The significance of tuberculin sensitivity among schoolchildren and its use as an index of the prevalence of tuberculosis.

Thesis presented for the degree of

Doctor of Medicine

by

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INTRODUCTION.

Local health authorities were invited by the Ministry of Health in 1953 to introduce schemes for the B.C.G. vaccination of school leavers and by the end of 1959 all but six authorities in England and Wales had such schemes (Ministry of Education, 1960).

The initial tuberculin test identifies those children who are tuberculin sensitive and their number is commonly used as an index of the amount of tubercular infection in the community (Ministry of Education, 1962.). The proportion of school leavers throughout the country who are tuberculin positive is published annually by the Ministry of Health and it is therefore possible for any local authority to compare its own with the national rate and thus, it is assumed, to compare its own with the national prevalence of tuberculosis.

It is the purpose of the writer to examine this assumption that the amount of tuberculin sensitivity amongst a small sample of schoolchildren is a reliable guide to the prevalence of tuberculosis.

The particular circumstances of a small community are used as a type to illustrate the general principles involved and the difficulties which may be created by the uncritical acceptance of the assumption.

Rawtenstall is a Lancashire manufacturing town of about 24,000 people. Thirteen year old children attending its schools have been offered B.C.G. vaccination since 1955. The proportion found to be tuberculin positive, (the reactor rate), in December 1962 (when the writer first was responsible for the B.C.G. programme) was 33.7 per cent. The national and the county rates for 1961 were 14.3 and 16.1 per cent. respectively.

In reviewing the rates for the previous years it was evident that in Rawtenstall it had not only been consistently high but

that it appeared to be getting higher:

Table 1: Per cent. school leavers tuberculin positive (to nearest whole number) in England and Wales, Lancashire County, and Rawtenstall, 1955-1962.

Year	E. & W.	Lancs. Admin. County	Rawtenstall
1955	-	-	31
1956	-	33	34
1957	-	26	-
1958	18	27	33
1959	14	19	33
1960	15	19	29
1961	14	16	41
1962 March Dec.	-	-	47 34 } 40

(The figures are calculated as a percentage of those tested and read. Routine testing was not done in Rawtenstall in 1957 and national rates are not available for the years before 1958.)

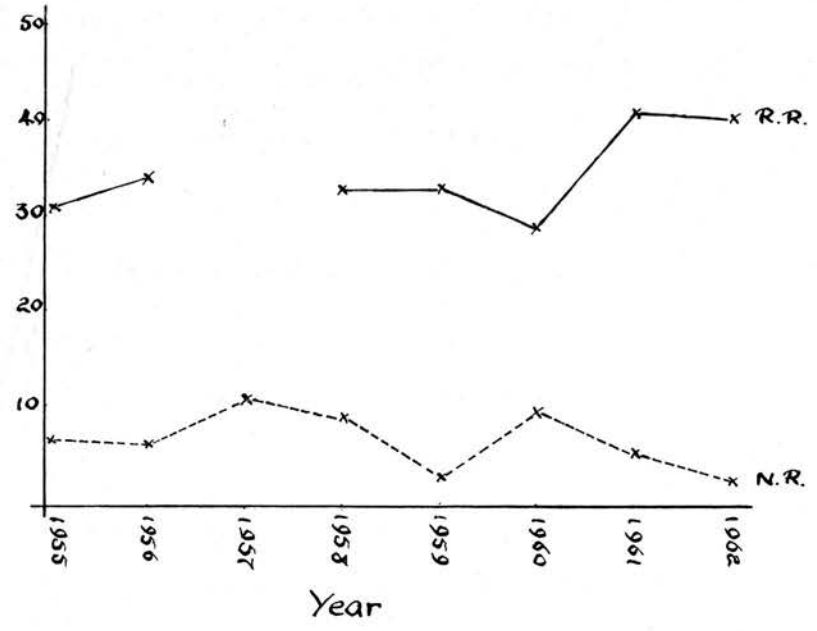
These rates could be taken to imply that tuberculosis was prevalent in Rawtenstall but this view was not shared by anyone with local experience in tuberculosis work nor was it reflected by either the notification or the mortality figures. These, although erratic, both suggested a decreasing incidence, particularly if viewed in five yearly periods.

