Growing Points in Medicine

Success and Failure in Human Virus Disease* IV—Immunization

SIR CHARLES STUART-HARRIS

British Medical Journal, 1971, 1, 446–448

The development of safe and effective virus vaccines is one of the striking consequences of increased technical knowledge in the cultivation of viruses in the laboratory. That the story is one of both success and failure can readily be appreciated by contrasting experiences with poliomyelitis and influenza. In England and Wales during 1969 there occurred a total of 11 notified cases of poliomyelitis and seven of paralytic disease, the lowest incidence for more than 20 years. In the U.S.A. during 1969 only 19 cases of paralytic disease were recorded in the entire country. Though probably one cannot achieve complete eradication of the disease, it is obvious that immunization with living Sabin vaccine in both countries has provided a remarkable degree of control. The experience of other countries where vaccine has been applied vigorously is the same, whereas elsewhere in developing countries, and particularly in the tropics, the disease continues and is even increasing.¹ The risk of importation of virulent viruses from such areas to Britain is considerable, and it is essential that the present high level of immunization, which varies from 60 to 80% of children in different areas, should be maintained. Contact tracing and focal use of vaccine in the vicinity of any suspected case of poliomyelitis must also continue.

The contrast between the effective control now achieved against poliomyelitis, even where, as in Sweden, reliance has been placed on inactivated Salk vaccine alone, and the recent bitter experience with Hong Kong influenza is indeed remarkable. After all, inactivated influenza vaccine has been known and has been used to a limited extent for years. Failure to exploit its use further has been due to a lack of confidence in its ability to produce durable immunity, to difficulty in using it in children because of its pyrogenic effect, and to the periodic major alterations in the antigens of both influenza viruses A and B in nature. Moreover, knowledge is still lacking concerning the mechanism of both individual and herd resistance to the influenza virus. Though countries elsewhere—principally the U.S.S.R. and Yugoslavia—have developed living attenuated virus vaccines against influenza, this has not prevented their suffering outbreaks of the disease. In spite of much experimental work, the best method of developing attenuation of virulence of influenza virus to the requisite level is still undecided.^{2,3} The effort of providing and using attenuated vaccine, even in a single town such as

Smolensk,⁴ is enormous, for it seems that over half of the working population must be immunized in order to lower the incidence, and vaccination has to be repeated periodically. Elsewhere I have attempted to summarize the requirements for the future,⁵ and shall not repeat them here.

Prospects for Control of Measles and Rubella

Live attenuated virus vaccines seem to be most successful in the case of diseases in which the viruses circulate in the blood and infection leads to a durable immunity. Measles and rubella belong to this category. Both these viruses exist in a stable form with unchanged antigenic structure, and antigenic subtypes have not so far been found. Attenuation of measles virus began with the work of Enders on the so-called Edmonston B vaccine.⁶ The early vaccines gave rise to a large proportion of febrile reactions, and further attenuation of the virus was effected. In the U.S.A. reliance has been placed on the Schwarz strain,⁷ and this has also been used by one British manufacturer. Goffe and Laurence⁸ modified another of Enders's strains, and their vaccine (Beckenham) was found to give a higher rate of reactions than the Schwarz strain in early trials in Britain. The M.R.C. Measles Vaccines Committee⁹⁻¹² found that Schwarz vaccine gave good immunity, which has been satisfactorily maintained for five years after immunization.

During the early phases of introduction of measles vaccine in Britain that prepared from the Schwarz strain and also Beckenham 31 were both used. Adverse reactions consisting of fever, rashes, and convulsions occurred with both, but were reported more often after the Beckenham vaccine. Matters reached a head in March 1969, when illnesses were reported of a neurological character resembling measles encephalitis. The tally of reactions reported to the Safety of Drugs Committee at this stage left no doubt that the Schwarz vaccine was preferable from the standpoint of all forms of reactions. Only vaccine made from the Schwarz strain has continued to be used in Britain since this unfortunate happening. A total of 25 neurological illnesses other than simple convulsions are now known to have occurred; 15 followed the use of Beckenham, nine occurred after Schwarz, and one after an unknown vaccine. They were varied clinical illnesses, sometimes with motor phenomena, sometimes with unconsciousness, and are grouped as "encephalitis." Four fatal illnesses have occurred after vaccine had been used—one from gastroenteritis, one as a "cot death," and one in a mentally retarded infant was diagnosed at necropsy as measles encephalitis. The fourth case died from subacute sclerosing panencephalitis, but had had measles five years before vaccine, which was given three months before neurological symptoms developed.

