A REINVESTIGATION OF CHILDREN PREVIOUSLY EXAMINED BY TUBERCULIN TESTS*

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In 1931 a report was published by this department on the incidence of tuberculous infection in children (Brompton Hospital Research Department, Report II) in which there were given the results of a series of von Pirquet and Mantoux tests on 1,220 children up to the age of 15 years. As many as possible of these have been retested and examined after an interval of one and a half to two years, with a view to finding whether there was any change in reaction to the tuberculin tests, and whether any of them had developed clinical signs and symptoms of tuberculosis. Of those previously tested 700 returned for re-examination.

In the previous report the children were separated into three groups: (1) those who had been in contact with a person known to have had tubercle bacilli in the sputum—that is, contacts; (2) those in contact with a person suffering from tuberculosis but without tubercle bacilli in the sputum; and (3) those without any known contact. It was found that the incidence of tuberculosis as shown by the Mantoux test was practically the same in groups (2) and (3); therefore in this investigation the children have been divided into two groups—namely, (1) contact, and (2) non-contact.

Of the 1,220 children tested in 1930-1, 200 were tested by the von Pirquet method and the remainder by that of Mantoux, with 0.1 c.cm. of these dilutions of old tuberculin: 1 in 10,000, 1 in 1,000, and 1 in 100. In the present investigation all the retests were done by the Mantoux method, the same brew of old tuberculin used in 1930-1 being employed and in similar dilutions. The readings were taken after an interval of forty-eight hours to prevent confusion with non-specific reactions; these were most frequent after injections with 1 in 100 old tuberculin, and usually occurred within twelve to twenty-four hours after injection; but in most cases they had disappeared within forty-eight hours or only showed very faintly.

CHANGES IN REACTION TO TUBERCULIN

A comparison was made between the results of the tests after an interval of one and a half to two years to determine whether sensitivity to tuberculin was retained or lost. The results are shown in Table I.

Thirty-three of these cases which gave a positive von Pirquet in 1930 gave positive Mantoux reactions (1 in 10,000 or 1 in 1,000) in 1932; eighty-two were negative to von Pirquet's test, and of these sixteen became positive (in varying dilutions) and sixty-six negative (1 in 100) to the Mantoux test. In the previous report it was shown that the Mantoux test is more sensitive than the von Pirquet, the latter being equivalent to 0.1 c.cm. of 1 in 10,000 old tuberculin (O.T.) given intracutaneously. Therefore the number of changes from negative to positive is higher than it would have been if the comparison had been made with the more sensitive Mantoux method in all cases. Out of 303 children there were twelve (4 per cent.) whose reaction changed from positive to negative. An analysis of these cases was made with the following results: three

of the children tested in 1932 were not seen for the reading, but the result was reported by the parent; two were positive to 1 in 1,000 O.T. in 1930, but the reaction was slight; one was positive to 1 in 10,000 in 1930 and

TABLE I

	Cases Retested					
	No. of Cases	Per-centage	Contact		Non-contact	
			No. of Cases	Per-centage	No. of Cases	Per-centage
Positive 1930-1:						
Remaining positive	291	96.0	112	96.6	179	95.6
Becoming negative	12	4.0	4	3.4	8	4.3
Total ...	303	—	116	—	187	—
Negative 1930-1:						
Remaining negative	343	85.4	38	79.2	305	87.4
Becoming positive	54	13.6	10	20.8	44	12.6
Total ...	397	—	48	—	349	—

negative to 1 in 1,000 in 1932, but it was not possible to test with 1 in 100; six were positive to 1 in 100 in 1930, and became negative to 1 in 100 in 1932. Therefore there are less than 4 per cent. who, without doubt, changed from positive to negative, and it is questionable if so low a figure as this is of any special significance.

In 1930-1 397 children were negative to the tuberculin test, and of these fifty-four (13.6 per cent.) became positive in 1932. These fifty-four, of whom ten were contacts, were further investigated by inquiry into their clinical history during the interval between the two tests. The past occurrence of any acute or definite illness would be ascertained in this way, although, admittedly, minor illnesses and indispositions might be overlooked. Six children had a definite history of illness, two having had pneumonia, one acute bronchitis, one tuberculous abscess of the neck, and two measles. Two children, both 4 years old, were debilitated and much below normal weight and development. In eleven cases the symptoms of asthma and chronic pulmonary catarrh, which were present at the first test, persisted. The other thirty-one children were reported to have been free from symptoms, and in these the primary infection by the tubercle bacillus was not accompanied by any disturbance worthy of note by the parents.

