Summary

Two trials were made to measure the effect of previous Salk vaccination on virus excretion by children fed with oral poliomyelitis vaccine viruses.

In the first trial a group of children received two doses of Salk vaccine and were then fed Sabin type II vaccine virus. A control group of children received only Sabin type II vaccine virus. Faecal virus excretion by the two groups of children was similar. No investigation of throat virus excretion was done.

In the second trial a group of children received either two or three doses of Salk-type vaccine, and were then fed Sabin type I vaccine virus. A control group of children received only Sabin type I vaccine virus. Faecal virus and throat virus were excreted in smaller amounts for a shorter time by the Salk-vaccinated group than by the control group.

The possibility that widespread use of Salk vaccine might influence the spread of naturally occurring virulent polioviruses is discussed.

The poliovirus research in the Department of Microbiology, the Queen's University of Belfast, is supported by the National Fund for Research into Poliomyelitis and Other Crippling Diseases and the Northern Ireland Hospitals Authority.

We are indebted to the sisters and nurses who helped with these studies. We thank Drs. J. R. L. Forsyth, Joan D. Henderson. and Lorna I. Scott for their help, and Professor F. M. B. Allen for lending us a laboratory in his department.

The outlines and objectives of this investigation were approved by the Medical Research Council Poliomyelitis Vaccines Committee.

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"In Ceylon the average expectation of life at birth last year was 62.5 years which is the highest so far recorded. That the child born in Ceylon to-day can reasonably expect to reach this age is in heartening contrast to the position about 40 years ago when a child born could have expected normally to live up to only 30 or 31 years." (Mr. A. P. Jayasuriya, Ceylon Minister of Health.)

VACCINATION AGAINST POLIOMYELITIS WITH LIVE VIRUS VACCINES

8. CHANGES IN SABIN TYPE I ORAL VACCINE VIRUS AFTER MULTIPLICATION IN THE INTESTINAL TRACT

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During the course of a trial of Sabin type I attenuated poliovirus (Dick *et al.*, 1961) some of the changes which occurred in the virus after human passage were investigated, and these are described below. The reason why changes in the characteristics of infectious vaccine viruses after human passage are of importance is discussed elsewhere (Dane *et al.*, 1961).

Materials and Methods.—These were as described in previous papers (Dane *et al.*, 1961 ; Dick *et al.*, 1961).

Results

Eleven children aged 7 to 17 months (average 11.6 months) who were without antibody—that is, <1 : 8—to type I poliovirus were fed with 10^6 TCD_{50} of Sabin type I attenuated poliovirus. After feeding, daily faecal specimens were collected for 21 days and again on the 28th and 35th days, and throat swabs were taken for the first 14 days. In addition, faecal specimens were collected daily from 23 children in contact with those who had been fed. All specimens were tested for the presence of type I poliovirus, and, if positive, the amount of virus was estimated by titration. Eight of the children fed became good faecal virus excreters and four of them also excreted virus from the throat. The immune status of the contacts was unknown, but three became infected during the study period.

Faecal and throat virus strains isolated from children fed the vaccine virus and from their contacts were tested for neurovirulence in monkeys and for the *t* and *d* marker character (Dane *et al.*, 1961).

Monkey Neurovirulence Tests.—In all, 10 strains of first- and second-human-passage type I vaccine viruses were tested in rhesus monkeys by the intracerebral inoculation of large amounts of virus ($10^{5.8}$ to $10^{6.8}$ TCD_{50}). The results of these tests are shown in Table I.

Paralysis and histological lesions were found in many of the monkeys, but were not as severe as is usually seen when virulent strains are tested in this manner.

T Marker Tests.—Forty-four virus strains, isolated after varying periods of growth in the human intestinal tract, were tested at 40° C. (Table II). None were $t+$, and only three strains were $t\pm$, the remaining 41 being $t-$ like the original vaccine virus. When the test was performed at 39° C. on 14 strains isolated from vaccinated children and on five strains from contacts more change in the *t* character of human-passage strains was found (Table III). There was a tendency for viruses to have a greater ability to multiply at 39° C. the longer they had multiplied in the intestinal tract.

D Marker Tests.—Ten human-passage strains of the type I vaccine virus were tested for the *d* marker. The original vaccine virus is $d-$: four of the strains tested were found to be $d\pm$, indicating that some change in the character of the virus had occurred (Table IV).

Community Surveillance

Twelve weeks after the type I vaccine virus had been fed, faecal specimens were collected and tested from all the 90 children living in the home where the virus had been fed. None were found to be excreting type I poliovirus, indicating that spread had been limited and may have involved only the three children who were shown to have contact infections during the study period of 35 days.

It was possible to discount any adverse effect of virus spread into the community from the Northern Ireland trials of Sabin type I and II vaccine viruses by reference to the types of poliovirus recovered recently from paralysed patients in Northern Ireland (see Diagram). There have been no cases of paralytic poliomyelitis due to type I or type II poliovirus since the trials of these vaccine viruses. Specimens were received and poliovirus isolations made from all but one of the clinically diagnosed cases of paralytic poliomyelitis in 1960 and 1961 (January to May).

