SERUM THERAPY IN POLIOMYELITIS

BY

JEAN MACNAMARA, M.D.(MELBOURNE)

In a recent article Dr. Simon Flexner[1] asks clinicians whether human immune serum which is able to inactivate, *in vitro*, infective doses of poliomyelitis virus, and which makes some difference in the severe infection induced experimentally in monkeys, may not be used to supplement and fortify the mechanisms pre-existing in man (as opposed to the monkey), tending to abort and confine the virus of this disease. Though twenty-two years have elapsed since A. Netter[2] first used the serum of convalescents as therapy in poliomyelitis, Dr. Flexner's question will receive at present many answers in the affirmative and some in the negative. The therapy was suggested before clinicians were ready for its application. One objection,[3] that it is impossible to obtain adequate supplies of human serum, has been overcome in several centres by preparation of serum before an epidemic occurs and by the provision of adequate after-care to potential donors[4 5 6 7] in the intervals between epidemics. Another objection, that the disease cannot be recognized before paralysis has developed, has faded with increased experience. There is now consensus of opinion that in the epidemics which have occurred recently in temperate climates it has been possible to recognize the disease in the preparalytic stage with a degree of certainty which increases with experience. The diagnosis rests upon the recognition of a syndrome, the failure of a careful clinical examination to discover any other cause for the illness, and the confirmation afforded by changes which usually occur in the cerebro-spinal fluid.

Serum therapy in poliomyelitis has been, and still is, handicapped by the lack of any uniform standard unit of virus or of serum. Ehrlich did much to promote uniformity of results from the use of diphtheria antitoxin by calling attention to the necessity for the use of a suitable toxin, and by distributing a dry standard antitoxin to various laboratories.[8] For the standardization of diphtheria antitoxin the inexpensive guinea-pig has provided a convenient animal. At present the expensive monkey is the only animal susceptible to poliomyelitis. Laboratory strains of virus are liable to variations, quantitative and possibly qualitative in nature.[9] While, as pointed out by Kramer,[10] the neutralization test, properly controlled, can be very useful in giving certain information, there is no standard unit of poliomyelitis virus or of serum to permit delicate, or standardized, or comparative measurement of potency.

VARIATIONS IN POTENCY OF SERUM

Experience with diphtheria antitoxin, made without undue haste, standardized, and concentrated, has not prepared clinicians for the variations in potency, at present inevitable, in the serum obtained from the blood of persons who have had poliomyelitis. In the former, the clinician has become accustomed to a weapon whose potency he knows, and whose dosage has become almost a standard figure. In the latter the product is liable to variations in potency induced by varying procedures in the selection of donors: the possibility of the inclusion of serum from non-immunes ; the varying time interval from the donors' initial disease ; the variation in potency of individual serums comparable to that found in individual horses immunized against diphtheria toxin ; the possibility that the immunity of some of the donors has been induced by a strain differing slightly from that of the epidemic for which the serum has been prepared; and the possibility of depreciation of the product from storage, or exposure to heat and antiseptic.

Some of the variables may be reduced—for example, by preliminary examinations to confirm the donors' statements that the disease from which they suffered has been poliomyelitis, and by shielding the product from exposure to heat even during transit ; but in view of uncontrollable variables, more is demanded of the doctor responsible for the treatment of patients than the inoculation of serum in the dosage written on the container. His difficulties are increased in that poliomyelitis does not run its course to any schedule. The duration of the preparalytic stage and the urgency of the condition vary in different epidemics and in individual patients. Because of these variations clinicians seeking to learn to use the only weapon at present available in such a manner as to protect from severe paralysis every one of those patients slow to develop immunity for themselves, have followed and gradually elaborated the procedure suggested by Amoss and Chesney[11] in 1917. This involves observation of the patient's response ; aiming at the administration of an initial dose large enough to produce the desired effect—namely, lowering of the temperature and improvement of the general condition ; ensuring by observation that if the first injection has been inadequate the necessity for a second or third will be recognized ; learning from one patient how to guess approximately the dose required by the next ; and using relatively larger doses when a new batch of serum is provided until there has been opportunity to compare its potency with that of the preceding batch. The study has been helped by lessons taught by serum therapy in other diseases. In the directions for the use of diphtheria antitoxin, Park and Williams[12] advise that it is the early and sufficient dose which is important ; that the size of the individual must be taken into consideration ; and that antitoxin injected intravenously passes out to the tissue fluids about ten times as rapidly as when the injection is given subcutaneously, and four times as rapidly as when given intramuscularly.