*Paper based on a lecture delivered to the Cardiff Medical Society on 10 November 1970.

University of Sheffield

SIR CHARLES STUART-HARRIS, M.D., F.R.C.P., Professor of Medicine

These reactions can be viewed only in perspective against the background of ordinary measles. The incidence of potentially serious complications was found by the Public Health Laboratory Service in 1963 to be one in 15.¹³ Most were respiratory illnesses, including otitis media, but four neurological complications, one of which was encephalitis, occurred among every 1,000 patients. The natural disease is infrequently fatal, and chiefly occurs in undernourished or immunologically defective children. But the incidence of complications far exceeds that of the unwelcome reactions occasionally induced by vaccine. Thus one and a quarter million doses of vaccine were estimated to have been given by March 1969, and many more children have been immunized since then. The expected winter epidemic of 1969 did not materialize, probably because of the vaccination campaign, but the summer wave of 1970 indicates that many more susceptible children must be immunized if control of the disease is to be achieved (see Chart).

Corrected quarterly notifications of measles in England and Wales.

Rubella

The need for a vaccine against rubella arises from the risk of congenital rubella in fetuses of mothers who have not suffered from natural infection. The first attenuated virus was prepared by Parkman *et al.*¹⁴ with the HPV strain. Since then other viruses have become available, including the Cendehill strain of Peetermans and Huygelen¹⁵ made in rabbit kidney cultures, and the RA virus of Plotkin *et al.*¹⁶ cultivated in human embryo fibroblasts. All of these viruses are attenuated in virulence for man and all have been used in large numbers of persons. There are three risks inherent in the use of rubella vaccine. Firstly, adult women and occasionally children may suffer from reactions in joints, including effusions, and the rate of reactions in British trials was higher with vaccines made from HPV than Cendehill virus.¹⁷ Secondly, persons receiving vaccine subcutaneously nevertheless excrete small amounts of virus into the throat. Fortunately, contact infection has not been proved in spite of careful study. Thirdly, virus may be passed to the fetus by a vaccinated mother, and though this may only occur relatively rarely the risk of damage to a very young fetus is appreciable. A recent report by Phillips *et al.*¹⁸ of a single case of fetal infection after rubella vaccination of a pregnant mother underlines this risk.

Though no controlled field trial of rubella vaccines has been made to estimate the level of protection which can be expected, the assumption is that immunity of a worth-while degree will be obtained. Immunization on a selected basis of girls of 11 to 13 now sanctioned in Britain is clearly necessary in order to gain wider experience of the vaccine. Schoolgirls who have not had rubella will thus avoid the problem of exposure to contact infection with its attendant anxiety when,

at a later age, they may become pregnant. It is important to realize that serological tests have shown the unreliability of a clinical history of a rubella-like illness. The seronegative woman who wished to be vaccinated must not be immunized with existing rubella vaccine unless pregnancy can be postponed for at least two months after its administration. As contraception by all known methods is attended by a small but significant number of failures recourse to abortion may be needed should pregnancy nevertheless occur. This moral and emotional problem cannot be avoided, and one can only hope that the issue will be clearly understood by the public. It will inevitably take some years before the transmission of rubella virus in the community is reduced, for this will necessitate routine immunization in early childhood, and such may even be undesirable.