That thirty-eight of the contact children remained negative is explained by the fact that their exposure to tuberculous infection during the one and a half to two years was slight, and, in fact, differed little from that of the non-contact children. Details of the degree of exposure to infection are as follows: in twenty-three cases the parent had at one time had tubercle bacilli in the sputum, but there had been no known positive sputum test since the birth of the child; therefore it may be argued that these were not strictly contact cases. In two instances the parent had died before the first test was done, so that there had been no known contact since that time. In no case in which the child remained negative was the parent or other relation known to have had a positive sputum test since 1930-1.

CHANGES IN DEGREE OF ALLERGY

Changes in the sensitivity to tuberculin were studied by comparing the lowest concentrations to which the children reacted on the two occasions. Each child who had reacted to 0.1 c.cm. of the 1 in 10,000 O.T. was retested with this strength, and, if negative, was tested

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with 1 in 1,000, and if negative to this with 1 in 100. Those who had been previously positive to 1 in 1,000 or to 1 in 100 were tested with each strength in turn, beginning with the 1 in 10,000 dilution, and, if necessary, increasing to 1 in 1,000 or to 1 in 100 until a positive reaction occurred.

TABLE II

	Positive 1 in 10,000 in 1930-1			Positive 1 in 1,000 in 1930-1			Positive 1 in 100 in 1930-1		
	No. of Cases	Contact	Non- contact	No. of Cases	Contact	Non- contact	No. of Cases	Contact	Non- contact
Positive, 1932:									
1 in 10,000 ...	140	59	81	39	14	25	3	1	2
1 in 1,000 ...	5	2	3	33	12	21	13	1	12
1 in 100 ...	0	0	0	5	0	5	7	0	7
Negative, 1932:									
1 in 100 ...	1	1	0	2	0	2	5	1	4
1 in 1,000 ...	3	2	1	1	0	1	0	0	0
Total...	149	64	85	80	26	54	28	3	25

Eighty children were positive to 1 in 1,000 and negative to 1 in 10,000 in 1930-1, and of these, thirty-nine (nearly 50 per cent.) now react to 1 in 10,000 dilution; in twenty-eight children a positive reaction was obtained with dilution 1 in 100 only in 1930-1, but in 1932, three react to 1 in 10,000 and thirteen to 1 in 1,000; therefore sixteen (more than 50 per cent.) respond to a weaker concentration. Out of all those who reacted positively in 1930-1, there are very few who have decreased their degree of allergy as shown by the above figures, and in about 50 per cent. there is an increase in sensitivity.

A comparison of the sensitivity of different age groups was made, and for this the result of the first test done on each child was used. The figures below are based chiefly on those given in Report II of the Brompton Hospital Research Department. Each child reported as positive to 1 in 1,000 or positive to 1 in 100 was negative to 1 in 10,000 or 1 in 1,000 respectively. The contact and non-contact children were considered separately, and were divided into four age groups.

TABLE III

Dilutions	Positive Reactors							
	0 to 5 years		5 to 10 years		10 to 15 years		15 yrs. & over	
	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.
Contact:								
1 in 10,000 ...	27	71.1	72	74.2	76	68.5	12	60.0
1 in 1,000 ...	10	26.3	20	20.6	30	27.0	8	40.0
1 in 100 ...	1	2.6	5	5.2	5	4.5	0	—
Non-contact:								
1 in 10,000 ...	13	52.0	97	62.8	81	52.6	15	60.0
1 in 1,000 ...	10	40.0	39	25.0	50	32.5	9	36.0
1 in 100 ...	2	8.0	20	12.2	23	14.9	1	4.0

A large percentage of the contact children are positive to 1 in 10,000 at an early age, and this percentage varies very little over the period 0-15 years. In the non-contact children the percentage positive to 1 in 10,000 in all age groups is comparatively low, and never reaches as high as that of the youngest group of the contacts. In the contact children there is apparently a quick process of reaching a high degree of allergy, while in the non-contact ones there is a smaller percentage which reaches the same

high degree of sensitivity. It has not been possible for us to test the majority of the contact children at a sufficiently early age to observe the change from negative to positive and to note with which dilution the first reaction after infection is obtained.

