Development of Tuberculosis in Infected Children*

ALTON S. POPE, M.D., F.A.P.H.A., PHILIP E. SARTWELL, M.D., AND DAVID ZACKS, M.D.

State Department of Public Health, Boston, Mass.

IN laboratory animals where time of infection and dose of bacilli can be controlled there is substantial agreement that primary infection with tuberculosis, if not overwhelming, results in a measurably increased resistance to subsequent inoculations with tubercle bacilli.[1, 2, 3] In man the picture is less clear. Although the typical parenchymal infiltration of primary infection, followed by resolution, fibrosis and calcification, is not infrequently observed roentgenologically, the exact date of reinfection and the duration of exposure are rarely known, and the dosage of bacilli is wholly problematical. Furthermore, it has not been demonstrated how far the results of inoculation experiments with tuberculosis in laboratory animals can be applied to natural infection in man.

From a public health standpoint the relationship between primary infection with tuberculosis and the development of subsequent progressive disease has become a problem of major importance. Is a primary infection acquired during childhood a relative safeguard against subsequent exposure? or does the sensitization acquired through such infection result in increased susceptibility to destructive lesions?

Much evidence might be cited to support both opinions, and the epidemiological findings so far reported appear to be contradictory.[4-9] Obviously the answer is not simple and the diversity of opinions based on extensive studies at least suggests that the end results may be strongly conditioned by such variables as the type of population exposed, the level of tuberculous infection in the community, and various environmental factors. Such complications make it difficult to compare directly the findings of different investigators, but for practical purposes the amount of tuberculous disease which in sufficient periods of time develops in properly controlled population groups appears to be the best measure of the significance of childhood infection in the evolution of phthisis.

In connection with its field clinic work on tuberculosis in school children, the Massachusetts Department of Public Health has during the past 15 years attempted to collect evidence on the relationship of childhood infection to the subsequent development of progressive tuberculosis in adolescents and young adults. On account of the long, indeterminate incubation period of tuberculosis and the slow development of clinical disease, it has been necessary to employ epidemiological methods which would give a perpendicular rather than the usual horizontal picture of the situation. The main object has been to obtain a quantitative measurement of

* Read before the Epidemiology Section of the American Public Health Association at the Sixty-eighth Annual Meeting in Pittsburgh, Pa., October 20, 1939.

the amount of progressive tuberculous disease subsequently developing in large groups of children examined in the clinics, classified according to age and sex, the initial reaction to the tuberculin test, roentgenological evidence of tuberculous disease, and known household contact with tuberculosis.

The basic material to be presented consists of the data on some 400,000 school children tuberculin tested in the Chadwick Clinics between 1924 and 1934, the reëxamination of certain groups of these children, and the cases of pulmonary tuberculosis subsequently reported in the entire group. During the first 3 years of the clinic children were selected for examination on the basis of known exposure to tuberculosis, underweight of 10 per cent or more, definite or suspicious symptoms or signs of pulmonary disease. For the next 2 years all school children for whom consents were received were examined, irrespective of special indications. During these 5 years complete physical examinations were made on all children examined, in addition to the von Pirquet test and roentgenogram of the chest of all positive reactors. During the last 5 years examination was limited to the tuberculin test of all children, with X-ray of reactors and physical examination only for children with positive roentgenograms. All children with roentgenological signs of either childhood or adult type tuberculosis were reëxamined annually with X-ray of the chest, and

TABLE 1

Reported Cases and Deaths from Tuberculosis in Children Previously Tested in Clinics, Excluding Those Who Had Tuberculosis When First Tested

	Number Originally Tested 1924–1934	*Cases Subsequently Reported 1924–1936*	*Deaths from Tuberculosis 1924–1936*	*Total Known Tuberculosis*
All tested	400,330	319	100	419
Reactors	99,769	189	52	241
Non-reactors	300,561	130	48	178

TABLE 2

Rates per 100,000 Children Tested

	Living Case Rate	*Death Rate*	*Rate for All Cases*	*Case Fatality Rate, Per cent*
All tested	79.7± 4.5	25.0±2.5	104.7± 5.1	23.9
Reactors	189.4±13.8	52.1±7.2	241.6±15.6	21.6
Non-reactors	43.2± 3.8	16.0±2.3	59.2± 4.4	27.0
R+ / R—	4.4	3.2	4.1	

TABLE 3

Distribution of Deaths from Tuberculosis

	Total	*Non-reactors*	*Reactors*
Median interval between test and death in years	5.7	5.9	5.6
Deaths 1– 3 years after test	18	8	10
" 4– 6 " " "	36	21	15
" 7– 9 " " "	34	16	18
" 10–12 " " "	11	6	5
Males	27	14	13
Females	73	39	34

whenever possible followed to the end of their school life.

