A Paper

ON

POLIOMYELITIS*

BY

F. M. R. WALSHE, M.D., F.R.C.P.

PHYSICIAN, NATIONAL HOSPITAL, QUEEN SQUARE

A notable advance in knowledge may raise as many questions as it solves, and a period of intensive and fruitful research may at first sight seem to leave us as far as ever from the solution of the problem we are investigating. This might plausibly be said of poliomyelitis.

Few affections of the nervous system have been more closely or successfully studied within the past few years, yet fresh pathological and epidemiological factors appear for elucidation, effective therapy remains as remote as ever, and many of our earlier certitudes have gone by the board. Yet we must necessarily be nearer a grasp of the many problems presented by poliomyelitis, and the present time is appropriate for a review of some recent advances in our knowledge. A comprehensive summary of these is not possible within the limits of my present opportunity, and I propose, therefore, to confine myself to a brief consideration of the question of the specific treatment of the disease in the light of our rapidly changing conception of its nature.

By way of definition we may say that poliomyelitis is one of a small group of infections of the nervous systems due to the action of ultra-microscopic viruses, the morphological identities of which are unknown to us. Other examples of the group are epidemic encephalitis and rabies, and in all three it is the grey matter which is the point of attack, whence these viruses are spoken of as "polioclastic." Of the characteristics they have in common perhaps the most striking are that they multiply only in contact with the living cell, within which their life and activity appear to be very brief, for after a short period they disappear. To this disappearance the name "auto-sterilization" has been applied, and in consequence of it virus diseases may be spoken of as "self-limiting."

CHANGED CONCEPTION OF POLIOMYELITIS

Perhaps the simplest way of indicating the considerable modification that has taken place recently in our conception of poliomyelitis is to give a brief statement of the views generally accepted up to five years ago, and to follow it by a summary of the conception which is now in process of development.

Up to four or five years ago poliomyelitis was generally regarded as an acute specific fever which, in its complete expression, presented three distinct clinical and pathological phases. Clinically, there was an initial and short-lived phase of systemic infection with its constitutional disturbance, then the signs and symptoms of meningeal irritation, and finally those of involvement of the nervous tissue—namely, paralysis. Each phase was thought to have an underlying pathological substratum. A general lymphatic hyperplasia marked the general infection, the invasion of the subarachnoid space was shown by a meningitis and by changes in the cerebro-spinal fluid, while the invasion of the nervous system was signalled by the development of inflammatory lesions in the ventral horns of the cord.

The primary nervous lesion was thus believed to be a meningitis, which spread along blood vessels into the cord, affecting first the interstitial tissue and secondarily the nerve cells. The port of entry of the virus was believed to be the nasopharynx, whence by the olfactory perineural lymphatics the virus reached the subarachnoid

space. In this the cerebro-spinal fluid acted as the vehicle for the further distribution of the virus through the nervous system.

Every item of this statement would now be challenged by workers at the problem of poliomyelitis, with the exception of that which regards the nasopharynx as the original port of entry of virus into the body.

Briefly, pathological investigation indicates that the virus reaches the nervous system by the axis cylinders of the olfactory nerve, enters the olfactory bulbs, and is spread thence within the nervous system by axonal channels. It has a special affinity for the nerve cells of the cervical and lumbar enlargements of the cord, within which it appears to multiply most easily. The primary nervous lesion is of the nerve cell, and not of the interstitial tissue. The cerebro-spinal fluid has been found to play no essential part in the carriage of the virus, while the meningeal reaction, the meningeal cellular infiltration, and the pleocytosis in the cerebro-spinal fluid have been found to be the results, and not the precursors, of the direct attack upon the nerve cell by the virus (Hurst, Hurst and Fairbrother).

It is to the study of the experimentally produced disease in the monkey that we owe the bulk of this new information. Such studies have many advantages over the clinicopathological investigation of the human disease, for the inoculated animal can be destroyed at any stage of the infection, early or late, and the whole sequence of events can thus be observed. In man the initial stages of the disease process are necessarily hidden from us, and we can study only its end-results.

