Levels of IgG and C1q-binding complexes ranked in order of level of IgG complexes in matched pre-eclamptic patients and normally pregnant controls

Patients with pre-eclampsia					Matched control			
Case No	Gestation (weeks)	Parity	Complexes (% inhibition)		Gestation (weeks)	Parity	Complexes (% inhibition)	
			IgG	C1q			IgG	C1q
1	40	0	3·0	3·7	40	0	32·5	27·5
2	32	0	5·5	17·7	32	0	Nil	7·8
3	29	0	6·3	33·2	29	0	9·5	11·3
4	29	1	16·0	20·5	29	1	26·5	29·9
5	31	0	19·1	21·6	31	0	16·3	24·7
6	35	0	26·1	15·2	35	0	9·0	7·5
7	28	0	27·5	24·0	28	0	Nil	3·4
8	33	0+1	27·8	35·1	33	1	23·3	14·4
9	31	4+1	29·7	29·7	31	3	15·2	19·2
10	29	0	32·2	37·0	29	0	0·4	1·0
11	28	0	33·5	41·6	28	0	17·5	19·0
12	34	1	33·5	34·3	34	1	Nil	5·1
13	36	0	34·5	33·9	36	0	Nil	Nil
14	34	0	41·5	30·9	34	0	8·5	10·5
15	34	0	45·3	49·3	34	0	29·8	26·3
16	35	0	50·5	46·8	35	0	Nil	13·8
Mean			27·0*	27·8†		Mean	11·8*	13·8†

*P<0·005; †P<0·005, Wilcoxon's rank sum test.

such clinical features of pre-eclampsia as the immunoglobulin and complement deposition in renal glomeruli,[5] the early activation of the coagulation system,[6] platelet consumption,[7] and IgG depletion.[8] The raised levels of immune complexes in normal pregnancies that have been observed by ourselves and others[1] support the view that circulating immune complexes are not in themselves necessarily pathological in human pregnancy. Immune complexes are, however, heterogenous in terms of immunoglobulin class, subclass, size, and complement-binding capacity as well as the antigen involved, and a detailed examination of these differences has yet to be made in pregnancy. Thus, in our two patients who had low levels of circulating IgG complexes associated with much greater C1q-binding the predominant antibody might have been IgM rather than IgG. Until the properties of the immune complexes in normal and pre-eclamptic pregnancies are better characterised, the significance and function of the complexes will not be understood. This problem is to be examined in the next phase of our investigations.

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Comparison of the tine and Mantoux tuberculin tests

Report of the Tuberculin Subcommittee of the Research Committee of the British Thoracic Association*

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Summary and conclusions

Intracutaneous (Mantoux 5 TU) and tine tuberculin tests were performed on the opposite arms of 307 people. The results of each test were read by two independent observers at either 48 or 72 hours. Positive readings were recorded in 59% of the Mantoux tests; induration was 10 mm or more in 34·7% of cases. Positive readings were recorded for 3·9% of the tine tests, and a further 15·5% were recorded in the doubtful category.

The tine test is unsuitable for epidemiological use because of the high proportion of negative and doubtful results in people positive on the Mantoux test. For the same reasons its usefulness in clinical practice is very limited.

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Introduction

One of us (JAL), who is responsible for many routine tine tuberculin tests in a large hospital and medical student population, gained the impression that fewer positive tuberculin reactions were being recorded than might be expected, especially

among those who had received BCG, certain immigrants, and the older age groups. There was also an increased number of accelerated and severe local reactions among the tine-negative subjects given BCG. A pilot study in which 30 nurses were tested by both tine and Mantoux methods showed substantial discrepancies between the results of the two tests. Because of this a similar but more detailed and controlled study on a larger group of subjects was undertaken.

Methods

Altogether 307 subjects, mainly medical students and student nurses, were studied. Age, sex, and BCG history were recorded, and permission to perform an additional test was obtained from each subject. Both tuberculin tests were given to each subject, and the presence or absence of a BCG scar was recorded.