Future Vaccines

The need to improve existing virus vaccines is equal in importance to the task of developing vaccines against disorders which cannot as yet be controlled. No one is satisfied, for instance, with smallpox vaccine, which whenever it is applied on a mass scale causes severe reactions, including encephalitis in previously unvaccinated adults and occasional deaths in infants under 1 year of age.¹⁹ There is hazard, too, in the use of inactivated rabies vaccine given as multiple injections to persons bitten by a supposedly rabid dog, for it is followed by postvaccinal encephalitis significantly often. Nevertheless, the urge to develop vaccines against other infectious diseases is strong, and in each case the problem posed by the disease requires evaluation before exploitation of a vaccine.

Mumps is a nuisance to the schoolchild and a hazard to the adult from the complications of aseptic meningitis, orchitis, deafness, and rarer disorders. The development of living attenuated vaccines both in the U.S.A.²⁰ and in the U.S.S.R.²¹ indicates that protection of older children and adults is now feasible. Nevertheless, routine immunization is not yet recommended for the younger child in Britain because of inadequate knowledge concerning the morbidity created by the natural disease. It is claimed that nearly two million persons in the U.S.A. have now received mumps vaccine.²²

A contrasting problem exists in the case of viral respiratory diseases. The morbidity from these is enormous and far outweighs any other groups of virus diseases in Britain. Yet prospects for control are gloomy in spite of prodigious efforts. Chanock²³ indeed considers prospects encouraging, at least in the case of adenovirus infections in Servicemen and young children, and also for parainfluenza and respiratory syncytial virus infections in babies and infants. Certainly if protection could be obtained safely and was effective vaccination regimens for children might be tolerated, provided that the schedule of immunization by other vaccines was not upset. There is some risk of the latter, however, in Britain; and in any case no one proposes vaccines for the 100 types of rhinoviruses, some of which are certainly significant pathogens in children. For the moment, therefore, vaccines against respiratory viruses other than influenza are not practical issues in spite of much desire and a good deal of basic research, particularly on living attenuated virus strains.

Conclusion

This review is inevitably incomplete and no attempts have been made to deal with the global problems of virus diseases. In Britain virology has had a distinguished record and, one may hope, an equally good future. The excellent facilities for virus diagnostic work provided by the Public Health Labora-

tory Service must, however, not be spread over relatively unrewarding sectors of human disease. Virus isolation is a costly procedure in both materials and manpower. The outstanding problem of respiratory virus disease demands a great deal of further basic work in order to define resistance more clearly. The serious problem of infectious and serum hepatitis challenges all of us to greater efforts to obtain control over this infection. New and better vaccines are required against old enemies such as influenza, and the use of existing vaccines against poliomyelitis, measles, and rubella must continue to be pressed. Other vaccines, such as, for instance, mumps, may become worth while. Who can say what may have been achieved in this vast field of human disease in another thirty years? Certainly the present disappointment of chemotherapy against virus diseases cannot be accepted as final.

I am grateful to Drs. A. Roden and W. Dunnnett, of the Department of Health and Social Security, for their help with the section on immunization and with the chart.