It may be argued that the mode of inoculation of the experimental animal is not comparable with the mode of infection in man, seeing that the former consists in bringing the virus into direct contact with nervous tissue, either by intracerebral or intrasciatic inoculation, whereas in man it appears likely that infection occurs through the olfactory mucosa. It will be remembered, however, that the olfactory nerve terminations lie exposed in this mucosa, and that here a direct contact of virus with nervous tissue is possible in man. Further, Faber and Gebhardt have infected monkeys by this route, and have traced the spread of the virus from the mucosa to its destination in the ventral horn cells.

We may therefore accept the train of events so closely studied in the monkey as reproducing with some fidelity the pathogenesis and progress of the human disease. With the mass of evidence in favour of the view that the carriage of the virus is axonal, and the nerve cell lesion the primary one, I shall not further deal, and we may now return to a clinical consideration of poliomyelitis in the light of these pathological observations.

CLINICAL BEARINGS OF EXPERIMENTAL WORK

It is clear that we are rapidly approaching a conception of poliomyelitis which regards it as primarily and exclusively an infection of nervous tissue, with no initial phase of systemic infection. Indeed, the strongest reason for assuming the presence of general infection has been the lymphatic hyperplasia found post mortem in fatal human cases, for the clinical manifestations of the disease are all readily capable of interpretation as nervous in origin. Hurst and Fairbrother have not found these lymphatic lesions in the experimental animal; in man the virus cannot be detected in them, and it may well prove that their constancy and significance have not been correctly assessed in the past.

A corollary of the pathological observations I have referred to is that the clinical division of poliomyelitis into preparalytic and paralytic stages does not correspond to distinct stages in the underlying pathological process. The development of paralysis does not—as we have assumed—indicate the entry of the virus into the nerve

* Read in opening a discussion in the Section of Neurology and Psychological Medicine at the Annual Meeting of the British Medical Association, Dublin, 1933.

cell or the onset of the attack upon this. It expresses no more than the climax of the action of the virus upon the cell, an action which has already been waxing in intensity for some hours or even days, prior to the appearance of paralysis. In other words, the attack upon the nerve cell has begun before diagnosis is possible, and we have no reason to assume that there is any clinically recognizable stage of the malady in which the nerve cell is intact and free from infection.

In a recently published critical analysis of the view that poliomyelitis is a general infection with secondary involvement of the nervous system, Faber has aptly quoted the clinical description of the opening phase of the disease given by Draper, himself one of the original and most authoritative exponents of the general infection theory. Draper's account is as follows:

"There seems little doubt in the minds of those who have seen much of the earliest hours of the disease that a very definite and characteristic clinical picture presents itself. But it is difficult by descriptive method to transfer an adequate impression of the subtle and striking difference between the onset hours of infantile paralysis and those of any other of the acute infectious illnesses of childhood. To say that the temperature is elevated, often as high as 103° or 104° and that the child is flushed and miserable; that vomiting occurs and that drowsiness supervenes, does not offer sufficiently distinguishing evidence of the special type of infection. Nevertheless, this common symptom-complex is shot through with delicate manifestations that are unmistakably specific, but which must still be viewed as clinical impressions—those helpful though indefinite aids to diagnosis. Now when infantile paralysis becomes epidemic in a locality which has been previously free from its presence, the physicians in that territory soon appreciate this difference from the usual illnesses of children . . . there is a look of mingled apprehension and resentfulness, quite unlike the alert, bright, and shining eye of other fevers. The psychic change responsible for this look finds further expression in a characteristically annoyed shrugging of the shoulder which occurs when the child is touched or simply spoken to. Indeed, there is frequently a snarling whine of resentment which is synchronous with this gesture of discontent . . . In cases of overwhelming infection . . . there are other striking phenomena. The child is restless, breathes rapidly, and seems to be busily and actively resisting some incomprehensible disturbance of its usual comfort. In these instances the irritability and resentful manner are not marked, but the whole organism seems to be composed of tensely drawn wires—a universal overstimulation. This pressor state of the nervous system is so marked that a sort of impulsive ataxic tremor is present in every motion, especially when that motion has intent. . . . It is interesting to recall at this point that the very earliest symptoms in the monkey are not at all unlike those just described, for the animal becomes highly excitable and seems to develop the same state of intense excitability of the entire nervous system. Usually a few cases are met with whose profound stupor masks all other signs and symptoms."