The problem has been approached from several angles and the data are presented in the form of two series of observations:

1. Reported subsequent morbidity and mortality from tuberculosis in the entire group of children tested
2. The development of tuberculosis in children under annual observation of the clinic

FIRST SERIES

Soon after the beginning of the Ten Year Program an alphabetical-geographical card index was set up for all children examined in the clinics, making it possible to check any subsequent developments against a child's status at the time of first examination. By means of this index all cases and deaths from pulmonary tuberculosis reported in Massachusetts from 1924 to 1936, inclusive, in the age groups covered by the Ten Year Program were checked to determine whether the individuals in question had ever been examined in our clinics. The diagnosis of tuberculosis in each report or death certificate was confirmed before it was included in the study. Thus a list was established of verified cases and deaths from tuberculosis which had developed in a period of 13 years in a group of some 400,000 children. The morbidity and mortality in this group up to 1934 have been reported previously by one of us.[10] It is probable that the reporting of cases is somewhat more complete in the group of reactors followed in the clinic than in the general population, but there is certainly no such weighting of the deaths reported. The cases and deaths from tuberculosis, together with morbidity and mortality rates, according to the tuberculin reaction on first examination are shown in Tables 1, 2 and 3.

In spite of the significantly higher morbidity and mortality among the children who reacted to the initial tuberculin test, the case fatality rate has been slightly higher among cases in children originally tuberculin negative. This would appear to cast some doubt on the benign character of first infections acquired between the ages 6 and 16. It will be noticed that the median interval between the tuberculin test and death in fatal cases is essentially the same among the originally negative and originally positive reactors.

SECOND SERIES

Of the children tested, X-rayed, and examined in the school clinics, a large number were, for reasons given above, kept under annual observation with X-rays and physical examinations. For statistical analysis all those were selected who did not have pulmonary tuberculosis or non-tuberculous pulmonary disease on first examination and who were reëxamined by X-ray at least once, a year or more subsequently. A total of 19,346 satisfied these requirements. Their mean age at the beginning of the period of observation was 11.4 years, and the mean period of observation was 3.4 years, with a maximum of 11 to 12 and a minimum of 1 to 2 years.

While these observations are based on a large experience, they have certain limitations which should be pointed out. The von Pirquet test was used throughout the study; however, specially trained physicians made both the tests and the interpretations, and multiple tests were often performed. Cases were classified as " contact " when a history of exposure to tuberculosis at any time since birth was obtained from either the parents or health department, and it was usually not possible to verify this by examination of the supposed contact or to find previously unsuspected sources of infection. In the majority of cases listed as contacts, contact had been broken when the child came under observation. A positive contact history was obtained in 33.9 per cent of the

TABLE 4

Cumulative Morbidity
Whole Group

Years of Observation x	*Number at Beginning* l_x	*Number Withdrawn During Year* w_x	*Number Developing Tuberculosis* d_x	*Average Number Under Observation During Year* $l_x - W_x$	*Per cent Developing Tuberculosis During Year* $100q_x$	$100p_x$	$100P_x$	*Per cent Cumulative Morbidity* $100(1-P)_x$
1– 2	19,346	3,060	21	17,816	0.118	99.882	99.88	0.12
2– 3	16,265	4,262	33	14,134	0.233	99.767	99.65	0.35
3– 4	11,970	3.937	28	10,001	0.280	99.720	99.37	0.63
4– 5	8,005	3,249	23	6,380	0.361	99.639	99.01	0.99
5– 6	4,733	2,025	21	3,720	0.564	99.436	98.45	1.55
6– 7	2,687	1,286	15	2,044	0.734	99.266	97.73	2.27
7– 8	1,386	655	10	1,058	0.945	99.055	96.81	3.19
8– 9	721	367	7	537	1.303	98.697	95.55	4.45
9–10	347	202	2	246	0.813	99.187	94.77	5.23
10–11	143	91	1	97	1.031	98.969	93.79	6.21
11–12	51	49	2	26	7.692	92.308	86.58	13.42

