a fourth dose of Salk vaccine. Unfortunately this was impracticable. However, the antibody response obtained seemed to be of much the same order as that to a fourth dose of Salk vaccine recorded by other observers. Wilt, Parker, Stackiw, and Hutchison (1961), in Canada, who were able to make such a comparison, found that the response to Salk vaccine was not quite as good as to living attenuated vaccine given by the mouth, but the difference was not significant. In Czechoslovakia, Žáček, Vonka, and Adam (1961) reported a much better response to the living vaccine than to a fourth dose of Salk vaccine. In the United States, Horstmann and her colleagues (1961), who compared different dosage schedules of living vaccine in 350 pre-school children, most of whom had received Salk vaccination but only 23% of whom had antibodies to all three types of poliovirus, obtained good responses whether judged by an increase in antibody titre or by excretion rate. These findings all agree in indicating that Salk-vaccinated children respond well to living vaccine by the mouth. It may therefore be concluded that, for the periodic reinforcement of immunity which seems to be desirable for the present, there is no need to continue with Salk vaccine: a single oral dose of Sabin vaccine should be sufficient.

Summary and Conclusions

A batch of oral living trivalent poliovirus vaccine made in Britain was compared with one made in the United States for Dr. Sabin. Both vaccines contained Sabin's attenuated strains. The trial was made in five different centres in England and Wales; 60 children received the British and 58 the American vaccine. The dose of each vaccine was 10^6 TCID₅₀ of each of the three types of virus.

The children, who were 5 to 7 years of age, had all received three doses of Salk inactivated vaccine more than 18 months previously.

Serum samples were taken before vaccination and again two to fourteen weeks later and titrated at a single centre for neutralizing poliomyelitis antibodies. Faecal specimens were collected, usually twice a week for six weeks after vaccination, and examined in local laboratories for poliovirus.

The results showed that the two vaccines behaved essentially alike, whether judged by antibody response or by ability to colonize the gut; both were able to reinforce the immunity of the children as judged by the increase in antibody.

It is concluded that the British living attenuated vaccine is similar in its immunizing properties to the American vaccine prepared for Dr. Sabin; and that for the reinforcement of immunity in Salk-vaccinated children a single dose of the oral vaccine may be given.

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EFFECT OF A SINGLE DOSE OF ORAL POLIOVIRUS VACCINE IN PERSONS PREVIOUSLY IMMUNIZED WITH INACTIVATED VACCINE

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An investigation of the effect of an oral dose of live poliovirus vaccine (Sabin) in persons who had previously been immunized with inactivated poliovirus vaccine (Salk) is described in this report. Two groups of subjects took part in the study; in one the ages ranged from 12 to 16 years and in the other from 18 to 45 years. The former younger group received Sabin vaccine type 1 and the latter type 2. The objects of the study were to observe the proportion of subjects susceptible to infection with live vaccine, to obtain information on the dose of virus necessary to establish infection, and to determine the antibody responses induced by the live vaccine.

Materials and Methods

Vaccine

Two monovalent batches of oral poliovirus vaccine were used. They were prepared by the Wellcome Research Laboratories from the Sabin strains LSc.2 ab type 1 and P72.Ch.2 ab type 2, which were two culture passages removed from Sabin's original vaccine. Three dilutions were made of each vaccine—the type 1 in 1:5 dilution steps and the type 2 in 1:3. The dilutions were dispensed into all-glass ampoules and sealed, each ampoule containing one human dose (0.5 ml.). These operations were done at the Hampstead Laboratories, where the ampoules were coded, so that the Sheffield investigators, who administered the vaccine and made the virus isolations from the faecal specimens, did not know which dose of vaccine had been given. Vaccine was held at -70° C. until used, at which time it was quickly thawed and the subjects were vaccinated by placing the contents of an ampoule on the back of the

tongue by means of a Pasteur pipette, an individual pipette being used for each subject.

Subjects

The type 1 vaccine was given in a single vaccination session of eight hours to 177 pupils 12 to 16 years of age in a secondary-modern school in Wombwell. All the children had already received three doses of inactivated poliovirus vaccine, the third dose being given at least nine months before the oral live vaccine, and no cases of poliomyelitis had been reported in the district within this period. The children in each school form were randomly divided into three groups by age and sex, and each group received vaccine of a different code letter. Serum samples were taken immediately before vaccination and also 28 days later. Faecal samples were collected at home 6 and 28 days after vaccination; six days was chosen as the most probable time of peak excretion of virus and 28 days to determine the duration of virus excretion. There was no evidence of untoward reactions to vaccination in any of the children.

The type 2 vaccine was given to 130 members of the clerical and professional staff of the West Riding County Council headquarters in Wakefield in a single eight-hour vaccination session. All subjects were living in private houses in urban and suburban Wakefield, and their ages ranged from 18 to 45 years. They had received a third dose of inactivated poliomyelitis vaccine four to twelve months previously, and no cases of poliomyelitis had been reported in the district during the nine-month period before the trial. The adults were randomly divided into three groups by age and sex, each group being given vaccine of a different code letter. As with the children, serum samples were taken at the time of vaccination and 28 days later, and faecal specimens were collected 6 and 28 days after vaccination. Each subject was asked to fill in a questionnaire at the end of the observation period recording any departure from normal health, and there were no complaints which could be attributed to vaccination.