Table 2: Tuberculosis notifications and deaths attributed to tuberculosis in Rawtenstall for five yearly periods 1943-1962.

Years	No. notifications	No. deaths
1943/1947	145	53
1948/1952	118	46
1953/1957	109	25
1958/1962	69	10

The estimated population had fluctuated little during this time.

The accompanying figure shows that the reactor and notification rates had recently diverged.



x——x Reactor rate = % +ve of all children tested and read.

x-------x Notification rate of tuberculosis, all forms, per 10,000 population.

All measurement is qualified by the methods and the materials used and what is being measured must be defined.

PART I. A consideration of the factors involved in measuring community tuberculosis.

I. The reactor rate.

The reactor rate, in this context, is the proportion of children in a given age group who are sensitive to tuberculin. It will vary not only with the actual frequency of sensitivity among the children but with a number of unrelated factors.

A. Variables in tuberculin testing.

1. The method of testing.

For many years the jelly patch test was preferred to other methods in this country because it was acceptable to children and because it was thought to be sufficiently reliable for all except research purposes. It received unqualified approval from Lendrum (1951) and qualified support from Dick (1950) and Murray, Petrie and Williamson (1955) but was condemned by Caplin, et al. (1954). Silver (1955) thought it useful in the testing of children under ten years but considered it unreliable in those over ten. It had been equated in sensitivity to the Mantoux intracutaneous test using 1.1000 O.T. (Dick, 1950: Clark, 1951: Lendrum, 1951) or 1.100 O.T. (Paterson, 1944) according to the details of technique and material used.

The question of which method of testing gave the most reliable results under routine conditions was a matter of increasing importance during the early 1950's because of the proposed extension of B.C.G. vaccination to schoolchildren. The British Tuberculosis Association undertook a comparison of four tests and in the first report (B.T.A. 1958) the jelly test was discredited. Despite its subsequent recommendation by Keeping and Cruikshank (1960) and by Miller, Seal and Taylor (1963) it is unlikely to have been in significant use since, and it has not had the approval of the Ministry of Health for pre-vaccination testing.

The Von Pirquet test did not come well out of the investigation but although it was conceded that this may have been due in part to unfamiliarity (since the test had never been in common use in this country) there did not seem sufficient cause to recommend its adoption.

The two remaining tests - the Mantoux (intra-cutaneous) and Heaf (multiple puncture) - were further compared and in the second report (B.T.A. 1959) it was concluded that the Heaf test was more suited than the Mantoux to routine use for epidemiological purposes in Britain.

The effective difference between the two methods cannot be stated simply because it varies with the materials used and with the manner of testing and reading. After reviewing the literature and the results of their own researches the British Tuberculosis Association inferred, however, that the Heaf multiple puncture test, read at seven days, was comparable to the two stage (5 T.U. and 100 T.U.) Mantoux intra-cutaneous test read at three days. The results of surveys by various authors comparing the two tests are shown in Table 3.

Table 3: Results of surveys comparing the 10 T.U. Mantoux test with the Heaf multiple puncture test.

Author(s)	Mantoux 10 T.U.			Heaf			Testing reading interval (hours)
	No. +ve	% +ve	Min. +ve (mms.)	No. +ve	% +ve	Min. +ve (No. of papules)	
Henshaw (1955)	487	41.6	6	504	43.0	4	72
Greening (1955)	319	27.4	6	396	34.0	?	72
Stott (1955)	801	72.6	6	813	73.6	?	72
Stewart & Carpenter (1955)	211	63.7	5	135	61.6	3	72 or 96
Low (1956)	153	24.7	6	201	32.4	1	48
Rathus (1956)	745	25.3	5	789	26.8	?	72
Briggs and Smith (1957)	366	31.8	7	424	36.9	4	72

2. The test materials.

Both tests can be performed either with Old Tuberculin (O.T.) or with Purified Protein Derivative (P.P.D.).

