PAPERS AND ORIGINALS

Interpretation of Positive Reactions to Heaf Tuberculin Test in London Schoolchildren

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Summary

A study of 289 children aged 12-14 years found to be Heaf test positive at routine testing was made to determine the likely cause of the positive tests. Only 12% of children grade 1 Heaf positive were likely to have had a previous infection with *Mycobacterium tuberculosis*, 49% were likely to have had infections with atypical mycobacteria, and in 39% no cause for the positive Heaf test was found.

The positive Heaf test seems to us to be too sensitive. Both a negative and grade 1 positive should be regarded as not significant and these children given B.C.G. vaccine. Heaf grades 2, 3, and 4 should be regarded as significant and the children investigated for *M. tuberculosis* infection.

Introduction

There has been controversy about the interpretation of positive reactions to the Heaf multiple-puncture tuberculin test (Collins, 1968) since the discovery in the United States that in adults exhibiting low-grade sensitivity to mammalian tuberculin the reaction may be due to atypical mycobacterial infection and not to infection with *Mycobacterium tuberculosis* (Palmer and Edwards, 1967).

The purpose of this investigation was to determine by differential Mantoux testing, with mammalian purified protein derivative (P.P.D.) prepared from *M. tuberculosis* and P.P.D.s

prepared from atypical mycobacteria, the likely cause of positive reactions found on routine Heaf testing of schoolchildren aged 12-14 years in London.

Subjects and Method

The investigation took place between November 1969 and June 1971 in children attending 23 secondary schools in the London borough of Newham. Children found to be Heaf test positive on routine testing in school who had not previously been given B.C.G. vaccine and whose parents consented to their participation in the study were Mantoux tested at least five weeks after the Heaf test.

In a pilot study which preceded the main investigation four Mantoux tests were performed on each child, but in the main investigation one of these was replaced by a repeat Heaf test (see Table I). Children in whom the Mantoux tests indicated that the tuberculin sensitivity was likely to be due to infection with *M. tuberculosis* were physically examined, had a chest x-ray examination, and were kept under observation for at least 12 months.

Routine Heaf Test.—The tests were performed with six-needle guns sterilized by flaming. The skin of the forearm was cleaned with isopropyl alcohol and the P.P.D. was applied by dropper and spread with the end-plate of the gun before firing. The tests were read at seven days by medical officers trained in this work, who were undertaking the usual B.C.G. vaccination programme in schools, and classified as follows: Heaf grade 0, no reaction or six faint marks on the skin without induration; Heaf grade 1, four or more discrete palpable papules at least 1 mm in diameter; Heaf grade 2, papules forming a ring with normal skin in the middle; Heaf grade 3, a plateau of induration; and Heaf grade 4, vesiculation or ulceration.

Mantoux Tests.—These tests were performed with disposable syringes and needles by one doctor, 0.1 ml of P.P.D. being injected intradermally into the forearm at least 2 in (5 cm) from the site of the initial routine Heaf test. The tests were read at three days by the same doctor, the transverse diameter of induration being measured with a plastic ruler. The repeat Heaf test given instead of the fourth Mantoux test in the main investigation was performed in the same way as the routine Heaf test already described but was read at three days with the Mantoux tests and not at seven days.

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Tuberculin.—(a) *Heaf tests*: mammalian tuberculin prepared from *M. tuberculosis*, three strains C, DT, and PN equally mixed, containing 2 mg of P.P.D. per ml, equivalent to 100,000 IU/ml, as normally supplied for routine Heaf testing in the United Kingdom. (b) *Mantoux tests*: a solution of known concentration of P.P.D. from each of four mycobacteria was diluted in phosphate-buffered saline to produce a solution containing the equivalent by weight of 5 tuberculin units per 0.1 ml—(1) *M. tuberculosis*, strains C, DT, and PN equally mixed; (2) *M. avium*, strain D4; (3) *M. intracellulare* (synonym Battey organism), strain 100616; (4) *M. scrofulaceum* (synonym *M. marinum*), strain Bu. The solutions were injected into the children within five days of preparation.

Results

Altogether 289 children took part in the investigation, of whom 213 were Heaf positive grade 1 on initial routine testing, 56 were grade 2, and 20 were grade 3 or 4 (Table I).

