A Continuing Study of the Acquisition of Natural Immunity to Poliomyelitis in Representative Louisiana Households

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A striking and significant finding of this intensive study of familial infection with poliomyelitis virus is the very high incidence among infants and young children—all infections being subclinical.

Adequate explanation of the occurrence of the disease poliomyelitis requires a full understanding of the factors influencing the dissemination of poliomyelitis viruses as well as of the conditions which determine that infection will result in disease. Until the recent advent of tissue culture technics for detecting poliomyelitis viruses and demonstrating the presence of their corresponding specific antibodies, recognition of past or present infection was a cumbersome procedure. Retrospective information has been forthcoming recently with increasing frequency as serologic surveys have been conducted in various, often widely contrasting, populations [1–5] and, in a few instances, study of sera collected serially from population samples has yielded evidence as to the frequency of immunizing infections within defined periods of time.[6, 7] Such studies have shown, in general, that such factors as poor environmental sanitation, large families and low economic status favor the early occurrence of immunizing infections.[4, 8, 9]

Efforts to detect current infection by demonstrating the excretion of poliomyelitis virus have been largely directed toward persons having a defined relation to cases of clinically recognizable disease, and they have shown that the probability of harboring virus increases with proximity to known, overt cases and is maximal in child household associates of such cases.[10–18] While a few purely random stool surveys have been reported, there is only one reported attempt to observe a population sample at frequent intervals over an extended period of time; this involved a small group of 16 newborn Negro infants in South Africa who were followed for more than a year.[19]

A similarly prospective study involving 156 representative households was

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initiated in 1953 in southern Louisiana with the primary objective of determining when and under what circumstances the average individual acquires his immunizing infections. This study also has centered about newborn infants but has included in addition the household associates of these index infants. In an initial report as of the end of 1954, 65 infections in these infants were described.[20] The present paper will report, still in preliminary fashion, observations related to a total of 109 episodes of household infection involving as many index infants.

Over-All Plan and Methods

As originally planned the study was to continue for at least five years. Clinical and epidemiologic information obtained during routine and special visits to the households was to be correlated with laboratory-derived information about the occurrence of infection as revealed by the examination of serum and stool specimens collected regularly from the newborn index children and on special occasions from other members of the households.

The composition of the original study group is indicated in Table 1. It was nearly evenly divided between three study areas, i.e., urban New Orleans and Baton Rouge (with low and high past incidences of poliomyelitis, respectively) and the semirural Evangeline area (with low past incidence of disease). Negroes, however, made up nearly half the group and were especially overrepresented in the Baton Rouge and Evangeline areas. The whites were divided on a family income basis using $3,500 per year as an arbitrary dividing

Table 1—Distribution of Households in the Study Group (As of Termination of Recruitment) by Area, Race, Economic Status, and Family Size

Area	Number of Older Siblings	Number of Households of Indicated Race or Economic Status			
		White Upper	White Lower	All Negro	Total
New Orleans *	0	3	5	6	14
	1 or 2	13	9	7	29
	3 plus	3	5	6	14
	All	19	19	19	57
Baton Rouge †	0	0	4	7	11
	1 or 2	8	5	9	22
	3 plus	4	3	9	16
	All	12	12	25	49
Evangeline Area ‡	0	1	1	8	10
	1 or 2	10	6	11	27
	3 plus	0	2	11	13
	All	11	9	30	50
All	0	4	10	21	35
	1 or 2	31	20	27	78
	3 plus	7	10	26	43
	All	42	40	74	156

* New Orleans includes the metropolitan area with a population of about 650,000.

† Baton Rouge includes all of East Baton Rouge Parish with a population of about 250,000.

