A study is described in which live poliovirus vaccine candidate strains were administered. Viremia was detected in two vaccine groups. The relationship of viremia to preimmunization antibody status and primary sites of infection and the importance of levels and duration of circulating virus are discussed.

VIREMIA FOLLOWING THE ADMINISTRATION OF LIVE POLIOVIRUS VACCINES

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VIREMIA in paralytic poliomyelitis was first reported by Ward, Horstmann, and Melnick[1] and soon thereafter by Koprowski, et al.[2] Subsequently, a number of investigators[3-12] have been concerned with the role and significance of viremia in the pathogenesis and immunology of naturally occurring poliovirus infections. In 1953, Horstmann[13] demonstrated viremia in four children with no central nervous system involvement during an epidemic of poliomyelitis. This finding was soon confirmed in other reports.[14-18] Thus it was established that viremia is found in polio infections during the so-called minor illness prior to the appearance of antibodies in the blood.

The frequency of viremia associated with the use of attenuated vaccine strains in comparison to natural infections is uncertain. Sabin[19] reported "traces of virus" in two of 11 human volunteers who were fed type 2 poliovirus simultaneously with other types. Poliovirus was recovered from the blood of both individuals on one occasion. More recently, Bauer, et al.,[20] demonstrated viremia following the administration of trivalent live poliovirus vaccine containing Lederle strains. The purpose of this investigation is to confirm the development of viremia following ingestion of any of several live poliovirus vaccines and to obtain pertinent quantitative data.

Experimental Procedure

The vaccines for this study were kindly provided by Dr. A. B. Sabin of the University of Cincinnati and Dr. H. Cox of Lederle Laboratories. In all cases, monovalent vaccines were used. The virus concentrations of the four vaccine strains, with log titers reported by the laboratory of origin and results of retitration in the CDC laboratory, are shown in Table 1. Titrations in the CDC laboratory were performed with the metabolic inhibition test[21] in sextuplicate and at half-log intervals.

Five hundred and eleven inmates from the United States Penitentiary, Atlanta, Ga., with no history of Salk vaccination or clinical poliomyelitis, volunteered for the study. Ten milliliters of blood were drawn from each individual for the determination of preimmunization antibody levels against the three poliovirus types. On the basis of these determinations, 96 individuals were selected for the study. Their preimmunization serums were subsequently

Table 1—Comparative Titrations of Vaccines and Vaccine Doses Employed

Vaccine	Titers of Vaccine per ml (in Logs Base 10)			Vaccine Dose	
	CDC	Lederle	Sabin	Log TCD_{50} (CDC)	ml
L-1	7.0	5.6–5.4	–	7.3	2.5
S-1	8.2	–	7.5	8.2	1.0
				7.2	1.0
S-2	7.6	–	7.2	6.6	1.0
S-3	7.4	–	7.2	6.4	1.0

retested for antibody levels concurrently with day 31 postimmunization serum specimens.

Participants were assigned to the five vaccine groups on the basis of absence of antibody to one or more of the three poliovirus types (Table 2). Because of the small number of "triple negative" individuals available, feedings in this group were limited to either of two vaccines, Lederle, type 1 (L-1), and one of the three Sabin (S) strains. The L-1 vaccine was selected because of its established capacity for inducing viremia. Of the Sabin strains, S-1 was selected as appropriate for comparison with the same antigenic type. Because the development of viremia may be related to the quantities of virus ingested, five "triple negative" individuals were fed undiluted S-1 vaccine, and two were given a tenfold dilution of the same S-1 vaccine, corresponding to the dose recommended by Dr. Sabin.[22] The remaining three triple negative individuals received 7.3 logs of L-1 strain.

"Double negative" individuals were randomly distributed among three equal groups to each of whom one of the three diluted Sabin vaccines were fed. Of those volunteers characterized as "single antibody negative" individuals, type 1 "negatives" were similarly divided and fed L-1 or diluted S-1 vaccine strains.