Study of the patient's condition and history, together with the clinician's previous experience with the batch of serum he is using, guides in the estimation of the dose required: the duration of the patient's illness ; his age and weight ; the degree of toxaemia ; the rapidity with which the illness has progressed through the stage of general symptoms to special warning signs. A patient who gives a history of illness lasting for a few days succeeded by an interval of apparent recovery, followed by the second phase of his illness, with pain in the neck and back, spine sign, fever and rapid pulse, and toxaemia lasting over twenty-four hours, has little time to lose, especially if tremor and hyperaesthesia have developed. Such symptoms suggest a larger dose than that required by a patient who has developed a spine sign within the past four hours after two days of observation for indefinite illness. The emergency is greater in patients in whom general symptoms are closely followed by the spine sign and tremor, especially if the pulse is rapid and toxaemia marked. Such cases approximate more closely to the fulminating cases of the older textbooks, and demand much larger initial doses than those in whom the progress of the disease is more leisurely, and the patient's resistance greater.

DIFFICULTIES IN GAUGING ITS VALUE

Human immune serum is expensive. In many countries large sums of public money have been spent on its preparation and administration. It is therefore important that any work which claims to give more accurate information of the value of serum than that of opinions gathered over years of observation should be carefully examined in order to ascertain whether the statistics presented have been so accurately compiled as to warrant any conclusion as to the therapy in general or to the methods of treatment adopted in the work reported. It is admitted that the only way to assess the value of serum on a statistical basis would be a study lasting for several years, during epidemics of varying virulence, carried out by clinicians experienced in this disease and enabled by their previous training in muscle examination to ensure that patients selected for the comparison had not progressed past the preparalytic stage. In this study, comparison would be made of the end-results of two groups of cases selected on a strictly alternate basis, in which one group would receive no serum and the patients in the other group would receive serum carefully prepared in the optimum initial dosage for each individual, the total dosage being determined by the response. The patients would be treated under conditions which would

allow observation, and records of the temperature would be kept.

No such comparison has yet been recorded. The experiences in New York City during 1931 have been quoted[13] as representing a controlled comparison. Examination of Dr. Park's report of the work undertaken in that epidemic shows that any claim to have made a controlled comparison is invalidated by the fact that the two groups of cases were not comparable. "There was accidental inclusion of a somewhat larger number of graver infections in the treated patients."[14] It is readily admitted by physicians whose work Dr. Park includes in his report that the emergency of the epidemic prevented an accurate comparison or treatment of the patients according to individual requirements. The report of Dr. Linsly R. Williams, the chairman of the Poliomyelitis Committee of the New York Academy of Medicine,[15] states: "The untreated group was indeed a much milder group than the treated group. The results were inconclusive. Many of the members of the committee and the physicians who took part in the study feel that more accurate and more intensive work should be done along these lines." Statistics derived from the study to which Dr. Williams referred were included in the statistics reported by Dr. Park. Some of the procedures adopted in the New York epidemic of 1931 have been discussed in a recent publication[16]—namely, the administration in some instances of doses as small as 25 c.cm.; the lack of detailed examinations of muscle power to ensure that the classification of cases as preparalytic was accurate or later to assess the end-results; the use of terms, such as "weakness," open to variable interpretations by different observers; the delay which occurred between withdrawal of cerebro-spinal fluid by lumbar puncture and the administration of serum to the cases which applied to the New York City Department of Health. These criticisms have been regarded by Dr. L. R. Williams as fair and just.[17]

