CONTROL OF ACUTE POLIOMYELITIS BY IMMUNIZATION

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Historical Note

Poliomyelitis now shares with epidemic influenza the place occupied during the 19th century by cholera, smallpox and typhus fever. Recurring yearly in some form in most highly industrialized countries, it may attack the most favoured with devastating effect, killing approximately 10 per cent. and maiming permanently a further 15 per cent. of those attacked. On the other hand, primitive, overcrowded, poverty-stricken regions generally escape these visitations, due almost certainly to universal infection in childhood. The successful reproduction of the disease in higher apes and proof of its virus nature by Landsteiner and Popper in 1908, and the demonstration of the mode of spread and invasion of its natural hosts by Flexner and Lewis in 1910 raised expectations that potent antisera and immunizing antigens would shortly be available. Convalescent serum was first used in Sweden in 1925 (Davide, 1928) and McNamara in Australia (1935) administered it intrathecally and/or intravenously in an endeavour to ward off, or prevent extension of paralysis. None of these measures met with conspicuous success and indeed I.M. and I.T. injections may conceivably conduce to paralysis in cases which otherwise would have remained aparalytic.

The first attempts at active immunization (Brodie in 1934-5, using a suspension of infected monkey spinal cord inactivated by formalin; Kolmer and Rule in 1934, using live virus attenuated by sodium ricinoleate) swiftly ended in disaster; although only a few thousand subjects were inoculated a dozen paralytic cases, some fatal, were encountered 6 to 14 days afterwards. A warning of the danger of these vaccines, issued by the United States Public Health Service (Leake, 1935), led to their disuse. In recent years the discovery (Enders *et al.*, 1949) that the Lansing strain could be grown in human embryo tissues and later other strains, in simian renal and testicular tissues (Li and Schaeffer, 1953) and the demonstration of the existence of different virus types each with

distinctive immunological characteristics (Morgan, 1948; Bodian *et al.*, 1949; Committee on typing, 1951, 1953), opened the way to the preparation of a safe, efficient, multivalent vaccine suitable for general issue and later for commercial production. But the early expectations of success, widely publicized in the lay and medical press, have proved far from being fulfilled and a re-assessment of the position is now being made at numerous research centres in U.S.A. and other countries including Great Britain.

Passive Immunization by Immune Serum

Following the successful use of convalescent serum in measles prophylaxis and to a less extent in rubella and mumps, it was natural to expect similar results against poliomyelitis. In actual trials these proved disappointing, partly on account of the low antibody levels encountered, in many poliomyelitis convalescents quite often lower than in contacts, and partly due to the existence of different immunological virus types (three so far identified) and even within these types of strains which may possess distinctive antigenic characteristics. The occasional occurrence of hepatitis, generally mild in adults but severe and even fatal in children, following administration of human serum whether from recent convalescent donors or normal adults, occasionally even when irradiated, led to its disrepute. Fortunately the gamma globulin fraction of serum or plasma obtained by means of precipitation by alcohol or ether at low temperatures, according to the technique introduced by Cohn and his co-workers in 1941, is virtually free from this hazard, presumably due to its twenty-fold antibody concentration compared with the parent serum. This preparation has actually been used with success in prophylaxis against infectious hepatitis as well as measles, whooping cough and similar diseases of childhood to which adults are commonly immune. Although communal immunity to poliomyelitis varies widely in different countries and even in different regions and social classes of the same country, experience

has shown that provided the plasma pool of donors is large enough (100,000 or so) a reasonably satisfactory titre can be expected. Before issue for poliomyelitis prophylaxis each batch or lot should be tested against a standard sample which has already proved its worth in field trials. Experimental work with susceptible monkeys has shown that if the serum is given with, or before, inoculation or ingestion of the virus, invasion is prevented but not infection, i.e., a symptomless carrier state is the expected sequel. The expense and scarcity of the product at the present time forbid any attempt at mass immunization even in face of a widespread, virulent epidemic; besides there are inherent limitations to its practical application, (1) the absence of a test of individual non-immunity; (2) the difficulty of ascertaining which contacts are actually infected; (3) the short duration of the protection afforded by a single dose; (4) the probability of re-exposure during a period of epidemic prevalence and hence the possible need for re-injection.