Table 2—Distribution of Individuals According to Their Preimmunization Status (MI Test) and the Type of Vaccine Administered

Preimmunization Antibody Status		Vaccine Administered				
Type Antibody Absent	No. Individuals	L-1	S-1 ($10^{8.2}$)	S-1 ($10^{7.2}$)	S-2	S-3
1, 2, 3	10	3	5	2	–	–
1, 2	12	–	–	6	6	–
1, 3	6	–	–	3	–	3
2, 3	9	–	–	–	5	4
1	33	17	–	16	–	–
2	12	–	–	–	12	–
3	14	–	–	–	–	14
Totals	96	20	5	27	23	21

Table 3—Schedule for Vaccine Administration and Collection of Specimens

Day	0	3	4	5	6	7	31
Vaccine administration	x						
Bleeding		x	x	x	x	x	x*
Pharyngeal swab	x	x	x	x	x	x	
Rectal swab	x		x	x	x		

* For postimmunization antibody determination only. Triple and double negatives were bled twice a day during Days 3 to 6.

The remaining "single negative" subjects received diluted S-2 and S-3 vaccines corresponding to their antibody deficiencies.

Table 3 is a diagrammatic representation of the schedule followed in the feeding phase of the study. On day 0, all subjects were interviewed and pertinent data including history of tonsillectomy, gastrointestinal or central nervous system illness, and a general statement of health were recorded. On subsequent days, each participant was questioned regarding any changes in his state of health. Complaints were recorded and followed as indicated.

Rectal swabs were collected with sterile, cotton-tipped applicators and immersed in Hanks' buffered saline solution with antibiotics added. These were immediately refrigerated and subsequently frozen within a few hours. Similarly, two cotton-tipped applicators were used in sequence for collection of pharyngeal swabs. They were then placed in 4 ml of Hanks' solution which was prepared and handled as with the rectal swabs.

Blood specimens were collected in 20 ml vacuum tubes. After clot formation, bloods were refrigerated until the serums were removed later in the same day. Clots and serums were then frozen and stored until processing. Two blood specimens (morning and afternoon) were drawn on days 3, 4, 5, and 6 from individuals in the "triple and double negative" groups, considered as having the greatest opportunity for the development of viremia. This was done to increase the probability of virus isolation in the event that significant diurnal variations should occur.

Administration of the vaccines was performed by three physicians according to a schedule designed to minimize the opportunity for cross-infection. In each case, the appropriate dose of vaccine was withdrawn from the ampule by syringe and the fluid delivered into the mouth. Immediately thereafter a cupful of water was given to assure passage of the vaccine to the gastrointestinal tract. Because of conflicts in assigned working and sleeping areas within the prison, no further arrangements to segregate the vaccinees could be made.

Materials and Methods

Cytopathic effect in primary monkey kidney monolayer cultures was used for the detection of viruses in collected samples. The cell cultures were grown in Melnick's Lactalbumin Hydrolysate growth medium with 5 per cent calf serum pretested for polio antibodies. Maintenance fluid was substituted before inoculation of cultures except when clots and serums were used as inoculums. Antibiotics in appropriate concentrations were added to all fluids.

Specimens were received in the laboratory under refrigeration at 6° C to 8° C within two to three hours of collection. Those that were not immediately processed for examination were frozen and stored at approximately −20° C. Clotted blood samples were ringed and the serums separated after light centrifugation. Serums and clots were frozen and stored separately.

For individuals bled twice daily, 5.0

ml mixtures of equal volumes of morning and afternoon serums were introduced into monolayer cell cultures prepared in 250 ml "milk dilution" bottles. Bottles were gently rocked at ten minute intervals for one hour to assure contact of the cells with the inoculums. Serums were then removed and maintenance medium was substituted. Cultures were incubated at 37° C and observed daily for eight days. When cytopathic changes were not evident at this time, each culture was subjected to a blind passage after a single cycle of freezing and thawing. Aliquots of 0.5 ml were used to inoculate four tubes of monkey kidney monolayers.

