BACKGROUND TO THE POLIOMYELITIS VACCINATION CAMPAIGN

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HISTORY OF POLIOMYELITIS IN SOUTHERN AFRICA

Epidemics of poliomyelitis were unknown in Southern Africa before World War I. Circumstances then arose which apparently favoured the spread of the paralytic disease, for in the summer of 1917/18, when soldiers were returning from the Middle East, the first epidemic occurred. Baumann[1] stated at that time: 'Poliomyelitis in its sporadic form has probably always been in existence in Southern Africa, as in other parts of the world. I have, each year, met with isolated cases of the disease in almost any season, during the hot weather in particular. Scarcely any year has passed in which there have not cropped up several such isolated cases. This summer, for the first time in the history of the country, so far as any records show, we have been visited with poliomyelitis in an extensive epidemic form'. During this epidemic, which ran its course from December to March, several hundred cases occurred in the towns of the Witwatersrand. Nearly all were in children under five years of age. At that time the disease was, therefore, still truly infantile paralysis.

In 1934 the disease was more prevalent than usual, and a sharp outbreak occurred in Bloemfontein,[2] which was characterized by a high mortality among those afflicted, but no extensive epidemics occurred again until World War II.

In 1941, during World War II, it was noted that an unexpectedly large number of cases of poliomyelitis were occurring in the soldiers of the New Zealand and Australian Expeditionary Forces in Egypt.[3] In 1942, Malta[4] suffered from its first recorded epidemic. In these outbreaks in the Mediterranean area the adult indigenous population largely escaped.[5] The disease affected the indigenous infants and the service personnel, particularly from Europe and North America.

With extensive troop movements taking place, there were opportunities for the wide dissemination of the virulent strains of virus, and serious epidemics occurred in many countries in succession.

South Africa was affected in its turn in 1944, when, in October, the disease assumed epidemic form.* It seems probable that the infection was introduced from the Middle East, for the first cases were seen in Durban. Severe outbreaks were then reported in succession from a number of towns, and most districts in South Africa were affected. An important exception was the Transkei, from which, out of a population of one-and-a-half million, only seven cases were reported. In the population generally, the incidence of paralytic cases was 10 times greater in the European section than in the Africans.[6]

It was suggested then, that in their primitive environment, the Africans are exposed early and often to endemic strains of virus, and in this way acquire an immunity not shared by those of European descent who enjoy the amenities of civilization.[6]

Another extensive epidemic occurred in South Africa in 1948, and the most severe epidemic so far experienced began in 1955 and continued into 1956 and 1957.* A significant change was first noted in 1956, in East London, where Sinclair Smith and van Heerden[7] reported nearly three times as many cases occurring among the Africans as compared with the Europeans. Subsequently similar findings were reported from other cities and towns in South Africa, and it was apparent that the paralytic disease would also involve the African population to an increasing degree.[8]

It appeared that epidemics were becoming more frequent, and each was more severe than the preceding one. There was reason to fear that this pattern of epidemics, of ever-increasing extent and severity, would continue to develop in Southern Africa, unless some means of prevention could be found and made generally available.

THE POLIOMYELITIS RESEARCH FOUNDATION

The 1948 epidemic was particularly severe in Johannesburg, and Mrs. Evelyn Gordon, the Mayoress, called a public meeting to consider the position. Representatives from all interested organizations were invited to attend. The meeting was addressed, at her suggestion, by Drs. E. H. Cluver and Gordon Laing, both of whom said that little could be done at the time to control the spread of infection, and emphasized that what was needed was more knowledge of the virus which caused the disease and the development of a means of preventing both its spread and its paralytic form. They also stated that South Africa offered unique opportunities for the study of some of the problems of poliomyelitis. At that time large-scale research was hindered in the countries which could otherwise have undertaken it, by lack of adequate numbers of monkeys. In South Africa, an abundant supply of vervet monkeys, most suitable for the investigation, was available. In South Africa, too, there were two distinct sections of the population living under a variety of conditions. It was considered that a study of the disease as it occurred here would yield valuable information.

It was therefore decided at this meeting to appeal to the public of Southern Africa for funds to support research into poliomyelitis. A committee was elected and, in turn, local committees to cover the whole of Southern Africa were appointed, and the Poliomyelitis Research Fund appeal was launched on a nation-wide basis. The response of the public was generous, and nearly £500,000 were collected in the year of the appeal, 1948/49. A Board of Trustees was then appointed to administer the fund. The objectives were set forth in the constitution and may be summarized as being 'to carry out research into poliomyelitis with a view to its prevention and to carry out research into other virus diseases, and into related problems'.