Despite these obstacles, a controlled field study was conducted in U.S.A. in 1951 and 1952, involving some 55,000 children, aged 1 to 11 years, half of whom were given 0.14 ml. gamma globulin per lb. body weight and half an equal volume of a dilute gelatin solution which so resembled the prophylactic in appearance that neither clinicians nor recipients knew which preparation was administered. Children of similar ages who received no injections were observed over the same period and subsequently used as a control group although these were in some respects not strictly comparable. The analysis of the results (Hammon *et al.*, 1953) revealed significant protection among the test individuals, lasting some 21 days (corresponding to the half life of the gamma globulin injected), compared with the two control groups; by doubling the dose or using a preparation twice as potent, the period of protection would theoretically be extended by another 21 days, but this assumption was not put to proof. Since the discovery (McCloskey, 1950; Geffen, 1950) that intramuscular inoculations, especially of irritating substances, favour production of paralysis in the limb injected, most severe in, or even limited to, the muscle or part of muscle traumatized, the use of control inoculations can no longer be countenanced even in the interests of science. When exposure can reasonably be presumed the subcutaneous route is preferable although absorption is slower and probably less complete.

Despite these hazards the Ministry of Health issued in 1954 a short memorandum on the prevention of poliomyelitis which incorporated a section on the use of gamma globulin, specifying

the centres where stocks are maintained in this country. The recommended priorities and dosage schedules were:

- (1) Babies exposed intimately in maternity wards or at home, 5 ml. (1 ampoule).
- (2) Hospitalized children, especially after recent tonsillectomy (1 to 7 years), 10 ml.
- (3) Nurses and medical students presumed to be encountering poliomyelitis for the first time, 15 ml.

If taken literally the last-named category would consume all available stocks in a few days as few hospitals do not admit the disease inadvertently, usually in the earliest and most infectious stage, during periods of epidemic prevalence. As a matter of experience, if reasonably careful precautions are taken in respect of a suspected case before transfer to an isolation unit or fever hospital, the staff do *not* ordinarily require specific prophylaxis. Although poliomyelitis in early pregnancy has not been observed to cause foetal defects, immune serum is justified for contacts near the end of pregnancy as labour complicating paralytic poliomyelitis or *vice versa* significantly worsens the prognosis. Familial contacts should also receive high priority, even in young adults if they had recently had an operation to the buccal cavity, including tooth extraction. As regards dosage, closer adjustment to body weight is advisable than the three scales specified in the memorandum, an easy task if more than one individual is inoculated at the same time.

Therapeutic Serum to Avert Paralysis

Recent experimental studies by Bodian (1953) have confirmed that potent gamma globulin will avert paralysis in animals already infected, and naturally roused hopes that intravenous administration of adequate amounts, say 10 to 20 ml. for children and 50 to 100 ml. for adults, may avert paralysis if given in the viraemic and even in the meningitic, pre-paralytic stage. But it is probable that when meningitis is present the full viral assault has already taken place, paralysis only appearing in a given area when over one-third of the motor neurones have been destroyed. Further spread of paralysis is usually attributed to secondary changes, notably oedema in the cord, and possibly also in the muscles. A serious difficulty in connection with intravenous gamma globulin is that severe, rarely fatal, reactions have been encountered, presumably due to the 'denatured' state of the molecules following the fractionation process. For this reason concentrated plasma (3 to 4 fold) is usually preferred when oedema, especially cerebral oedema, is considered a factor influencing the prognosis.