Comparable accounts have been given by Heine, Muller, and many other observers, and they certainly bear out the contention that the opening clinical phase of poliomyelitis is more consonant with a primary nervous involvement than with any theory of systemic infection. It may reasonably be submitted, therefore, that from their onset the symptoms betoken the actual invasion of nervous tissues by the responsible virus.

In elaborating this hypothesis Faber refers to some experiments carried out by Gebhardt and himself, and already mentioned. Having infected a series of monkeys by the intranasal route, an animal was destroyed and its nervous system examined for the presence of virus and that of lesions on each of the succeeding eight days. The virus was found to be successively present in the olfactory bulbs, the hypothalamic region, the medulla, the posterior horn cells, the posterior root ganglia, and the ventral horn cells. He attributes the preparalytic symptoms to the successive presence and action of the

virus upon each of these regions. I cannot here follow his argument in detail, but though some of it yet lacks confirmation, at least in outline it is reasonably in accord with the facts of clinical observation, and is perhaps less speculative than the theory of an initial systemic infection. A further clinical distinction may now be reconsidered—namely, that into *abortive* cases, in which only the symptoms of a supposed systemic infection are present, and *non-paralysed* cases, in which the symptoms of a supposed meningeal involvement occur, but in which recovery ensues without the development of paralysis. Clearly, this distinction ceases to have any meaning, for there are only paralysed cases and non-paralysed cases. The real distinction between the two is that in the latter the virus has been neutralized before it has damaged the ventral horn cells sufficiently to impair their function.

RESPONSE TO SERUM TREATMENT

In summary, then, we may say that the trend of recent work is to show that poliomyelitis is probably from the outset and exclusively an infection of the nervous system; that the evidence hitherto accepted as proving the occurrence of general infection is capable of another interpretation; and that the hypothesis of a primary meningitis which determines and precedes the invasion of the nervous tissue must be abandoned. The preparalytic stage of poliomyelitis is simply that stage of the disease in which the damage to the nerve cells has not yet destroyed them or paralysed their activity. This conception of poliomyelitis may explain much that has been obscure in the response of the disease to serum administration, and it may provide a clue as to the lines upon which the question of treatment may have to be approached.

For it seems clear that this problem of serum treatment is not what we have hitherto supposed it to be. It has been assumed that the preparalytic stage was a brief period during which we might hope to neutralize the virus before it reached and began to attack the nerve cell. There is probably no such period, and all we can hope for is to neutralize virus already in the cell before the latter is damaged beyond repair. The experiments of Flexner and Lewis hold out little hope that this is possible, for they showed that the intrathecal injection of convalescent serum had the power of preventing paralysis or of prolonging the incubation period only if given within twenty-four hours after the inoculation of the virus. Flexner¹ believes that in monkeys the suppression of the virus "is only possible 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."

There have always been observers who have failed to discover any efficacy in the serum treatment of the human disease, though their observations have been largely ignored by those who hold the opposite view, and on going through the published reports of the twenty-two-year period which has elapsed since Netter first employed convalescent serum certain very interesting and significant features emerge. They are as follows:

(1) The doses employed by the earliest workers were by present standards ludicrously inadequate, yet the results claimed for them have not been surpassed by those of the heavier dosage now in favour. Thus Netter, in 1911, gave from 5 to 15 c.cm. serum, some of his patients receiving but a single dose.

(ii) In most instances the serum employed has been of unmeasured and unknown neutralizing power. It has been assumed that every convalescent serum possessed this power in considerable degree, an assumption we now know to be unwarranted, for the blood of recovered individuals may be of feeble potency in this regard (Shaughnessy, Harmon and Gordon, and others).