Titration of Antibody and Isolation of Virus

Antibody in serum samples was titrated by the metabolic inhibition test. Dilutions of the sera were mixed with a test dose of virus (100TCD_{50}) and allowed to combine for three and a half hours at 37°C . and held overnight at $+4^{\circ}\text{C}$. A suspension of monkey-kidney cells was then added to the mixtures and the neutralizing titres were read after incubation at 37°C . for seven days. Virus isolations were made in monkey-kidney-cell cultures from extracts of faeces obtained after emulsifying and centrifuging. No enteroviruses other than polioviruses were isolated.

Results with Type 1 Poliovirus

The results of isolations of poliovirus type 1 from faecal specimens are shown in the Table. Of the 177

Activity of Oral Poliovirus Vaccine, Types 1 and 2, in Two Groups of Subjects

Oral Vaccine	Age-group	Virus Dose	No. of Subjects	No. (and %) of Subjects Excreting Virus	
				Day 6	Day 28
Type 1	12-16 years (Wombwell)	$10^{6.0}$	65	18 (28)	2 (3)
		$10^{5.3}$	57	5 (9)	1 (2)
		$10^{4.6}$	55	6 (11)	0 (0)
		Total	177	29 (16)	3 (2)
Type 2	18-45 years (Wakefield)	$10^{5.8}$	39	20 (51)	3 (8)
		$10^{5.3}$	45	20 (45)	8 (18)
		$10^{4.8}$	46	13 (28)	3 (7)
		Total	130	53 (40)	14 (11)

children who received type 1 vaccine, 29 excreted virus six days later, but only three of these were excreting virus at 28 days. It is clear that the highest dose of $10^{6.0}\text{TCD}_{50}$ was more effective in establishing infection than the lower doses, since infection was established in 28% of those who received $10^{6.0}\text{TCD}_{50}$ but only in 9% and 11% of those who received $10^{5.3}$ and $10^{4.6}\text{TCD}_{50}$ respectively.

The antibody responses are shown in Fig. 1. It does not record the titres of all subjects, since for some

FIG. 1.—Antibody responses of schoolchildren to a single dose of type 1 poliomyelitis vaccine (oral). ○=Excreting virus. ●=Not excreting virus.

paired sera were not obtained. It is clear that the dose of $10^{6.0}$ TCD₅₀ was the most effective in establishing infection in those children with high antibody titres, since it infected 11 of 47 children having antibody titres of 512 or more, whereas the lower virus doses infected only 2 of 78 subjects with antibody titres in this range.

Taking the three groups together it is seen that not all children excreting virus showed a rise in antibody titre, and this was especially true of those with high titres before vaccination. When, however, only those with titres of less than 512 are considered, all 15 who excreted virus showed an increase in antibody titre of fourfold or more. It is also noted that 10 children who showed no virus excretion had a fourfold or greater rise in titre. It is probable that, in these, virus excretion was of short duration and might have been detected if faecal samples had been examined more often.

Results with Type 2 Poliovirus

The results of the poliovirus type 2 isolations from faecal samples of the adults are also shown in the Table. Of the 130 subjects 53 excreted virus six days after vaccination and 14 of them were still excreting virus at 28 days. The two highest doses of vaccine showed a similarity in their ability to infect and were slightly more effective than the smallest dose. Virus was excreted by 20 of the 39 who received $10^{5.8}$, also by 20 of the 45 who received $10^{5.3}$ but by a smaller proportion, 13 out of 46, of those who received $10^{4.8}$ TCD₅₀.

The antibody titres before and after vaccination are shown in Fig. 2. It does not record the titres of all subjects, since for some paired sera were not obtained. When all three groups are considered together it is seen, as in the case of the children, that not all those who excreted virus showed a rise in antibody titre, and again this is especially true of those with high antibody titres. When, however, only those with titres of 512 or less are considered, 22 out of 25 who excreted virus showed a rise of antibody of fourfold or more. There were six subjects who showed no virus excretion and had a four-

fold or greater rise in antibody titre. In these, as with the children, virus might have been detected if more faecal samples had been taken.

Conclusions

The subjects who took part in this study were aged 12 to 45 years, and thus their immunity before oral vaccine was given would in some cases have been due not only to Salk vaccination but also to previous sub-clinical poliomyelitis. It may be that those who became infected after receiving the type 1 and 2 oral poliovirus vaccines had not experienced a previous infection with the poliovirus of the corresponding type, but certainty about this could have been obtained only by determining the antibody titres of sera taken before the subjects had received Salk vaccine.

Nevertheless, it is clear from the results obtained with the groups who received the highest doses of the vaccines that many of the subjects were still susceptible to infection with poliovirus—about 30% to type 1 and 50% to type 2. It is also clear that of these susceptibles a high proportion, especially those with low antibody titres, gave good antibody responses after infection with vaccine. It was observed, however, that reducing the dose of virus in the oral vaccine reduces its ability to infect, and on the basis of these results it is suggested that doses of about $10^{6.0}$ for type 1 and $10^{5.0}$ TCD₅₀ for type 2 would be suitable to use in order to immunize those who remain susceptible to poliovirus infection after immunization with Salk vaccine.

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FIG. 2.—Antibody responses of adults to a single dose of type 2 poliomyelitis vaccine (oral). ○=Excreting virus. ●=Not excreting virus.