longer duration. This, however, has not been found. A single injection of A.C.T.H. produced an initial rise in reticulocyte counts from about 2 to about 3% within two hours (outflow), followed by a drop to normal values after about 24 hours. A repeated injection of A.C.T.H., then, gives the same results.

By injection of 1 mg. of A.C.T.H. twice a day into normal mice it has been possible to keep the animals on a raised reticulocyte level for some time. In spite of continued injections of A.C.T.H., however, the reticulocyte counts decrease little by little, and after about 10 days the average reticulocyte counts have reached the normal level.

These findings make it doubtful whether the increased haemoglobin values seen after administration of A.C.T.H. are related to the increased titre of K.F.

The working hypothesis adopted is that the increased haemoglobin values, at least in part, may be related to an increased release of cells from the bone-marrow (outflow) caused by A.C.T.H. This release may act as a stimulus for increased production of erythrocytes. If polycythaemia tended to develop in this way, it might be counteracted by decreased amounts of erythropoiesis-stimulating substances (erythropoietin) in animals with intact mechanism for regulation of erythrocyte and haemoglobin levels. In accordance with this, no marked degree of polycythaemia seems to have been observed in animals after administration of A.C.T.H. Problems related to outflow will be discussed in more detail in another paper.

The mechanism regulating the titre of K.F. has been discussed in this paper. In a preceding paper it was shown that the titre of K.F. increases in cordotomized mice after bleeding, whereas the titre of erythropoietin does not. Two patients with hepatitis showed increased titre of K.F., whereas erythropoietin could not be detected, indicating the liver as a place of formation of erythropoietin. This suggests a mechanism in the production and regulation of K.F. and erythropoietin as shown in Fig. 10.

Summary

Hypophysectomized bled rats show impaired reticulocytosis and their titre of K.F. is not raised as in normal bled rats, whereas their titre of erythropoietin is raised.

Adrenalectomized bled mice show reticulocytosis of the same degree as normal bled mice and their titre of a specific erythropoietic principle (K.F.) as well as of erythropoietin is raised.

Hypophysectomized rats respond with considerable reticulocytosis after injection of adrenocorticotrophic preparation.

Normal mice injected with adrenocorticotrophic preparation have an elevated titre of K.F. in their serum, whereas nephrectomized mice injected with adrenocorticotrophic preparation have no traceable amounts of K.F. in their serum.

Adrenalectomized unbled mice have a raised titre of K.F. in their serum.

Mice injected with large doses of cortisone show impaired reticulocytosis and their titre of K.F. is not elevated as in normal mice after bleeding, whereas their titre of erythropoietin is.

The findings here presented have led to the conclusion that the adrenocorticotrophic hormone, by an extra-

adrenal mechanism, stimulates the secretion (production) of the erythropoietic principle produced in the kidney.

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RESPONSE OF CUBAN CHILDREN TO ORAL VACCINATION WITH LIVING ATTENUATED POLIOVIRUS VACCINES

A CLINICAL AND SEROLOGICAL STUDY

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Paralytic poliomyelitis occurs in Cuba as a sporadic disease in early childhood, with periodic relatively small outbreaks. Most of the cases are in children under 5 years of age, and less than 15% are in those over 10 years. In the period 1946 to 1957, with the exception of three years, the annual number of reported cases varied from 10 to 100. In 1946, 1952, and 1955 there were reported respectively 343, 494, and 267 cases (Pan-American Sanitary Bureau, 1958a, 1958b). Paul, Melnick, and Riordan (1952) suggest that perhaps only 50 to 75% of the actual cases occurring in Cuba are recorded. These authors collected 82 sera in a 1950 survey, and demonstrated the presence of Lansing-type poliovirus antibodies in 64% of the children aged 1 to 4 years and in 75% of those aged 5 to 9 years.

Our data indicate that all three types of poliovirus are widespread in the Havana metropolitan districts, and

additional studies now in progress will greatly expand the surveyed areas and the age-group samples. While Salk-type vaccine was administered to several thousand individuals shortly after this product became available, it has had no national sponsorship, and its use has been largely restricted to the practice of a small number of paediatricians and in a few institutions.

