during the first two years. This greater susceptibility to infection is found among premature children even when they are reared in an apparently favourable home environment.

In general, premature children—after they have reached the age of 2—appear to be as healthy as those born at term.

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REFERENCES

- Capper, A. (1928). *Amer. J. Dis. Child.*, 35, 443.
 Crosse, V. M., and Evans, P. J. (1952). *Arch. Ophthalm.*, Chicago, 48, 83.
 Douglas, J. W. B. (1951). *Lancet*, 2, 440.
 Drillien, C. M. (1948). *Arch. Dis. Child.*, 23, 69.
 Ferguson, A. E., Brown, A. C., and Ferguson, T. (1952). *Glasg. med. J.*, 33, 143.
 Hess, J. H., Mohr, G. J., and Bartelme, P. F. (1934). *The Physical and Mental Growth of Prematurely Born Children*. University of Chicago Press.
 Kinsey, V. E., and Zacharias, L. (1949). *J. Amer. med. Ass.*, 139, 572.
 Mohr, G. J., and Bartelme, P. F. (1934). See Hess, Mohr, Bartelme (1934).
 Reese, A. B. (1949). *Arch. Ophthalm.*, Chicago, 41, 527.
 Rowntree, G. (1950). *Monthly Bull. Minist. Hlth.*, 9, 134.
 Royal College of Obstetricians and Gynaecologists and Population Investigation Committee (1948). *Maternity in Great Britain*. Oxford Univ. Press, London.
 Terry, T. L. (1942). *Amer. J. Ophthalm.*, 25, 203.
 — (1945). *J. Amer. med. Ass.*, 128, 582.

REPORT OF TUBERCULIN SURVEY IN THE RHONDDA FACH

BY

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The tuberculin test has long been recognized not only as a useful measure in clinical diagnosis but as an essential part of epidemiological investigations appertaining to tuberculosis (Ustvedt, 1942). Myers (1946) declares that "as an epidemiological agent, the test excels every other procedure of examination," and he regards repeated testing of special groups as an excellent method of determining the effectiveness of a tuberculosis control programme. Though a more accurate index of the success of such control measures is undoubtedly the number of new cases of tuberculosis occurring in a community subject to intensive and repeated mass x-ray surveys, the tuberculin-testing of large groups does provide evidence on the existing degree of total communal infectivity. It was therefore decided to carry out skin tuberculin-testing of the school population in the Rhondda Fach as an integral part of the research scheme.

This scheme has as one of its main objectives the determination of the total prevalence of pulmonary tuberculosis in a defined community, the isolation and treatment of all known active cases, and the estimation of the rate of occurrence of new cases subsequent to the application of such measures (Cochrane, Cox, and Jarman, 1952).

The schoolchildren in the Rhondda Fach were tuberculin-tested during the months of February, March, and April, 1951, and a sample of the schoolchildren in another valley were tested during September, 1951. When the Rhondda Fach is resurveyed radiographically in 1953 the school population will again be

tuberculin-tested and the results of such retesting will be compared with those of the 1951 survey. A sample of the schoolchildren in the "control" valley, drawn from the same schools as were those in this 1951 survey, will also be retested in 1953, and the results will serve for comparison with those obtained from the Rhondda Fach.

Such retesting will be combined with a follow-up study of children who were tuberculin-negative in 1951, and this will permit a determination of the attack rate of infection in the two valleys.

Method of Testing

In 2,301 cases the usual Mantoux technique was employed: 0.1 ml. of a 1/10,000 dilution of standardized O.T.—that is, 1 T.U.—was injected intradermally, and all negative reactors were retested with 0.1 ml. of a 1/100 dilution—that is, 100 T.U. The criteria adopted for the reading of these tests was that any reaction producing less than 5 mm. diameter of induration was regarded as negative. The reactions were recorded as measurements in millimetres of induration wherever this was possible, even when they were less than 5 mm. and, qualitatively, negative tests.

