BRITISH MEDICAL JOURNAL
LONDON
SATURDAY JULY 16 1955

IMMUNIZATION AGAINST VIRUSES

The prospect of controlling poliomyelitis by immunization has aroused intense interest throughout the world, but opinion at present differs on the method to be adopted, whether a killed or attenuated vaccine should be used. It would seem profitable therefore to consider what has already been achieved with immunization against other virus diseases. Of the many factors to be taken into account, a proper understanding of the natural history and pathogenesis of disease comes first.[1 2] A method of protection in one disease may be valueless in another. In herpes simplex, for example, primary infection commonly occurs as an asymptomatic infection in childhood.[3] Antibody develops at this stage, but the virus remains latent in the person infected. Recurrent infection due to virus reactivation occurs in the presence of antibody, so that immunization with the object of stimulating antibody is not likely to be effective. Measles presents a very different picture. The incubation period is long, invasion is by the blood stream, the clinical attack rate is high, and immunity, as judged by second attacks, long-lasting. As the date of exposure and probable date of appearance of symptoms can usually be determined, measles presents an ideal case for immunization. Recent reports of the use of gamma globulin and its advantages over convalescent serum show how successful this can be.[4] Indeed, the main disadvantage is in complete suppression of the disease, which is inadvisable except in certain clear-cut cases. The most effective use of such a valuable product is to modify the natural infective process with a small dose, producing combined passive-active immunization. J. Stokes and others have suggested that similar conditions prevail in infective hepatitis.[5] Rabies has several features in common with measles, in contrast to poliomyelitis, and on theoretical grounds passive immunization should be of value. H. Koprowski *et al.*[6] and K. Habel[7] have recommended the use of hyperimmune serum in the treatment of rabies, if necessary combined with active immunization. An attenuated vaccine produced in the chick embryo (Flury strain) has now been developed and is an important advance on the classical Pasteurian treatment of the disease with its limitations and dangers.[8]

Influenza presents still different problems. The incubation period is short, virus invades along the respiratory mucosa and not by the blood stream, and, although high levels of antibody can be produced with formolized vaccine produced in the chick embryo, the effectiveness of immunization is limited by several factors. The level of antibody in the secretions of the respiratory tract is lower than in the blood and the duration of antibody response is comparatively short. Another factor is the difference in antigenic character among the influenza A strains. Under the best conditions, when immunization is carried out before an epidemic with a vaccine incorporating the correct virus strains, protection can be demonstrated.[9] Recent advances with mineral-oil adjuvants to boost antibody production suggest that a more effective immune response can be obtained. Meanwhile preliminary reports from Russia refer to the use of live virus given intranasally; apparently it is not toxic, produces an immune response, and is easy to administer to large numbers.[10]

Immunization with attenuated virus vaccines, of which there are many examples in human and veterinary medicine, gives on the whole a more long-lasting immunity.[11-13] Nevertheless attenuated vaccines are not without their limitations. For the majority of persons vaccinated in infancy against smallpox in Great Britain immunity is effective because the risk of exposure is so small; for people likely to be exposed to the disease, such as members of the armed Forces, revaccination at regular intervals

[1] Salk, J. E., *The Dynamics of Virus and Rickettsial Infections*, edited by Hartman, F. W., *et al.*, 1954, p. 219, New York.
[2] Horstmann, D. M., *Bull. N.Y. Acad. Med.*, 1953, **29**, 910.
[3] Scott, T. F. MacNair, *New Engl. J. Med.*, 1953, **250**, 183.
[4] McDonald, J. C., and Cockburn, W. C., *British Medical Journal*, 1954, **2**, 1076.
[5] Stokes, J., jun., *et al.*, *J. Amer. med. Ass.*, 1951, **147**, 714.
[6] Koprowski, H., *et al.*, *Amer. J. Hyg.*, 1950, **8**, 412.
[7] Habel, K., 1953, 6th International Congress in Microbiology, Rome.
[8] Fox, J. P., 1953, ibid.
[9] Francis, T., jun., *Poliomyelitis, Wld Hlth Org. Monogr. Ser.*, 1954, No. 20, p. 125, Geneva.
[10] In *Abstracts of World Medicine*, 1955, **17**, 263 (No 878c).
[11] Cox, H. R., *British Medical Journal*, 1954, **2**, 259.
[12] Habel, K., *The Dynamics of Virus and Rickettsial Infections*, edited by Hartman, F. W., *et al.*, 1954, p. 259, New York.
[13] Koprowski, H., ibid., 1954, p. 270.
[14] Theiler, M., *Virus and Rickettsial Infections of Man*, edited by Rivers, T. M., 1952, p. 531, Philadelphia.
[15] Dick, G. W. A., *Brit. med. Bull.*, 1953, **9**, 215.
[16] *British Medical Journal*, 1952, **2**, 551.
[17] Ibid., 1954, **2**, 259.
[18] Ibid., 1955, **1**, 1061.
[19] Report on 1954 Field Trial, 1955, sponsored by National Fund for Infantile Paralysis.
[20] See *British Medical Journal*, 1955, July 9, p. 150.
[21] Koprowski, H., *et al.*, *Amer. J. Hyg.*, 1952, **55**, 108.
[22] —— *Poliomyelitis, Wld Hlth Org. Monograph Ser.*, 1955, No. 20, p. 335, Geneva.
[23] Sabin, A. B., *Amer. J. Dis. Child.*, 1953, **86**, 301.
[24] —— *The Dynamics of Virus and Rickettsial Infections*, edited by Hartman, F. W., *et al.*, 1954, p. 289, New York.
[25] —— *Poliomyelitis, Wld Hlth Org. Monogr. Ser.*, 1955, No. 20, p. 247, Geneva.
[26] Zitcer, E. M., *et al.*, *Science*, 1955, **122**, 30.
[27] *British Medical Journal*, 1955, **1**, 1144.
[28] Ibid., 1955, **1**, 1204.