The use of the Salk-type vaccine presents a number of problems for countries whose social and economic conditions are like those of Cuba. For this reason, and because of the long and successful use of smallpox and yellow-fever live virus vaccines in Latin America, the initiation and pursuit of the work with oral attenuated poliovirus vaccines by the Lederle group (Koprowski, Jervis, and Norton, 1952), and the later entrance of Sabin (1955) in this field have been followed with great interest.

After contact with Dr. H. R. Cox, of Lederle Laboratories, and consultation with Dr. F. L. Soper, then Director of the Pan-American Sanitary Bureau, a series of studies were undertaken in Cuba. It has been possible to explore several aspects of oral poliovirus vaccination in different groups of subjects under close medical supervision. Their ages ranged from 1 to 21 years, but most were between 5 and 12. Less than 10% of those vaccinated belong to "open" groups. These were dispensary patients on whom follow-up work was difficult or impossible in a few instances. Most of the children were members of what might be called institutional populations. These included several successive groups of underprivileged children who resided in recreation camps for 90-day periods, occupants of a foundling home and an orphanage, as well as children who lived in a Cuban "boys town"* and others who attended dormitory schools but often returned home for weekends. Observations are being continued on several of these, but serological data are now complete on the six groups which are the subject of this report.

The vaccines for these studies were provided by the Lederle Laboratories Division of the American Cyanamid Company, and the serological assays were done in its Viral and Rickettsial Research Laboratory by methods described elsewhere (Cox *et al.*, 1960) and at the Microbiological Associates Inc. laboratory in Washington, D.C.

Group 1

Since the swallowing of capsules is usually difficult without the aid of fluids, this test was designed to determine whether or not the highly acid carbonated beverages commonly enjoyed by children would inactivate the strains of vaccine virus if ingested with the virus-containing capsules.

For this trial 16 children (10 males and 6 females) aged 4 to 11 years were selected. They were daily dispensary patients at Mantilla, a suburb of Havana. Twelve of them were white. They were residents of multiple-family dwellings in an economically depressed area. Many were harbouring a variety of intestinal parasites and most of them were undernourished.

The capsules containing the vaccine strains of poliovirus were administered at intervals of 21 days in the following order and contained the indicated concentrations of virus per capsule: first feeding, type II, $10^{4.9}$ TCD₅₀; second feeding, type I, $10^{4.8}$ TCD₅₀; third feeding, type III, $10^{5.2}$ TCD₅₀. Each child was given

approximately 100 ml. of a popular beverage, having a pH of 3.2, with which to wash down the capsules. The children were not all started on the programme at the same time, but the first feeding was done on February 19, 1958, and the entire group had received all three strains of virus by April 18. A blood sample was collected from each child at the time of the initial feeding and again 26 to 28 days after administration of the third feeding. The sera were refrigerated until both the pre- and post-vaccination samples from all children had been obtained. The paired sera from each child were titrated simultaneously.

The serological titrations showed that at the time of the first feeding 8 of the 16 children lacked antibody for one or more types of poliovirus. The distribution of these sero-negatives was as follows:

Type I only ..	2	Total negatives:	
" III ..	3	Type I ..	4
Types I and III ..	1	" II ..	2
" II and III ..	1	" III ..	6
" I, II, and III ..	1		

The post-vaccination sera contained only two negatives, both for type III virus; thus the conversion rate was 83%. In addition fourfold or greater booster responses were observed in many of the children who possessed antibody prior to feeding.

The general level of response for each of the three types of poliovirus is indicated by the pre- and post-vaccination geometric mean titres and fold gains (Table I). The two type III negatives that failed to

TABLE I.—Group 1. Geometric Mean Antibody Titres

Poliovirus Type	Before	After	Fold Gain
I	33	111	3.4 ×
II	128	412	3.2 ×
III	15	38	2.5 ×

respond occurred in a 6-year-old who was previously negative only for this strain and a 7-year-old who was negative for both types I and III. These were the only type III misses in the 6- and 7-year-old children of the entire study, which included the total of 22 type III negatives (see Chart). The 7-year-old had excellent responses with both types I and II, these being from 1:4 to 1:128 and from 1:256 to 1:1,024 respectively. Since the other four type III negatives all responded satisfactorily it cannot be concluded that this virus strain is more readily inactivated than the other strains by an acid beverage such as that employed.