‡ The Evangeline area comprises St. Mary's, Iberia, St. Martin's, and Lafayette Parishes with an aggregate population in 1950 of 160,003, including 77,834 urban and 82,169 classed as rural.

line. The Negro family incomes were comparable to those of the white-lower group but the degree of household crowding was greater. Small (one child) and large (four or more children) families were also underrepresented in all three areas. A bias of possible importance derives from the fact that, during recruitment, preference was given to families that seemed both cooperative and likely to continue residing in the study areas.

As each household was admitted, a family record was prepared containing information of future epidemiologic interest and base line sera were taken from all household members. Each month thereafter the household was revisited to obtain interval information and to collect specimens from the index child. Blood specimens during the first year were obtained by heel-puncture; thereafter, venapuncture from a cubital vein was usually possible. Early in 1954 and again in 1955 "annual" sera were collected from all family members to seek evidence of household infection which had not involved the index child. Specimens from the index children were examined on a current basis and evidence of infection, i.e., new appearance of antibody or isolation of virus, resulted in an immediate return to the household for further information and specimens from household and other indicated contacts. In the Baton Rouge and Evangeline areas this field work has been carried out largely by nurses attached to the local health departments, to whom we are deeply indebted.

All laboratory examinations have been by currently accepted tissue culture technics. Until the end of 1954, HeLa cell monolayer cultures were employed exclusively. Since then, monolayer films of monkey-kidney cells have been used for both virus isolation attempts and tests for neutralizing antibodies. Stools are routinely tested as 10–20 per cent extracts in saline, prepared by simple centrifugation (4,500 rpm for one hour) and cytopathic agents isolated are identified by neutralization with potent type-specific antisera furnished by Dr. H. A. Wenner. All stools previously tested and found "negative" in HeLa cells have been retested using the more sensitive kidney-cell cultures. Sera are screened in final dilution of 1:2 (venapuncture specimens) or 1:10 (heel-puncture specimens) against approximately 100 tissue culture doses of virus, using established prototype strains as described elsewhere.[18] When indicated, antibody titrations have been carried out using two culture tubes per serial fourfold dilution of serum.

The initial group of 156 households contained 161 index children including five sets of twins and 686 other, older members. As of August 31, 1955, there remained 141 households containing 624 older associates and 180 children being followed at monthly intervals of whom 144 were original index children and 36 were recently born siblings.

Infections in Index Children

Through September, 1955, a total of 109 infections with poliomyelitis viruses had been experienced by the index children as indicated by seroimmune response. In three instances of children infected during the first six months of life it has not been possible to determine more precisely the time at which infection took place. The remaining 106 infections could be defined in time on the basis of virus isolation or the new appearance of specific antibody. The distribution of these infections by month of age, shown in Table 2, reveals several peaks, i.e., at 12, 16, 17, and 22 months, which are believed merely to reflect the fact that many of the infants were of about the same age during periods of relative abundance of virus in their respective communities. Special interest pertains to the 15 infec-

Table 2—Distribution of Infections with Poliomyelitis Viruses in Index Children by Month of Age

Age in Months	Number of Infections	Age in Months	Number of Infections	Age in Months	Number of Infections
Unknown *	3	11	6	23	5
< 1 †	1	12	10	24	3
1	0	13	4	25	3
2	2	14	5	26	2
3	2	15	4	27	1
4	3	16	9	28	2
5	1	17	9	29	1
6	3	18	2	30	0
7	1	19	1	31	0
8	1	20	1	32	0
9	4	21	3	33	0
10	6	22	10	34	1

* These occurred during the first six months of life but the precise month is not known.
† Virus was found in stool collected on the third day of life.

tions that occurred during the first seven months of life. Excluding the three infections occurring at an unknown but early age, only four infections (including one in a three-day-old infant) took place in the face of the demonstrated presence of persisting maternal antibody.