Morning and afternoon blood clots were ground with 8 ml of Hanks' balanced salt solution in a single pool containing 1 gm of each clot. A 5.0 ml volume of this mixture was inoculated into a bottle culture following the same procedure as with the serums.

When only single blood samples were drawn daily, the serum inoculum consisted of 2.5 ml and the clot inoculum was prepared as above employing 2 gm of the clot. Cultures negative after eight days were subcultured as described above.

Rectal swabs were received with the cotton points immersed in 2 ml of Hanks' solution with antibiotics. These specimens were frozen and thawed, the immersed swabs thoroughly agitated, and the fluid expressed. The absence of excessive suspended debris permitted direct inoculation of 0.2 ml volumes of fluid into each of four primary monkey kidney culture tubes. The same procedure was followed for pharyngeal swabs. If none of the four tubes showed cytopathic changes in eight days, the tubes were frozen and thawed once and 0.2 ml of pooled fluids were blind passaged in duplicate tissue-culture tubes.

For virus quantitation, 1 ml volumes of each single serum positive in the original 2.5 ml inoculum were inoculated individually into bottle cultures. In the event that the originally tested 5.0 ml pool of A.M. and P.M. serums yielded a positive culture, each serum component was tested individually. In addition, 0.1 ml of undiluted serum and 1 ml volumes of further tenfold dilutions were inoculated to provide 10^{-1}, 10^{-2}, and 10^{-3} aliquots of serum. Four culture tubes were inoculated for each dilution.

All virus isolates from serums and swabs were typed, and in every case they were found to be identical with the virus types administered.

From the group of individuals originally available for this study, 96 were selected on the basis of serum antibody levels determined by the metabolic-inhibition test. Failure of serum dilutions in 0.25 ml volumes to inactivate 100 TCD_{50} units of type 1 (Mahoney), type 2 (Stattler), and type 3 (Saukett) poliovirus contained in equal volumes was used as the criterion for dividing 96 volunteers into single, double, and triple antibody negative groups. Serums were initially tested in dilutions of 1:4, 1:8, and 1:16. Thirty-one days after vaccine administration, postimmunization serums were collected and the preimmunization serums were retested concurrently with postimmunization serums against the poliovirus type administered. Metabolic-inhibition tests were repeated with the first serums in dilutions of 1:4 and 1:8 and the second serums in dilutions of 1:25, 50, 100, and 800. In addition, the paired serums were tested for neutralizing (cytopathogenicity inhibiting) antibodies against the same virus type as the vaccine administered. The first serums were tested in dilutions of 1:2, 4, and 8; the second serums in twofold dilutions from 1:100 to 1:1,600.

Results

The original design of this study intended grouping volunteers according to seronegative types and feeding one of

the corresponding monovalent polio vaccines. Redetermination of the preimmunization antibody levels by the neutralization test confirmed seronegativity to the vaccine type administered in only 46 of the 96 volunteers initially selected. This finding necessitated a further breakdown of the individual vaccine groups into preimmunization "antibody negative" and "low antibody positive" subgroups.

A summary of individual results is given in Table 4. Subjects are grouped according to preimmunization antibody levels and the vaccine types administered. Isolation and immunization results are presented. In each instance, positive isolates were identified with the polio type administered. The preimmunization and 31-day postimmunization antibody levels presented in the last two columns represent titers determined by neutralization of cytopathic effect.

Viremia was detectable only among individuals confirmed to be seronegative by neutralization test and was further limited to groups receiving L-1 and S-2 vaccines. The ratios of the numbers of seronegative individuals with viremia were 5:14 in the L-1 group and 6:13 in the S-2 group. Five individuals originally considered to be triple negative received undiluted S-1 vaccine. Subsequently, they were found to have preimmunization neutralizing antibody titers somewhat greater than 1:8 for type 1 and therefore cannot be considered as valid candidates for viremia.

