pass final judgment on available means of preventing poliomyelitis in the young during the prevalence of an epidemic, it is desirable that the nature of such means shall become widely known, since epidemic poliomyelitis continues to appear annually in some parts of America and Europe during the summer and autumn season.

The observation of Lewis and myself, already referred to, that monkeys which had recovered from an attack—irrespective of its severity—of experimentally induced poliomyelitis were not subject to reinfection, led quickly to the testing of the blood of recovered monkeys and human beings for immune substances to which the protection might be attributable.[3] Tests made almost simultaneously in France, Germany and the United States disclosed the existence in the blood, after recovery from the disease, of neutralizing, antiviral bodies. A mixture consisting of the virus of poliomyelitis and the serum of the blood was injected into monkeys. No symptoms of disease tended to arise from this injection; while mixtures of virus and normal monkey serum, or the serum of many, but not all persons not known to have had poliomyelitis, proved incapable of protecting the animals against the onset of the symptoms, including paralysis, characteristic of the experimental disease. I shall return a little later to a consideration of the circumstances under which the blood of supposedly normal individuals acts in a measure similar to that of persons known to have had paralytic poliomyelitis, since this action has come to have such pregnant meaning.

Let me repeat, the blood of normal monkeys invariably failed to act upon or neutralize the virus of

[1] Abstracted from the John M. Anders Lecture on Poliomyelitis delivered at the College of Physicians, Philadelphia, January 6, 1932.

[2] S. Flexner and P. A. Lewis, *Jour. Am. Med. Assn.*, liv, 45, 1910; *Jour. Exp. Med.*, xii, 227, 1910.

[3] P. H. Römer and K. Joseph, *Münch. med. Woch.*, lvii, 568, 1910; C. Levaditi and K. Landsteiner, *Compt. rend. Soc. biol.*, lxviii, 311, 1910; S. Flexner and P. A. Lewis, *Jour. Am. Med. Assn.*, liv, 1780, 1910; A. Netter and C. Levaditi, *Presse méd.*, xviii, 268, 1910.

poliomyelitis. The neutralizing property was detectable only when the inoculated monkeys had shown unmistakable signs of infection, although these signs may have been fleeting in character and wholly devoid of a paralyzing effect. Monkeys which receive the virus in the ordinary process of inoculation and resist all infection—either because the virus employed is too weak or too small a quantity is used, or because individual monkeys are exceptionally refractory—remain normal in regard to the antiviral action of the blood and capacity to respond with paralytic symptoms when a more effective inoculation is made.

In the light of the fact that monkeys are not naturally afflicted with poliomyelitis, as is man, it is significant to note not only that normal monkeys do not exhibit the blood antiviral property, but that the blood of recovered monkeys is weaker in antiviral substances than is the blood of recovered persons. For the sake of convenience it is customary to speak of the neutralizing, antiviral blood serum obtained from recovered persons and monkeys as "convalescent serum." Thus, monkey convalescent serum is less potent than human convalescent serum. But the potency of the former can be markedly increased by the additional injection of virus into recovered monkeys, a process which Lewis and I called reinforcement.[4] Reinforced (or hyperimmune) monkey serum equals or even surpasses in neutralizing power the convalescent serum obtained from human beings.

Neutralization of the virus by convalescent serum, monkey and human, was established originally by test tube experiments. As already stated, virus and serum were mixed before the mixture was injected into monkeys. Since under such conditions no infection occurred, the immediate question which arose was whether neutralization could also be effected inside the animal body, that is, when virus and convalescent serum were injected separately. While the test tube, or *in vitro* demonstration, of the presence of antiviral bodies in the blood undoubtedly threw light on immunity in poliomyelitis, it was thought that the determination of neutralization *in vivo* might possibly lead to therapeutic application. The tests carried out by Lewis and myself[5] consisted of the intracerebral inoculation of virus and the intraspinal injection of convalescent serum into monkeys. The intracerebral method is the most effective that is known for inducing the infection; the intrathecal injection is the most certain and efficient procedure for bringing the neutralizing serum into intimate relation with the nervous tissues, including the nerve cells, and hence for the blocking of the cells against the entrance of the virus, the injurious effects of which are responsible for the severe symptoms of the disease. While it is true that under physiological conditions the flow of the cerebrospinal fluid, into which the serum is introduced, is away from the nerve tissues, the small rise in pressure produced by the injection suffices to reverse the current, bringing the serum into intimate contact with all the constituents of the tissues, including the nerve cells.[6]