The data as to seasonal occurrence are shown in Table 3. Since the index children were being born into the study from April through October of 1953, the year 1953 contributed very little exposure experience. From the 1954 and 1955 data, however, it is evident that, while some appreciable risk of infection persists throughout the year, there is a significantly greater risk during the summer and early fall. Table 3 also indicates the distribution of infections by virus type. The chief points of interest are the predominance of type 3 virus in the 1953–1954 period and of type 1 virus in 1955. These findings were closely paralleled in the clinical cases from the study areas which yielded types 1, 2, and 3 virus, respectively, in 6, 3, and 8 cases in 1954 and in 11, 5, and 3 cases in 1955. The proportional

Table 3—Distribution of Infections with Poliomyelitis Viruses in Index Children by Year and Calendar Month and by Virus Type

	Number of Infections in Month Indicated												Number of Infections with Virus Type		
Year	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	All	1	2	3
1953				0	0	0	0	0	0	4	1	1	9*	3	1	5
1954	0	0	1	0	3	7	20	8	7	10	3	2	61	9	23	29
1955	5	1	2	4	4	5	11	7					39	27	8	4
All	5	1	3	4	7	12	31	15	7	14	4	3	109	39	32	38

* Includes 3 infections, mentioned in Table 2, which could not be assigned to a specific month.

Table 4—Distribution of Infections with Poliomyelitis Viruses in Index Children by Area, Year, and Virus Type

Year	Virus Type	Number of Infections in Area Indicated			
		Evangeline	Baton Rouge	New Orleans	All
1953–1954	1	3	1	8	12
	2	12	7	5	24
	3	12	11	11	34
1955	1	6	7	14	27
	2	0	7	1	8
	3	4	0	0	4
1953–1955	All	37	33	39	109

distributions of virus types in overt infections, thus, were not too different from those in our study group in the corresponding periods.

Area, year, and virus type are considered in Table 4. While over-all infections were nearly equally frequent in the three areas, there were possibly important differences in respect to virus type. Both in 1953–1954 and in 1955 the greatest number of type 1 infections occurred in New Orleans, while in 1955 types 2 and 3 infections were confined almost completely to Baton Rouge and the Evangeline areas, respectively. The relation of infections to race or economic status and to family size is shown in Table 5 in which are presented both the numbers of infections and crude rates which do not take into account variations in the periods of observation. The over-all risk of infection was greatest for Negro children. Perhaps because there were disproportionately few

Table 5—Distribution of Infections with Poliomyelitis Viruses in Index Children by Race or Economic Status and by Number of Older Siblings *

Race or Economic Status	Infections in Children with Indicated Number of Older Siblings						Infections in All Children	
	None		1 or 2		3 or more			
	Number	Rate Per cent †	Number	Rate Per cent	Number	Rate Per cent	Number	Rate Per cent
Negro	9	16	29	46	21	30	59	31
White Lower	5	19	12	21	9	25	26	22
White Upper	1	9	20	25	3	14	24	21
All	15	16	61	30	33	26	109	26

* Older siblings mean, in this case, other children under 15 years of age.

† Since nearly all of the infections recorded were in original index children, the rates have been computed using only the numbers of original index children as the bases for the denominators. Actually, since each child can experience three infections with different virus types, the denominators were obtained by multiplying the numbers of children by three.

first-born index children in the white-upper group, the over-all rates for the two white groups are not different. Finally, while the number of older siblings does not seem very important, it is clear that having one or more older (and presumably nonimmune) siblings materially increases the risk of infection.

Excretion of virus by infected index children deserves comment which, however, will be restricted to the 61 children infected during 1954, all of whose stool specimens have been completely examined. Poliomyelitis virus was isolated not at all from eight, on only one occasion from 17 and on two or more occasions from 36 children with a maximum interval of 64 days between first and last positive specimens. The average period of observed virus excretion for the 53 children actually yielding virus was 21 days. The true average period of virus excretion is probably much longer, perhaps 50 days, since specimens were collected usually at 30-day intervals. Also, in 20 instances, including five of the children from whom no poliomyelitis virus was obtained, a possibly crucial or limiting specimen yielded an untypable cytopathic agent which may have masked the presence of poliomyelitis virus.