Active Immunization

Inoculation with Formalin-inactivated Virus

As in 1934, two rival vaccines now hold the field in U.S.A. and once again the formalized preparation, developed largely by Salk at Pittsburg University, appeared first on the scene and received widespread acceptance, despite the fact that, in the interval, the principle of employing live virus for immunization had been well established. Cox (1954) has listed 13 kinds of vaccine in which virus are being used in attenuated form in human and veterinary prophylaxis. However, poliomyelitis virus stands in a class by itself by reason of its known mutational unpredictability, a circumstance closely associated with high potential virulence to human susceptibles. Early in 1953 Salk reported success in some 600 children (474 between 4 and 12 years) with a trivalent vaccine, none developing poliomyelitis during the following period of epidemic prevalence although seven were intimately exposed and three showed afterwards demonstrable serum antibody increases, presumably as a result of the exposure.

Preparation of Vaccine. In the endeavour to render the vaccine innocuous without impairing its immunizing properties, Salk treated virus tissue culture fluid (using monkey kidneys) with 0.4 per cent. formalin (37 per cent. formaldehyde) in a bath of melting ice (1°C.) for ten days. It was found that while Type 3 strains were sensitive to the chemical, Types 2 (M.E.F.—1) and Type 1 (Mahoney) were more resistant in that order. These differences may be due to different concentrations of virus rather than to inherent resistance to formalin. The vaccine was then emulsified with a purified mineral oil and emulsifying agent and passed through a Seitz filter to eliminate possible bacterial contamination, and as an additional precaution merthiolate in a concentration of 1:10,000 was added as an antiseptic. Tests in monkeys as well as human subjects indicated that the intramuscular route was clearly the most efficient. Aqueous solutions which permitted intradermal inoculation only produced significant antibody against Type 2 strains. Three injections were recommended; in his latest communication Salk (1955) advocated that an interval of two weeks should separate the first two injections (each 1 ml.), the third ('booster') dose given as long afterwards as practicable, preferably seven to eight months, provided it antedates the next period of epidemic prevalence.

In the autumn of 1953, the Medical Advisory Committee of the National Foundation for Infantile Paralysis recommended planned extensive trials of the vaccine which were commenced in April 1954, with the assistance of six major commercial manufacturers of biological products.

The results of the inoculations, evaluated by Francis and his team of the Department of Epidemiology and the Virus Laboratory, University of Michigan, were announced on April 12, and published in May 1955. Altogether 1,080,680 children formed the vaccine group and 749,236 the placebo (i.e. received injections without antigen but ignorant of contents) or control group. Children of similar age living in the same area but not necessarily of the same socio-economic class who received no injections were observed and placed in a third group for comparative purposes as intramuscular injections of any kind are known to predispose to paralytic poliomyelitis. The incidence of paralytic poliomyelitis in the three groups over the period of observation may be simply expressed in the form of a ratio, viz. 1; 3.5; 3.3, respectively. Immediately the Francis report was presented licences were granted to six commercial firms to release vaccine without restriction but in the last week of April cases of paralytic poliomyelitis were reported to occur shortly after the injections, at first from Cutter preparations (issues suspended on April 27) and later from those of other firms (all inoculations suspended on May 7); towards the end of the month some batches were released after further testing and administered on a 'voluntary' basis. Finally, a permanent Technical Committee under government control was set up to recommend action on standards and supervise testing of vaccine batches (lots) and inoculation was gradually resumed in different states. The general 'all clear' was given in a television programme in which the new Secretary for Health Education and Welfare appeared, on September 4.

Among the numerous objections to the Salk vaccine the most important are:

- (1) Although monkey and virus-inhibition or tissue culture tests indicate that the vaccine is free from risk, these are not necessarily applicable to humans who are known to be more susceptible to the virus.
- (2) Formalin coagulates albumin, a necessary ingredient of tissue culture media, and may form protective covering to the dormant virus.
- (3) Monkey renal tissue may induce dangerous allergic reactions in human organs especially if injections are repeated.
- (4) The Mahoney strain, which is known to cause severe paralysis, was unjustifiably incorporated in the vaccine.
- (5) The use of penicillin and streptomycin to obviate bacterial contamination in tissue culture may induce allergic reactions in sensitized subjects.
- (6) No evidence is available regarding the duration of the immunity conferred.