In 1,109 cases the initial test used was the multiple puncture test, employing standardized, adrenaized O.T. This is a modification of the Finnish Trambusti (1928) test and that described by Chester Stewart (1928). The reason for using this method, and the possible source of error involved, are discussed later.

A preliminary report on the multiple puncture test has been made recently (Heaf, 1951). The test is performed as follows: a drop of undiluted adrenaized O.T. is spread over an area on the forearm about the size of a shilling by means of a sterilized platinum loop; the multiple puncture instrument is then applied and pressed home; any excess of O.T. is wiped away with cotton-wool and the test is read at the end of 48 hours. The criteria adopted for the reading of this test were as follows: 0=no reaction,

TABLE I.—Results of Tuberculin-testing of School Children

Age in Years	No. who Completed Tests	No. Positive to 1/10,000 O.T.	No. Positive to 1/100 O.T.	No. Positive to Multiple Puncture Only	Total Positive	% Positive
(a) Rhondda Fach						
3	97	2	3	1	6	6.2
4	208	4	4	4	12	5.8
5	263	9	8	7	24	9.1
6	294	13	12	10	35	11.9
7	323	12	30	10	52	16.1
8	348	15	14	12	41	11.8
9	251	14	23	21	58	23.1
10	296	16	40	24	80	27.0
11	313	31	31	29	91	29.1
12	334	23	36	49	108	32.3
13	255	23	39	29	91	35.7
14	280	38	48	31	117	41.8
15	78	11	16	4	31	39.7
16	43	9	12	—	21	48.8
17	21	5	7	—	12	57.1
18	6	3	3	—	6	100.0
	3,410	228	326	231	785	23.0
(b) Other Valley						
3	16	2	1	—	3	18.8
4	56	2	2	—	5	8.9
5	96	1	3	—	4	4.2
6	83	3	5	—	8	9.6
7	112	9	5	—	14	12.5
8	115	6	9	—	15	13.0
9	104	13	7	—	20	19.2
10	139	21	7	—	28	20.1
11	179	34	19	—	53	29.6
12	232	40	22	—	62	26.7
13	225	41	27	—	68	30.2
14	203	53	26	—	79	38.9
15	111	39	19	—	58	52.3
16	58	11	3	—	14	24.1
17	26	7	5	—	12	46.2
18	10	3	2	—	5	50.0
19	3	1	1	—	2	66.7
	1,768	286	164	—	450	25.5

or small points of trauma or commencing induration; 1=larger but discrete circles of induration; 2=a ring of induration; 3=a plaque of induration. Reactions up to and including category 1 were regarded as negative and retested with an intradermal injection of 0.1 ml. of 1/100 dilution of O.T. (100 T.U.).

Results.—The results of tuberculin-testing in the Rhondda Fach are summarized in Table 1 (a) and represented graphically in Fig. 1. The tuberculin-testing carried out in

FIG. 1.—Results of tuberculin-testing in the Rhondda Fach, compared with those of a similar valley in South Wales.

another mining valley comparable to that of the Rhondda Fach, but in which no intensive survey technique is being carried out, is summarized in Table 1 (b) and represented graphically in Fig. 1, and the results serve for comparison with those obtained in the Rhondda Fach.

Number Tested and Analysis of Lapses

It was ascertained that 4,743 schoolchildren were on the school register in the Rhondda Fach area. Of these, 4,522 (95.3%) were x-rayed, but only 3,410 (71.9%) completed the tests. This illustrates the difficulties encountered during mass tuberculin surveys. The lapses resulting from absenteeism occurred at all stages of the survey. It should be noted here that most of the tuberculin-testing was done during the winter months, when thick snow lay on the ground.

Many children who were absent for the reading of the second test were visited at home for this purpose. The

TABLE II.—Stages at Which Lapses Occurred During Tuberculin Survey. Number of Children on School Register, 4,743

Reason for Lapsing	No. Not Tested	No. Remaining	%
Absent from school ..	259	4,484	4.9
Test refused	480	4,004	10.5
Absent at reading of first test ..	287	3,717	6.5
Absent at reading of second test (excluding those positive at the first test) ..	307		6.2
Completed tests		3,410	
Total	1,333 (28.1%)	3,410 (71.9%)	(28.1%)

stages at which lapses occurred during the survey are summarized in Table II. The 480 children who were x-rayed but not skin-tested represent parents' refusals.