TABLE 5

Cumulative Morbidity Rates from Tuberculosis Among School Children According to Sex, Tuberculin Reaction and Roentgenological Findings at First Examination

Years of Observation	*Total*	*Males*	*Females*	*Negative von Pirquet* *	*Positive von Pirquet*	*Positive von Pirquet Negative X-ray*	*Positive von Pirquet Positive X-ray*
1– 2 Years	0.12	0.11	0.12	...	0.13	0.04	0.23
2– 3 "	0.35	0.22	0.46	...	0.38	0.10	0.68
3– 4 "	0.63	0.40	0.82	...	0.68	0.16	1.21
4– 5 "	0.99	0.58	1.32	...	1.05	0.30	1.80
5– 6 "	1.55	0.82	2.13	...	1.63	0.74	2.49
6– 7 "	2.27	1.14	3.18	...	2.38	0.86	3.67
7– 8 "	3.19	1.72	4.41	2.4	3.24	0.86	5.09
8– 9 "	4.45	3.19	5.47	2.4	4.55	1.36	6.89
9–10 "	5.23	4.02	6.21	2.4	5.36	2.44	7.54
10–11 "	6.21	4.02	8.12	2.4	6.40	2.44	9.08
Mean age of group at beginning of observation	11.43	11.51	11.38	10.38	11.52	11.43	11.65
Mean period of observation	3.4	3.3	3.4	2.8	3.5	3.4	3.6

* Only one breakdown occurred in this group.