The standardisation of successive batches of P.P.D. is difficult - indeed Guld, et al. (1958) concluded that it was almost impossible since they found that the ratio of potency for two batches varied with the population tested and with the standard of reading test results.

The tuberculin used in the Heaf test is prepared to contain 2 m.g. of tuberculoprotein in 1 ml. of solution but the tuberculin used in the Mantoux test is further diluted. The particular dilution injected will affect the response, since the greater the dilution the smaller the dose of antigen and a linear relationship exists between the logarithm of the dose and the response - whether this is measured as the area of induration (Bruce, 1961) or as the diameter of induration (Birmingham, 1962). The dose is identified in terms of Tuberculin Units (T.U.), one T.U. being equal to 0.00002 mg. of P.P.D.

Dilutions of purified tuberculin are subject to variations in potency due to adsorption of tuberculin on to the glass container, the degree of adsorption varying with the strength of the dilution, the temperature, and the degree of filling of the ampoule (Waaler, et al., 1958). These authors estimated the loss in a 5 T.U. dilution to be 60 per cent. of the active substance but they pointed out that it differed unpredictably from one ampoule to another. The diluent used also influences the degree of adsorption (Magnusson, et al., 1958) as does the inclusion of merthiolate (B.T.A. 1957) or Tween 80 (Waaler, et al., 1958). The effect of storage was studied by Edwards, Cross and Hopwood (1963) who concluded that there was no loss in potency after the first 24 hours, storage being at 2°-4°C and the diluent being a borate buffer. Exposure to light is known to depreciate the potency of

tuberculin preparations (Guld, Deck and Buchman-Olsen, 1955).

Recent confirmation of the instability of P.P.D. dilutions due to adsorption has come from Marks (1964) who observed that it also occurred in the syringe used for injection. The syringe can influence the response to tuberculin in other ways. It has been accepted that the frequency distribution of the tuberculin reactions of most populations (unselected in terms of tuberculin sensitivity) is bimodal, the left hand group representing those with no tuberculin sensitivity and those showing a minimal response to the diluent (Palmer, Ferebee and Petersen, 1950: Edwards, Palmer and Edwards, 1955: Edwards, Edwards and Palmer, 1959). Griep and Bleiker (1957), however, have demonstrated that the distribution becomes unimodal if the reflux action which always occurs with the usual type of tuberculin syringe is prevented by fitting a one-way valve. In testing the same population with the same tuberculin but with the two syringes - one with, and the other without, a one-way valve - they obtained reactor rates of 33.8 and 26.3 per cent. respectively. This back-tracking of tuberculin is from the intradermal wheal into the syringe and it depends on the pressure created intradermally by the injection. This in turn varies with the volume of the injection and the depth of the injection. These factors are considered later with other variables which can be classified together as experimental errors. The reflux may, however, occur between the piston and the barrel of the syringe, the tuberculin being lost from the top of the barrel. This leakage is an expression of the pressure created within the syringe and it varies with the tightness of the fit between piston and barrel. Guld and Rud (1953) described a simple method of testing a syringe for the amount of leakage it allowed. They set a standard allowance and discarded syringes which failedto keep within it.

The standard allowed a loss by leakage of up to 3 - 4 per cent. of a 0.1 ml. injection and the discard rate of new syringes from batches of different brands was never less than one quarter.

Less variation is possible in the materials used in the Heaf test, since the P.P.D., being undiluted, is stable. The machine used to inject the tuberculin in the Heaf test has been subjected to alterations in design and these have influenced both the frequency and the size of reactions, although not in a consistent fashion nor to any marked degree (Carpenter and Stewart, 1959).