The ages of the 259 who were absent for the first test were unfortunately not ascertained at the time of the survey, but it can be stated that they are distributed in a relatively equal manner throughout every type of school, and were therefore not confined mainly to one or two age groups.

The ages of the remaining 1,074 who lapsed are known, and the percentages of those available for the initial skin test who completed each stage of the course are represented graphically by age groups in Fig. 2.

FIG. 2.—Percentage of children available for first test who completed each stage of the course.

Reference to this graph shows that most of the lapses occurred in the age group 5 to 6, and it would appear that the refusal of parents to have their children skin-tested is mainly determined by the age of the child. It is interesting that the percentage lapse rate of those available for skin-testing is fairly equally distributed between each stage of the course and between the different age groups. This suggests that the 3,410 children who completed the test do represent a truly random sample.

Comparison between Tuberculin-testing in the Rhondda Fach and the M.R.C. Surveys of England and Wales

Fig. 3 shows the comparison between the prevalence of positive tuberculin reactions among schoolchildren in the Rhondda Fach and those in the M.R.C. surveys in England and Wales (Daniels, 1952). This comparison suggests that if tuberculin surveys do in fact reflect the total amount of human tuberculous infectivity in a community the amount of such infectivity in the Rhondda Fach is rather less than that in the urban areas of Northern England and Wales and rather more than that in the urban area of Southern England. As the total prevalence of cases of active tuberculosis among those over 15 years of age in the Rhondda Fach was found to be 12 per 1,000, out of which 6 per 1,000 were infectious, the conclusion might reasonably be drawn that estimated prevalence figures for active disease in England and Wales based on these findings are likely to be nearer the truth than those based on findings in routine mass radiography surveys (Cochrane, 1952). Such an estimated prevalence rate, based on a population at June 30, 1952, of 34,000,000 persons over 15 years of age, would mean that there are about 400,000 cases of active tuberculosis in England and Wales, of which 200,000 are infectious.

FIG. 3.—Results of tuberculin-testing in the Rhondda Fach compared with those of the M.R.C. surveys in England and Wales.

The Rhondda Fach and the Control Valley

Fig. 1 shows the prevalence of positive reactors among schoolchildren in the Rhondda Fach and in the control valley, and this reveals that there is a somewhat lower rate of conversion at comparable age groups in the control valley. Presumably there is rather less tuberculosis in this valley than in the Rhondda Fach. It will be noted that there is a sharp drop in the percentage of reactors in the Rhondda Fach at age 8. It is possible that this may be due to some error the nature of which has not been ascertained. Several re-checks on the sorting and counting of the appropriate cards were carried out in this connexion. Table I (a) shows, however, that more children were tested in this age group than in any other, while Fig. 2 shows that the percentage of lapses which occurred at this age is about the average of all age groups from 6 to 16 years. The source of error, therefore, if such exists, remains unexplained.

Sources of Error

(1) Observer Error

Error can arise in the performance and reading of the tests. It has been shown (Meyer *et al.*, 1951) that in duplicate Mantoux tests performed on the right and left arms in which the reactions were read independently but by one person there was disparity in the reading of negative and positive tests in 8% of cases. Sources of error here, however, were both in the performance of separate tests and in the reading of them. In the present survey the only error studied was that involved in the qualitative reading of single tests given by one person.

Double-observer readings were carried out in a sample of Mantoux tests in order to ascertain whether two observers would be necessary throughout the whole survey in order to achieve scientific accuracy. A total of 1,228 Mantoux tests were read by two observers (Dr. V. W. J. Hetreed and myself) reading independently and using the agreed criteria of 5 mm. or more of induration to indicate a positive reaction. The two observers were in a large room out of earshot from each other and seated back to back. The examinee approached the first observer, whose reading was recorded by the clerk attending him. This was recorded in red on the record card and the card was then handed back to the examinee, who proceeded to the second observer.