(iii) Three methods of administration have been in use—intrathecal, intramuscular, and intravenous. Equally

favourable results have been claimed for all three, yet it is difficult to believe that all three can be equally effective. The earliest possible action of the serum upon the virus is of the very essence of the situation, yet intramuscular injection must involve maximal delay, while intrathecal injection can be little better, since it seems probable that re-absorption into the blood stream is a necessary preliminary to the reaching of the nerve cell. In the light of modern pathological conceptions of poliomyelitis the rational method is intravenous administration. If in fact, then, all these methods are of equal value it is possibly because this value is negligible and the method of administration therefore indifferent.

(iv) Adequate control of the results of treatment has only exceptionally been undertaken. There may be obvious reasons for not withholding serum from any case, yet, nevertheless, the omission to establish controls in this way has rendered a sound assessment of serum treatment impossible, and has left us for twenty years uncertain as to its value.

(v) It is significant that beneficial results of an even more striking character than those claimed for convalescent serum have been advanced by several observers on behalf of Rosenow's anti-streptococcal serum, for the use of which there is no scientific basis. The evidence for these now generally rejected claims is of the same order as that so widely accepted as valid in the case of convalescent serum. In both cases adequate controls are lacking. There is surely a lesson for us in this—namely, that the standards often adopted in evaluating therapeutic methods are of a kind that would not be accepted in any other field of scientific inquiry.

(vi) Finally, and of more positive significance, are two small series of cases treated by Schwarz and by Draper in which an equal number of control cases were observed, to whom serum was not given. In both series the untreated cases fared as well as those given serum, and in Draper's series definitely better.

We may conclude, then, that with the exception of these two series, and of a larger one now to be considered, serum treatment in the past has not been conducted on a basis that makes an assessment of its value possible, and that so far no convincing evidence of its value has been forthcoming.

Last year, however, some definite and reliable information emerged. In 1931 the beginning of an epidemic in New York led to a concerted effort by several observers to make a scientific study of serum treatment. In all, over a thousand cases of poliomyelitis were observed, half being given serum and half not receiving it. The figures are to be seen in the volume entitled *Poliomyelitis*, published at the instance of the International Committee for the Study of Infantile paralysis. I will only cite the conclusions expressed as the result of this experiment:

"A group of over a thousand cases, including those of Aycock and Kramer, diagnosed in the preparalytic stage, with approximately half treated by convalescent serum, shows nothing to indicate the therapeutic value of the serum, either in reducing case fatality or in preventing paralysis. Indeed, the slight differences between the treated and the untreated groups are against the use of serum. Since the same results were shown by three groups of workers it may be concluded that these cases were diagnosed and treated without personal bias. It is fair to say, however, that there is a belief that the percentage of moderately severe cases was a little greater in the treated children in the group studied under the direction of the Academy of Medicine. This number of cases seemed large enough to equalize in each group the individual differences that cannot be exactly measured in clinical medicine" (p. 240).

ASSESSMENT OF WORTH OF CONVALESCENT SERUM

If any still remain unconvinced that serum treatment as hitherto employed has proved a broken reed in our hands, there is yet another means by which we may seek to assess its worth. Let us compare it with the other specific treatments that have come into general use and

acceptance during our own time. On the one hand we have the treatment of diphtheria and tetanus and the prevention of typhoid, on the other insulin treatment of diabetes and the liver treatment of pernicious anaemia. There are also the treatment of syphilis by the salvarsan compounds and other chemotherapeutic successes of more recent date. What stamps all these is the remarkable rapidity with which they established their efficacy. The exact indications for their use and the quantitative assessment of their actions may have required some years of experience, but their specific value was never long in doubt.

In the convalescent serum treatment of poliomyelitis we have, by way of contrast, a method that has been increasingly used for over twenty years. Belief in its value, never universal, has steadily waned, until it has reached its lowest point in the conclusions just cited. There could scarcely be a more impressive illustration of its inefficacy.