3. The manner of testing and reading.

It has been reported that the tuberculin reaction varies both quantitatively and qualitatively with the site chosen for injection. Wasz-Hockert (1950), in reviewing the literature, found general agreement that tests performed on the trunk gave stronger reactions than those performed on the limbs. His own experience in testing adults was similar but in children under ten, despite great individual variation, he found no generally significant difference. In this respect he related tuberculin sensitivity directly to the thickness of the epidermis at the site of injection and inversely to the vascularity of the skin in the area of injection. Aronson and Taylor (1955) performed simultaneous tests on 139 persons, one into the skin of the forearm, theother into the skin of the shoulder. At the former site 92 of the tests were unequivocally positive, at the latter, 136. Carpenter and Stewart (1959) noted that Heaf tests on the upper forearm were larger than those on the lower forearm and concluded that reactions tend to become smaller as the site of injection is moved peripherally. This was not, however, the experience of Gillis and Stradling (1957) who noted a slight but statistically significant trend in the opposite direction.

These authors were unable to confirm the finding by Heaf

(1955) that local desensitisation to tuberculoprotein develops at the site of injection and persists for more than twelve months. Edwards and Magnus (1955) reported that, in retesting after three months, reactions appeared earlier, attained a greater maximum size and faded earlier at the previously used site than at a previously unused site - although by the third day early differences had resolved and the frequency and mean size of reaction at either site was then the same. Duboczy (1964) confirmed these findings in retesting at monthly intervals for three months. At the first repeat test at the used site the per cent. positive on the third day was the same as with the original test. Further repeat testing and later reading progressively lowered the positivity rate. Reactions to repeat tests at the same site appeared earlier, attained a greater size sooner and disappeared earlier than the reactions to the original test. The author refers to the phenomenon as "local sensitization" and observes that it is demonstrable up to twelve years after the original test. It is difficult to reconcile these reports with that of Heaf. However, the anergy suggested by Heaf has been found to pervert estimates of tuberculin sensitivity, particularly following B.C.G. vaccination (British Student Health Officers Association, 1960).

Results of both Mantoux and Heaf testing may vary with the interval between testing and reading. Stewart, Carpenter and McCauley (1958) found the proportion positive to a 5 T.U. dose on the seventh day after Mantoux testing to be greater than on the third or fourth day by between 1.5 and 5.5 per cent. according to the tester. After Heaf testing the proportion positive on the seventh day was greater than on the third or fourth day by between 3.7 and 5.9 per cent. according to the tester. Approximately three-quarters of the population tested were tuberculin positive. The British Tuberculosis Association (1959) had found

that in Mantoux testing the proportion positive to a 5 T.U. dose was the same on the third as on the seventh day (45.6 per cent.) although 6.4 per cent. of those positive on the third day were negative on the seventh day and 6.5 per cent. of those negative on the third day were positive on the seventh. By the tenth day the proportion positive had dropped to 24.1 per cent. although between the seventh and the tenth day 1.3 per cent. had changed from negative to positive. In Heaf testing the proportions positive on the third, seventh and tenth days were 74.3, 78.0 and 78.3 per cent. respectively, although 1.0 per cent. became negative between the third and the seventh day and 2.6 per cent. between the seventh and the tenth day. Busk, Magnus and Blöcher (1955) reported no significant difference in the proportion positive to the Mantoux test between daily readings from the second to the fifth day.

Tuberculin sensitivity is a quantitative, continuous variable and there is in consequence always a problem of deciding where the line shall be drawn between what is to be called negative and what is to be called positive. Although there is an inherent fallacy in attempting to divide any population in such a way circumstances may demand that it be done. Reactions to the Mantoux test are commonly expressed as millimetres diameter of induration and since, as has been mentioned, this varies with the dose of tuberculin injected, the criterion of positivity may be altered accordingly. There is not, however, any universally adopted standard for any dilution; indeed, it has been suggested by Edwards, Palmer and Edwards (1955) that there should not be, since, they claim, the significance of tuberculin sensitivity shows geographic variations which can be met only by using criteria determined by local circumstances. In this country alone a number of different standards have been used, as may be seen from Table 4.

Table 4: Varying criteria of positivity adopted in Mantoux tuberculin testing surveys in the U.K.