The record card was taken by the clerk attending the second observer in a way which precluded him from inadvertently seeing what was already recorded on it by the first observer. The second observer then made his reading, and this was recorded in blue by the attending clerk. Any examinee whose test was recorded as negative or doubtful by either observer was retested with 0.1 ml. of 1/100 O.T.—that is, 100 T.U. The final tests were also read by the two observers. The results are summarized in Table III.

TABLE III.—Summary of Double-observer Readings

1st Test, 1/10,000 O.T.	No.	2nd Test, 1/100 O.T.			No Second Test
		Neg.—Neg.	Neg.—Pos.	Pos.—Pos.	
Neg.—neg. ..	990	912	1	77	152
Neg.—doubtful ..	16			16	
Neg.—pos. ..	9			9	
Doubtful—doubtful ..	38			38	
Doubtful—pos. ..	23			23	
Pos.—pos. ..	152				
Total ..	1,228	912	1	163	152

Only qualitative differences in reading the tests are shown, though both qualitative and quantitative—that is, differences in millimetres of induration measured—differences were noted.

There are only two categories of double-observer readings: those of “negative-positive” and “doubtful-positive,” which include examinees who may not have been given a second test had there been only one observer. There are nine in the category “negative-positive” and 23 in the category “doubtful-positive.” All of these reacted positively to the second test. Thus had these 32 cases not been retested because a single observer had read them as positive on the first test this would have made no difference to the final figures of positive and negative reactors.

It was concluded from these results that no appreciable error was likely to arise through the qualitative reading of the tuberculin tests by one experienced person. One and the same reader only was therefore employed during the rest of the survey.

(2) Non-specific Reactions

Attention has been drawn (Palmer, Ferebee, and Petersen, 1950) to the possible occurrence of reactions of a non-specific character when using the larger doses of tuberculin. Positive reactors to a low dose of tuberculin among 10,000 white student nurses in the U.S.A., arranged according to lifetime residency in different States, occurred with a frequency which corresponded to known geographic variations in the prevalence of tuberculosis, whereas positive reactors to a higher dose showed a peculiar geographic distribution unrelated to known prevalence. This suggested “a local widespread non-specific sensitivity to tuberculin.”

This possible source of error is fully discussed in the M.R.C. tuberculin survey (Daniels, 1952). The conclusion is drawn that there is no evidence that with a dose of 100 T.U. the proportion of non-specific reactions is so high in this country as to warrant ignoring those positive only to doses greater than 10 T.U.—that is, 0.1 ml. of 1/1,000.

(3) Bovine Infection

Another possible source of error in using the results of a tuberculin survey as an index of total communal infection from human pulmonary sources is the existence in the community of the bovine type of infection. By comparing the percentage of positive reactors among children in an area in which tuberculosis in cattle was non-existent with that among children of similar age groups in an area where infection in cattle was frequent, it has been shown (Madsen, Holm, and Jensen, 1942) that infection with bovine bacilli may influence the results of tuberculin-testing surveys. That this may be a factor influencing the results is also borne out by the differences in percentages of positive reactors among children of school entry age from rural and urban areas in England and Wales (Daniels, 1952).

So far as the Rhondda Fach is concerned the proportion of notified cases of tuberculosis which are designated as non-pulmonary may give some indication of the prevalence of bovine tuberculous infection.

Table IV shows the number of respiratory and non-respiratory cases of tuberculosis notified during the years 1949, 1950, and 1951 in the Rhondda Fach area. The sharp

TABLE IV.—*Notified Cases of Respiratory and Non-respiratory Tuberculosis in the Rhondda Fach*

Year	Respiratory Tuberculosis	Non-respiratory Tuberculosis	Meningitis
1949 ..	59	6	—
1950 ..	87	9	2
1951 ..	66	5	2
Total ..	212	20	4

increase in the notifications for 1950 reflects the discovery of an abnormally large number of early cases of pulmonary tuberculosis through the intensive mass radiographic survey carried out in connexion with the research scheme.