The clinical observations on this and the succeeding five groups are discussed collectively below.

Group 2

At the suggestion of Dr. H. R. Cox it was decided to reinvestigate the problem of feeding all three virus strains simultaneously. For this purpose 62 female children, aged 4 to 17 years (median 10 years) were chosen: 55 were white. They were residents of what may be described as a dormitory school in the environs of Havana. The girls lived in the institution, but were free to return to their homes for week-end holidays every three to four weeks. The school was operated by the Church, and many of the children held scholarships contributed by various charitable organizations. The students represented families of modest incomes, and they were healthy and well nourished.

*A "city" for orphan and destitute children similar to Father Flanagan's in "Boys-Town," Indiana, U.S.A.

All the children were fed on May 13, 1958, at which time a blood sample was collected from each. Post-vaccination sera were obtained 38 days later. The same three lots of vaccine employed in group 1 were used in this trial. Each child received one capsule of type I, one of type III, and two type II poliovirus simultaneously, 30 minutes after a meal. The swallowing of the capsules was facilitated by the ingestion of approximately 100 ml. of a suspension of non-fat dry milk solids ("star-lac").* The girls were under the daily observation of nuns, and were visited at frequent intervals by the staff physician.

Serum neutralization tests on the pre-vaccination sera revealed 36 sero-negatives among the 62 children. They were distributed in the following combinations:

Type I only	1	Total negatives:	
" III	12	Type I ..	11
Types I and II ..	2	" II ..	4
" I and III ..	7	" III ..	21
" II and III ..	1		
" I, II, and III ..	1		

The post-vaccination serum studies disclosed four residual negatives. An 11-year-old, negative only to type I prior to vaccination, and a 12-year-old who had been negative for both types I and II, had both failed to respond to type I strain. The other two misses were for type III virus, one in an 11-year-old, negative only for type III, and the other in a 14-year-old who had been without antibodies for type II and III before the simultaneous feeding of all three virus strains. The conversion rate for the pre-feeding negatives was 89%, and, in addition, 21 out of 50 children whose antibody titres had ranged from 1:4 to 1:512 in their pre-vaccination sera manifested fourfold or greater gains in titre. The composite antibody gains are reflected in the geometric mean titres before and after simultaneous virus feeding (Table II).

TABLE II.—Group 2. Geometric Mean Antibody Titres

Poliovirus Type	Before	After	Fold Gain
I	35	126	3.6 ×
II	162	462	2.8 ×
III	13	115	8.8 ×

It is of interest to note that the triple negative in this group, a 10-year-old girl, responded with titres of 128, 16, and 1.024 for types I, II, and III respectively.

Group 3

In order to gain some information regarding the flexibility of the feeding schedule, 91 children (50 males and 41 females) were fed the three strains of poliovirus with a 7-day interval between the ingestion of each type. Their ages ranged from 6 to 11 (median 8 years), 72 of the children being white. All were residents of the Matanzas City Recreation Camp. They were heavily parasitized and came from the poorest economic strata of the rural areas, where malnutrition is a way of life. The children stayed for 90 days in the recreational camp, and during this time were well fed and well cared for. The primary activity of the resident physician at the camp is to restore the health of the children, rid them of parasites, and return them to their homes in good physical condition. The camp is approximately 75 miles (120 km.) east of Havana. The first feeding was two capsules of type II virus containing $15^{5.3}\text{TCD}_{50}$ of virus on September 6, 1958. A week later the children were fed two capsules of type III virus containing $10^{5.6}\text{TCD}_{50}$,

and the final feeding was $10^{5.5}\text{TCD}_{50}$ of type I virus in a single capsule. At each feeding the children were given a glass of fat-free dry milk with a pH of 6.7. Serum samples were collected at the time of the first feeding and 34 days after the administration of the type I strain.

At the time of the primary feeding there were 23 sero-negatives, distributed among 16 children as follows:

Type I only	5	Total negatives:	
" II	1	Type I ..	10
" III	3	" II ..	3
Types I and III ..	5	" III ..	10
" II and III ..	2		

Post-vaccination serum-neutralization tests showed that the negative-to-positive conversion rate was 96%. A single type I negative remained. This was in a 9-year-old girl who had previously been without antibodies for both types I and III poliovirus; her type II titre remained unchanged at 1:512.