CLINICAL STUDIES

The second part of the investigation was concerned with the incidence of clinical tuberculosis in the 700 children retested. Of these, seven were suffering from pulmonary tuberculosis when first tested, but when seen at the time of the second test they had all improved and the disease was quiescent. Their ages were 8, 10, 11 (two), 13 (two), and 14 years, and four of them had a history of contact with open tuberculosis. Besides these seven, there were five children with pulmonary tuberculosis who were tested in 1930 only, of whom four—13, 14, 15, and 16 years old respectively in 1930—have died of the disease; and one, aged 14 years, is in a sanatorium at present. Of the other 693, none has developed clinical tuberculosis during the interval between the two tests. This number includes 303 who were originally positive reactors to von Pirquet or Mantoux tests. Their ages are given below, and it will be seen that twenty-four of these were under the age of 5 years when first tested.

TABLE IV

Age	Contact	Non-contact	Total
0 to 5 years ...	14	10	24
5 to 10 years ...	62	93	155
10 to 15 years ...	38	76	114
15 years and over ...	5	5	10

A more detailed investigation of these twenty-four children is given below.

POSITIVE REACTORS UNDER 5 YEARS OF AGE

The group of positive reactors under 5 years of age consists of twenty-four children, fourteen of whom were contacts. Their ages at the time of the first test are given in the following table.

TABLE V

Age	Contact	Non-contact	Total
0 to 1 year ...	0	0	0
1 to 2 years ...	2	0	2
2 to 3 years ...	2	3	5
3 to 4 years ...	2	4	6
4 to 5 years ...	6	5	11

The history of each child during the interval between the tests, the general and pulmonary condition in 1932, and the degree of exposure to tuberculous infection in the case of the contact children, were noted. In five of the contact cases the infected parent had died before the first test, and there had been no known contact since; in four the tuberculous relative had apparently been well, and had not been known to have had a positive sputum during the past two years; in five the parent had had tubercule bacilli in the sputum since 1930-1, and the child had been in close contact. Therefore in five cases out of the twenty-four there was a history of continuous exposure to tuberculous infection.

The history and clinical condition of the twenty-four children was as follows: eighteen had had no symptoms or signs during the one and a half or two years, and their

general and pulmonary condition in 1932 was normal; one child had had no symptoms, but there were signs of fibrosis at the base of one lung following collapse of the lower lobe, which was recognized in 1930 but for which no definite cause was ascertained on investigation; one had had no symptoms, but his general condition was poor, although there were no definite abnormal physical signs; one had bronchitis when the second test was done; one had rheumatic myocarditis at the time of the second test, but had had no pulmonary symptoms during the two years, and there were no abnormal signs in the lungs in 1932; one had enlarged and unhealthy tonsils in 1932, but was otherwise healthy; and one had slightly enlarged discrete cervical glands, which had remained unaltered since 1930. Three children under 5 years of age, who were positive in 1930, cannot be traced.

None of the children examined was ill, and with one exception their general condition was good. Although the numbers are small, it is interesting to note that of these twenty-four children under 5 years (two of whom were under 2) who had been infected with the tubercle bacillus none had had an acute dissemination of the disease, and none, except perhaps the child with cervical adenitis, had clinical tuberculosis.

CONCLUSIONS

The results of the repetition of the tuberculin test on 700 children whose ages varied from 1 to 15 years at the time of the first test show that allergy, once it is produced, persists in over 96 per cent. of cases throughout childhood.

A comparison of the different dilutions of old tuberculin which will produce a positive tuberculin reaction demonstrates the fact that there is a tendency for the degree of sensitivity to increase after an interval of one and a half to two years. Further, on separating the children into contact and non-contact groups, it is evident that a high degree of sensitivity in contact children is reached at an early age, whereas in a large percentage of non-contact children this degree of allergy is not reached at any age.