In the four cases of meningitis human-type bacilli were recovered from the cerebrospinal fluid. In 9 out of the 20 cases of non-respiratory tuberculosis, tissue fluid was available for examination; in five of these, cultures were positive for tubercle bacilli and all were of human type (J. Glyn Cox, 1952, personal communication).

Information supplied by the Central Tuberculosis Laboratory of the Welsh Regional Hospital Board (J. Marks, 1952, personal communication), shows (Table V) that since 1943

TABLE V.—*Isolations of Human and Bovine Type of Tubercle Bacilli from Tuberculous Patients in Wales*

Year	Total Positive Cultures	Human Type	Bovine Type
1943 ..	554	499	55
1944 ..	511	463	48
1945 ..	484	453	31
1946 ..	442	416	26
1947 ..	536	519	17
1948 ..	569	541	28
1949 ..	1,041*	1,026	15
1950 ..	1,539*	1,534	5

* The increase in positive cultures reflects wider use of the laboratory.

there has been a steady decrease in the number of isolations of the bovine type of bacillus, suggesting that infection with this type has been responsible for only a small and steadily decreasing proportion of the total number of cases of tuberculosis.

This laboratory receives specimens from all over Wales, though about three-quarters of them come from the South Wales area, which includes the more densely populated counties of Monmouth and Glamorgan.

In Glan Ely Hospital, Fairwater, there are 110 beds for non-pulmonary tuberculosis, and most of such cases occurring in the South Wales area, including the Rhondda Fach, are admitted to this hospital. Information was made available by the medical superintendent (V. Emrys Jones, 1952, personal communication) to the effect that during the past five years not one of the large number of cases yielding positive cultures was due to a bovine infection.

The likelihood of bovine infection affecting the percentage of positive reactors in different age groups amongst the schoolchildren of the Rhondda Fach can also be related to the sources of milk supply to the school and homes. From information supplied by the Rhondda Urban District Council Health Department (D. J. Thomas, 1952, personal communication) it has been ascertained that licensed retail distributors of milk in the Rhondda Fach area obtain their supplies from four main wholesale sources. All of the milk so supplied is sterilized, pasteurized, or from tuberculin-tested herds. Of the 25 distributors, 23 supply milk which is from tuberculin-tested herds and pasteurized as well, and

the remaining two supply milk which is pasteurized or sterilized. These conditions of milk supply have been in existence in the Rhondda Fach for at least ten years, with the exception of three small farms which supplied raw milk in small localized areas until five years ago. One distributor, however, who possesses a small farm, produces about 8 gallons (36.4 litres) of milk a day, and this he retails intermittently in a very small locality. The sale of 8 gallons (36.4 litres) of untreated milk represents about 0.8% of the total milk sold daily in the entire valley. The bulk of the milk has for decades been imported into the district and, on account of the method of milk marketing during the past 20 years, heat treatment has been a commercial necessity.

It is therefore reasonable to conclude that bovine infection is unlikely to contribute to the number of positive reactors amongst the Rhondda Fach schoolchildren to an extent which would invalidate tuberculin surveys as an index of human tuberculous infectivity in that community.

A contrast is provided by the survey carried out in the Calder Valley in the county of Yorkshire (Keidan *et al.*, 1952). Out of a total school population of 6,532 in the Calder Valley 85% completed the skin-testing programme. A high prevalence of positive tuberculin reactors was found amongst the schoolchildren in this rural area when compared with those from Hull and Leeds. The reactor rates from Hull and Leeds closely approximate to those from the Rhondda Fach and to those from the urban areas of England and Wales, whereas the rates from the Calder Valley are much higher at every age group and exceed also the rates for rural England and Wales (Fig. 4). Table VI

FIG. 4.—Results of tuberculin-testing in the Rhondda Fach compared with those of the Calder Valley and Leeds.