Detailed information from the 11 subjects with viremia is presented in Table 5. The three triple or double negative individuals in this group were bled twice a day during days 3 to 6, the remaining eight single negative individuals had one bleeding per day. The levels reported in Table 5 represent the maximum level of viremia attained in each case. Virus concentrations did not exceed one TCD_{50} per ml of serum in most volunteers, however, four subjects had maximum levels of 10 to 100 TCD_{50}. Numbers 38 and 281, the only subjects with viremia throughout the testing period, are of special interest. Number 38 showed less than one TCD_{50} of virus per ml of serum until the morning of day 6 at which time the viremia level rose to 10 TCD_{50} and remained there through day 7. Volunteer number 281 maintained viremia levels of 10 TCD_{50} per ml of serum in the four specimens drawn on days 3 and 4 after which the concentration dropped to one TCD_{50} on day 5 and to less than one TCD_{50} on day 7. These data reflect the differences seen in the distribution of viremia days as plotted in Figure 1. The peak time for viremia in six individuals receiving S-2 vaccine was three to five days after feeding. In the L-1 group, positive isolations appeared to be more evenly distributed throughout the testing period with a peak on days 5 and 6. As had been expected, the subjects with viremia also had high recovery rates from rectal and pharyngeal swabs.

In Table 4, the infection rates of the "low antibody positive" group and the confirmed "antibody negative" group are compared. It was accepted that infection had been established when one or more isolations were made from rectal or pharyngeal swabs. In the absence of preimmunization antibody, infection was achieved in every case except in the group receiving $10^{7.2}$ TCD_{50} of S-1 vaccine, in which only seven of ten individuals were infected. The infection rates of all vaccine groups appeared to be significantly depressed when low levels of antibody were present at the time of feeding. Although vaccine strains may differ in infectivity, we have taken the liberty of totaling the infection ratios within the "antibody negative" and the "low antibody positive" groups. This seems justifiable inasmuch as individual ratios within each group fall in the same range. Thus 43 of 46 "antibody negative" subjects be-

Table 4—Virus Isolations and Antibody Titers from the 96 Individuals Participating in this Study

Study No.	Vaccine	Undetected abs by Polio Type in Preimmunization MI Test	Days on Which Virus Isolated			Neutral abs to Vaccine Administered	
			Rectum	Pharynx	Serums	Pre	Post
38	L-1	1,2,3	4–6	4–7	3–7	<2	400
416	L-1	1,2,3	4–6	–	–	>8	>1,600
457	L-1	1,2,3	–	–	–	>8	800
358	L-1	1	4–6	3–7	4	<2	400
279	L-1	1	5	3–7	5,6	<2	100
381	L-1	1	4–6	7	5	<2	100
350	L-1	1	4–6	–	6,7	<2	400
40	L-1	1	4–6	4–7	–	<2	100
131	L-1	1	4,5	3–7	–	<2	800
427	L-1	1	4–6	3–7	–	<2	nd
387	L-1	1	4–6	3–7	–	4	1,600
439	L-1	1	4–6	–	–	<2	< 100
175	L-1	1	4–6	–	–	<2	< 100
212	L-1	1	4–6	–	–	<2	< 100
239	L-1	1	5,6	–	–	<2	< 100
314	L-1	1	5,6	–	–	<2	< 100
395	L-1	1	4–6	–	–	4	< 100
452	L-1	1	4–6	–	–	4	< 100
277	L-1	1	–	3–7	–	<2	> 400
462	L-1	1	–	–	–	>8	100
22	S-1	1,2,3	4,5	–	–	>8	nd
456	S-1	1,2,3	–	3,5–7	–	>8	>1,600
62	S-1	1,2,3	–	5	–	>8	400
213	S-1	1,2,3	–	–	–	>8	> 100
91	S-1	1,2,3	–	–	–	>8	400
216	S-1/10	1,2,3	–	–	–	>8	800
66	S-1/10	1,2,3	–	–	–	>8	>1,600
426	S-1/10	1,2	4–6	3–7	–	<2	100
189	S-1/10	1,2	4–6	–	–	<2	< 100
460	S-1/10	1,2	–	3–7	–	<2	< 100
257	S-1/10	1,2	–	–	–	<2	< 100
80	S-1/10	1,2	–	–	–	>8	400
421	S-1/10	1,2	–	–	–	>8	800
489	S-1/10	1,3	5,6	4	–	<2	100
229	S-1/10	1,3	4–6	3–7	–	4	nd
92	S-1/10	1,3	4–6	3–7	–	>8	>1,600
476	S-1/10	1	4,6	3–7	–	<2	400
215	S-1/10	1	4–6	3–7	–	2	100
278	S-1/10	1	6	3–7	–	2	> 400
282	S-1/10	1	4,6	3–7	–	2	400
482	S-1/10	1	5,6	3–7	–	4	100
128	S-1/10	1	4–6	–	–	<2	< 100
315	S-1/10	1	4–6	–	–	<2	< 100
360	S-1/10	1	–	3–7	–	8	> 800
433	S-1/10	1	–	–	–	<2	< 100