In addition to the 22 negatives which were converted, 21 out of 71 children whose pre-vaccination titres ranged from 1:4 to 1:512 showed booster responses for type I virus, 20 out of 55 for type II, and 59 out of 76 for type III. The magnitude of the collective response is suggested by the geometric mean antibody titres before and after feeding the three virus types at seven-day intervals (Table III).

TABLE III.—Group 3. Geometric Mean Antibody Titres

Poliovirus Type	Before	After	Fold Gain
I	72	159	2.2 ×
II	371	709	1.9 ×
III	56	382	6.8 ×

Group 4

In a foundling home near the centre of Havana, where the majority of children had received two or three doses of Salk vaccine, an opportunity was afforded to observe the response of children to oral vaccination after artificial immunization. It is not to be presumed that their pre-vaccination antibodies were entirely the result of the Salk vaccine. The group of 105 children included 20 who had had no Salk vaccine; 10 who had received two vaccine injections, the second being given in April, 1957; and 75 who had completed their third Salk injection in May, 1957, approximately 18 months prior to the initiation of the oral vaccination programme on November 27, 1958.

Approximately 80% of the children had been resident in the institution for several years. Their ages varied from 4 to 10 years, the median being 7 years. One child was an epileptic. Fifty-six were white; 95 were males. A physician was in residence at the home. Eighteen children who had received three Salk vaccine injections and who were randomly located in dormitory quarters, were left as unvaccinated contact controls at the time the other children were given the oral poliovirus vaccine.

Capsules containing $10^{5.0}\text{TCD}_{50}$ of type II virus were administered on November 27, 1958; and on December 17, $10^{5.5}\text{TCD}_{50}$ of type III virus was fed. The final capsule, representing $10^{5.5}\text{TCD}_{50}$ of type I poliovirus, was ingested on January 20, 1959. Approximately 100 ml. of the resuspended dry fat-free mild solids at pH 6.7 was given with each feeding. Blood samples were collected from the vaccinated and control children at the time of the first feeding and again 34 days after the last strain was fed.

At the time the feeding programme started there were 15 sero-negative children given oral vaccine. They were distributed as follows:

Type I only ..	1	Total negatives:	
" II ..	4	Type I ..	3
" III ..	4	" II ..	6
Types I and II ..	1	" III ..	6
" I and III ..	1		
" II and III ..	1		

In addition, there was a single negative (type III) among the control children who had received three Salk vaccine injections.

Examination of the post-vaccination serum specimens revealed five residual negatives in the orally vaccinated children, a conversion rate of 67%. The type III negative control child was still negative and still unchanged in titre for the other two strains. Four of the five post-vaccination negatives were for type II virus, and three of these were in children who had had no Salk injections. While only 10 of 15 negatives converted, there were many booster responses among those whose pre-feeding antibody levels were from 1:4 and 1:512. Only one of the control children who had been in contact with the orally vaccinated children, but had not received the live virus vaccine, manifested a fourfold increase in titre for type II virus. Distributed among the other 17 unvaccinated controls there were nine instances of a two-fold titre increase, 13 of a twofold titre decrease, and four in which there were fourfold titre decreases.

The composite titre changes for subgroups are illustrated by the geometric titres before and after the feeding programme was started (Table IV).

TABLE IV.—Group 4. Geometric Mean Antibody Titres

History of Salk Injections	No. of Children	Type I			Type II			Type III		
		Pre	Post	Fold Gain	Pre	Post	Fold Gain	Pre	Post	Fold Gain
None ..	20	54	194	3.6 ×	79	187	2.4 ×	24	132	5.5 ×
Two ..	10	157	294	1.9 ×	415	446	1.1 ×	79	208	2.1 ×
Three ..	57	229	386	1.5 ×	496	711	1.4 ×	109	288	2.6 ×
Controls	18	246	237		438	406		114	87	

Group 5

This trial, like that with group 3, was carried out in a recreation camp about 50 miles east of Havana. The group consisted of 111 children, of whom 77 were white; 59 were male. They ranged in age from 6 to 12 years, with a median of 8 years. The conditions of the camp and in the homes from which the children came were comparable to those described for group 3.