TABLE VI.—*Tuberculosis Morbidity in the Calder Valley and in the Rhondda Fach*

	Total Cases Notified, All Types, per 100,000	Non-respiratory Cases Notified per 100,000	Percentage of Cases Non-respiratory
Calder Valley, 1948	460	215	46.7
Rhondda Fach, 1949	244	24	9.8

shows that the greater total morbidity from tuberculosis in the Calder Valley compared with that in the Rhondda Fach is almost entirely accounted for by the much higher proportion of non-respiratory cases notified in the former valley. These figures suggest, moreover, that the higher incidence of positive reactors found in the Calder Valley might be attributed to an excessive amount of bovine infection, a supposition which is supported by other direct evidence. The conditions appertaining to the supply of milk in the Calder Valley are in marked contrast to those in the Rhondda Fach, Hull, and Leeds. As much as 80% of all milk consumed in the Calder Valley is untreated, and about 40% of the cows in the area are positive tuberculin reactors. These findings therefore amount to strong circumstantial evidence that the difference in prevalence of positive tuberculin reactors in the Calder Valley and in the Rhondda Fach is related to a high incidence of bovine infection in the former and a low incidence in the latter.

(4) The Negative Reaction

Attention has been drawn (Rich, 1951) to the fact that a negative tuberculin test is not necessarily proof that a person has not been infected. He quotes many workers who have demonstrated the phenomenon of "reversion" from a positive to a negative test and have shown that such reversion can occur in as short a time as two years. He suggests that, in the past, available evidence tended to support the view that only in exceptional cases will the test be negative in healthy persons who have been previously infected, but that in the face of greatly changed conditions "it becomes possible that the results of the tuberculin test in present-day surveys no longer mirror so well the actual incidence of infection." The average duration of tuberculin sensitivity following a slight well-resisted infection is not known.

It is believed that reversion tends to occur only where the incidence of active disease, and therefore the chance of reinfection or superinfection, is very low. It may therefore influence the figures in schoolchildren living in rural and semi-rural areas with a milk supply free from infection, but it is less likely to affect those resulting from a survey in an urban area such as the Rhondda Fach.

(5) Use of the Multiple-puncture Test

It was recognized during the early stages of the survey that a number of children were "lost" on account of absenteeism during the routine of first testing, reading, re-testing, and again reading. Needle-puncture methods of tuberculin-testing have been described (Trambusti, 1928; Stewart, 1928) which presumably possess a number of advantages over Mantoux testing in mass surveys, chief of which are that it is a single procedure and that only 1% of complicated reactions occur, in contrast to 10% produced by Mantoux testing with 1/1,000 O.T. (Edwards and Savonen, 1951).

In order to ascertain whether a needle-puncture technique similar to the Trambusti test but employing multiple punctures and using undiluted adrenalized O.T. might prove to be a satisfactory single test, it was used in 1,109 cases as the initial test. The method and criteria adopted have already been described.

To ascertain whether the results in these cases could be included in the total figures, a comparability study between the multiple-puncture test and the accepted intradermal routine was undertaken in 692 cases.

Method of Comparability Study.—A multiple-puncture test was performed on the right arm and at the same time an intradermal test with 0.1 ml. of 1/10,000 O.T. was performed on the left arm. The tests were read 48 hours later in groups of 20 in the following way. The right arm of each examinee was exposed, the left arm being placed behind the back. The observer read the multiple-puncture test, keeping his attention deliberately and strictly only on the arm of the examinee. Whilst the observer left the room

the whole group was "shuffled." The right arm was now placed behind the back and the result of the intradermal test on the left arm was then read. Cases in which either test was read as negative were retested with 1/100 O.T.

Results of the Comparability Study.—It will be noted from Table VII that one false positive occurs in Category 2 multiple-puncture reactions and none in Category 3. Thus in 102 cases that would have been read as positive if multiple puncture alone had been used as the initial test, one would have been in error. Reference to Table I (a) shows that 231 cases were read as positive to the initial multiple-puncture test and were not retested. Two of these may have been "false positives"—an error which does not affect the validity of the total results.