TABLE II.—*T-character at 40° C. of 44 Strains of Human-passage Virus After 1 to 5 Weeks' Multiplication in the Intestinal Tract*

Week of Virus Multiplication in Intestinal Tract	No. of Human Passages	No. of Strains Tested	*t* Marker: 40° C.		
			t+	*t*±	*t*−
1st ..	1	13	0	0	13*
2nd	1	12	0	1	11†
	2	1	0	0	1
3rd	1	5	0	0	5
	2	2	0	0	2
4th	1	3	0	0	3
	2	1	0	0	1
5th	1	5	0	1	4
	2	2	0	1	1
Total		44	0	3	41

* Includes 1 strain of throat virus. † Includes 4 strains of throat virus.

TABLE III.—*T-character at 39° C. of 14 Strains of First-human-passage and 5 Strains of Second-human-passage Virus After 1 to 5 Weeks' Multiplication in the Intestinal Tract*

Human-passage	Week after Feeding	No. of Strains Tested	*t* Marker: 39° C.		
			t+	*t*±	*t*−
1st	1	3	0	3	0
	2	3	0	3	0
	3	3	1	2	0
	4	3	3	0	0
	5	2	2	0	0
2nd (contacts)	2	1	0	0	1
	3	2	0	2	0
	5	2	1	1	0
Total		19	7	11	1

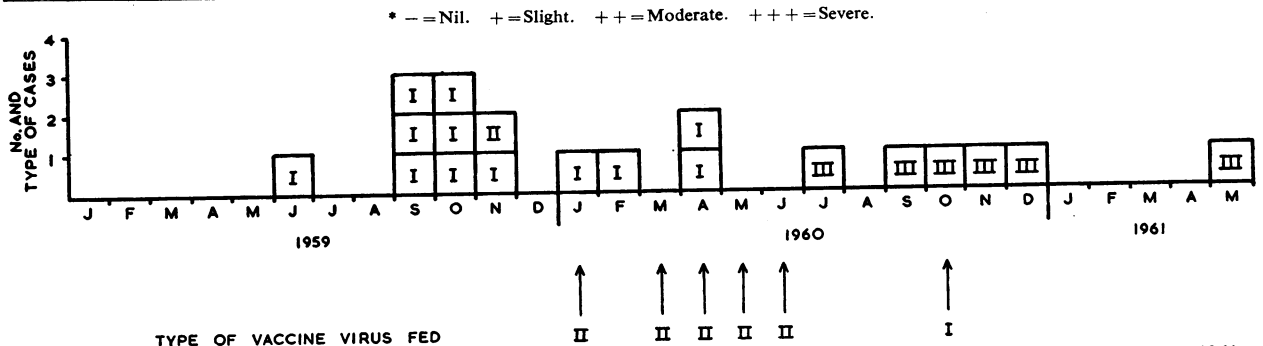
TABLE IV.—*D-character of 10 Strains of Human-passage Virus*

Virus	No. of Human Passages	Days after Feeding	*d* Marker
D. McK.	1	7	*d*−
		20	*d*−
		34	*d*±
M. McC.	1	5	*d*−
		28	*d*−
P. McH.	1	7	*d*±
		28	*d*±
E. Ba.	2	34	*d*−
B. Co.	2	15	*d*−
J. Mo.	2	35	*d*±

TABLE I.—*Intracerebral Neurovirulence in Rhesus Monkeys of First- and Second-human-passage Viruses*

Child	Human-passage	Days after Feeding	Titre Log_{10} TCD_{50}/ml.	No. of Monkeys with Paralysis*					No. of Monkeys with Lesions*				
				−	+	++	+++	Total	−	+	++	+++	Total
M. Sw.	1st	6	5·8	1	0	1	0	1/2	0	2	0	0	2/2
M. Sw.	,,	14	5·8	1	0	1	0	1/2	1	0	1	0	1/2
D. McK.	,,	7	6·4	2	0	0	0	0/2	1	1	0	0	1/2
D. McK.	,,	34	6·3	1	0	1	0	1/2	0	1	1	0	2/2
M. McC.	,,	14	6·1	2	0	0	0	0/2	1	1	0	0	1/2
M. McC.	,,	34	6·4	1	0	1	0	1/2	0	1	1	0	2/2
P. To.	,,	13	5·8	1	1	0	0	1/2	1	1	0	0	1/2
B. Co.	2nd (contact infection)	15	6·5	1	0	1	0	1/2	0	1	1	0	2/2
E. Ba.	,,	34	6·8	2	0	0	0	0/2	0	2	0	0	2/2
J. Mo.	,,	35	6·8	1	1	0	0	1/2	0	1	1	0	2/2

* − = Nil. + = Slight. ++ = Moderate. +++ = Severe.



Numbers and types of polioviruses recovered from paralytic cases in Northern Ireland from January, 1959, to May, 1961, and times of feeding Sabin types I and II vaccine. N.B.—No acute-phase specimens were received from the type II case in November, 1959 ; retrospective clinical and serological diagnosis.