LESSONS FROM NEW YORK AND ELSEWHERE

Nevertheless, the work done in New York City made two useful contributions to the problem: (1) the demonstration that during that epidemic many cases recovered without treatment, though a spine sign and cerebro-spinal fluid changes were observed (unfortunately no indications have been recorded by the New York workers by means of which such cases could be differentiated with certainty from the remainder who proceeded to paralysis); (2) the demonstration that the use of a variable product against variable conditions in a dosage decided arbitrarily rather than by the requirements or response of individual patients was followed by a percentage of failures—3.8 per cent. mortality, 19.6 per cent. paralysis, and 7.7 per cent. "weakness." In a smaller series Kramer and Aycock and their associates[18] were able to do more accurate work, but the preliminary examinations to ensure the accuracy of the classification "preparalytic" were limited to examinations in the recumbent and sitting positions, and the dosage administered was arbitrarily decided. These workers did not claim that their study represented a controlled experiment, but that it more nearly approached one than any they had previously been able to make, and they concluded that the study should be continued. Five of their treated cases developed severe paralysis. The authors state that there was some indication that these irregular results may be accounted for by the lateness of the treatment; but no temperature charts were published.

In some circles, where there has been no opportunity afforded by recurrent epidemics of judging the effect of serum in doses adapted to individual requirements, the publication of the New York work has been followed by a reaction of opinion more extreme than would appear warranted by the failure of Kramer and Aycock and their associates to avert paralysis in five patients by the administration of an arbitrary dose of serum. Surgeons have not discarded operative intervention for intussusception on the grounds that some of the patients recover unaided, nor are they influenced by the fact that results in any series are not 100 per cent. successful when in some instances the operation is delayed or the reduction incomplete. The value of the treatment is assessed by the results achieved in series of cases where every effort is made to diagnose early, to avoid delay between diagnosis and treatment, and to reduce the intussusception completely.

Levinson, McDougall, and Thalhimer,[19] in reporting the results of the work in Chicago, state that in none of their treated cases was the involvement severe. They stressed the clinical response following a large initial dose of serum. "There were many patients treated who showed such a prompt and favourable response within twenty-four hours, a temperature drop to normal, and complete subsidence of symptoms and signs (except for some increased neck rigidity following spinal serum administration), that it seemed almost specific." Paterson,[20] reporting experiences in Brisbane during the epidemic of 1931–2, described reactions which occurred in some of his patients, beginning about four hours after injection of serum and lasting on an average for twelve hours—characterized by a rise in temperature, extreme discomfort, and headache. "Suddenly the picture would change, the child would feel a lot better, and the headache was gone; food and drink were wanted, and from being very irritable the child showed pride in attempting the various actions asked for." Within twenty-four hours there was a considerable drop in temperature, but it was generally two or three days before the temperature became actually normal. Paterson explained that as Brisbane was unprepared for an epidemic, serum had to be obtained from Melbourne, and therefore the doses given were smaller than those he would use in the future. The report does not state whether any other treatment was undertaken after serum had been given. From the clinical study of Dr. S. F. McDonald,[21] it appears that many of the Brisbane patients were toxic. A "dengue state" is described. In Victoria it was found that patients were frequently constipated, dehydrated, and acidotic, the pain in the neck having prevented adequate ingestion of fluid. The administration of an aperient, carbohydrate, and fluid by means of a bent glass tube or feeding cup helped to eliminate from the picture such features which mask the indications for a second dose. It is too early to ascertain from the Brisbane workers whether the discomfort of which the children complained was more than that experienced by any toxic febrile child after an anaesthetic, or whether the reactions occurred after any particular batch of serum. McDonald stressed the importance of having serum and facilities for examination of the cerebro-spinal fluid available at the bedside. "To do as is not infrequently done—to do a lumbar puncture and bring in fluid five miles for examination and to return with serum—meant delay, so that rapid extensions may occur."