References

- Cockburn, W. C., and Drozdov, S. G., *Bulletin of the World Health Organization*, 1970, **42**, 405.
- Beare, A. S., Bynoe, M. L., and Tyrrell, D. A. J., *British Medical Journal*, 1968, **4**, 482.
- Mills, J., Van Kirk, J., Hill, D. A., and Chanock, R. M., *Bulletin of the World Health Organization*, 1969, **41**, 599.
- Slepuškin, A. N., et al., *Bulletin of the World Health Organization*, 1967, **36**, 385.
- Stuart-Harris, C. H., *Archives of Environmental Health*, 1970, **21**, 276.
- Enders, J. F., Katz, S. L., Milovanović, M. V., and Holloway, A., *New England Journal of Medicine*, 1960, **263**, 153.
- Schwarz, A. J. F., *American Journal of Diseases of Children*, 1962, **103**, 386.
- Goffe, A. P., and Laurence, G. D., *British Medical Journal*, 1961, **2**, 1244.
- M.R.C. Measles Vaccines Committee, *British Medical Journal*, 1965, **1**, 817.
- M.R.C. Measles Vaccines Committee, *British Medical Journal*, 1966, **1**, 441.
- M.R.C. Measles Vaccines Committee, *British Medical Journal*, 1968, **2**, 449.
- M.R.C. Measles Vaccines Committee, 1970, unpublished.
- Miller, D. L., *British Medical Journal*, 1964, **2**, 75.
- Parkman, P. D., Meyer, H. M., jun., Kirschstein, R. L., and Hopps, H. E., *New England Journal of Medicine*, 1966, **275**, 569.
- Peetermans, J., and Huygelen, C., *Archiv für die gesamte Virusforschung*, 1967, **21**, 133.
- Plotkin, S. A., Farquhar, J. D., Katz, M., and Ingalls, T. H., *American Journal of Epidemiology*, 1967, **86**, 468.
- Dudgeon, J. A., Marshall, W. C., Peckham, C. S., and Hawkins, G. T., *British Medical Journal*, 1969, **1**, 271.
- Phillips, C. A., Maeck, J. V. S., Rogers, W. A., and Savel, H., *Journal of the American Medical Association*, 1970, **213**, 624.
- Dick, G., *Progress in Medical Virology*, 1966, **8**, 1.
- Hilleman, M. R., Buynak, E. B., Weibel, R. E., and Stokes, J., jun., *New England Journal of Medicine*, 1968, **278**, 227.
- Smorodintsev, A. A., Klyachko, N. S., Nasibov, M. N., and Shickina, E. S., In *Papers and Discussions presented at the 1st International Conference on Vaccines against Viral and Rickettsial Diseases of Man*, p. 422. Washington, Pan American Health Organization, 1967.
- Weibel, R. E., et al., *Journal of the American Medical Association*, 1969, **207**, 1667.
- Chanock, R. M., *Science*, 1970, **169**, 248.

“For Debate . . .”

Halothane Hepatitis—A Preventable Disease?

PAUL SHARPSTONE, D. R. K. MEDLEY, ROGER WILLIAMS

British Medical Journal, 1971, **1**, 448–450

Summary

Eleven patients with acute hepatitis following multiple anaesthetics with halothane have been seen at two hospitals during the last four years. Six had massive hepatic necrosis and died. Unexplained fever occurred in nine of the patients; two of these and one other had had previous episodes of jaundice after halothane anaesthesia. Thus, in ten patients the disease could have been avoided.

Introduction

Numerous reports of acute hepatic necrosis occurring after anaesthesia with halothane followed the earliest mention of this association in 1958.^{1,2} Subsequently, large retrospective surveys^{3,4} showed that this was a rare complication and that it occurred no more frequently after halothane than after

other anaesthetic agents. However, since there are several potential causes of liver failure in most patients who have had a surgical operation, it was not possible to implicate halothane as the specific cause in many of the reported cases. But the consistency of the clinical features,⁵ the recurrence of hepatitis after re-exposure,^{6,7} the specificity of the histological changes seen on electron microscopy,⁵ and, in particular, the provocation of hepatitis by deliberate challenge of previously affected individuals^{8,9} leave little doubt that halothane-induced hepatitis is an entity.

Though the reported mortality of 67 to 96%^{5,10} is probably biased because of the inclusion of more severe cases, halothane hepatitis must, nevertheless, be regarded as a very dangerous condition. However, its occurrence is still disputed by anaesthetists.^{11–13} This, together with our experience that at least some of the cases could have been avoided, prompted us to report the 11 patients seen at two hospitals during the last four years.

Clinical Features

The clinical and laboratory data are summarized in the Table. Seven patients (Cases 1–7) were referred from other hospitals to a unit specializing in liver disease and four (Cases 8–11) were treated at a regional general hospital. Presumably the higher mortality of the former group is the result of the referral of more severe cases.

King's College Hospital, London S.E.5

PAUL SHARPSTONE, M.B., M.R.C.P., Senior Medical Registrar (Present address: Consultant Physician, Royal Sussex County Hospital, Brighton)

ROGER WILLIAMS, M.D., F.R.C.P., Consultant Physician and Director of Liver Unit

St. Margaret's Hospital, Epping, Essex

D. R. K. MEDLEY, D.M., M.R.C.P., Consultant Physician