STUDY AND TREATMENT OF SMALLPOX

A SERIES of investigations was carried out in Madras, India, during the early part of 1960 to shed new light on a number of problems still unsolved in the epidemiology, immunology, pathogenesis, prevention and treatment of smallpox.

This work was sponsored by the World Health Organization, the Indian Council of Medical Research, the Governments of India and Madras, and other bodies, and were supported by grants from the World Health Organization, the Virus and Rickettsial Disease Study Section, National Institutes of Health, Bethesda, and the Marcus Tullius Reynolds III Fund. Some of the findings have been reported in the *WHO Chronicle* (16, No. 1; January 1962).

It has long been accepted that smallpox patients are normally not infective in the first few days of the disease before the rash appears. Indeed, the effectiveness of the isolation of patients in the early stages of the disease as a step towards controlling outbreaks depends largely on the correctness of this belief. If patients were infective from the beginning, early isolation of the contacts of known cases when they begin to run a temperature would fail to prevent the disease from spreading to those in contact with them. To determine how long the non-infective period lasts and when oral infectiveness ceases, Downie and his colleagues examined mouth washings and garglings from 119 patients in the Infectious Diseases Hospital, Madras, for the presence of virus. They found that specimens taken on the first and second day of illness were negative. Since, at this stage of the disease, lesions are not usually present in the mouth, this finding conforms with the accepted view that smallpox is not usually infective in the pre-eruptive phase. Positive results were most frequently obtained between the sixth and the ninth day, at a time when the lesions in the mouth tend to ulcerate and so discharge virus into the saliva. After twelve days patients suffering from a mild or moderate attack have very little virus left in the saliva. This is the time, however, in which the pustules in the skin are breaking down and providing a fresh source of infection.

The duration of the immunity conferred by vaccination against smallpox in infancy is known to be of variable extent, and the presence of a good vaccination scar does not mean that the person possessing it will not contract the disease. Vaccination is widely practised in Madras, yet smallpox is endemic; a series of studies carried out in 1960 showed that more than half the cases of the disease admitted to the Madras Infectious Diseases Hospital had good scars from vaccination in early life. In an attempt to find out to what extent antibody—and thereore immunity—is lost in people successfully vaccinated in early life, Downie, Hobday, Vincent and Kempe collected sera from more than 300 adults in Madras and estimated the antibody content. The individuals from whom sera were collected were mostly young adult males and thus did not form a representative cross-section of the population of Madras. The similarity between the three groups tested (blood donors, patients admitted to the Infectious Diseases Hospital, Madras, with chickenpox, and patients in the World Health Organization Tuberculosis Chemotherapy Centre in Madras), suggested that the results might be typical of the antibody-levels in the vaccinated adult population of Madras. Downie and his co-workers found that approximately 10 per cent of this population had little or no neutralizing antibody in their sera. They suggest that this percentage of the population, added to the 10–20 per cent which are not vaccinated, may provide a sufficient number of non-immune persons to permit smallpox to remain endemic in the city. The crowded conditions in which a large part of the population lives probably also contributes to the persistence of the disease.

The case mortality in variola major is approximately 20 per cent, although in unvaccinated patients it may be 40–50 per cent. By contrast, in variola minor or alastrim it is only 1 per cent or less. In limited outbreaks of smallpox, however, even if the disease is variola major, there may be no deaths (especially if the patients have been vaccinated), and there is no means of telling from the clinical picture which of the two forms is active in the community. Dumbell, Bedson and Rossier, after comparing several laboratory methods of differentiating the virus of variola major from that of variola minor, recommend a simple diagnostic test applicable to material taken directly from the patient. This test, based on the findings that the virus of variola major will produce pocks on the chorioallantois of chick embryos incubated at 38·25° C., whereas the virus of variola minor will not, will enable a differential diagnosis to be made within two days.

Since its introduction by Calmette and Guérin at the beginning of the century, the rabbit scarification method of assaying potency and standardizing smallpox vaccine has been in regular use throughout the world. It has been objected to on the grounds that the estimates of potency are qualitative, the errors due to different techniques and animal variation, and the total number of infective virus particles undetectable. Other test methods have been devised; but, in the view of Kolb, Cox and Aylor, they, too, have their limitations. Thus, the rabbit intracutaneous method is not sufficiently sensitive for titrating vaccines of dubious quality or unstable character because of inconsistent or poor development of the intracutaneous lesions. Some authors hold that the count variance in the method of counting pocks in the chick chorioallantois is so great that no valid estimate of the over-all coefficient of variation is possible. Tissue culture in monkey kidney provides a very much more sensitive titration system than rabbit scarification, but the method cannot be adopted until correlation is established between the virus titre found in it and successful human vaccination. Intravenous injection of embryonated eggs, because of time and expense, is not a practical procedure in the routine assay of vaccines.