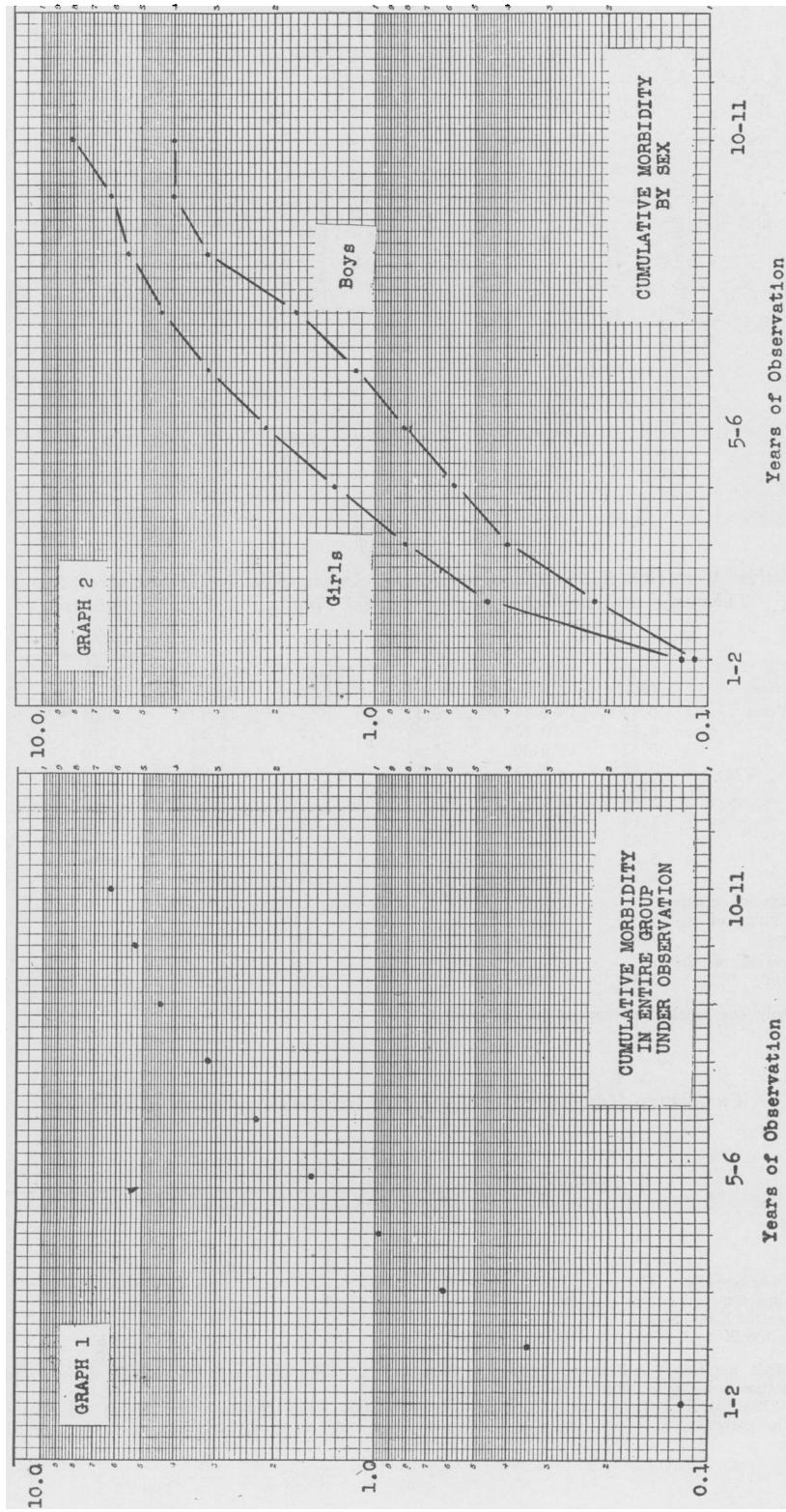
TABLE 6

Cumulative Morbidity After 7–8 Years According to History of Exposure

	Contacts		*Non-contacts*		*Combined*	
	Number Developing Tuberculosis [1]	*Per cent Morbidity*	*Number*	*Per cent*	*Number*	*Per cent*
All cases	106	5.1	45	1.8	151	3.2
Males	23	2.4	16	0.48	39	1.7
Females	83	7.5	29	2.31	112	4.4
Original non-reactors	1	5.0	..	....	1	2.4
Original reactors	105	5.3	45	1.9	150	3.2
With negative X-ray	15	1.5	7	0.6	22	0.9
With positive X-ray [2]	90	7.7	38	3.0	128	5.1

1. This applies to all cases developing pulmonary or extrapulmonary tuberculosis during study, and includes those who have subsequently died.

2. " Positive X-ray " here refers to those who when first tested and examined showed old childhood-type lesions in parenchyma, hilum, or both locations. These were generally calcified, and might be single or multiple.


GRAPH 1
CUMULATIVE MORBIDITY IN ENTIRE GROUP UNDER OBSERVATION
10.0
1.0
0.1
1-2
5-6
10-11
Years of Observation
GRAPH 2
CUMULATIVE MORBIDITY BY SEX
Boys
Girls
10.0
1.0
0.1
1-2
5-6
10-11
Years of Observation

cases of childhood type tuberculosis, in 27.4 per cent of the reactors with negative X-ray, and in 67.7 per cent of the non-reactors in this series; the high figure for non-reactors means of course that the usual reason for keeping them under observation was a contact history.

Two methods of analysis were applied to determine the frequency of breakdown from tuberculosis. The first, or cumulative morbidity method, was suggested by Frost and used by Brailey [11]; a description of the mathematics involved is given by Puffer, Stewart, and Gass.[12] Table 4 illustrates its application to the entire series; Table 5 shows the cumulative morbidity as derived in the last column of Table 4, by years for each group. While some children were followed for 11–12 years, the figures for the last few years are unduly influenced by a single breakdown, since the number remaining under observation is small; therefore in Table 6, which divides the groups according to contact, the morbidity is taken only at the end of 7–8 years of observation. Since no differences were noted in the distribution of cases of pulmonary tuberculosis and of other reinfection forms of the disease, all are included together in the tables. There was a total of 142 pulmonary cases, 8 pleural effusions, and 13 extrapulmonary cases; 31 deaths from tuberculosis occurred during the study.

As this method takes into account years of observation but not age, it was felt that another approach based on age might further illuminate the problem. The method adopted is one used by Herlitz [6] and is illustrated in Table 7.