Of the 213 children who were initially Heaf grade 1, in only 16 (8%) was the mammalian P.P.D. reaction greater than the atypical reaction, and in a further 9 (4%) the reactions were equal $\pm$ 1 mm. These 25 (12%) children were the maximum number likely to have been infected with *M. tuberculosis*. Of the 56 children initially Heaf grade 2 the proportion likely to have

been infected with *M. tuberculosis* was 38%, and of the 20 children who were Heaf grade 3 or 4 all were likely to have been infected (Table II).

Over one-third (39%) of the children initially Heaf positive grade 1 were Mantoux negative (induration less than 5 mm) to mammalian and atypical P.P.D.s (Table II). If the mammalian Mantoux test is considered alone 161 (76%) of the children were Mantoux negative; the proportion Mantoux negative did not differ significantly between children tested 35 to 40 days after the Heaf test and those tested 41 to 55 days after the Heaf test. Although, as was expected, there was variability between the grades recorded at the initial and second Heaf tests a similar proportion (77%) of the children classified as grade 1 at the second test were Mantoux negative.

The reaction to atypical P.P.D. was greater than that to mammalian P.P.D. in 135 (46%) children, and *M. avium* P.P.D. produced a larger reaction than Battey P.P.D. in about two-thirds of them (Table II). The results in boys and girls were similar.

In children with Heaf grade 1 reactions 63% (37 children) of those born abroad had a positive reaction to atypical P.P.D. compared with only 44% (67 children) of those born in the United Kingdom. In a greater proportion of children born abroad Battey P.P.D. produced a larger reaction than *M. avium* P.P.D. (Table III). However, the number of children born abroad was small and these differences were not statistically significant.

TABLE I—Schedule of Study and Numbers of Children Taking Part

		Heaf Grade			Total
		1	2	3 or 4	
Day 0	Routine Heaf test (read at 7 days)	213	56	20	289
Day 35	Pilot study. Mantoux tests* (read at 3 days)	30	8	3	41
	1. Mammalian P.P.D.				
	2. Avium P.P.D.				
	3. Battey P.P.D.				
	4. Scrofulaceum P.P.D.				
Days 35 to 55 ..	Main study. Mantoux tests* (read at 3 days)	183	48	17	248
	1. Mammalian P.P.D.				
	2. Avium P.P.D.				
	3. Battey P.P.D.				
	4. Heaf test† (read at 3 days)				

* The four Mantoux tests were given at the same time avoiding the site of the initial routine Heaf test.

† The repeat Heaf test was omitted in the 17 children initially Heaf grade 3 or 4.

TABLE II—Relation of Mantoux Reactions to Initial Heaf Test

Initial Routine Heaf Test Grade	No. (%) of Children					Total Mantoux Tested
	Mantoux Negative (Induration <5 mm)	Mantoux Positive (Induration $\geq$ 5 mm)				
		Mammalian (2 mm or more > atypical)	Mammalian/ Atypical (equal $\pm$ 1 mm)	Atypical (2 mm or more > mammalian)		
				Avium		
1	84 (39)	16 (8)	5 (4)	68 (32)*	36 (17)	213 (100)
2	4 (7)	13 (24)	8 (14)	23 (41)	8 (14)	56 (100)
3 or 4	0	13 (65)	7 (35)	0	0	20 (100)
Total Heaf positive	88 (31)	42 (15)	24 (8)	91 (31)*	44 (15)	289 (100)

* One child had equal avium and Battey Mantoux reactions.

TABLE III—Relation of Mantoux Reactions to Place of Birth in the 213 Heaf Test Grade 1 Children

Place of Birth	No. (%) of Children					Total Mantoux Tested
	Mantoux Negative (Induration < 5 mm)	Mantoux Positive (Induration ≥ 5 mm)				
		Mammalian (2 mm or more > atypical)	Mammalian/ Atypical (equal ± 1 mm)	Atypical (2 mm or more > mammalian)		
				Avium		
United Kingdom	68 (44)	11 (7)	8 (5)	46 (30)	21 (14)	154 (100)
Africa	3 (33)	1 (11)	0	4 (45)	1 (11)	9 (100)
Asia	7 (47)	1 (7)	1 (7)	2 (13)	4 (26)	15 (100)
West Indies	6 (17)	3 (8)	0	16 (46)*	10 (29)	35 (100)
Total	84 (39)	16 (8)	9 (4)	68 (32)*	36 (17)	213 (100)

* One child had equal avium and Battey Mantoux reactions.