Infections in Household Associates of Index Children

The sera collected from the household associates on admission to the study and again in 1954 and 1955 have been screened for neutralizing antibodies. The results indicate that, in six instances, the index child escaped infection experienced by others in the same household. In these households, six out of a total of 16 homologously nonimmune other family members also escaped infection. In contrast, only four escaped out of 86 previously nonimmune persons in households in which the index child was infected during 1953–1954. Examination has been completed of single stool specimens taken soon after infection of the index child from 69 of these 86 persons and has revealed poliomyelitis viruses in 34 or 49 per cent. Another eight stools yielded possibly interfering untypable agents.

The response of previously immune household associates to identical conditions of exposure is in sharp contrast to the foregoing. While 31 (19 per cent) of 161 homologously immune persons presumably became reinfected during 1953–1954, since they responded to exposure with a significant antibody rise (usually much greater than fourfold), virus was found on only one occasion in the stool specimens collected from these individuals. It is also of interest that reinfection occurred chiefly in persons with low antibody titers (median titer 1:40) and that the range of post-reinfection titers (1:320 to 1:40,960) and the median value (1:2,560) are substantially higher than those we have observed following primary infection (range 1:20–1:5,120, median 1:320 to 1:640).

Clinical and Epidemiologic Aspects of the Household Infections

Although there has been no clinically diagnosed case of poliomyelitis in the study group, histories of possibly significant minor illness were often obtained. Among 149 persons experiencing primary infection, including 67 index children and 82 associates for whom the records are complete, a history of minor illness at an appropriate time was elicited for 23 index children, 22 child siblings, and eight adult associates or about 36 per cent of the group. Fever was the single common denominator but headache, nausea or vomiting, sore throat and irritability were other common manifestations. In five instances a story of nuchal rigidity or muscle pain and stiffness suggested

possible CNS involvement but in no case was there major muscular impairment.

Evidence has already been presented in relation to the influence of such factors as season, area, race, or economic status, age, and family size upon the occurrence of infection. Unfortunately, efforts to trace the specific pathways by which infection gained entrance into specific households have not been highly rewarding. On two occasions possible links to cases of paralytic disease were uncovered: in one, the immune physician father had cared for a patient; and in the other, more probable instance a nonimmune sibling who became infected himself had contact with a case of overt infection with virus of the appropriate type. Investigations of only 56 household episodes have been completed in that all of the related laboratory work is finished. In 12 of these, histories of intimate contact with other households were obtained. All children in 11 contact households were shown to have antibodies for the homologous virus and some were found still shedding virus. In the final household, however, in spite of intimate daily contact, the single child escaped infection. Nonetheless, it would seem that intimate contact between households favors virus spread. The remaining investigations yielded no obviously pertinent information.

Patterns of Seroimmunity in the Study Group

While the study group has serious deficiencies as a truly representative population sample, it does constitute a fairly good sample of the families with small children in each of the three study areas. In this light it is of interest to consider the type-specific seroimmunity of the household associates upon admission to the study in 1953 and the changes revealed by the results of screening sera taken from the same persons early in 1955. Persons no longer in the study in 1955 will not be considered, except

Table 6—Seroimmunity to Poliomyelitis Viruses in Household Associates * of Index Children, by Age and by Virus Type, in 1953 and 1955

Age in 1953 (Years)	Number of Persons	Per cent of Persons Immune to Virus of Indicated Type in Indicated Year							
		Type 1		Type 2		Type 3		Mean for All Types †	
		1953	1955	1953	1955	1953	1955	1953	1955
1	30	27	30	13	20	13	50	18	36
2	40	48	50	38	50	13	50	32	50
3	49	37	41	37	51	20	43	31	45
4	30	60	60	50	50	60	83	57	64
5– 6	59	70	78	64	71	78	86	71	78
7– 9	53	66	76	79	85	70	74	71	84
10–19	60	87	88	88	90	88	90	88	90
20–29	144	89	90	90	90	88	89	89	90
30 plus	159	87	88	93	94	91	92	90	91
All	624	72	76	74	78	71	80	73	78

* Limited to persons still in study when 1955 sera were collected.