It should be noted (Table VII) that, had the multiple-puncture test been used as a single test only, the Category 2 reaction would have been too high for reading a positive

TABLE VII.—Comparison Between Results of Multiple Puncture and Intradermal Tuberculin Testing in School Children

Reactions to Multiple-puncture Test			Reactions to Mantoux Tests			
Presumed Negative 0 1	Presumed Positive 2 3		1/10,000 O.T.		1/100 O.T.	
			Pos.	Neg.	Pos.	Neg.
561 29	60 42		—	561	22	539
			7	22	14	8
			43	17	16	1
			40	2	2	—
Total ..	692		90	602	54	548

test, since out of 29 reactions designated as Category 1 as many as 21 were positive to Mantoux testing. If, however, Category 1 reactions had been accepted as positive then 8 out of the 29 would have been in error. This is preliminary work with this test, and further investigations on the reading of the lowest category of reaction that can be regarded as positive is necessary before the multiple-puncture test can be used as a satisfactory single test in survey work requiring scientific accuracy.

Criteria for Reading a Positive Reaction

Although qualitative results only are shown in Table I, any measurable induration was recorded. The results on retesting cases which were read as qualitatively negative but in which some measurable induration was present are shown in Table VIII. Since only 12 out of 124 of such

TABLE VIII.—Results of Retesting with 1/100 Intradermal O.T. a Sample of Cases Designated after the First Test as "Negative," but Showing Some Measurable Induration

Reaction to 1st Test with 1/10,000 O.T.	Reaction to 2nd Test with 1/100 O.T. Induration Measured in mm.					
	0-5 mm.	5-10 mm.	10-20 mm.	20-30 mm.	30-40 mm.	40+ mm.
Negative "with measurement" .. 51	12		6	23	7	3
Doubtful "with measurement" .. 73			8	41	21	3
Total .. 124	12		14	64	28	6

cases proved negative on second testing with 1/100 O.T. and the measured induration of those reacting positively was high, the results suggest that the criterion of 5 mm. of induration for a positive test with 0.01 mg. of O.T. is probably too high.

Summary and Conclusions

Of the children on the school registers in the Rhondda Fach area, 71.9% were tuberculin-tested. The stages at which lapses occurred are presented and three-quarters of the total lapses are analysed by age groups.

Evidence is presented which suggests that the sample is adequate for the results to be considered as an accurate reflection of the total tuberculous infection in the community.

The trend of conversion rates at different age groups in the Rhondda Fach and in another valley are presented. These form a satisfactory basis for later comparison applicable to the studies which are to be continued in the future to ascertain the effect of the control of tuberculous infectivity in the Rhondda Fach.

Possible sources of error have been considered, including that of error in the qualitative reading of tuberculin tests by experienced observers, and none of these are regarded as invalidating the results and purpose of the survey.

A comparability study was carried out in 692 cases between the multiple-puncture method of tuberculin-testing and the normal intradermal method. The inclusion of figures obtained by the use of the multiple-puncture method of testing does not invalidate the results or conclusions drawn from the study. As yet the multiple-puncture test cannot be regarded as a satisfactory single test for survey work requiring scientific accuracy.

Evidence is presented that the criterion of 5 mm. of induration for the reading of a positive test with 0.01 mg. of O.T. is probably too high.