The Laboratories of the Poliomyelitis Research Foundation

To achieve these objects it was decided to build special virus laboratories to provide the necessary accommodation. Although no promising leads of the development of a vaccine were apparent at the time, these virus laboratories were planned on the assumption that a preventive vaccine would soon be developed and would require production on a large scale, and one half of the institution was set aside for this purpose.

The other half provided space and equipment for research

* See graph on p. 505.

into poliomyelitis and other virus diseases and related problems. It was divided into a number of units, respectively concerned with the study of: (1) alimentary virus infections, (2) respiratory virus infections, (3) arthropod-borne virus infections, and (4) serology immunity studies. In addition, accommodation was provided for a biochemical and biophysical department in which were housed special items of equipment, including an electrophoresis apparatus, an ultracentrifuge and an electron microscope.

THE RESEARCH PROGRAMME

The aim of the research programme was to define the extent of infection with poliovirus and to determine the number and incidence of its serological types. To achieve this object, arrangements were made for comprehensive virus studies and immunity surveys to cover the territories of Southern Africa, the neighbouring islands, and countries even further afield.

Virus Studies

Patients with poliomyelitis and aseptic meningitis admitted to the fever and isolation hospitals in the strategic centres of Cape Town, Port Elizabeth, East London, Durban, Johannesburg, Bulawayo, Salisbury and Nairobi were investigated to determine the cause of their illness. When epidemics of poliomyelitis occurred elsewhere, specimens were collected from a representative sample of the patients for the isolation and identification and typing of the responsible virus.

The specimens collected from patients in the acute phase of their illness were — throat swab, faeces, blood, and cerebrospinal fluid. The specimens collected in the hospitals other than the Johannesburg hospitals were sent by air transport and usually arrived at the laboratory, even from the most remote places, within 24 hours of their despatch.

At the laboratory, suspensions were prepared from the throat swabs and faeces, and 500 units of penicillin and 500 mg. of streptomycin per ml. were added. Each suspension was then inoculated in 0·2 ml. amounts into two tissue-culture tubes of vervet monkey kidney. These were observed for up to 28 days for signs of degeneration, the maintenance medium being changed when indicated. Each suspension was also inoculated into one litter of one-day-old mice. These mice were observed for 14 days for weakness, tremors and other signs of illness. When indicated, animals were sacrificed, pieces of organs and tissues were taken for histological section, and a portion of the carcass was taken for the preparation of suspension per passage into other litters of baby mice.

The serum separated from the blood, and the cerebrospinal fluid, without the addition of antibiotics, were similarly inoculated into tissue-culture tubes and into baby mice.

The serum of the blood collected during the acute phase and that of the blood collected in the convalescent phase two to four weeks later were both tested for poliovirus antibodies in a tissue-culture neutralization test. These sera were also tested as a routine in complement fixation tests against rickettsial antigens, including *R. burneti*, the cause of 'Q' fever, and against *Herpes simplex*, mumps and lymphocytic choriomeningitis viruses.

When a virus was isolated, the patient's acute and convalescent phase sera, if available, were tested for antibodies against it.

When a virus was isolated in tissue culture and it produced an enterovirus type of destruction, it was tested against types 1, 2 and 3 poliovirus antisera. If it was neutralized by one of these antisera, its identity was established. If it was not neutralized by any of the type-specific antisera, the virus suspension was passed on to the Coxsackie virus team for inoculation into baby mice. If it proved to be a Coxsackie virus it was serologically typed in baby-mouse neutralization tests. If the virus was not pathogenic for baby mice, it was handed on to the ECHO virus team for further studies.

For the present, attention will be directed only to the poliovirus isolations and typing. The findings of these studies during the past decade are given in Table I.

From these results it is apparent that all three types of virus are commonly responsible for paralytic poliomyelitis, that each of the three is widespread in Southern Africa, as in the rest of the world, and that the extensive

TABLE I. TYPES OF POLIOVIRUS ISOLATED IN SOUTH AFRICA*

	Type 1	*Type 2*	*Type 3*
1953/4	10	9	10
1954/5	53	0	15
1956	662	24	50
1957	532	21	74
1958	48	77	90
1959	177	85	19
1960	325	43	62
1961	114	53	66

* This table reflects the incidence of the different types of poliovirus causing poliomyelitis in each year. It does not give the total incidence of cases.

severe epidemics have all been due to type 1 poliovirus infection. However, several small but severe outbreaks, with a high proportion of the cases showing severe paralysis, were due to type 3, and type 2 poliovirus also frequently gave rise to paralytic cases.