Beginning on September 13, the children were fed two capsules of type II virus containing $10^{5.0}$ TCD₅₀ of virus; seven days later two capsules, each representing $10^{5.2}$ TCD₅₀ of type III virus; and a week later a single capsule of type I virus containing $10^{5.5}$ TCD₅₀. A blood sample was collected from each child at the time of the first feeding and again four weeks after the feeding of the type I virus.

During the period of virus feeding 15 of the children developed clinical influenza. Six of the affected children were 6 years old and the others were scattered in age distribution.

Serum neutralization tests showed that at the time of the first virus feeding there were 38 sero-negatives among 33 of the children. These were distributed as follows:

Type I ..	8	Total negatives:	
" II ..	4	Type I ..	13
" III ..	16	" II ..	4
Types I and III ..	5	" III ..	21

Post-vaccination sera were found to include one type I and one type III negative; thus the conversion rate was 94.7%. Neither of the residual negatives was in a child who suffered from influenza during immunization.

In addition to positive results in those who were previously without antibody, there were fourfold or greater increases in titre among those whose pre-vaccination levels varied from 1:4 to 1:512. The booster response rates for such children were 41% for type I virus, 66% for type II, and 75% for type III.

The general response to vaccination is shown by the increases in geometric mean antibody titres (Table V).

TABLE V.—Group 5. Geometric Mean Antibody Titres

	Type I			Type II			Type III		
	Pre	Post	Fold Gain	Pre	Post	Fold Gain	Pre	Post	Fold Gain
All children ..	43	123	2.9 ×	130	417	3.2 ×	19	190	10 ×
Children having influenza ..	58	134	2.3 ×	140	445	3.2 ×	12	140	12 ×

Group 6

In November, 1958, 159 inmates of a girls' institution were vaccinated with the three strains of oral poliovirus vaccine. The same lots of vaccines as those used in group 5 were employed. The feeding order was types II, III, I, with a seven-day interval between feedings. The capsules were administered with approximately 100 ml. of resuspended dry milk solids at pH 6.7, 30 minutes after a meal. Two doses of Salk vaccine had been given to 121 of the children in November, 1957, one year prior to the initiation of the oral vaccination programme.

The ages of the girls ranged from 6 to 19 years. The median age of the 38 who had received no Salk vaccine was 9 years, while that of those who had been given two injections of Salk vaccine was 12. Pre-vaccination serum samples were collected from each child at the time of the first feeding, and a second sample was obtained approximately one month after the third feeding.

Serological study of the blood specimens revealed a total of 15 sero-negatives at the beginning of the feeding programme (Table VI). After oral vaccination the

TABLE VI

Poliovirus Type	No Salk	2 × Salk	Total Negatives
I	1	2	4
II	1	0	4
III	2	3	7
I and II	1	0	
II and III	2	0	
Totals ..	7	5	15

serum studies showed that one child remained without demonstrable antibody for type I virus and two without antibody for type II. The conversion rate was therefore 80%. The residual negatives were, for type II virus, 7- and 8-year-old children who had not received Salk vaccine, and the type I negative was a 14-year-old girl who had been Salk-vaccinated.

Table VII shows the booster response rates among children with antibody titres varying from 1:4 to 1:512 prior to vaccination with the oral poliovirus vaccine. The general responses of the two subgroups are reflected in the geometric mean titres of their poliovirus antibodies pre- and post-vaccination with oral poliomyelitis vaccine.

TABLE VII

	Type I	Type II	Type III
No Salk vaccine ...	36%	33%	53%
2 Salk injections ...	22%	28%	35%

TABLE VIII.—Group 6. Geometric Mean Antibody Titres

	Type I			Type II			Type III		
	Pre	Post	Fold Gain	Pre	Post	Fold Gain	Pre	Post	Fold Gain
No Salk vaccine	102	125	1.2 x	73	140	2.0 x	34	110	3.2 x
2 Salk injections	135	139	1.0 x	272	253	0.9 x	110	167	1.4 x

In the six groups there were a total of 139 sero-negatives. Of these, 17 were still negative after vaccination. This represents a conversion rate of 88%. The distribution of the 139 sero-negatives according to age of individual and virus type is shown in the Chart.