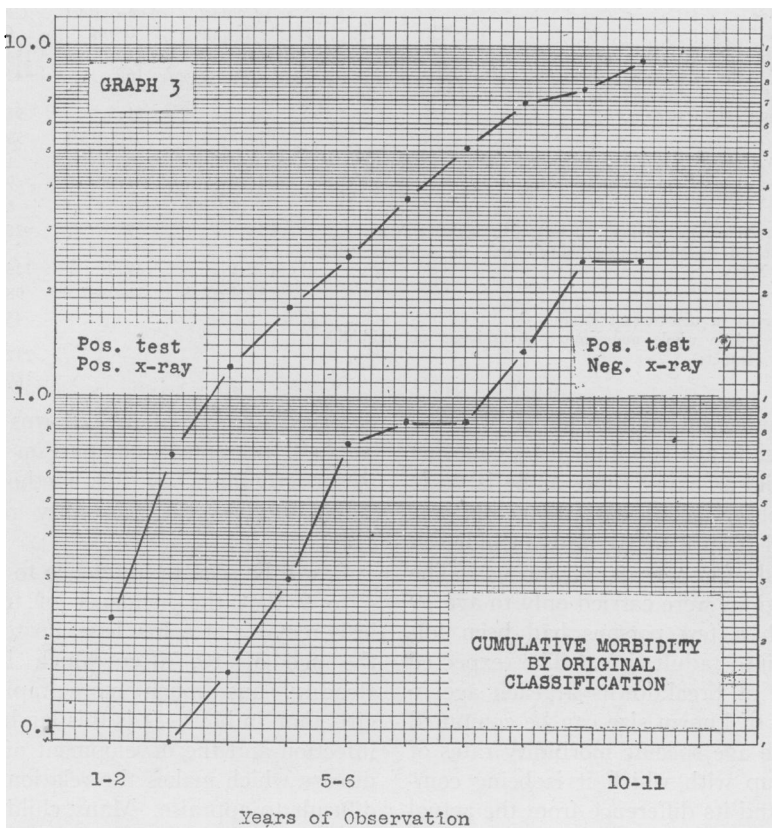


TABLE 7

Age-specific Morbidity from Tuberculosis in Reacting and Non-reacting Children

Age	Group I Original Reactors: Number Under Observation	Group I Original Reactors: Number Developing Tuberculosis	Group II Original Non-reactors: Number Under Observation	Group II Original Non-reactors: Number Developing Tuberculosis	Expected Cases Among Non-reactors
6	90	0	26	0	0.0
7	556	2	117	0	0.4
8	1,470	0	287	0	0.0
9	2,603	0	390	0	0.0
10	3,968	6	454	0	0.7
11	5,288	10	478	0	0.9
12	6,616	8	503	0	0.6
13	7,806	14	519	0	0.9
14	8,464	22	466	0	1.2
15	8,245	24	409	0	1.2
16	6,754	27	298	0	1.2
17	4,632	18	202	0	0.8
18	2,601	10	221	0	0.8
19	1,324	12	47	1	0.5
Total		153±12.4		1±1	9.2±0.7

Difference=8.2±1.2

TABLE 8

Observed and Expected Cases of Tuberculosis (All Forms) Developing Subsequent to Initial Examination According to Sex, Tuberculin Reaction, X-ray Findings and Contact

Age 6–19

	Contact Group	Non-contact Group	Combined Group
Total number of cases developing tuberculosis	111	43	154
Number of males developing tuberculosis	26	16	42
Number of males expected to develop tuberculosis based on female morbidity rates	77.7	21.8	95.4
Difference	51.7±9.8	5.8±5.8	53.4±11.4
Number of cases of tuberculosis observed among non-reactors	1	0	1
Cases expected based on morbidity rates of original reactors	12.0	1.7	9.2
Difference	11.0±1.6		8.2±1.2
Cases observed among original reactors with negative X-ray	18	7	25
Cases expected based on morbidity rates of reactors with positive X-ray	72.9	39.9	123
Difference	55.4±8.8	32.9±7.2	98±12
Cases observed in non-contact group			43
Cases expected in whole non-contact group based on morbidity rates of contacts			212.3
Difference			169.3±21.1

The number of children under observation at each age is obtained by counting each child as many times as he is years under observation; e.g., if a child was followed from 8 to 10, he is included in the totals for ages 8, 9, and 10. The observations were carried only to age 19 although a few persons had been followed into adult life. The expected number of breakdowns at each age in a group of known size can be computed from the age specific morbidity rates of the group with which it is being compared, and its difference from the actual observed number of breakdowns noted. Table 8 presents a comparison of the major groupings by this method, and Table 9 gives the morbidity rate by ages.