(Continued on following page.)

Table 4—(Cont.)

Study No.	Vaccine	Undetected abs by Polio Type in Preimmunization MI Test	Days on Which Virus Isolated			Neutral abs to Vaccine Administered	
			Rectum	Pharynx	Serums	Pre	Post
240	S-1/10	1	–	–	–	<2	< 100
20	S-1/10	1	–	–	–	2	< 100
41	S-1/10	1	–	–	–	2	nd
177	S-1/10	1	–	–	–	4	100
372	S-1/10	1	–	–	–	4	800
313	S-1/10	1	–	–	–	8	< 100
164	S-1/10	1	–	–	–	>8	< 100
281	S-2	1,2	4,6	3–7	3–5,7	<2	< 100
425	S-2	1,2	4–6	3–7	3,4	<2	< 100
454	S-2	1,2	4–6	–	–	<2	< 100
84	S-2	1,2	–	5	–	<2	< 100
383	S-2	1,2	–	–	–	>8	100
461	S-2	1,2	–	–	–	>8	>1,600
111	S-2	2,3	4–6	3–5	–	>8	1,600
13	S-2	2,3	4	–	–	>2	nd
415	S-2	2,3	5,6	–	–	>8	< 100
105	S-2	2,3	–	–	–	>8	< 100
259	S-2	2,3	–	–	–	>8	1,600
280	S-2	2	4–6	3–7	5	<2	< 100
235	S-2	2	5,6	3–7	3,4	<2	< 100
184	S-2	2	4,5	3–7	3–5	<2	400
327	S-2	2	5	4,5,7	–	<2	100
185	S-2	2	5	3–7	–	<2	> 800
341	S-2	2	5	6,7	–	4	>1,600
311	S-2	2	6	3–7	–	8	>1,600
158	S-2	2	4–6	–	–	<2	< 100
378	S-2	2	4–6	–	–	<2	< 100
385	S-2	2	5	–	–	<2	< 100
122	S-2	2	–	6,7	5,6	<2	100
509	S-2	2	–	–	–	>8	>1,600
504	S-3	1,3	–	4	–	<2	< 100
160	S-3	1,3	–	–	–	>2	< 100
455	S-3	1,3	–	–	–	>8	< 100
125	S-3	2,3	4–6	–	–	<2	< 100
100	S-3	2,3	–	7	–	4	400
23	S-3	2,3	–	5	–	>8	< 100
302	S-3	2,3	–	–	–	>8	100
230	S-3	3	4–6	3–7	–	<2	< 100
391	S-3	3	4–6	3–7	–	<2	< 100
178	S-3	3	4,5	3	–	<2	< 100
463	S-3	3	4–6	6,7	–	>8	400
162	S-3	3	5,6	4,5,7	–	>8	> 800
64	S-3	3	4,5	–	–	<2	< 100
348	S-3	3	4–6	–	–	<2	< 100
432	S-3	3	4	–	–	<2	< 100
276	S-3	3	4–6	–	–	<2	100
322	S-3	3	4	–	–	>8	> 100
376	S-3	3	–	–	–	>2	100
33	S-3	3	–	–	–	4	nd
414	S-3	3	–	–	–	>8	< 100
90	S-3	3	–	–	–	>8	100

came infected, while only 24 of 50 became infected in the presence of low-level homotypic antibodies. This is a highly significant difference. Thirty-five per cent of the individuals in the L-1 group and 46 per cent in the S-2 group developed viremia when no homotypic antibody was found. However, in the presence of even low levels of antibody, viremia was not detected. Virus was never isolated from clots even when the viremia level in the serum portions of the blood was high.