Combined data on distribution of poliomyelitis sero-negatives among 526 children, by age and virus type, before and after oral vaccination with poliovirus vaccine.

Discussion

In addition to these six groups vaccinated with the oral poliovirus vaccine described above, we have vaccinated eight other groups during the past year. The 14 groups comprised approximately 2,000 subjects. In none of these have nervous symptoms or other disturbances been observed which were suspected of association with the administration of the vaccines. Not only was the clinical course of the normal children entirely uneventful while undergoing immunization, but so also was that of many children who developed acute infectious diseases, such as mumps, rubella, or influenza, while participating in the oral vaccination trials. Similarly, there were no adverse reactions in one epileptic, one diabetic, and several children suffering from cardiac and kidney ailments. There were numerous minor illnesses, such as are invariably seen in undernourished, parasitized children when brought together in recreation camps and institutions, but these illnesses were no more numerous and no more severe than those observed prior to the initiation of the oral poliovirus vaccination.

We believe it is important to record that the infectious diseases mentioned above were not aggravated in any

way by their concurrence with an induced infection with attenuated strains of poliovirus. Conversely, it is equally important to find that these induced infections are not altered in any clinically discernible manner by the presence of certain common diseases of childhood which are likely to occur during an immunization programme.

Since the serological studies on a large proportion of these 2,000 subjects are not yet completed it remains to be determined whether or not concurrence of these fortuitous acute infections has adversely affected the establishment of the vaccine strain in the gastro-intestinal tract. A number of vaccinated children were undergoing mepacrine treatment for infestations with *Giardia lamblia*, and this may have adversely affected the outcome of the oral vaccination. Completion of the serological tests on the sera of these individuals should provide answers to these important questions.

It should be emphasized also that several of these small-scale trials were conducted under conditions that were not likely to be favourable to the vaccines. This was done because it was thought desirable, as a guide in planning future and larger-scale programmes, to know or to have some indication of what might be expected when administrators encounter the numerous conditions and complications that are certain to develop with expanding use of the vaccine under all conditions. Our experiences to date have been most reassuring, and therefore we plan to continue our studies and to seek evidence of circumstances and conditions, both medical and environmental, which may contraindicate the use of the vaccines.

Though small in scope and number of subjects, the first trial provided an indication that common carbonated beverages having a high degree of acidity were not markedly inhibitory when consumed immediately after the ingestion of the vaccine strains in capsule form. Group 2 was large enough to give clear evidence of the fact that the simultaneous administration of all three strains can be a practical, effective procedure. This fact, now confirmed by other larger trials, is of great practical importance. The result in group 3, contrary to expectation, implies that interference between these three strains of poliovirus is not a major factor when they are given at intervals of seven days in the order: types II, III, I, since 22 of the 23 negatives converted and many of the 91 children showed good booster responses to this system of administration.

While the fourth trial provided no substantial evidence of contact spread of the vaccine strain under our test conditions, the relative titre stability of the controls during the trial period of approximately 12 weeks underscores the significance of titre changes yielded by the assay method. The number and magnitude of the responses in the vaccinated children were not remarkable, in part perhaps because of the relatively high pre-vaccination titres.

Group 5 gave similar information to that of group 3. The concurrent influenza observed in a number of children in this group was not affected by immunization with poliovirus, nor was the induced infection with poliovirus altered by the presence of the influenza. Neither of the children who failed to respond to immunization in the group was among those experiencing influenza. The children with influenza responded in the same manner to immunization, qualitatively and quantitatively, as those without concurrent influenza.

The sixth trial resembles somewhat the fourth in the general population involved, the ages represented, and the history of Salk injections. The most interesting point of comparison is the fate of sero-negatives (there were 15 sero-negatives in each group, 10 of which occurred in non-Salk-injected individuals) in the light of the different schedules of administration employed. In the fourth group, in which the capsules were fed individually over long intervals (three to five weeks) the conversion rate was 70%. In group 6, seven-day intervals were used and the conversion rate was 80%, suggesting that interference among the three strains of virus fed is not a problem.