CONCLUSION

It is unlikely that Dr. Flexner's question will be answered from statistics as long as a uniform standard unit of serum and of virus is lacking. In New Zealand,[22 23] Canada,[7 24] Australia,[6 20] and the United States of America[11 19] experience has led many workers to consider human immune serum a therapy of value in promoting prompt recovery and protecting from severe paralysis. In Wellington, during the epidemic of 1924–5, Dr. W. S. Robertson,[25] to whose example of early and adequate dosage Victorian work is greatly indebted, found that occasions arose when the supply of serum was too small to allow doses he considered adequate for all the cases which came for treatment. Rather than divide the available supply among them so that each would have a subeffective dose, some were treated adequately and others left without serum. In March, 1927, Dr. Robertson's demonstration of the untreated cases still in hospital severely paralysed provided a stimulus for the provision of an adequate supply of serum in Victoria. The ideal of using serum in such a manner as to protect from severe paralysis every one of the patients unable to deal adequately with the disease is more likely to be accomplished if it is realized that the clinicians treating the patients have to assume

the additional responsibility of judging the dosage—responsibility reduced in the use of other serums by laboratory standardization. Observation of each patient, study of the temperature chart, and experience with the disease and the serum available tend to make the estimation of the necessary dosage more accurate. In Victoria, critical analysis of the methods one had adopted in the handling of the seven failures of the series of 133 patients suggested that in these instances remission of watchfulness and delay were responsible for the development of paralysis. When a method of controlling the cause or conferring protection upon the child population or an easier or better therapy is introduced, human immune serum will be no longer necessary as a therapy in poliomyelitis.

REFERENCES

[1] Flexner, S.: *British Medical Journal*, 1933, i, 134.
[2] Netter, A., Gendron, A., and Touraine: *C. R. Soc. de Biol.*, 1911, lxx, 525.
[3] Walshe, F. M. R.: *Lancet*, 1927, i, 227.
[4] Tebbutt, A. H., and Helms, K.: *Med. Journ. Australia*, 1933, i, 51.
[5] *Health News*, New York State Department of Health, Albany, 1931, viii, 142.
[6] Macnamara, J., and Morgan, F. G.: *Lancet*, 1932, i, 532.
[7] Lomer, T. A., and Shirren, W. T.: *Canadian Med. Assoc. Journ.*, 1930, xxii, 230.
[8] Medical Research Council: "Diphtheria," London, H.M. Stationery Office, 1923, p. 150.
[9] Flexner, S.: *Journ. Amer. Med. Assoc.*, 1932, xcix, 1246.
[10] Kramer, S. D.: Ibid., 1932, xcix, 1057.
[11] Amoss, H. L., and Chesney, A. M.: *Journ. Exper. Med.*, 1917, xxv, 606.
[12] Park, W. H., and Williams, A. W.: *Pathogenic Microorganisms*, Philadelphia and New York, Lea and Febiger, 1920, p. 665.
[13] *Brain*, 1932, lv, 604.
[14] Park, W. H.: *New York State Journ. Med.*, 1933, xxxiii, 93.
[15] Williams, L. R.: *Bull. New York Acad. Med.*, 1932, viii, 620.
[16] Macnamara, J.: *Lancet*, 1932, ii, 1354.
[17] Williams, L. R.: Ibid., 1932, ii, 1355.
[18] Kramer, S. D., Aycock, W. L., Solomon, C. I., and Thenebe, C. L.: *New England Journ. Med.*, 1932, ccvi, 432.
[19] Levinson, S. O., McDougall, C., and Thalhimer, W.: *Journ. Amer. Med. Assoc.*, 1932, xcix, 1062.
[20] Paterson, A.: *Med. Journ. Australia*, 1933, i, 8.
[21] McDonald, S. F.: Ibid., 1933, i, 2, 38.
[22] Hector, C. M.: Ibid., Supplement, October 8th, 1927, p. 258.
[23] Robertson, W. S.: *New Zealand Med. Journ.*, October, 1925, p. 235.
[24] McEachern, J. M., Chown, B., Bell, G. L., and McKenzie, M.: Report on the Poliomyelitis Epidemic in Manitoba, Winnipeg, 1928. Department of Health and Public Welfare, Report No. 1, p. 53.
[25] Robertson, W. S.: Personal communication.

MEDICAL RESEARCH COUNCIL

ANNUAL REPORT FOR 1931–2

In a leading article in the *Journal* of March 11th (p. 421) attention was drawn to some of the general conclusions arrived at in the annual report of the Medical Research Council.[1] In this, and a later issue, it is proposed to make a more detailed comment on the various researches that are being carried out.