Discussion

The ultimate significance of viremia following the use of attenuated poliovirus vaccines cannot be determined within the scope of this study. The fact that viremia is found associated with attenuated poliovirus immunization introduces questions which affect factors of safety and efficacy in the use of live virus vaccines. The question to what degree the development of central nervous system infection depends on the quantity and duration of circulating virus and how much on its neurotropic and invasive properties remains open. However, one may reason that some form of viremia may be necessary for antibody stimulation.

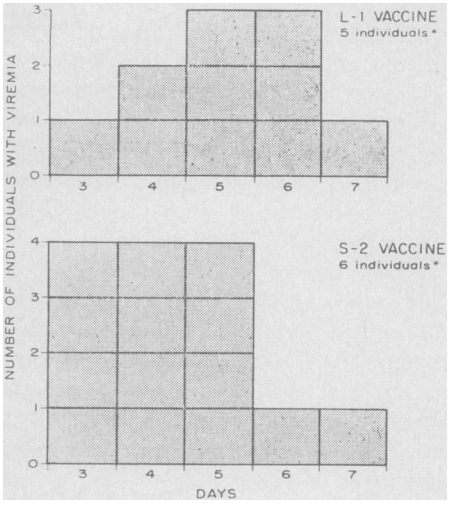
Due to extensive polio immunization, suitable subjects for studies designed to answer questions provoked by the demonstration of viremia following administration of live polio vaccine are increasingly hard to find; and considerable laboratory effort in preliminary screening of candidates is required. The number of confirmed homotypic "negatives" in our study is small, and the limited available volumes of pre-immunization serums permitted confirmation of antibody grouping by neutralization of cytopathic effect for only the single polio types administered. The assignment of triple, double, and single "negative" categories was based on metabolic-inhibition tests. Thus it is recognized that any error in antibody determination would be in the direction of failure to detect the presence of low-level heterotypic antibodies. Although this may prejudice the accuracy of the established categories, it also emphasizes the occurrence of viremia in spite of the presence of heterotypic antibodies and the inference of past heterotypic infection. In Table 6, the relationship of absence of homotypic antibody to

Table 5—Composite Results in Subjects with Viremia

Study No.	Vaccine Administered	Days Viremia Demonstrated	Max. Level of Viremia TCD_{50} ml Serum	Days Rectal Positive	Days Pharynx Positive	31 Day* Antibody Level
38	L-1	3,4,5,6,7	10	4,5,6	4,5,6,7	400
279	L-1	5,6	1	5	3,4,5,6,7	100
350	L-1	6,7	>100 <1,000	4,5,6	–	400
358	L-1	4	<1	4,5,6	3,4,5,6,7	400
381	L-1	5	<1	4,5,6	7	100
122	S-2	5,6	1	–	6,7	100
184	S-2	3,4,5	1	4,5	3,4,5,6,7	400
235	S-2	3,4	<1	5,6	3,4,5,6,7	100
280	S-2	5	<1	4,5,6	3,4,5,6,7	<100
281	S-2	3,4,5,7	10	4,5,6	3,4,5,6,7	<100
425	S-2	3,4	100	4,5,6	3,4,5,6,7	<100

* Reciprocal of antibody to polio type fed as determined by neutralization test.

Figure 1—Distribution of Viremia Days



* See Table 5 for days viremia demonstrated.

high infection rates and subsequent viremia with two vaccine strains is illustrated.