That these criticisms were not without foundation

tion are confirmed by subsequent investigations and recommendations;

- (a) Salk (1955) disclosed that the 1953 vaccine was found to be less potent antigenically in 1954 and recommended the addition of edathamil to thimerosal (merthiolate) to act as a stabilizing agent.
- (b) The amended standards officially issued on May 13, were that one litre of vaccine should contain 5 (or more) virus particles (or particulates) less than once in 100,000 times (Scheele and Shannon, 1955), tacitly admitting that it may be impossible to kill all living virus.
- (c) The use of the Brunhilde strain was recommended in the vaccine in substitution of the highly virulent Mahoney strain (both belong to Type 1).
- (d) As the consensus of scientific opinion was that formalin did not necessarily kill all virus, and the immunization mechanism probably depended on the presence of living virus, it appeared that some risk in connection with the Salk vaccine was inevitable; but as no alternative was available, it was considered justifiable to continue its use in regions where poliomyelitis remained a serious problem.

Support for the Salk-type vaccine was provided by the Canadian experience (vaccine produced under stringent conditions in the Connaught Laboratories, Toronto) in which no untoward effects were encountered amongst 400,000 children inoculated; protection appeared adequate, judging by the subsequent attack rate although probably the hazard of exposure is less in its scattered population than in U.S.A. In Denmark where the Brunhilde strain was incorporated in the vaccine in place of the Mahoney strain, no untoward effects had been experienced.

The present position is illustrated by the conclusions at two recent conferences on poliomyelitis.

(1) Meeting of American Public Health Association at Kansas City, Mo.; the vaccine is now safe and one injection is as effective as were three in the previous year; preliminary results from 11 States showed the attack-rates to be two to five times greater in unvaccinated children (*Times*, November 16).

(2) W.H.O. Conference at Stockholm; since the new regulations came into force in U.S.A. there were no proved instances of harmful effects from the vaccine although a potential risk was admitted. In South Africa 15,000 children had been inoculated and in Western Germany 100,000, in both instances without ill effects and apparently with protection, but immunization was suspended

pending the application of further safety tests. In Great Britain vaccines made by Glaxo Laboratories, Ltd. and the Wellcome Research Foundation, were to be used in the autumn of 1955, but deferred in the light of American experience until the Spring of 1956, when a safer vaccine will be available. Whether it will be as effective remains to be seen. Some workers consider that use of human amniotic tissue or the growing chick embryo may eliminate all risk provided virus strains can be adapted without antigenic loss (*Times*, November 27).

Ingestion of Live Attenuated Virus

Advocacy of living virus as the most effective antigen for active immunization has come mainly from Sabin (1953) and Koprowski (1955). The advantages and objections of this method are obvious but the former undoubtedly outweigh the latter if the risk of mutational reversion to a virulent state could be eliminated. So far the problems connected with this essential condition have not been satisfactorily solved. The suggestion that gamma globulin might be given at the same time to neutralize residual or potential paralyticogenic activity in attenuated virus, quite apart from involving an injection which the ingestion method primarily seeks to obviate, is pointless as long as this reagent is costly and scarce. There remains the possibility that a new strain or type may emerge, which would not be neutralized by gamma globulin until a sufficient number of suitable donors were immunized, either artificially or by natural disease, to provide the immune plasma from which gamma globulin is extracted.

Despite all the difficulties, the scientific and organizational climate remains hopeful that poliomyelitis can be outlawed as completely as diphtheria, although early optimism has been dampened by recent setbacks.

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