Survey Author(s)	Tuberculin preparation	Tuberculin Strength (T.U.)	Maximum Neg. reaction in mms. induration	Minimum Pos. reaction in mms. induration
Jarman (1953).	O.T.	1	4	5
Palmer, Nash, Nyboe (1954).	P.P.D.	1	7	8
Hart, et al. (1962).	O.T.	3	4	5
Pollock, Sutherland, Hart (1959)	O.T.	3	7	8
Stewart, Carpenter, McCauley (1958)	O.T.	5	4	5
B.T.A. (1959)	P.P.D.	5	5	6
Palmer, Nash, Nyboe (1954)	P.P.D.	5	7	8
Stewart, Carpenter (1955)	O.T.	10	4	5
Stott (1955)	O.T.	10	5	6
Clark (1951)	O.T.	10	9 *	10 *
Wolman (1952)	O.T.	10	10	11
Murray, Petrie, Williamson (1955)	O.T.	100	4	5
Johnston, Ritchie, Murray (1963)	O.T.	100	5	6

(* The criterion in this survey was "an area of erythema at least 1 cm. in diameter with palpable induration")

Clearly it was easier to be a tuberculin positive schoolchild in Musselburgh (Murray, Petrie and Williamson, 1955) than in London (Palmer, Nash and Nyboe, 1954).

In a more empiric approach Narain, et al. (1963) attempted

to define a positive Mantoux reaction in terms which were related to the known incidence of local tuberculous disease. Their inability to do so led them to accept an arbitrary division as the only possibility.

Birmingham (1962) established - in effect - that in a small series of tuberculous patients doubling the dose of tuberculin added, on average, 2.3 mms. to the mean diameter of their response. In testing large population groups with either 5 T.U. or 10 T.U. doses of tuberculin Guld (1955) found the difference between the reactions to the two doses to lie between two and three mms. This difference was not associated with significant changes in the reactor rate however, even with the same criterion for positivity for either dose - a finding dependant, perhaps, on the distribution of the sensitivity of the particular population tested.

The distinction between a negative and a positive result to the Heaf test is no more strictly defined. When first described (Heaf, 1951) it was recommended that the presence or absence of induration be the sole criterion, and this was later amplified, first so that "six definitely indurated papules", but subsequently "four or more palpable indurated papules", became the minimal acceptable, positive reaction (Heaf, 1953; 1953a.) Low (1956) acceptedinduration at one or more puncture sites as positive and Carpenter and Stewart (1959) at three or more.

In addition to the variables so far mentioned there are others which are imposed by errors in human judgement and technique.

Palmer and Edwards (1953) studied the effect of variations in either the volume of tuberculin injected or the depth at which it was injected (the other factor, as near as was possible, being constant), believing these to be the two ways in which an intra-cutaneous injection may deviate from the recommended technique. They found that the average size of induration increased with the

volume injected and decreased with increasing depth of injection. Bruce (1961) however reported that with increasing volume the diameter of induration first increased and then decreased. To these sort of errors in Mantoux testing must be added errors of judgement in reading the results. Meyer, Hougen and Edwards (1951) estimated that, except at low levels of sensitivity, the standard deviation of the total experimental error of an observed size of induration was about 2 mms., that for the reading error alone being about 1.3 mms. In effect they found that in simultaneous testing on either arm this degree of error led to positive reactions being recorded on the R. arm in 10.5 per cent. of persons who had negative reactions on the L. arm and to weak positive reactions being recorded on the L. arm in 16.2 per cent. of those negative on the R. arm. Magnus and Edwards (1955) reported that amongst 126 vaccinated persons given two 5 T.U. tuberculin tests at three months interval sixteen were negative on one or other occasion but only four on both. Stewart, Carpenter and McCauley (1958) estimated the combined experimental error to be such that experienced workers would differ in about 18 per cent. of cases as to whether the subjects were positive or negative to a 5 T.U. Mantoux test, approximately 15 per cent. being testing error and 3 per cent. reading error. In a large scale tuberculosis study in South India involving the annual retesting of many thousands of persons Frimodt-Møller (1960) found such variation between results from successive 5 T.U. Mantoux tests that he questioned the parts played by experimental error and by alterations in individual allergy. Quoting experience gained from duplicate Mantoux testing of tuberculous patients in a local sanatorium he gave 4.54 mms. and 2.13 mms. as the variance attributable to tester and reader errors respectively, the total standard error being 3.03 mms., and subsequently concluded that more of the scatter in the general

population was due to experimental error than to true changes in allergy. Hart et al. (1962) in repeat Mantoux testing, at a short interval, found that fifteen per cent. of those who had reacted to the first test failed to do so to the second, and that in those who reacted to both the standard deviation of the difference between the two tests was a little over 4 mms.