Those subjects not developing viremia also stimulate some interesting speculations. Was the failure to detect viremia in these individuals due to failure to sample at optimum intervals, insensitivity of current technics to detect minimal virus concentrations or, in fact, the absence of virus in the blood stream? Once a primary infection is established, the failure of virus to enter the blood stream must be attributed to differences in some specific virus properties, to individual factors of host resistance, or to both. Although viremia in naturally occurring nonparalytic infections has been demonstrated, to our knowledge there is no available information on viremia rates in such cases. Such data would furnish a valuable baseline for comparison of the observed viremia rates with the oral vaccine strains and would allow for more accurate interpretation of conditions producing viremia in some individuals and not in others when equally challenged. One may reasonably expect that refinements in technic and a critical selection of the population would reveal even more subjects with viremia with the use of L-1 and S-2 vaccines and perhaps also with those attenuated vaccine strains which in our study remained negative.

All of the attenuated vaccine strains considered here appear to be equally efficient in producing alimentary infection. It is known that type 2 poliovirus is dominant over the other two strains of the Sabin vaccines in producing alimentary infections when all three types are administered simultaneously, whereas among the Lederle strains, type 3 dominates types 1 and 2.[23] The S-2 strain appears to be both dominant and invasive as demonstrated by its ability to produce viremia. However, notwithstanding the dominance of type L-3, studies by Bauer, et al.,[20] have shown that seven of eight individuals developed type 1 viremia and only one individual had type 3 viremia when administered trivalent vaccine. This lat-

Table 6—Relationship of Infections with Vaccine Strains to the Preimmunization Neutralizing Antibody Level

Vaccine Administered	Total No. of Individuals	Proportion of Individuals Developing Infection* in ab Groups†	
		<2	≥2
L-1	20	14/14‡	4/6
S-1($10^{8.2}$)	5	–	3/5
S-1($10^{7.2}$)	27	7/10	7/17
S-2	23	13/13§	5/10
S-3	21	9/9	5/12
Totals	96	43/46	24/50

* Isolation of poliovirus from pharyngeal or rectal swab.
† Numerator: No. of individuals developed infection. Denominator: No. of individuals having antibody titers indicated.
‡ 5/14 in this group developed viremia.
§ 6/13 in this group developed viremia.

ter subject had preimmunization titers of 16 and 64 for types 1 and 2, respectively. Four of five "triple negative" individuals in that study developed type 1 viremia. Virus was isolated from the pharynx in 105 occasions, 49 isolations were type 3, and 41 were type 1. Thus, although L-3 is the dominant strain of the Lederle vaccine group, type 1 seems to be more invasive.

Some variations in the time when viremia developed after feeding was observed. Here again information from humans with "wild virus" infections would be a helpful baseline for comparison with the attenuated strains. In our experience, viremia with S-2 vaccine occurred earlier in relation to feeding than with L-1 strain (Figure 1). In the Minnesota studies[20] viremia with Lederle type 1 was found four times on days 3 and 5 and twice on day 7 in seven individuals. These figures do not correspond exactly to our experience with the same vaccine strain. However, four of the seven subjects in Bauer's study were "triple negative," while in our L-1 group, four of five individuals with viremia were known to have heterotypic polio antibodies. The numbers in these two studies are too small to draw definitive comparisons but it is suggestive that viremia may appear earlier in "triple negative" than in double and single "negative" subjects. Aside from individual host factors, strain characteristics such as infectivity and invasiveness undoubtedly influence the rapidity with which viremia is manifest.