In the pilot study 41 children were Mantoux tested with *M. scrofulaceum* P.P.D. (Table I); only seven were positive, and in all of them the reaction was smaller than that caused by *M. avium* or Battey P.P.D.

All except one of the 25 children initially grade 1 whose Mantoux reactions indicated possible infection with *M. tuberculosis* were seen at least 12 months after the Heaf test. Nothing abnormal was found on physical examination or in the chest x-ray picture. Similarly 19 of the 21 children initially Heaf grade 2 were seen; all were normal on physical and radiological examination. One of the 20 children initially grade 3 or 4 had hilar lymph-node enlargement with a Ghon focus and was given anti-tuberculous drugs, 3 showed evidence of a calcified primary complex, and the remaining 16 were clinically and radiologically normal both immediately after the Heaf test and on follow-up at least 12 months later.

Discussion

The purpose of the routine Heaf testing of children aged 12-14 years in the United Kingdom is to separate them into two groups, those requiring B.C.G. vaccination and those requiring investigation of possible *M. tuberculosis* infection. Hitherto, Heaf-negative children have been vaccinated and Heaf-positive children have been examined clinically and radiologically.

This study of Heaf-positive children in Newham shows that the Heaf test as at present interpreted is too sensitive for this purpose—only 25 (12%) of 213 children who were initially grade 1 positive were likely to have been infected with *M. tuberculosis*; the other grade 1 positive reactions were not significant. None of these 25 children, 24 of whom were followed up for at least 12 months, had evidence of active tuberculosis, and our previous experience has been that neither the children with Heaf grade 1 reactions nor their families have active tuberculosis.

Our findings indicate that the investigation of all the Heaf grade 1 children would subject 88% of them to unnecessary chest x-ray examination and deny them the protection afforded by B.C.G. vaccine.

We recommend the routine B.C.G. vaccination of children

with Heaf grade 1 reactions because we think that the risk of missing active tuberculosis in a small proportion of these children or their families is remote and far outweighed by the advantages to nearly 90% of the children of B.C.G. vaccination and the avoidance of unnecessary chest x-ray examination. We have already shown that the vaccination of children who are Heaf positive grade 1 does not give rise to any untoward reactions (Report, 1969).

We suggest, therefore, that Heaf grades 0 and 1 should be regarded as not significant and agree with Collins (1968) that the terms Heaf-negative and Heaf-positive should be abandoned in favour of "not significant" and "significant."

A more accurate division of the children into those likely to have been previously infected with *M. tuberculosis* and those who have not been infected could be made by double Mantoux testing using mammalian P.P.D. and atypical P.P.D. (Palmer and Edwards, 1968). Our results suggest that *M. avium* P.P.D. would be the most suitable in this country. Such a double Mantoux test would not be practicable in Newham, however, where the Heaf test is used because of its acceptability to school-children and the ease and rapidity of performance. It is for this reason that we recommend the continued use of the Heaf test in 12-14-year-old children provided that the children with Heaf grades 0 and 1 are vaccinated and only those with grades 2, 3, and 4 are investigated for infection with *M. tuberculosis*.

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Assessment of the Need for Continued Oral Therapy in Diabetics

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Summary

Hypoglycaemic agents were replaced by placebos in diabetic patients attending a hospital clinic. Of 62 patients observed, 43 (69%) relapsed within six months but blood sugar control remained unchanged in 19 (31%) during the period of observation.

Introduction

Tablet therapy for diabetes came into general use in 1956, and tolbutamide was one of the first drugs so to be used. Since then

this type of treatment has been extended by the use of other compounds in the sulphonylurea group and by the introduction of the biguanides. From the beginning it had been realized that although oral therapy was successful in reducing blood sugar levels in mild diabetes, the long-term effects were less certain. In particular, it could not be predicted whether or not these compounds would be able to delay the appearance of the degenerative disorders that occur in long-standing diabetes. In 1959 a group of American clinicians and statisticians met to discuss this problem and by 1961 a co-operative prospective study had been started in six university centres, later expanded to 12, under the title of the University Group Diabetes Program (1970, 1971).

More than 800 recently diagnosed diabetic patients were assigned at random to various treatment groups. After a follow-up period ranging from five to eight years it emerged that the death rate from cardiovascular disease, both in the tolbutamide-treated group and in the phenformin-treated group, was sig-

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