In the six trial groups described above there were 526 children who were fed all three types of virus and from whom pre- and post-vaccination samples of sera were assayed for antibodies. Most of the children were between 6 and 10 years of age, and they represented a variety of social and economic conditions which are typical of those to be encountered in Cuba and many other Latin American countries. The results obtained in terms of responses to the three strains of poliovirus have been somewhat variable, but so have the test conditions. Some of the groups have been too small to give clear-cut answers, but they have been useful in spite of this limitation. An inherent invariable in all such studies is the degree of pre-existing immunity for each type of virus as indicated by antibody levels. Our subjects were selected on the basis of availability rather than whether or not they represented optimum media for obtaining results that would be most favourable to the vaccines. For this reason we believe that we are observing the performance of the oral vaccines in a reasonable cross-section of conditions as they exist in the field.

In assessing the value of the vaccine there are several criteria that may be applied. First, of course, is that of safety, and this we have already discussed. Second is the reduction of the hazard of paralytic poliomyelitis by the elimination of susceptibles. The conversion rate was approximately 88% in the six trial groups. The few failures have been scattered over the whole age range investigated, and they have not been confined to a single type of virus, as can be seen in the Chart.

In individual trials the conversion rates ranged from 67 to 96%. When the three strains of virus were fed simultaneously the rate was 89%. Associated with the reduction of the number of susceptibles is the frequency of booster responses. Directing attention to those children whose pre-vaccination titres varied from 1:4 to 1:512, because the titrations were not done at dilutions high enough to detect fourfold increases at levels higher than 1:52, 36% of 329 children had booster responses for type I virus, 45% of 287 for type II, and 62% of 328 for type III. The mean titres show clearly that the least gains were made in groups which had the highest antibody levels at the time of feeding. Gains for type II virus in general were less marked than for the other two types of virus. Fortunately, this is the type which appears to be associated with epidemics least often, and further work in the selection of strains will doubtlessly provide a blend of more equally balanced strains for the oral vaccine. We believe that the collective data argue effectively for the efficiency of the present strains and the method of application.

Another criterion that may be applied in evaluating results of our trials is that of practicality and utility of the method of application. Here there would appear to

be a strong argument in its favour. With the increasing evidence of the high response rates to the simultaneous feeding of all three strains of virus, vaccination against poliomyelitis is transformed from a clinical procedure into a beautifully simple tool for mass application. It lends itself to emergency conditions as well as to the less urgent demands of routine prophylaxis in the clinic, the office, or institution. As regards speed and ease of application, the trivalent oral vaccination against poliomyelitis may be favourably compared with the mass dusting with insecticides in control of epidemic typhus. And from the standpoint of cost, which is always an important consideration for the public health administrator, trivalent oral vaccinations should certainly make smaller demands on our resources.

Summary

The serological and clinical responses of 526 children who were given the three sero-types of attenuated poliovirus as an oral vaccine are described, and reference is made to the clinical observations during eight additional trials comprising in all approximately 2,000 subjects ranging in age from 1 to 21 years. They represent a variety of field conditions in Cuba.

Clinical evidence of nervous or other disturbances attributable to the vaccine was not observed, and vaccination in the presence of acute infectious diseases such as mumps, rubella, and influenza, as well as in certain chronic diseases, was uneventful.

Conversion rates for sero-negatives to positives varied for the three types of poliovirus and in the six trial groups; the overall rate for the study was 88%. In addition, booster responses were shown by children whose pre-feeding titres were between 1:4 and 1:512. The response rates in such children were 36% for type I poliovirus, 45% for type II, and 62% for type III.

The high rates of response when all three strains of poliovirus were administered simultaneously is a finding of considerable practical importance, and its implications are discussed.

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There are 18,588 young men and women from the United Kingdom dependent territories studying in Britain and the Irish Republic compared with just over 4,000 ten years ago. More than one out of every three of the present students are nurses, of whom there are 6,365. Of the total number, 3,383 are studying at universities. After nursing, the most popular subject is law, which is the choice of 2,237 of the students. There are 1,814 G.C.E. students, and 1,297 are studying engineering and technology, 1,135 arts and economics, and 1,004 medicine and pharmacy.—(Colonial Office Information Department.)