The role of the concentration of virus in the blood serum and the length of time that it is detectable must be defined before any meaning can be attributed to viremia associated with attenuated poliovirus vaccines. One may speculate that smaller amounts of virus circulating over a shorter period of time do not pose as great a threat to the host. On the other hand, high levels of viremia and long periods during which virus is circulating in the blood provide good opportunity for invasion of the central nervous system. In 11 subjects with viremia, virus levels ranging from less than one TCD_{50} to greater than 100 TCD_{50} per ml with a duration range of one to five days were found. Viremia lasting for periods of four and five days, as in volunteers 38 and 281, has not been previously reported. Neither of these individuals was in a poor state of health, nor were any signs of illness noted during the study. Either one may have had viremia for more than the five-day testing period. Number 38 had a level of 10 TCD_{50} in the last specimen on day 7, and number 281 began the testing period on day 3 with a level of 10 TCD_{50} per ml of serum. The virus levels in the blood might be expected to build up gradually to a maximum level and then taper off before falling below detectable levels. Thus with an extended testing period, viremia might have been demonstrated before or beyond the sampling period used in this study. Factors influencing the level of virus in the serum are elusive. Four subjects had viremia levels of 10 TCD_{50} or greater per ml of serum and four had less than one TCD_{50}. A multiplicity of secondary sites of multiplication may influence viremia level,[6,12] or perhaps the body mechanisms for clearing virus from the blood stream vary in efficiency. However, evidence for either of these hypotheses is not available in this study. The viremia level did not appear to be related to the duration of viremia. Quantitation of virus in the pharynx or gastrointestinal tract might have furnished some correlation of viremia with virus concentration in the primary sites.

The demonstration of viremia appears to be largely dependent upon the size of serum inoculation used for virus isolation. Bauer, et al.,[20] obtained greater than a twofold increase in virus isolations with 2 ml serum inoculums

as opposed to 0.2 ml quantities. In our study, four individuals, two from each of the L-1 and the S-2 groups, yielded positive isolations with 2.5 ml but not with 1.0 ml serum inoculums. In the event that 2.0 ml specimens had been used as proposed by the WHO Expert Committee on Poliomyelitis,[24] it is conceivable that at least some of these four individuals may have been regarded as negative. We can only conclude that by increasing the size of the serum inoculums within the limits of practicability, the incidence of detectable viremia would be increased.

Summary

Ninety-six adults were found to lack antibodies against one or more of the three poliovirus types by metabolic-inhibition test. Single, double, and triple "negative" subjects were assigned to vaccine groups for the administration of monovalent attenuated poliovirus strains. The vaccines and doses employed were as follows: Lederle type 1, $10^{7.3}$ TCD_{50}; Sabin type 1, $10^{8.2}$ or $10^{7.2}$ TCD_{50}; Sabin type 2, $10^{6.6}$ TCD_{50}; and Sabin type 3, $10^{6.4}$ TCD_{50}.

Simultaneously with the determination of the 31-day postimmunization antibody levels, titrations of the preimmunization serums were repeated by the neutralization test. The lack of homotypic antibodies against the poliovirus type administered was confirmed in 46 cases, whereas low antibody levels were found in the remainder.

In the absence of demonstrable homotypic antibody, viremia of varying duration and levels of virus concentration was detected in two vaccine groups.

Viremia rates were 5 of 14 for Lederle type 1, and 6 of 13 for Sabin type 2 vaccines. In each case, the virus type isolated from the blood stream coincided with the poliovirus type administered. The relationship of viremia to preimmunization antibody status and to primary sites of infection and the importance of levels and duration of circulating virus are discussed.

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Addendum

The study reported above was conducted concurrently with that of Melnick, et al., which was reported in the Abstracts of the 61st Annual Meeting of the Society of American Bacteriologists (Bacteriological Proceedings, 1961, p. 145). In spite of the difference in experimental design, the findings with type 2 Sabin vaccine are in essential agreement in the two studies.

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Annotations on Recent Home Care Literature

A bibliography on "Organized Home Care Programs for the Homebound Disabled" is available from the National Society for Crippled Children and Adults (2023 W. Ogden Ave., Chicago 12, Ill.; single copies free). This is a selection of recent references indexed in "Rehabilitation Literature," almost all of them published since 1959. The bibliography is devoted exclusively to references pertaining to medical care programs for the homebound and to auxiliary services incorporated in them, and thus does not include general references on employment, recreation, or education for the homebound. References are classified under Surveying the Problem (leading off with APHA's "Chronic Disease and Rehabilitation: a Program Guide for State and Local Health Agencies"); the Program's Organization and Operation; Specific Programs and the Services Provided; and Related Home Service.