VIRUS DISEASES

Further work has been done in measuring, by Dr. W. J. Elford's method of critical filtration, the size of the infective units of viruses. Dr. Wilson Smith and Mr. Barnard, using the latter's optical methods, have succeeded in photographing the infective particles of vaccinia, the size of which, estimated in this way, closely agrees with the measurements determined by filtration. These particles, photographed in the living state and unstained, undoubtedly correspond to the Paschen bodies seen in stained preparations of vaccinia. Drs. Perdrau and Wilson Smith have measured the diameter of the herpes virus particles, which are found to be similar in size to those of infectious ectromelia and vaccinia. The infective units of Borna disease (a central nervous disease of horses and cattle) appear, according to the work of Dr. Elford and Mr. Galloway, to be smaller than the last two mentioned but within the range of visual and photographic demonstration. The particles of the "louping-ill" (a disease of sheep) virus pass through much smaller filters, and, as with the still smaller units of the foot-and-mouth disease virus, are too minute to form a microscopical image by the methods yet available.

Dochez, in New York, has put forward the claim that the virus or viruses of the common cold can be artificially cultivated in a medium containing living embryonic cells of a chicken. Dr. Andrewes, working with Dr. Oakley of St. Bartholomew's Hospital, has been able to infect students with the filtered virus obtained directly from human cases, but not with cultures of the virus made on the Dochez medium. Nor were they able to produce colds in their human volunteers with the culture preparations made by Dochez himself, which the latter had found infective for American volunteers. The common cold still remains the *enfant terrible* of medicine. It has not yet been possible to infect animals with the viruses of measles, mumps, or chicken-pox, and attempts are being made to propagate these viruses in cultures of human tissue cells.

BACTERIOPHAGES

Continued investigations into the nature of bacteriophages support d'Herelle's view that they are separate, self-multiplying, particulate organisms. Dr. Andrewes and Dr. Elford, using the latter's method of critical filtration, have found that the diameter of the smallest bacteriophage yet examined is identical with that of the virus of foot-and-mouth disease. The largest bacteriophage is stopped by a filter of such relative coarseness as to suggest that its particles are almost within the range of microscopical detection. Dr. Burnet has shown that bacteriophage may be used as a sensitive indicator of certain strains of bacteria in the Salmonella group, and has prepared a number of serums which specifically neutralize the action of different bacteriophages. Bacteriophages can be inactivated by methylene-blue in the presence of oxygen and on exposure to light. This is another point of correspondence between these substances and viruses, as it has been shown that the viruses of vaccinia, herpes, Borna disease, "louping-ill," and fowl plague can be similarly inactivated. It is possible that this action of methylene-blue may have some medical application.

INFECTIVE TUMOURS OF BIRDS

Drs. Gye, Purdy, and Andrewes have continued their observations on malignant tumours of birds. The interesting thing about these tumours is that they can be transmitted by cell-free extracts, the infective agents exhibiting many properties in common with the viruses. By injecting a cell-free filtrate Dr. Gye has produced in the duckling the fowl sarcoma discovered by Fujinami, and by similar filtrates has propagated the tumour from duckling to duckling through twenty "generations." When transmitted to the duck, the Fujinami tumour consists of duck cells. Thus, in this instance, the conception of rigid species limitation of tumours does not hold water. Dr. Andrewes has already shown that the fowl sarcoma of Rous is transmissible to the pheasant, and Dr. Purdy has succeeded in producing it in the duckling. The process here, however, is one of grafting, and the cells of this tumour, successively transferred from duck to duck, still retain the specific characters of fowl cells; this is analogous to the method of propagation of mammalian tumours.

BACTERIA

Drs. Dudley and Gough, investigating the chemistry of the tubercle bacillus, have separated fractions having the properties of an albumin and of a pseudo-globulin, the former having a carbohydrate constituent absent in the latter. As announced in last year's report, Dr. Gough has investigated the carbohydrate "haptene" of the tubercle bacillus; using the same methods, he has now

[1] Report of the Medical Research Council for the Year 1931–2. 1933. H.M. Stationery Office. (2s. net.)