It will be seen by reference to Tables 4 to 9 that the incidence of tuberculosis remains at a low level up to about the age of 10, after which it rises steadily, and much more rapidly in girls than in boys. It is this lag between infection and the development of active disease which makes the relationship so difficult to appraise. Many children are

TABLE 9

Morbidity by Age

Age	Number Under Observation	Number Developing Tuberculosis	Per cent Morbidity
6	116	..	...
7	673	2	0.3
8	1,757	..	...
9	2,993	..	...
10	4,422	6	0.1
11	5,766	10	0.2
12	7,119	8	0.1
13	8,325	14	0.2
14	8,930	22	0.2
15	8,654	24	0.3
16	7,052	27	0.4
17	4,834	18	0.4
18	2,822	10	0.4
19	1,371	13	0.9

lost from observation before they reach an age at which they are likely to develop tuberculosis, and among those who are followed it is often impossible to determine with any certainty the time and degree of any subsequent exposure. All of our evidence indicates that in school children it is the age of the individual rather than the time of exposure or any environmental factor which determines the time at which tuberculosis develops. It will also be noted that the incidence of tuberculosis is higher among original reactors to the tuberculin test than among non-reactors, and significantly higher among those whose original X-rays showed evidence of childhood type tuberculosis than among reactors with negative films; and that it is higher in each group among contacts than non-contacts.

SUMMARY AND CONCLUSIONS

In a group of some 400,000 Massachusetts school children tuberculin tested in the period 1924–1934 the subsequent reported morbidity and mortality from tuberculosis has been determined to the end of 1936, and rates have been computed on the basis of the original reaction.

Among the reactors the morbidity from adult type tuberculosis has been approximately 4 times that in the non-reactors. The death rate has been 3 times as great in the reactors, and the case fatality essentially the same in the two groups.

The cumulative morbidity from tuberculosis in children reëxamined annually for 10–11 years was over 6 per cent. This rate was approximately twice as high in females as in males, was substantially higher among reactors than among non-reactors and among reactors was over 3 times as high in those with originally positive roentgenograms.

For this second series the tuberculosis morbidity among children with a history of family exposure to the disease was 2½ times that in children without known exposure.

Age specific morbidity rates in the series show that significant tuberculosis in school children is infrequent below the age of 10, that the incidence rises rapidly after this age, and much more rapidly in girls than in boys.

REFERENCES

1. Lurie, M. B. Experimental Epidemiology of Tuberculosis. *J. Exper. Med.*, 58:305 (Sept.), 1933.

2. Opie, E. L., and Freund, J. An Experimental Study of Protective Inoculation with Heat Killed Tubercle Bacilli. *J. Exper. Med.*, 66:761 (Dec.), 1937.

3. Clawson, B. J. Experiments Relative to Vaccination Against Tuberculosis with BCG. *Arch. Path.*, 20:343 (Sept.), 1935.

4. Opie, E. L. Present Concepts of Tuberculous Infection and Disease. *Am. Rev. Tuberc.*, 32:617 (Dec.), 1935.

5. Wallgren, A. Pulmonary Tuberculosis; Relation of Childhood Infection to Disease in Adults. *Lancet*, 1:417 (Feb. 19), 1938.

6. Herlitz, G. Studien über die Prognose der okkulten Kindertuberculose. *Acta paediat.* (supp. 2), 19:1–157, 1937.

7. Ustvedt, J. H. Frequency of Tuberculous Disease Among the Recently Infected. *Nord. med. tidskr.*, V, 4:956, 1932.

8. Myers, J. A., and Harrington, F. E. Effect of Initial Tuberculous Infection on Subsequent Tuberculous Lesions. *J.A.M.A.*, 103:1530 (Nov. 17), 1934.

9. Jacobs, A. L. Investigations Upon Tuberculosis Among Students in Scandinavia. *Tubercle*, 19:481 (Aug.), 1938.

10. Pope, A. S. Application of Our Knowledge of Tuberculosis Through Case Finding. *Tr. Nat. Tuberc. Assoc.*, 31:317, 1935.

11. Brailey, M. Mortality in Tuberculin-Positive Infants. *Bull. Johns Hopkins Hosp.*, 59:1 (July), 1936.

12. Puffer, R. R., Stewart, H. C., and Gass, R. S. Tuberculosis Studies in Tennessee. *Am. J. Hyg.*, 28:490 (Nov.), 1938.

NOTE: Our indebtedness is acknowledged to the International Health Division of the Rockefeller Foundation whose support made possible the collection of part of these data.