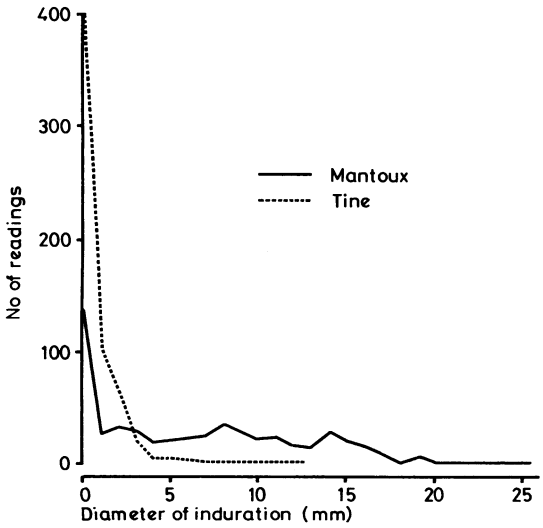
For the Mantoux test tuberculin purified protein derivative diluted to 5 tuberculin units in 0·1 ml was used. Two batches of tine discs (Lederle) were used to determine any batch variability (batch expiry dates were 10 September 1978 and 20 December 1978). The standard Mantoux test was performed on the left arm and the tine test on the right arm carefully following the manufacturer's recommendations.

Two testers were alternated between the two tuberculin methods every 10 subjects. The two tine batches were alternated every 20 subjects. There was no selection for previous BCG.

Results were read at 48 or 72 hours. Four observers were used, two independently reading each tine test and two reading the Mantoux site without the test on the other arm being visible. On the Mantoux test the transverse diameter of induration (in millimetres) was used for determining reaction size, while the diameter (in millimetres) of the largest indurated papule was used on the tine test; when papules were fused the combined diameter was measured. In both Mantoux and tine readings the lower size was recorded if the measurement fell between divisions on the millimetre scale.

Results

The readings of each observer were combined for each test in the figure. The distribution of the Mantoux test readings showed a small number of readings in the range of 4-7 mm, whereas no antimode was present in the tine test distribution. More small diameter readings occurred on the tine test than on the Mantoux test. Readings of the Mantoux test were grouped as negative (0-4 mm) and positive (⩾5 mm). The tine test readings were grouped according to the manufacturer's recommendations (0-1 mm negative, 2-4 mm doubtful, and ⩾5 mm positive) from the National Tuberculosis and Respiratory Diseases Association classification.[1] As each of the 307 subjects underwent two tests and each test was read by two observers 1228 pairs of readings were available for analysis (table I). Altogether 59% of Mantoux readings were positive while only 3·9% of tine test readings were definitely positive with 15·5% falling into the doubtful category, giving 19·4% with either positive or doubtful tine test results. The difference between the number of positive Mantoux readings and the number of positive plus doubtful tine readings was highly significant ($P < 0.001$).* Altogether 40·1% of all readings were tine-test negative and Mantoux-test positive. This false negative rate was equally divided between small (5-9 mm) and large (⩾10 mm) positive Mantoux readings. No subject had a positive tine test reading but negative Mantoux test reading; there were seven doubtful tine test readings in subjects negative on the Mantoux test. For one pair of readers there were 120 subjects with positive Mantoux but negative tine results and two subjects with negative Mantoux but doubtful tine results. For the other pair of readers there were 127 people with positive Mantoux but negative tine results and two with negative Mantoux but doubtful tine results. There was a decreasing proportion of positive Mantoux readings with decreasing evidence of BCG vaccination (table II). This trend was also apparent in the doubtful tine category but not with positive tine readings. There was no significant difference for time of reading, readers, different batches, or sex of subjects for either Mantoux or tine tests, but there was a significant difference between the two tine testers (table III).



Distribution of readings on tine and Mantoux tests.

TABLE I—*Comparison of tine and Mantoux tuberculin tests based on two readings of each test on 307 people (four readings for each person). Results are numbers (and percentages) of readings*

Reading of Mantoux test	Reading of tine test			Total
	Negative (0–1 mm)	Doubtful (2–4 mm)	Positive (⩾5 mm)	
Negative (0–4 mm)	497 (40·5)	7 (0·6)	0	504 (41·0)
Positive:				
5–9 mm	252 (20·5)	43 (3·5)	3 (0·2)	298 (24·3)
⩾10 mm	241 (19·6)	140 (11·4)	45 (3·7)	426 (34·7)
Total	990 (80·6)	190 (15·5)	48 (3·9)	1228 (100·0)

TABLE II—*Results of tine and Mantoux tuberculin tests related to evidence of previous BCG vaccination*

	Evidence of previous BCG vaccination			All groups combined
	History positive, scar present	History positive, no scar	History negative, no scar	
No of patients	135	99	73	307
No (%) positive on Mantoux test	101 (75·1)	50 (50·0)	30 (41·1)	181 (59·0)
No (%) positive on tine test	3 (2·2)	6 (5·6)	3 (4·4)	12 (3·9)
No (%) doubtful on tine test	27 (20·0)	15 (15·0)	6 (8·2)	48 (15·5)

TABLE III—*Results of tine tuberculin test readings related to giver of test*

	Tine test readings			Total
	Negative (0–1 mm)	Doubtful (2–4 mm)	Positive (⩾5 mm)	
No (%) given by tester 1	269 (85·1)	40 (12·7)	7 (2·2)	316
No (%) given by tester 2	226 (75·8)	55 (18·5)	17 (5·7)	298

Difference between testers in negative and combined doubtful and positive groups was significant ($P < 0.05$).