† Represents the average experience with a single type virus; computed by summing the number of persons in an age group immune to each type virus and referring this sum to a denominator equal to three times the total number of persons in the age group.

as noted, so that the 1953 and 1955 results can be compared directly.

Table 6 indicates the per cent of seroimmunity to each virus type by age for the group as a whole. With one important exception, the seroimmune patterns for the three virus types are closely parallel and show a fairly rapid rise to about 60 per cent by age four and 90 per cent in the age groups 10 years and older. In the interval between collection of the 1953 and 1955 sera (average of about 18 months) about 4 per cent of the population were infected with type 1 virus, the same proportion with type 2 virus, and about 9 per cent with type 3 virus. Nearly all of those infected were less than 10 years of age. The major lack of parallelism in the 1953 type-specific seroimmune patterns was in the group under four years of age which was seriously deficient in type 3 immunity. This is shown in graphic form in Figure 1 which depicts, for comparison, the age curves for type 1 and 3 immunity in the same younger individuals in 1953 and 1955. As the result of the predominance of type 3 infections in the 1953–1954 period the deficiency in type 3 immunity has been more than made up and there now exists a relative lack of type 1 immunity. This is of special interest in view of the predominance in 1955 of infections with type 1 virus.

Figure 1—Seroimmunity to Types 1 and 3 Poliomyelitis Viruses in 1953 and 1955 Among Household Associates Under 20 Years of Age in 1953

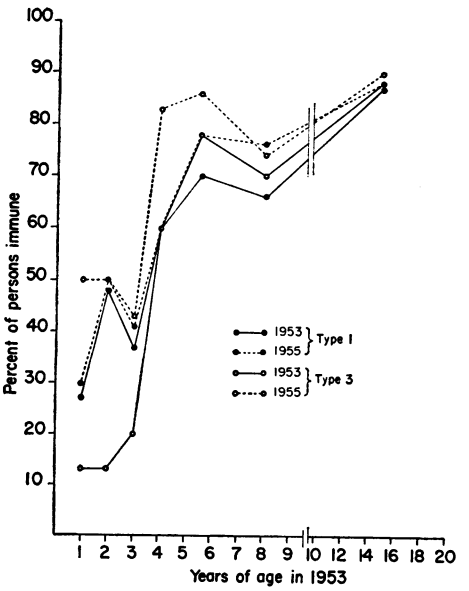
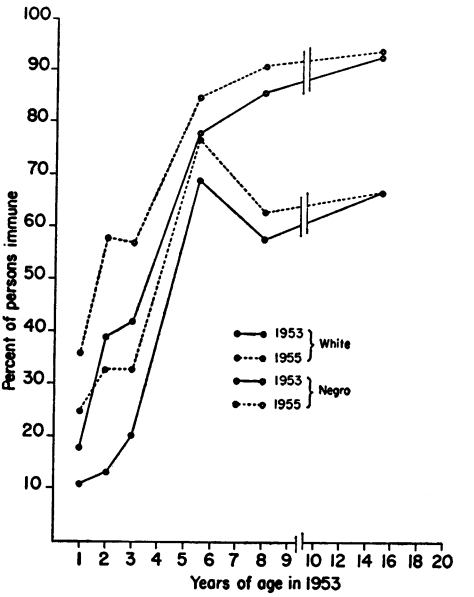


Figure 2—Mean Seroimmunity to Poliomyelitis Viruses (All Types) in 1953 and 1955 Among Negro and White Upper Economic Household Associates Under 20 Years of Age in 1953