It was concluded that, to be effective, a vaccine would have to include each of the three types of poliovirus.

Immunity to Poliomyelitis — Serological Surveys

The immunity status of any individual can be determined by testing his blood for the presence of antibodies. In the case of poliomyelitis two tests have been widely used. These are the Lansing mouse-protection test which determines immunity to type 2 poliovirus only, and the tissue-culture protection tests which can be used to determine immunity to each of the three types of poliovirus.

Surveys of representative samples of the population of Southern Africa and the neighbouring islands have been carried out over the last 15 years. In the early surveys reliance was placed on the Lansing protection test, which tests antibodies against type 2 poliovirus only, but since 1953 the tissue-culture protection test for each of the three types of poliovirus has been used. The results will be reported in detail in a separate paper.

In general, it was noted that in each age group a larger proportion of Africans had acquired immunity than Europeans in the corresponding age group. It was noted, too, that by the time they are six years old, most Africans had acquired immunity to all three types of poliovirus, whereas a number of Europeans were lacking antibodies to one or more types of poliovirus in adolescence and even in young adult life. Some adults were lacking immunity to all three types of poliovirus.

With regard to the islands, it was noted that more than 90% of the population of Madagascar showed immunity when

tested in the Lansing protection test, and that the immunity in the inhabitants of Mauritius was not as high as in the corresponding age groups in the Africans of the continent of Africa. It was also found that the islanders of Tristan da Cunha, when tested in 1955, had all acquired immunity to type 3, only one had acquired immunity to type 1, and about 25% had acquired immunity to type 2. It was considered that the immunity shown to type 3 was a group immunity resulting from a wave of infection of type 3 virus which had occurred within the preceding two years. In the survey carried out in 1961, this conclusion was confirmed, in that all those over the age of six still had immunity to type 3, none had immunity to type 1 except those who had been elsewhere during their lifetime, and none had immunity to type 2. In other words, those who had previously shown immunity to type 2 had, in the intervening period, lost these antibodies.

As far as South Africa is concerned, this immunity survey gave clear evidence of the need of the various sections of the population for immunization by vaccine. On the basis of this information, and also on the incidence of paralytic cases, it was concluded that Africans over the age of six did not need the vaccine. Since there were many young adult Europeans lacking immunity to one or other of the poliovirus types, however, it was decided that those of European descent up to the age of 30 required immunization.

In the mass vaccination campaign, therefore, it was decided to offer vaccine to all Africans up to the age of 10, to all Coloureds and Indians up to school-leaving age, and to all Europeans up to the age of 30, unless they were recent immigrants from North-West Europe, when they were offered vaccine up to the age of 40.

Development of the Vaccine

When the buildings of the Poliomyelitis Research Foundation were planned, no vaccine against poliomyelitis was available, nor did it seem likely that one would be developed in the immediate future. However, in drawing up these plans, provision was made for each of the procedures which held promise of achieving this. A set of laboratories was designed for tissue-culture work, and facilities for egg-culture work and ample laboratory space for animal experiments were provided.

In the same year (1949) Weller *et al.*[9] showed that the poliovirus would grow prolifically in tissue culture. It appeared that this finding marked the beginning of a new era, when great advances could be expected. This anticipation has been fully realized; the application of the tissue-culture technique to the study of virus diseases has completely transformed the picture and, within the last decade, nearly 200 serologically distinct viruses have been recognized.

It was anticipated that this technique could be used to produce large amounts of virus suitable for the production of a killed inactivated type of virus, and also that it could be applied to the development of attenuated viruses of the three different types.

Dr. Jonas Salk,[10] in the USA, undertook the development of the inactivated type of vaccine and Dr. P. A. D. Winter and his team undertook the same task in the laboratories of the Poliomyelitis Research Foundation. Our team was kept fully informed of the procedures in use in the USA, and the development of the vaccine proceeded in parallel with its development there. On 12 April 1955, on the anniversary of the death of President Roosevelt (the first President of the National Foundation for Infantile Paralysis), vaccine was released for issue in the USA.

At the same time, vaccine prepared in the vaccine division by the team under Dr. Winter was available for issue in South Africa. This vaccine was also submitted to a comprehensive series of tests designed to prove its safety, by a team under Dr. H. H. Malherbe. The results of these tests indicated that it was free from live poliovirus as well as from other infective agents and from toxicity.