That the Heaf test is subject to smaller experimental error than the Mantoux test is suggested by the findings of Stewart, Carpenter and McCauley (1958). These authors assessed the effect of the reading error made by independent observers, and found a difference of 3.1 per cent. in the positivity rate when reading on the third or fourth day and of 0.7 per cent. when reading on the seventh day. They thought that tester and reader errors combined accounted for differences of less than 5 per cent.- as opposed to about 18 per cent. for the Mantoux test. Gillis and Stradling (1957) had previously investigated the effect of the errors made by two independent readers of 116 Heaf tests - one reported 28 as negative, the other 26. The British Tuberculosis Association (1958) found no difference between the reading error of either test. Carpenter and Stewart (1959), reporting the trial of a self-firing Heaf multiple puncture machine, made use of two testers whose work had been previously reported (Stewart, Carpenter and McCauley, 1958). Measurable differences in technique had persisted and apparently were characteristic of the individual. The implication was that while the reactions produced by one tester were comparable over a period of time those of different testers were not.

For these reasons, and for reasons connected with the varying significance of tuberculin sensitivity, to be discussed, there is little justification for expressing the results of a tuberculin testing programme in terms of "percentage positive" and "percentage negative".

It might be worthwhile to review the relevance of these variables to the schools' B.C.G. programme in general and to the programme in Rawtenstall in particular.

In memoranda addressed to Medical Officers concerned with the vaccination of school leavers the Ministry of Health (1955) recommended the Mantoux test but added that others could be used on the responsibility of the vaccinator. Later, (Ministry of Health 1958) the Heaf test was a suggested alternative although preference was still expressed for the Mantoux test. The extent to which each has been favoured is not precisely known but it is probable that the more widely used in the early years of the schools programme was the Mantoux test and in recent years the Heaf test. The Ministry had likewise recommended (1955) that an initial dose of 1 T.U. be used and that "negative reactors" be retested with a 10 T.U. dose, but no objection was made to the use of a single 10 T.U. test and this had been the practice in Rawtenstall up to 1961 when the Heaf test was substituted. The change was associated with an increased reactor rate, as might have been expected even had other factors remained constant. However, the increase, from 29 per cent. positive to 41 per cent. positive is larger than any reported in the literature. (See Table 3).

Purified protein derivative had always been recommended by the Ministry of Health (1955) for pre-vaccination tuberculin testing; this has always been used in Rawtenstall and almost certainly elsewhere, since P.P.D. has been issued free of charge by the Ministry whereas O.T. has had to be obtained and paid for through the ordinary commercial channels. The P.P.D. issued by them is prepared in the Central Veterinary Laboratory of the Ministry of Agriculture, Fisheries and Food. Local health authorities were notified that two batches issued in 1961 and 1962

(V.47 and V.49 respectively) were of enhanced potency and that their use would result in a number of false positive reactions. In a personal communication the Ministry of Health stated that V.49 was the more potent and that one local authority had reported that 35 per cent. of those children tested with this batch were thought to have given a false positive reaction. Neither batch was issued for use in Rawtenstall, V.43 being used in the 1961 B.C.G. programme and V.46 in 1962. This variable therefore operated in a manner likely to depress local results in relation to national results - whether significantly or not would depend upon the distribution and usage of the offending batches.