The results of the *in vivo* experiments can be stated briefly. When the virus is injected not longer than from 18 to 24 hours before the serum, and the amount of virus introduced into the brain does not exceed a fixed quantity, neutralization *in vivo* can be accomplished. Neutralization may be complete, when no symptoms whatever arise; or it may be partial, in which instance mild symptoms appear after a longer incubation period. Ordinarily the experimentally produced paralytic disease in the monkey is severer than the paralytic disease in man. While the mortality of the human affection is 20 per cent. or less, that of the frankly paralyzed monkey is 60 per cent. or more. When monkeys recover at all, they have as a rule merely passed through a mild attack of the experimental disease, such as is produced with weak virus strains or after partial neutralization of the virus. The *in vivo* experiments showed, therefore, that the action of the virus already present in the animal body could, under certain conditions, be suppressed. Suppression is, however, possible only when the immune serum is injected before symptoms of infection arise; once signs of infection are present, the serum is incapable of preventing the ordinary course of the disease from supervening.

The test by intracerebral inoculation is the most drastic one that can be devised. It exceeds in severity the conditions of infection occurring in man. In the human being, the virus is believed both to enter and to leave the nervous system by way of the nasal mucous membrane; we[7] early found that the virus implanted in the brain escapes into the nasal mucosa. This observation was quickly followed by the induction of the experimental paralytic disease through the instillation of the virus into the nares,[8] which finding in turn soon gave rise to the discovery that the intrathecal injection of serum prevents the development of infection by way of the nasal membrane.[9] It has,

[4] S. Flexner and P. A. Lewis, *Jour. Am. Med. Assn.*, liv, 1780, 1910; lv, 662.

[5] S. Flexner and P. A. Lewis, *Jour. Am. Med. Assn.*, liv, 1780, 1910.

[6] L. H. Weed and P. S. McKibben, *Am. Jour. Physiol.*, xlviii, 512, 1919.

[7] S. Flexner and P. A. Lewis, *Jour. Am. Med. Assn.*, liv, 535, 1910.

[8] S. Flexner and P. A. Lewis, *Jour. Am. Med. Assn.*, liv, 1140, 1910; S. Flexner, *Jour. Am. Med. Assn.*, lv, 1105, 1910.

[9] S. Flexner and P. A. Lewis, *Jour. Am. Med. Assn.*,

indeed, proven easier to prevent infection by the nasal than by the cerebral route of inoculation.[10] An important consideration is that the time interval between the nasal instillation of virus and the intrameningeal injection of serum may be lengthened with security beyond the period of safety that has been determined when the virus is inoculated into the brain. Moreover, convalescent serum injected into the meninges is equally capable of preventing infection by virus introduced into the blood;[11] and the immune serum is also protective, under certain circumstances, when the injection is made into the blood stream instead of into the membranes surrounding the brain and spinal cord.[12]

Professor Netter, of Paris, in 1911,[13] seized upon these experimental results and introduced into practice the convalescent serum treatment of poliomyelitis which has since been the subject of so much discussion. It soon became apparent that, once paralysis had appeared in human beings, the serum was quite powerless to influence the disease. As means of diagnosis became more accurate and instances of preparalytic poliomyelitis could be diagnosed with greater certainty, the use of the convalescent serum was increasingly restricted to these early cases. Medical opinion is still divided as to whether the serum is effective even under these circumstances. The matter has indeed become largely a statistical one, and hence it is not likely that a definite decision will be made immediately.[14] Epidemic poliomyelitis is a protean disease, symptomatically considered, and its effects are so varied that the outcome of individual preparalytic cases can not be predicted with certainty. Even the comparison of alternate cases in which serum is given with those from which it is withheld, is at best but a rough measure of effectiveness, since so much may depend on the way in which the choice of cases is made. I have attempted to formulate my own views on this debated subject[15] which I venture to restate here:

> My own experience has been chiefly with the experimental disease in monkeys. There the use of immune serum does make a difference. As between human beings and monkeys, the conditions are not identical; but the advantage is in part with human beings. Among them we find far more of the mild or preparalytic cases. In man there is, therefore, an inherently effective agency at work in aborting poliomyelitis. This agency is far less effective in monkeys in which the experimental disease tends to be severe and fatal. The severe form of the experimental disease in monkeys can be prevented or mitigated by means of immune serum. Since the practice of medicine is applied to individual cases of disease and does not, except statistically, deal with disease in mass, the question may fairly be asked whether the preexisting mechanisms in man tending to confine and abort the virus infection, can not in some instances be supplemented and fortified by convalescent serum. It is generally agreed that the use of the serum does no harm. Since it can not be affirmed that in individual cases it does no good, and a body of medical opinion exists in its favor, the question arises of whether its use should be withheld. This question is to be answered not by the pathologist, but by the physician. If a better, more calculable method of preventing paralysis were known, that is, a surer way of supplementing the normal mechanism tending to restrain the action of the virus before it causes functional injury to the nerve cells, this question would not arise. But there is no better or more calculable method known. The choice is, therefore, between no therapeutic intervention at all and a kind of intervention believed to be harmless and not known actually not to be sometimes useful in cases of this tragic disease.

Up to this point we have dealt with the restraint of the virus when it is mixed with immune serum in the test tube, or when the virus introduced into the animal body is followed by the injection of serum before symptoms of infection have arisen. The next problem to be considered related to the possibility of restraint of the virus when the serum is injected several days in advance of the virus. The answer to this question received from experimental work promises to bear on a possible preventive measure—passive serum protection—against epidemic poliomyelitis.

Stewart and I on addressing ourselves to the solution of this problem found that serum prevention is not only experimentally possible, but that the blocking effect against the entrance of the virus into the nerve cells endures for several days after an intraspinal injection, and occurs even after an intravenous injection of convalescent serum. Having in mind the practical implications of these observations, we proposed "that in the event of severe outbreaks of epidemic poliomyelitis, convalescent human serum be employed to afford passive protection to persons—children especially—menaced by the disease."[16]

The experimental results having been successful, we regarded it desirable to apply the method of protection to children and young adults exposed to epidemic

liv, 1780, 1910; S. Flexner, *Tr. Assn. Am. Physn.*, xxvi, 67, 1911.

[10] S. Flexner and H. L. Amoss, *Jour. Exp. Med.*, xxxi, 123, 1920.

[11] S. Flexner and H. L. Amoss, *Jour. Exp. Med.*, xxv, 525, 1917.

[12] S. Flexner and F. W. Stewart, *Jour. Am. Med. Assn.*, xci, 383, 1928; *New England Jour. Med.*, cxcix, 213, 1928.

[13] A. Netter, A. Gendron and Touraine, *Compt. rend. Soc. biol.*, lxx, 625, 1911.

[14] S. D. Kramer, W. L. Aycock, C. I. Solomon and C. L. Thenebe, *New England Jour. Med.*, ccvi, 432, 1932; W. H. Park, *Tr. Assn. Am. Physn.*, xlvii, 123, 1932.

[15] S. Flexner, *Jour. Am. Med. Assn.*, xcix, 70, 1932.

[16] S. Flexner and F. W. Stewart, *Jour. Am. Med. Assn.*, xci, 383, 1928; *New England Jour. Med.*, cxcix, 213, 1928.

poliomyelitis. During the next two or three years, of a number of such persons injected with convalescent serum, none developed the disease; but the number was too small to permit decisive conclusions. An opportunity came, however, with the overwhelming New York City epidemic of 1931, at which time we recommended the protective injection of convalescent serum or its near equivalent, blood from normal adults, parents by preference.[17] The amounts of convalescent serum available are too limited to serve for mass immunization. Several thousand children were treated in this manner, and among them the incidence of poliomyelitis was believed to be lower than in the uninjected population. The procedure employed was to withdraw from parents blood taken under sterile conditions and to inject 30 cubic centimeters or more of the uncoagulated blood intramuscularly into the children.