The absence of any development of clinical tuberculosis in 700 children during the period of one and a half to two years is interesting, more especially as this number includes two children of 1 to 2 years of age and seven under 3 years. That these children have remained apparently healthy throws doubt on the view which is held by some authors that a positive tuberculin reaction in a child under 2 years of age is evidence of active tuberculous disease.

SUMMARY

1. After an interval of one and a half to two years 700 children, 164 of whom were contact cases, were retested with tuberculin with the Mantoux method, and were examined for signs of tuberculosis.

2. Investigation has shown that in over 96 per cent. of cases positive reactors have remained positive after an interval of one and a half to two years. The change from negative to positive reaction, in at least thirty-one out of fifty-four cases, took place without any notable disturbance to the health of the child.

3. By using dilutions of 1 in 10,000, 1 in 1,000, and 1 in 100 O.T. it was shown that there is a tendency for the reactions to occur with higher dilutions of O.T. after one and a half to two years' interval.

4. Seven of the 700 children had pulmonary tuberculosis when first examined, but had improved in 1932. Of the remainder none has developed clinical tuberculosis. This number includes twenty-four who were under 5 years when first positive to the tuberculin test, and of these two were under 2 years of age.

We wish to express our thanks to the honorary medical staff of the hospital for permission to make use of their cases, and to the lady almoner, Miss Marx, for valuable help in tracing the children.

SEVERE ANAEMIA WITH ACHLORHYDRIA*

BY

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We come across three different clinical forms of severe anaemia associated with the absence of free hydrochloric acid from the gastric juice: (1) pernicious anaemia; (2) anaemia associated with carcinoma of the stomach; and (3) a form of anaemia of secondary type associated with neither of the above conditions.

I

Pernicious anaemia shows all the characteristic signs and symptoms met with in severe anaemia due to any cause. But it may or may not show, in addition, certain other features affecting the alimentary tract, as sore tongue, nausea, vomiting, and diarrhoea, or the nervous system as postero-lateral sclerosis. But the final decision must rest on the blood examination, and this is characteristic and absolutely diagnostic. There is great diminution both of the red corpuscles and of the haemoglobin, but the special feature is that the red corpuscles are proportionately more reduced than the haemoglobin, so that each corpuscle on the average contains *more* haemoglobin than does a normal red corpuscle. This is expressed in the statement that the colour index is above 1. Accordingly on examining a film it is recognized that on the average the corpuscles are larger than normal. This may be confirmed by an elaborate process of measurement, though this is rarely necessary. The presence of these large corpuscles, macrocytes, is a characteristic feature of the anaemia, and is found in no other condition, except certain unusual and rarely met with conditions. There is also marked variation in size. In addition to the macrocytes, microcytes—corpuscles smaller than normal—are encountered, and their presence makes the macrocytic condition more strikingly evident than even the raised colour index would indicate. In addition to this macrocytosis and anisocytosis there is marked departure from the normal shape—poikilocytosis—and the corpuscles may be oval or pear-shaped or depart still more from the normal rounded form. It is not that an occasional corpuscle here or there departs from its natural form (that may happen in any kind of severe anaemia), but that the great majority do so, and one may have to look carefully for any of the normal round shape. This tendency for the corpuscles to be oval† instead of round is one that I have emphasized for a long time back, and is sometimes even more striking than the large average size. There are other departures from the normal—the presence of nucleated and abnormally staining red corpuscles, departures from the normal proportions of the various forms of leucocytes, and diminution of the blood platelets—but the features of the red corpuscles that I have already described are the most important, and are in themselves diagnostic.

A good many patients with pernicious anaemia appear to digest their food well and maintain their body weight. But on looking through my record of cases over the last twenty or thirty years I come across a fair number of patients with pernicious anaemia in whom anorexia or complete loss of any inclination for food was present. This is a symptom that one had commonly come to associate with absence of free hydrochloric acid from the gastric juice, and accordingly in these patients I was accustomed to use medicinal doses of hydrochloric or

* Post-graduate lecture, Manchester Royal Infirmary, November 29th, 1932.

† On showing a film of his patient's blood to one practitioner, who had a clear recollection of his biological days, he exclaimed, "Why! it's just like frog's blood."