In considering the relation of seroimmunity to race, economic status and area, mean values for immunity to the three virus types have been employed to simplify the presentation. In Table 7 the data for 1953 and 1955 are presented by race and economic status. From the 1953 figures it is evident that immunity developed most rapidly in the Negro group with the white lower-economic group following fairly closely and the white-upper group lagging well

Table 7—Mean Seroimmunity to Poliomyelitis Viruses (All Types) † in Household Associates * of Index Children in 1953 and 1955, by Age, Race and Economic Status

Age in 1953 (Years)	White Upper Economic Group			White Lower Economic Group			All Negroes		
	No. of Persons	Per cent Immune in		No. of Persons	Per cent Immune in		No. of Persons	Per cent Immune in	
		1953	1955		1953	1955		1953	1955
1	12	11	25	7	29	43	11	18	36
2	8	13	33	9	33	44	23	39	58
3	14	21	33	15	27	42	20	42	57
4	7	38	48	7	76	76	16	56	67
5- 6	16	69	77	9	63	72	24	78	85
7- 9	19	58	63	15	71	78	19	86	91
10-19	6	67	67	21	86	89	33	93	94
20-29	37	78	80	46	89	89	61	95	96
30 plus	61	85	87	34	92	93	64	95	95
All	180	64	69	173	74	78	271	79	84

See * and † as in Table 6.

behind. The relative positions changed very little by 1955 with each group experiencing about the same degree of change, i.e., an increase in immunity of about 4 or 5 per cent. The 1953 and 1955 data for the younger members of the contrasting Negro and white-upper groups are presented graphically in Figure 2. Not only had immunity developed more rapidly in the Negroes by 1953 but during an additional 18 months of experience the white-upper group failed to achieve immunity equal to that of the Negroes in 1953.

Because of the marked overrepresentation of Negroes in the Baton Rouge and Evangeline area groups, direct comparison of area figures is not warranted. In order to see the possible relation of area to seroimmunity, Table 8 was pre-

Table 8—Mean Seroimmunity * to Poliomyelitis Viruses (All Types) in Initial Sera from All Participants † in Study Through June 30, 1955, Index Children Excepted, by Study Area, Race, and Economic Status

Study Area	Persons in Indicated Racial or Economic Group							
	White Upper		White Lower		Negro		All Groups	
	Number	Per cent Immune	Number	Per cent Immune	Number	Per cent Immune	Number	Per cent Immune
New Orleans	90	63	141	84	99	79	330	77
Baton Rouge	70	54	44	61	123	82	237	70
Evangeline	62	78	34	75	136	80	232	79
All	222	64	219	78	358	80	799	75

* See footnote 2 to Table 6.
† See text for explanation.

pared with separate figures for the three racial or economic groups in each area. Further, in order to increase the size of the populations to be compared, the figures are based on examination of the admission sera of all participants in the study other than index children, even though many are no longer under observation. Although age-specific figures have been omitted, it should be indicated that the distributions of the various groups by age are reasonably similar. While the figures for the Negro groups in the three areas are very similar, there are possibly significant differences between the corresponding white groups. Fitting well with the high past incidence of poliomyelitis in Baton Rouge is the fact that immunity in both white groups in that city is considerably less frequent than in the corresponding groups in either New Orleans or the Evangeline area. Also, the white-upper group in urban New Orleans has distinctly less immunity than the corresponding group in the semirural Evangeline area.

Discussion and Summary

Since early 1953, about 150 representative households from three areas in southern Louisiana have been observed for an average period of 27 months in an effort to learn more about when and under what circumstances the usual immunizing infections with poliomyelitis viruses occur. Examination by tissue culture methods of stool and blood specimens collected monthly since birth from the index infant in each household has revealed the occurrence of 109 episodes of household infection. Six additional episodes in which the index child escaped were revealed by examination of sera collected annually from the other household members.