Allusion has been made to the fact that the blood of normal adults offers a substitute for the convalescent serum. The history of the discovery of the virus neutralizing property possessed by the blood serum of normal adults on the virus of poliomyelitis is instructive. In the year 1911, Anderson and Frost[18] investigated the so-called "abortive cases" of poliomyelitis to which Wickman's attention has been forcibly directed in the Swedish epidemic of 1905–1906.[19] The American investigators paid particular attention to the blood neutralizing reaction which had been described a short time before[20] by the employment of which they endeavored to establish the poliomyelitic nature of certain indefinite cases of illness which accompanied those of frank paralysis arising in the epidemic of poliomyelitis at Mason City, Iowa. In the course of their studies they made two observations, since confirmed, which are of special significance: first, that the blood of adults who had shown no signs of illness may possess considerable antiviral properties; and second, that the blood of young children, even when they have had an attack of the disease, may not develop promptly neutralizing power against poliomyelitis, or may develop it in a lesser degree than adults. Similar observations were made by Peabody, Draper and Dochez,[21] who studied the New York City epidemic of 1911. But it was Aycock and his associates[22] who studied the phenomenon more widely and concluded that a process of unperceived—subclinical—immunization of the adult population is taking place extensively to-day, thus explaining the antiviral activities now so generally found in the blood of normal persons. Aycock relates this subtle process to the similar one long known to be occurring in widely prevalent infectious diseases such as diphtheria and scarlet fever. Normal adult blood not only tends to contain the neutralizing substances in appreciable amounts, but in rare instances in quantities surpassing those present in the blood of persons who have recovered from undoubted attacks of poliomyelitis.[23]

However, it was not until the epidemic of 1932 in Philadelphia and other places in Pennsylvania that the method of passive immunization by the use of normal adult blood received not only wide, but more measured application. The analysis of these tests is being awaited with great interest. Certain favorable results have already been reported. But the completion of final results, and especially their interpretation, will require time and critical judgment. It is obvious, of course, that comparison should be made, where practicable, between large groups of children, injected and uninjected, both groups being similarly circumstanced as to age, environment and exposure. But it is also desirable to take into account the fact that certain adults are known not to possess the antiviral blood property; hence a standardized protective material can not be generally employed in the effort to produce passive immunization.

Finally, it must be remembered that tests on monkeys have disclosed two modes of intra-vitam action of the convalescent serum. In one, the virus is completely suppressed and no symptoms of infection arise; in the other, the action of the virus is mitigated, the incubation period before the appearance of symptoms being prolonged, and the symptoms themselves are milder. It is probable, therefore, that among the passively immunized children many will escape all signs of disease, and others—depending on all the circumstances stated—will fail to be protected, or will develop milder symptoms, taking into account the number receiving the adult blood in comparison with a corresponding number not so treated. We must await future events before attempting any general prediction on this important subject; but enough would appear to have been achieved already to warrant a further and wider trial of this safe and readily available means of preventing epidemic paliomyelitis which continues to be a serious menace on a world-wide scale.

One aspect of the subject of immunity in polio-

[17] S. Flexner, SCIENCE, lxxiv, 251, 1931.

[18] J. F. Anderson and W. H. Frost, *Jour. Am. Med. Assn.*, lvi, 663, 1911.

[19] I. Wickman, Beiträge zur Kenntnis der Heine-Medinischen Krankheit (Poliomyelitis acuta und verwandter Erkrankungen), Berlin, S. Karger, 1907.

[20] P. H. Römer and K. Joseph, etc., *loc. cit.*

[21] F. W. Peabody, G. Draper and A. R. Dochez, Monographs of The Rockefeller Institute No. 4, 1912.

[22] W. L. Aycock and S. D. Kramer, *Jour. Prevent. Med.*, iv, 189, 1930.