During the latter half of 1960 there were five cases of paralytic poliomyelitis caused by type III virus. These occurred as a small outbreak which followed an importation of type III virus from a town in England (Virus Reference Laboratory Report, 1961). A child came on holiday to Northern Ireland in July and became paralysed the day after arrival; the chain of infection spreading from this source was clearly defined. Cases of acute poliomyelitis caused by type III virus had occurred early in 1960 in some parts of England, but none were recorded in the town from which the child came until November. All three types of attenuated poliovirus vaccine had been fed to a small number of children in that town during the spring.

Discussion

Murray *et al.* (1959) found no evidence of paralysis or C.N.S. lesions in rhesus monkeys inoculated intrathalamically with Sabin type I vaccine virus. Using a similar technique, we found that passage strains of this virus isolated after one to five weeks' multiplication in the human host showed a definite increase in neurotropism. Twenty monkeys were inoculated with high-titre ($10^{5.8}$ to $10^{6.8}$ TCD_{50}) virus from 10 isolations. Seven monkeys became paralysed and 16 had definite lesions in the C.N.S. Though none of these passage viruses had a neuropathogenicity comparable to that of "wild" polioviruses isolated from paralysed patients, they would nevertheless be regarded as quite unsuitable for use as vaccine viruses.

No attempt was made in this trial to assess whether the changes in the virus which occur after multiplication in the human intestinal tract tend to be progressive. The results of the *t* marker test, however, indicate that over the short period studied the changes in this character were in fact progressive.

In our opinion the changes observed in both the type I virus studied in this trial and the type II virus studied in an early trial (Dane *et al.*, 1961) indicate a need for careful, open-minded community surveillance if and when these viruses are used for routine vaccination as opposed to mass "area vaccination." Due consideration should be given in advance to the fact that it would not be an easy matter to acknowledge that an infectious living vaccine had probably been responsible for a case or cases of poliomyelitis.

Our own surveillance of the small trials in Northern Ireland illustrates the need for a more certain and accepted method of intratypic strain differentiation than is now available. It would have been satisfactory if we could have shown conclusively by some simple test that the type III poliovirus imported from England in July was not of vaccine virus origin. We think it most unlikely that it was, but is that enough?

The type I vaccine virus showed less capacity for spread in this trial than had type II vaccine virus in a previous trial under somewhat similar conditions. We were able to show by the absence of cases of paralytic poliomyelitis due to these two types of poliovirus that no serious effects had resulted from the possibly quite extensive community spread of type II vaccine virus and the probably very limited spread of type I vaccine virus.

Summary

Eleven children were fed Sabin type I vaccine virus. During the following month three other children in contact with them became infected with the virus. The laboratory marker characteristics of faecal and throat viruses excreted by the children were compared with those of the original vaccine virus.

The original vaccine virus has been shown by others to produce neither paralysis nor lesions when inoculated intracerebrally into rhesus monkeys. In contrast the human passage viruses recovered in this trial were found to produce paralysis and histological lesions in a proportion of the monkeys inoculated.

Some changes in the *t* and *d* marker characters of the virus were also found to occur after human passage.

The community surveillance which formed part of this and other trials is described, and the difficulties involved in such surveillance programmes are discussed. No case of paralytic poliomyelitis caused by type I poliovirus has occurred in Northern Ireland since the type I vaccine virus was fed.

The poliovirus research in the Department of Microbiology, the Queen's University of Belfast, is supported by the National Fund for Research into Poliomyelitis and Other Crippling Diseases and the Northern Ireland Hospitals Authority.

We are indebted to the sisters and nurses who helped with these studies. We thank Drs. J. R. L. Forsyth, Joan D. Henderson, and Lorna I. Scott for their help; and Professor F. M. B. Allen for lending us a laboratory in his department.

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Returns received from India, Pakistan, and Burma show that in the Homes and Leprosaria owned, managed, or aided by the Mission to Lepers 14,000 patients received treatment, 2,800 became free from active symptoms, and 8,100 showed marked improvement. At the same time 67,000 were treated as out-patients, with "arrest" in 4,200 and marked improvement in 24,500. From Africa returns are inevitably incomplete, but there are recorded more than 6,000 patients in the Homes aided by the Mission and more than 20,000 out-patients have been treated. From Taegu, in Korea, comes news of the Mission's roadside and village clinics which treat 660 patients, and of 32 admitted to the four-bed unit of the Mission attached to the Kyungbuk University Hospital. In the Katmandu Valley of Nepal out-patients are coming forward in increasing numbers to the clinics at the Shanta Bhawan Hospital (more than 130); to the clinics in the Bhat Gaon and Chapagaon villages (more than 30 to each), and at Anandaban Leprosarium (more than 10). The Hong Kong report shows that 540 patients were under treatment on the Isle of Happy Healing, with 119 new patients admitted during the year and 69 discharged with certificates of "arrest." New members have been admitted to the Church at many of the centres mentioned above. The records received show 3,488 Church members at the beginning of the year under review, with 795 added to their number in the course of the year. (*Witness unto Me*, describing the work of the Mission to Lepers in 1960, price 1s., from the Mission's headquarters, 7 Bloomsbury Square, London W.C.1.)