Analysis of the infections in index infants indicates that, while infections occur in the region under study throughout the year, there is a pronounced seasonal increase in late summer and early fall. However, all three virus types are not constantly and equally represented. In reviewing other similar evidence Sabin [21] has suggested that type 2 virus is usually endemically present whereas types 1 and 3 are present only "on certain epidemic occasions." Our data suggest that the cyclic occurrence of type 3 and type 1 virus may be conditioned by specific deficiencies in immunity among children under four years of age.

Our observations as to the patterns of seroimmunity in the over-all study group and as to the observed infections in the index children support concepts previously advanced as to the importance of economic status and family size to the early acquisition of infection,[4, 8, 9] i.e., infection occurs significantly earlier in Negro children and in children with one or more older siblings. Also, just as in families with cases of overt disease,[16–18] intra-household spread of these silent immunizing infections to all nonimmune members is the general rule.

This fact of generalized exposure within the household makes possible a unique opportunity to correlate naturally and actively induced seroimmunity with ability to resist infection. Our findings, in agreement with other data reviewed by Sabin,[21] indicate that reinfection is most apt to occur in persons with low antibody titers and that, when it does occur, it is not associated with prolonged, epidemiologically significant shedding of virus. Finally, while only four of 15 infections occurring in the first seven months of life took place in the face of demonstrated persisting maternal antibody, this cannot be taken to mean that maternal antibody protects against infection. Our still incomplete data indicate that maternally derived antibody does not persist for more than three months unless the maternal antibody titer was unusually high.

Although some evidence has been obtained for ready spread of virus between closely associated households as well as within households, no direct information has been obtained so far as to specific mechanisms of virus transmission. Also, no direct insight has been gained as to the conditions which determine that infection will result in disease. Among the index children and their nonimmune household associates an estimated 240 infections * have occurred during the period of observation with no instance of paralytic disease, although a history of minor febrile illness, possibly due to poliomyelitis virus infection, has been elicited in relation to about one-third of the verified infections. While there is a suggestive similarity in distribution of virus types among the household infections and the cases of overt disease, which occurred concurrently in the study areas, it remains possible that the household infections were caused predominantly by strains of low virulence. However, if one accepts the age-specific infection rates observed in our study group as applicable to the aggregate population of the three study areas (just over a million in 1950), there were in 1954 about 77,000 infections with 109 reported cases of paralytic disease or a ratio of one paralytic case per 710 infections with viruses of all types. In this light, absence of paralytic disease in our study hardly requires explanation.

Addendum

Since this manuscript was prepared, a preliminary report [22] has been published of a very interesting study, similar in many ways to that described here, of the occurrence of poliomyelitis virus infections in about 200 households of United States Air Force personnel stationed in the Philippine Islands during a four-month period in 1953. While differences in objective, environment, and composition of the study groups render direct comparisons between the Philippine and Louisiana studies difficult, it is worth noting that in the Philippine study numerous infections with all three virus types were also observed unassociated with clinically recognized poliomyelitis.

* The estimate (based on 1.2 infections in household associates per infection in an index child) is necessary because examination of specimens collected from members of households infected in 1955 has not been completed.

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Fellowships in Pediatric Neuropsychiatry

Pediatricians and psychiatrists are invited to apply for fellowships being offered jointly by the Department of Pediatrics, Ohio State University, and the Children's Hospital of Columbus. A Clinic of Child Development has been established jointly, which will concern itself with deviations from normal behavioral development in the preschool period. Fellows will have an opportunity to teach and to engage in research projects designed to throw light on the etiology of the neuropsychiatric disorders of childhood.

Fellowships will be granted for one year with a stipend of $5,000. The first will be available beginning July 1, 1956, and one is provided for each six months.

Further information from Dr. Earl H. Baxter, chairman, Department of Pediatrics, or Dr. Hilda Knobloch, associate professor of pediatrics and director of the clinic, Ohio State University, Columbus.