Discussion

The acceptability of an alternative tuberculin test depends on how closely it reproduces the number of positive reactions recorded in a given population when simultaneously tested by a standard test, the most generally accepted being the Mantoux method. It also depends on whether a significant number of positive reactions from the alternative test are recorded in

*Statistical analyses were performed using the standard error of the difference of two proportions based on the number of subjects tested.

subjects who have negative Mantoux responses. In comparing tests it is essential to consider the positive reactors as a separate group. If this is not done a large difference in positive responses can be masked, especially if a higher proportion of the subjects are tuberculin negative

Our results have shown a greater disagreement than previous studies, although these have generally shown a tendency for the tine test to produce fewer positive responses than the Mantoux or Heaf tests.[2-5] Expressed in terms of people whose test responses were read by one pair of readers, 120 (67·8%) of the 177 subjects positive on the Mantoux test had negative tine responses, but there were only two (3·4%) with negative Mantoux results among the 59 subjects with positive tine results. The very pronounced disagreement in positive responses in our study compared with that in earlier reports raises the possibility that the tine discs we used were not giving results similar to those of the discs used in previous studies. It should be emphasised that we took particular care to follow the manufacturer's instructions for applying the test.

The general advantages claimed for the tine disc method of tuberculin testing have not been confirmed. Although the disc is technically simple to apply, table III shows that in this series there was a significant difference in the number of tine reactions over 2 mm between the two testers, both of whom were experienced in the use of the method. It is unlikely that non-medical personnel would obtain consistent responses. The speed with which the test can be applied is offset by the need to confirm by further Mantoux testing a high percentage of tine readings.

Our results indicate that the tine method for selecting tuberculin-negative subjects for BCG vaccination will result in many (67·8%) Mantoux-positive subjects receiving BCG. This probably accounts for the high number of accelerated reactions observed when subjects have been selected for BCG vaccination by the tine method. It is also a matter of concern that in hospital staff exposed to open cases of tuberculosis the low rate of tuberculin-positive selection by the tine test may result in missed tuberculin conversion. A feature of the present study has been the high proportion (over half) of people with negative tine responses among those with considerable responses ($\geqslant$ 10 mm) on the Mantoux test (table I). This leads to the possibility of failure to diagnose active tuberculosis by missing strong tuberculin reactors in any population in which the tine method is used—for example, among those served by the Schools Medical Service.

Our results indicate that the tine disc tuberculin test cannot be regarded as satisfactory for epidemiological use and little confidence can be placed in negative readings. Because of this the test cannot be recommended for clinical use. The probability of missing active tuberculosis in children and of failing to detect tuberculin conversion in exposed adults is a factor that renders the test additionally unsuitable.

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Requests for reprints should be addressed to Dr J A Lunn.

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Evidence for intestinal origin of transcobalamin II during vitamin B_{12} absorption

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Summary and conclusions

The plasma binding of newly absorbed, radioactively labelled vitamin B_{12} was studied during a urinary excretion (Schilling) test. Vitamin B_{12}, after being absorbed from the gut, enters blood attached to transcobalamin II, which seems to be derived from the ileal enterocyte. The absorbed B_{12} re-enters the blood stream after the transcobalamin II-B_{12} complex is cleared by the liver and it is then excreted into the urine during the Schilling test.

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Introduction

It is still uncertain whether newly absorbed vitamin B_{12} (B_{12}) enters portal blood in the free state and then attaches itself to plasma B_{12} transport protein—transcobalamin (TC) II—as well as to other vitamin B_{12} binding proteins (transcobalamins) or enters portal blood as a TC II-B_{12} complex.[1 2] Further investigation of the events in the urinary excretion test for B_{12} absorption (Schilling test) is likely to throw light on this problem.

In this test a small dose of labelled B_{12} is given by mouth and accompanied by an injection of 1000 μg of unlabelled cyanocobalamin. The injected B_{12} is such a large amount that all the serum B_{12}-binding proteins become saturated with B_{12}. The remaining B_{12} (more than 80% of the intramuscular dose) remains unbound to protein, is filtered by the glomerulus, and excreted in the urine. Absorbed, labelled B_{12} joins, directly or