[23] H. J. Shaughnessy, P. H. Harmon and F. B. Gordon, *Jour. Prevent. Med.*, iv, 463, 1930; M. Brodie, *Jour. Exp. Med.*, lvi, 507, 1932.

myelitis remains to be considered. We have long known that monkeys may be rendered actively immune by successive small injections, or one large injection, of poliomyelitis virus made beneath the skin[24] or by successive inoculations made into the skin.[25] Both these methods of securing immunity suffer from the disadvantage that occasionally monkeys develop paralysis instead of immunity. It appears that monkeys, in common with human beings, exhibit varying degrees of susceptibility to the presence of the virus in the body. An effort is being made to improve and perfect this means of active immunization in order to avoid the rare onset of disease. The combined use of immune serum and virus offers greater security. That active immunity can be obtained by the injection of mixtures of the serum and virus has been shown by Rhoads.[26] Recently we have carried out experiments on a larger scale, in which virus and serum have been injected separately into the body of monkeys. These animals developed active immunity and, up to the present, without the appearance of symptoms of infection in any case. Moreover, evidence is accumulating that as the original, human virus is passed from monkey to monkey, it undergoes modification, and while retaining its immunizing properties, changes its infective power. Whether or not use may be made of this transformation in securing active immunization of human beings when menaced by epidemic poliomyelitis, future study alone can determine.[27]

OBITUARY

RUFUS LOT GREEN

PROFESSOR RUFUS LOT GREEN, professor emeritus of mathematics at Stanford University, died in Palo Alto, California, on November 19 at the age of 71. With the death of Professor Green, Stanford University loses one of its most faithful servants, teachers, counselors and friends, and the community one of its most serviceable citizens.

It does not fall to the lot of every man in academic work to stand out as a teacher par excellence, a counselor with wise judgment, a citizen with a high sense of public duty and a friend with understanding mind and heart. So did this man, best known, however, only to his colleagues, students and friends. The name of Professor Green does not stand out in the annals of science, nor will historians of science record any great achievements of his in mathematical research or published monographs—but in the hearts of his students are indelibly impressed the sterling and modest qualities of a quiet and unassuming teacher, endowed with high ideals of true scholarship. For a period of over 40 years, teaching mathematics was his one great task.

Professor Green was born in Rush County, Indiana, on March 3, 1862, the son of Samuel and Elizabeth Anne (McKee) Green. He showed early aptitude for both mathematics and natural history. His first two years in college were spent at the University of Indiana from 1879 to 1881 under Daniel Kirkwood in mathematics and David Starr Jordan in natural history. From 1881 to 1883 he attended Cornell University, after which he returned to Indiana University, where he graduated in 1885 with a B.S. degree, and immediately became an instructor in mathematics at his alma mater. During this time he prepared for his master's degree, which he received in 1888. His long teaching career was interrupted only once when he spent one year as a graduate student and fellow by courtesy at Johns Hopkins University in 1887–88 under Sylvester. Professor Green's advancement was rapid; he filled successfully the position of associate professor (1886–90) and attained the position of full professor at the age of 28 (1890–93) during the period of David Starr Jordan's presidency of Indiana University (1885–91). Two years after the new university Leland Stanford first opened its doors in 1891 with Dr. Jordan as president, Professor Green received a call to become associate professor of mathematics, and in 1894 he was promoted to full professorship. He was just a year too late to be classified with the "Old Guards," an affectionate term for the pioneer professors who came with Dr. Jordan. (It was three years later that the writer became a student of his and formed a friendship which endured until Professor Green's death.) He became executive head of the department of mathematics in 1925, from which position he retired in 1927.

In the councils of affairs of the university he assumed more than his full responsibility on various committees. He was best known, however, as chairman of the students' affairs committee. His fairness and justice in administering student disciplinary cases won him great respect and esteem. The students recognized in Professor Green a man of high principles and this made him a favorite among them.

The work in his classroom was unusually interesting

[24] S. Flexner and P. A. Lewis, *Jour. Am. Med. Assn.*, lv, 662, 1910; C. P. Rhoads, *Jour. Exp. Med.*, li, 1, 1930.

[25] W. L. Aycock and J. R. Kagan, *Jour. Immunol.*, xiv, 85, 1927; F. W. Stewart and C. P. Rhoads, *Jour. Exp. Med.*, xlix, 959, 1929.

[26] C. P. Rhoads, *Jour. Exp. Med.*, liii, 115, 1931.

[27] S. Flexner, *Jour. Am. Med. Assn.*, xcix, 1244, 1932.