The vaccine was tested for its potency in monkeys and guinea-pigs in the serology unit, and was found to stimulate antibodies against all three types of poliovirus. The response of type 1 and type 2 antibodies was good, that of type 3 antibodies was relatively poor. Since most cases in epidemics had been shown to be due to type 1 infection, it was considered that the use of the vaccine would greatly diminish the incidence of paralytic cases. However, following the giving of polio vaccine and the so-called 'Cutter incident', the Health Department Committee, newly appointed to review the situation, decided not to release the vaccine for issue until it had been re-tested. These tests were completed in August 1955 and the first vaccine was released for issue during that month.

The vaccination campaign gathered force slowly, but with the advent of a widespread epidemic in 1956 and 1957, the demand for vaccine greatly exceeded the amount available. It was not until 1958 that the Poliomyelitis Research Foundation was in a position to meet all needs. It is estimated that about 750,000 individuals, mostly European children and infants, were given the vaccine.

In the following years, the incidence of poliomyelitis in vaccinated children was very much less than in unvaccinated children. However, a large number of cases continued to occur. A new trend of the disease was apparent for the first time in 1956, when, in the epidemic in East London, it was noted that there were three times as many cases in African children as in European children, and in the epidemic in 1956 - 57 there were more African than European cases in the country as a whole for the first time since records were kept.

It appeared that a live virus vaccine would meet this situation better than a killed vaccine. An attempt to develop an attenuated strain for this use was begun at the Institute in 1946, when the serial passage of the Lansing strain of poliovirus in *Mystromys albicaudatus*, a common South African veld rodent, readily adaptable to laboratory conditions, was initiated.

At the beginning of this study the virus paralysed nine of ten monkeys *(Cercopithecus aethiops pygerythrus)* inoculated intracerebrally, two of seven after 47 passages, and only one of ten after 100 passages, and again after 150 passages, indicating that some attenuation of the virus in these monkeys had occurred.

A feeding trial of the virus was contemplated at this stage and arrangements were discussed with Dr. J. Rauch, Medical Officer of Health of Germiston, and Dr. G. Faer-

ber, Medical Officer in charge of the non-European clinics in Germiston African Township. However, for various reasons this trial was not carried out.

Soon after this, Koprowski *et al.*[11] reported the first trials of the TN strain of type 2 virus, which had been found to be relatively avirulent for monkeys when originally isolated. It was further attenuated by serial intracerebral passage in cotton rats. After the first trial in 20 children, this strain of virus was fed to several hundred children without ill-effect. Most of those lacking antibodies to type 2 virus before the feeding, developed an immunizing infection associated with the appearance of type 2 poliovirus antibodies.

It was apparent that this strain could be used to immunize against type 2 poliovirus. Unfortunately, most extensive epidemics are caused by type 1, and the use of a type 2 strain as a live oral vaccine could not be expected to prevent them, although it would probably prevent some paralytic infections. There was clearly a need for a trivalent vaccine.

Following on preliminary studies undertaken by Prof. J. F. Enders, who showed that the Brunhilde strain of type 1 virus after 20 tissue-culture passages had become relatively attenuated for monkeys, Sabin and his associates[12] began a systematic attempt to produce attenuated strains. After several years of intensive and painstaking work, he reported the successful development of attenuated strains of each of the three types of poliovirus. He sent these three strains to the Poliomyelitis Research Foundation for study under South African conditions in 1958. The oral vaccine used in the mass vaccination campaigns was prepared from them.

Koprowski,[13] more or less simultaneously, also applied the tissue-culture technique to the development of attenuated strains of type 1 and type 3 poliovirus, the Chat and Fox strains respectively. These were also made freely available to the Poliomyelitis Research Foundation and are still under study.

This is an appropriate time to acknowledge the great help given to the workers of the Poliomyelitis Research Foundation by Dr. T. H. Weller, who was one of the team of Enders, Robbins and Weller whose successful culture of the poliovirus ushered in the modern tissue-culture era of virology. In 1952 he spent several months working with and initiating the South African team in the technique of tissue culture, which was the main basis of the work reported in this and succeeding articles.

It is also a pleasure to express our thanks to Dr. H. Koprowski, Dr. A. B. Sabin and Dr. J. E. Salk, who kept us informed of the results of their work and freely made available the strains of poliovirus which they had developed, and to the National Foundation for Infantile Paralysis of America whose officers arranged for the free exchange of information. We are also grateful to the State Health Department, in particular the former Secretary for Health, Dr. J. J. du Pré le Roux, and his successor, Dr. B. M. Clark; the Senior Pathologist, Dr. R. Turner, and the members of the Virology Committee, for their encouragement and support.

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