Kolb, Cox and Aylor accordingly suggest refinements of the rabbit scarification method to meet some of the objections against it. The use of more animals, a calibrated gradient ensuring more precise measurement of individual pocks and confluent areas, and a simple mathematical scheme for quantitating potency of unknown vaccines in terms of a reference will help make the method of greater value

for the assay of vaccines to be used for human inoculations. The rabbit scarification method has considerable advantages: the results have been sufficiently correlated with those of human vaccination. It is economical in that two test vaccines can be directly compared with a control on three animals, and a minimum amount of training of personnel is required. By the use of the modifications suggested, test results can be determined and expressed in relative terms by simple mathematical means.

THE ROCKEFELLER FOUNDATION

THE annual report of the Rockefeller Foundation for 1960* includes, besides the President's review, the more general aspects of which have been discussed in the November 18 issue of *Nature* (192, 587; 1961), reports on the major features of the Foundation's support during the year for work in the medical and natural sciences, the humanities, the social sciences and the agricultural sciences. In agriculture, the Foundation's operating programme is devoted primarily on research to overcome or minimize the hazards to the production of food crops and livestock, and to train competent local scientists to direct their countries' agricultural research services. Of some 2·8 million dollars in aid of research and teaching, 405,350 dollars were for agricultural and veterinary science at eight different institutions in Africa, 300,000 dollars to the Ministry of Agriculture, Peru, and the Agrarian University for co-operative crop improvement programmes. The substantial assistance given to the Mexican, Colombian, Chilean and Indian Agricultural Programmes and the results of these programmes are outlined in the President's review and, besides. in the Inter-American Maize Improvement Project a very successful pattern of co-operation has been established among the six Central American republics which in seven years has greatly increased maize production in these countries and built up a corps of well-trained specialists in maize production. This project is now being organized into regional units beginning with a Central American programme and an Andean zone programme. Among other grants in this field may be mentioned those to the Boyce Thompson Institute for Plant Research for the study of obligate parasitism, to four Polish Institutions for the purchase abroad of equipment for research and teaching in the plant and animal sciences, and to the Kansas State University of Agriculture and Applied Science for research in the biological and physiological changes in wheat during storage.

In the medical and natural sciences, the President reviews more particularly the Foundation's support for virology, to which nearly 1·5 million dollars were devoted in 1960, and especially to the work on arthropod-borne (arbor) viruses, where it now appears that the HeLa cell line, originally isolated from a human carcinoma, can be used for the propagation and study of all the 'arbor' viruses so far tested when cultivated under special conditions. It has already proved extremely useful in studying the chemical and physical properties of Semliki Forest virus, a prototype group *A* agent. Besides the central laboratories in New York, where the programme is co-ordinated, field stations are maintained in North and South America and in India, and surveys of arbor virus diseases have been made in Mozambique, in Bechuanaland and Angola as well as parts of South Africa. The programme is basically a fact-finding undertaking to determine the incidence, epidemiology and importance of the various 'arbor' viruses, which are largely regional. Continuity of land surfaces may lead to a wide distribution of agents, as illustrated recently by the dramatic appearance in India of African horse-sickness, the causative virus being transmitted by a species of very small biting midges of the *Culicoides* species.

Among other grants for the medical and natural sciences, in which field more than 4 million dollars were for professional education, are those to the National University of Mexico for its research on the chemistry of natural products; to the University of Valle, Colombia, for research in experimental medicine; to the University of Melbourne for research in experimental physiology; to Kyoto University for behaviour studies in two species of monkeys; to the Population Council, New York, for its co-operative programme on population problems; to Oberlin College, Ohio, for a new natural science building; to the University College of Rhodesia and Nyasaland for research on sleeping sickness and bilharziasis by the Department of Zoology; to University College, London, for research in human genetics; to Harvard University, to establish a Centre for the Study of Nutritional Disease; for research in enzyme chemistry at the Karolinska Institute, Stockholm, and the University of Amsterdam; for studies of cellular metabolism at the University of Oxford; for biochemical research at the University of Rome; and for research in biophysics at King's College, London, and at the Indian Cancer Research Centre, Bombay.

In the social sciences, grants totalling 1·3 million dollars to assist the quest for rapid political and economic development included a grant to enable the International Bank for Reconstruction and Development to furnish basic working libraries on economic development to ministries of finance or economic affairs, development corporations, or central banks in emergent nations. Other grants in this field went to the Centre for International Studies, Mexico City, to the Institute of Public Administration, University of the Philippines, and to Hitotsubashi University, Tokyo, for a study of economic growth in Japan. The 875,000 dollars in support of the social sciences and basic disciplines included grants to the National Bureau of Economic Research, New York, for research on international trade; to the University of Michigan for a study of voting behaviour; and to Harvard University towards the costs of a conference on input–output techniques. The 478,000 dollars in support of studies of the fundamental problems of contemporary society included grants to the Centre for Studies and Research in International Law and International Relations at the Hague Academy of International Law; to the Free University of Brussels for the study of the national economic problems of the West; to the American Council of Learned Societies for a current digest of the Soviet Press and to Harvard University and the Massachusetts Institute of Technology for an arms control seminar.

* The Rockefeller Foundation Annual Report, 1960. (Rockefeller Foundation, 111 West 50th Street, New York, 1961.)