It is difficult to escape the conclusion that Flexner's observations as to the inability of immune serum to influence the course of the experimentally produced disease, unless it be administered before the onset of symptoms of infection, must apply equally to the treatment of the human disease. Park has also expressed the view that once the virus has produced within the nervous system changes sufficient to allow of diagnosis, it is already too late for serum to exert influence upon the course of events. But if, as now appears to be the case, we must regard all the symptoms of poliomyelitis, including those of the entire preparalytic stage, as indicating the action of virus upon the nerve cell, then it is always too late to combat infection. This may well be why serum treatment has failed us.

Therapeutic enthusiasm is notoriously proof against hard facts, and we may therefore expect this treatment to be continued by those who already believe in it. But something will have been gained if the lessons and disappointments of the past lead to the more scientific planning and administration of this mode of treatment in the future. We might almost say that convalescent serum has not had a fair trial. Unstandardized serums of unknown potency have been administered in varying dosage by varying routes in different stages of the malady, and control observations have almost uniformly been neglected. It would indeed be surprising if such haphazard methods allowed of any reliable conclusions.

It is known that the blood of most healthy adults possesses virus-neutralizing powers of considerable potency, and it seems clear that the method of choice in the administration of immune serum is the intravenous route. For these reasons Faber has suggested that the testing and standardization of blood transfusion donors in respect of virus-neutralizing powers, and the therapeutic employment of blood transfusion from donors of known potency and appropriate grouping, and in maximal amount, promises to be the most useful method of attack. It has manifest advantages over the use of convalescent serum or of foreign immune serums.

Seeing that the value of such treatment must for the present be regarded as problematical, there can be no sound objection to the making of proper control observations and to the careful selection of cases for treatment upon some consistent basis. Only an unwise publicity and the making of extravagant claims are likely to stand in the way of such a selection during the course of an epidemic. Where these errors have not already been made they can surely be avoided.

In this way the value of immune serum may be given a thorough trial during the next few years if—unhappily—further epidemics of poliomyelitis occur. The commonly adopted method of pooling convalescent serums, without any attempt at their standardization, can no longer be

regarded as an adequate provision for an outbreak of the disease, and the treatment must be put upon the same basis of precise measurements and employment as obtain with other modes of serum treatment. That this may entail technical difficulties is not a reason for continuing the present haphazard methods.

It is as well to look the situation in the face, and to realize that from the very nature of the disease with which we have to deal we cannot be very sanguine about any method of treatment that can come into action only after the nerve cells already harbour the virus and are suffering from its attack. It is for this reason that Flexner's recent suggestion of the production of an active immunity in the child, of the kind achieved in the case of small-pox, is so important, and it is to be hoped that further study may provide us with such a weapon against this most disabling of diseases.

A comprehensive summary of contributions to every aspect of the study of poliomyelitis is to be found in a volume referred to earlier and published by the International Committee for the Study of Infantile Paralysis, under the title of *Poliomyelitis* (Williams and Wilkins Company, Baltimore, 1932). It contains an exhaustive bibliography. A more critical survey has recently appeared from the pen of H. K. Faber in the review *Medicine* (publishers as above) for May, 1933. It is entitled "Acute Poliomyelitis as a Primary Disease of the Central Nervous System: a reconsideration of the pathology, symptomatology, and treatment, based on the hypothesis of axonal propagation of the infective agent."

REFERENCE

- ¹ *British Medical Journal*, 1933, i, 132.

THE BEARING OF RECENT WORK ON CERTAIN ASPECTS OF POLIOMYELITIS *

BY

J. PURDON MARTIN, M.A., M.D., F.R.C.P.

PHYSICIAN TO OUT-PATIENTS, NATIONAL HOSPITAL FOR NERVOUS
DISEASES, QUEEN SQUARE

Nothing in recent work has been more important for the understanding of poliomyelitis—and of virus diseases of the nervous system as a whole—than the demonstration by Drs. Fairbrother and Hurst⁶ that the infection is conveyed along the axis cylinders. The degree to which this doctrine of axonal transmission of the virus might alter the general conception of poliomyelitis is exemplified in Dr. Walshe's paper (see p. 1197), where he upholds the view that the disease is exclusively nervous. This argument, if carried to the implication that infection without nervous involvement does not commonly occur, would not only alter our general conception of the disease, but would be subversive of many of our ideas of its epidemiology. For to infection without nervous involvement we have attributed the immunity that is widespread among the general population. This immunity is acquired, and it does not depend merely on age, for it varies as regards its age distribution in different communities. To this immunity, in turn, we have attributed the low incidence of poliomyelitis on the population and its incidence on the younger members. Such ideas would have to be radically modified if Dr. Walshe's argument were to prevail.