is necessary to maintain immunity. Such complications as generalized vaccinia and post-vaccinal encephalitis are a potential risk, but they are risks which are well known and accepted under the circumstances. Yellow fever is another instance of the success of an attenuated vaccine.[14] Two vaccines are now in use—the 17 D strain produced in the chick embryo, and the French neurotropic strain administered by skin scarification with or without the addition of vaccinia virus as well. The immunity may last for eight to ten years or longer.[15] Again, in the early stages of vaccination against yellow fever a number of fatalities occurred, either from encephalitis or from post-vaccinal jaundice following the use of icterogenic serum in the vaccine.

The problem of immunization against poliomyelitis has been discussed in this *Journal* on a number of occasions.[16-18] The point at issue at present is whether formolized vaccines are safe and sufficiently effective to warrant their use. The alternative is to use an attenuated vaccine, or possibly a combination of the two. Last year's vaccine trial in America showed that the formolized vaccine stimulated antibody production, but unfortunately there are few quantitative data on the duration of the immune response.[19] The 1954 trial also established that with strict control vaccination was a safe process. This appears to be corroborated by the trials at present being carried out in Canada with a similar vaccine. As an additional safeguard it has been recommended that the existing Type I (Mahoney strain) should be replaced by a less virulent one.[20]

A number of other workers favour the idea of an attenuated vaccine, and considerable progress has already been made in this direction. Koprowski *et al.*[21 22] have shown that an avirulent Type II strain given by mouth produces a symptomless infection accompanied by the development of antibody. Progress has also been made with the attenuation of a Type I strain. Of considerable significance is the fact that a number of persons vaccinated had high levels of antibody more than three years later. An obvious disadvantage is the fact that vaccinated subjects excrete virus in the faeces, a situation which may well be difficult to control. Sabin has produced in tissue culture (using monkeys' kidneys) attenuated viruses of all three serological types which have lost their power to produce paralysis,[23-25] and in this issue of the *Journal* he gives a preliminary report (p. 160) on the effect of inoculating such viruses into non-immune human volunteers. A comparatively small inoculum produced a symptomless alimentary infection and the development of antibody. Cox, on the other hand, considers[11] that monkey and human tissues are potentially pathogenic and has concentrated on the adaptation of virus to the chick embryo. Progress has been made. A recent report[26] from the U.S.A. on the growth of virus in human amniotic membrane describes an interesting development, though subject to the general criticism that Cox has made.

Safety testing of poliomyelitis vaccines, whether formolized or attenuated, will always be a major task; each will present its own problems. But there seems no reason why with strict control a reasonable guarantee of safety cannot be given.[27 28] While great progress has been made in the development of attenuated vaccines, they are clearly still in the experimental stage. It would seem that formolized vaccines have a place at present while alternative methods are being developed. In any case it is most unlikely the final answer to the control of poliomyelitis will be achieved in one step.

CEREBRAL PALSY

Cerebral palsy is a term that embraces a group of disorders of motor function in children, often accompanied by mental defect, caused by a cerebral lesion of some kind. It is therefore not a clinical, pathological, or aetiological entity. This being so, it is not surprising that many classifications of its various forms have been introduced, with resulting confusion and misunderstanding. There is a clear need for an agreed terminology and classification. An article by Drs. C. L. Balf and T. T. S. Ingram in the *Journal* this week (p. 163) is an attempt to provide a simple classification, based on recognized neurological syndromes, which, the authors hope, will prove useful to both research and clinical workers. It was used with success in a study of cerebral palsy in Edinburgh, recently reported by Ingram,[1] and the authors claim that it has proved equally useful in routine clinical practice.

The Edinburgh survey by Ingram revealed an incidence of cerebral palsy of 2 to 2.5 cases per 1,000 children, and his study of the results of other surveys suggests that the incidence does not differ greatly in different large towns. Considering how common the condition is, the gravity of the disability it causes, and the interest now taken in the care and welfare of handicapped children, it may seem strange that knowledge of the pathology and aetiology of cerebral palsies is still incomplete; but opportunities for pathological studies are less frequent than might be

[1] Ingram, T. T. S., *Arch. Dis. Childh.*, 1955, **30**, 85.
[2] Towbin, A., *Arch. Path. (Chicago)*, 1955, **59**, 397 and 529.
[3] Eastman, N. J., and DeLion, M., *Amer. J. Obstet. Gynec.*, 1955, **69**, 950.