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REFERENCES

- Cochrane, A. L., Cox, J. Glyn, and Jarman, T. F. (1952). *British Medical Journal*, 2, 843.
 Daniels, M. (1952). *Lancet*, 1, 775.
 Edwards, P. Q., and Savoner, S. (1951). *Publ. Hlth Rep., Wash.*, 66, 1625.
 Heaf, F. (1951). *Lancet*, 2, 151.
 Keidan, S., Lyons, J., Mann, B., and Wilthew, G. A. (1952). *British Medical Journal*, 1, 1390.
 Madsen, T., Holm, J., and Jensen, K. A. (1942). *Acta tuberc. scand.*, 16, Suppl. 6, p. 9.
 Meyer, S. N., Hougen, A., and Edwards, P. (1951). *Publ. Hlth Rep., Wash.*, 66, 561.
 Myers, J. A. (1946). *Ibid.*, 61, 1563.
 Palmer, Carol E., Ferebee, S. H., and Petersen, O. S. (1950). *Ibid.*, 65, 1411.
 Rich, Arnold R. (1951). *The Pathogenesis of Pulmonary Tuberculosis*. Thomas, Springfield, Ill.
 Stewart, Chester A. (1928). *Amer. J. Dis. Child.*, 35, 388.
 Trambusti, Brune (1928). *Boll. Ist. sieroter. milan.*, 7, 371.
 Ustvedt, H. J. (1942). *Pulmonary Tuberculosis and its Treatment*, translated by A. L. Jacobs. John Bale Medical Publications, London.

Dr. Max J. Miller, of the Institute of Parasitology, McGill University, has recently been appointed Research Director of the Liberian Institute of the American Foundation for Tropical Medicine. The Foundation was incorporated in 1934, and is associated with the American Society of Tropical Medicine and the American Academy of Tropical Medicine. The Foundation supports the teaching of tropical medicine in medical schools and promotes research into tropical disorders. The Liberian Institute was established in 1946 to carry on comprehensive research on the origins, treatment, and control of tropical diseases. The Institute's immediate objective is to provide an international laboratory centre where medical, governmental, educational, and industrial scientists of all nationalities can unite in a common attack on diseases of man and domestic animals, and on the production of balanced food crops for both man and animals.

CHLORAMPHENICOL TREATMENT OF THE NEWBORN

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The synthesis and large-scale production of chloramphenicol has made available everywhere a valuable antibiotic, effective against a wide range of pathogenic organisms, including strains resistant to penicillin. As the drug can be taken by mouth, vast numbers of patients, old and young, have been treated somewhat empirically, and it is not surprising that some of the hundreds of papers describing successful therapy disclose serious toxic effects. Most of the reports of fatal aplasia of bone marrow are associated with relatively large doses, or prolonged or repeated treatment with the drug (Hawkins and Lederer, 1952; Sturgeon, 1952; Smiley *et al.*, 1952; Claudon and Holbrook, 1952; Wolman, 1952).

It has therefore become necessary that the clinician should know exactly what serum concentration to expect from a recommended dose. In the case of adults this was provided by Ley *et al.* (1948) and by Hewitt and Williams (1950). For children, Kelly *et al.* (1951) have reported blood-serum levels, and shown how long they persist. As their series contained only one baby less than 6 kg. in weight, an investigation was undertaken in order to establish serum levels obtained in babies during the first fortnight of life.

A group of babies suffering from staphylococcal infections was therefore selected for trial with chloramphenicol therapy.

Present Investigation

Methods.—Blood was obtained in sterile Wright's capillaries from heel puncture. With this method quite small quantities of blood yielded enough serum for assay.

Assay.—Numerous different organisms have been used for the biological assay of chloramphenicol levels in blood serum. The organism most commonly recommended is *Sh. sonnei*. We have tested various other bacteria and found that, using the capillary technique of Fleming (1944), one of our strains of Group A beta-haemolytic streptococci (9570) was conveniently inhibited by exactly 1 µg. of chloramphenicol per ml. The use of this strain clearly simplified the estimation of chloramphenicol levels when a result in µg. per ml. of serum was required.

Test.—The results were read after incubation at 37° C. overnight, the end-point being the tube in which the test organism just failed to grow. This was confirmed by Gram-staining where there was any doubt.

Dosage of Drug.—In order to ensure that all of the intended dose was taken by the babies, chloramphenicol was dispensed as a powder, each powder being made up separately in a waxed paper packet, according to the infant's weight. The powder was given by teaspoon, together with a small amount of syrup. By the dosage scheme, only a limited series of weighed powders need be held by the dispensary to meet the requirements of babies of different sizes, and powders of appropriate amount were available at all times of the day and night. As will be seen from the Table, even at the extremes of each weight range the