Personally I do not feel that anything in the recently acquired knowledge justifies such a complete abandonment of our former views. I am convinced that the disease ordinarily consists of a *general* as well as a *nervous* infection, and, further, that in the majority of infected persons the nervous system is not involved.

* Paper read in the Section of Neurology and Psychological Medicine at the Annual Meeting of the British Medical Association, Dublin, July, 1933.

EVIDENCE FAVOURING GENERAL INFECTION

The evidence of general infection seems to me indisputable. The first striking fact is the enlargement of the lymph glands found post mortem in human cases. This has been emphasized by those who have had extensive pathological experience of the acute disease. Burrows,⁹ who was resident pathologist at the Johns Hopkins Hospital during an epidemic of poliomyelitis in Baltimore in 1916, described a general lymphoid hyperplasia as the most marked pathological feature of the disease, and in a recent paper he has even argued that poliomyelitis may be more correctly classed with the diseases of the lymphatic system. The structures most affected are the solitary lymph follicles of the intestinal tract, Peyer's patches, and the mesenteric lymph glands, but the peripheral lymph glands may also be involved, and one may also see hyperplasia in the thymus and in the Malpighian corpuscles of the spleen. Smith's report on the 1931 epidemic in New York also stresses the changes in the lymphoid tissue, including the tonsils, thymus, and spleen (134 fatal cases, 81 examined completely). Flexner and Lewis actually demonstrated the presence of the virus in human mesenteric lymph nodes, and others have shown its presence in the mesenteric lymph glands of experimental monkeys, even when the infection of the animal has been by intracerebral inoculation. The virus has not been detected in human blood—a fact which is not surprising in view of the technical difficulties of demonstrating its presence—but Flexner and Lewis, Clarke, Fraser and Amoss, and others have been successful in finding it in the blood of experimental monkeys, following intracerebral inoculation.

A fact which is strongly suggestive of general infection is the development of immune bodies in the blood. It is apparent from many and various findings that a general immunity is developed, and it seems unlikely that any strong blood reaction of this kind would occur if the infection or noxious substances were confined to the nervous system and did not enter the blood itself. There are, moreover, occasional cases encountered clinically, which seem inexplicable by any other theory than that of general infection. These are instances in which the onset of poliomyelitis has followed an injury, and in which the paralysis has been maximal in the injured limb. I have seen one in which paralysis of the left leg in a young man came on seven days after an injury of the left buttock sustained at football. A few years ago (1926), at a meeting of the Association of Physicians, Dr. Abercrombie¹ described three cases in which children had been attacked by acute poliomyelitis after fractures. The intervals between the fracture and the onset of paralysis were respectively eleven, twelve, and about twenty days, and in each case the fractured limb sustained an extensive and severe paralysis, whereas the other limbs recovered. He quoted similar cases described by Charcot. In the subsequent discussion on that paper Professor Fraser referred to similar cases observed during an epidemic in New York. The injuries in these cases were not compound, and, in the light of to-day's knowledge, the only explanation of the determination of the paralysis to the injured limb seems to be that an infection circulating in the blood obtained entrance to a damaged nerve at the site of the injury, and that consequently the maximal dose of virus was transmitted to the corresponding portion of the spinal cord. It is a fair argument that in the absence of trauma some, at least, of these patients would have escaped nervous involvement.

RELATION BETWEEN GENERAL AND NERVOUS INFECTION

General infection undoubtedly occurs; but what is its relation to the all-important nervous infection, and does it influence the early symptoms?