Other Ministry recommendations covered the storage of tuberculin, particularly as regards conditions of temperature and light, and the degree of ampoule filling; advice was given as to the choice of test site and exact criteria of positivity for both the Mantoux and the Heaf test were stipulated. More latitude was given in the choice of testing-reading interval, particularly with the Heaf test in which the recommendation was that reading may be at "any time from 72 hours to 7 days" (Ministry of Health, 1958). Reading has always been on the third day in Rawtenstall. Where so much variation is uncontrollable it may seem a pity that the opportunity was not taken to standardise that which could be controlled, but the effect of this permissiveness must be very small bearing in mind the level of tuberculin sensitivity in the age group to be tested. The "used site" phenomenon mentioned by Heaf (1955) is clearly a factor of no importance in the circumstances of the schools' B.C.G. programme. Syringe leakage in Mantoux testing was a random factor unlikely to be responsible for trends in tuberculin sensitivity in succeeding years in any locality. In any event the period of greatest disparity between local and national rates in Rawtenstall was after the

introduction of the Heaf test.

The remaining variable is that due to experimental error. Prevaccination tuberculin testing, and reading, is performed, in Lancashire County, by Assistant Divisional Medical Officers (A.D.M.O's.). There had been three changes in the tester-reader in Rawtenstall between 1955 and March, 1962. Table 5 shows that from 1955 to 1960 there had been no significant change in the measured frequency of tuberculin sensitivity amongst Rawtenstall schoolchildren - a constancy which increasingly isolated it from the County as the latter's reactor rate fell. It also shows that there was a large increase in 1961 followed by a lesser increase in March, 1962 and by a substantial fall in December, 1962 which returned the rate to its earlier level. The association between the identity of the tester-reader and the results of tuberculin testing suggested the possibility of a causal relationship.

Table 5: Association between tester-reader, method of testing and the results of tuberculin testing in Rawtenstall schoolchildren 1955-1962.

Year	Tester-Reader (A.D.M.O.)	Test	% Reactor Rate
1955	1	Mantoux 10 T.U.	31
1956	1	Mantoux-10 T.U.	34
1957	-	-	-
1958	2	Mantoux 10 T.U.	33
1959	2	Mantoux 10 T.U.	32
1960	3	Mantoux 10 T.U.	29
1961	4	Heaf	41
1962			
March	4	Heaf	47
Dec.	5 + 6	Heaf	34

When the significance of these figures was first being questioned, early in 1963, there was no way of telling whether such a relationship existed or not. Indirect evidence available since then makes the suggestion less probable. A.D.M.O. "4" (in the table) transferred to another borough within Lancashire Administrative County in 1962 and thereafter performed and read

the Heaf tests in that Borough's B.C.G. programme. Its reactor rate, together with Rawtenstall's, is given in Table 6, those rates measured by the same A.D.M.O. being shown in red.

Table 6: Tuberculin sensitivity in two Lancashire boroughs, 1955-1963, that measured by the same A.D.M.O. being shown in red.

Year	Rawtenstall	Borough "2"
1955	31	23
1956	34	21
1957	-	23
1958	33	9
1959	32	13
1960	29	-
1961	41	8
1962	47 : 34	43
1963	22	8

This record does not support the view that thepeak rates in Rawtenstall were due to experimental error. In this context the finding of Stewart, Carpenter and McCauley (1958) that unfamiliarity with the Heaf test had no significant effect on the observed reactor rate is interesting.

However, further analysis of the figures quoted in Table 5 strengthens the view that experimental error has been a factor in inflating the reactor rate. It will be noted that in December, 1962 there were two tester-readers, one of whom was the writer. All tests were done in similar circumstances and the results appear in Table 7 (excluding the results from one school in which only three pupils were tested, two being positive).

Table 7: Heaf test results by two tester-readers in 13 year old Rawtenstall school children in December, 1962.

School	Tester-Reader 5						Tester-Reader 6						Total % +ve.
	No. tested	Heaf Grade			No. +ve	% +ve	No. tested	Heaf Grade			No. +ve	% +ve	
		1	2	3				1	2	3			
1	18	7	2	3	12	66.7	50	1	4	8	13	26.0	36.8
2	15	0	1	3	4	26.7	53	6	10	3	19	35.8	33.8
3	7	1	0	2	3	42.9	35	3	4	1	8	22.8	26.2
Totals	40	8	3	8	19	47.5	138	10	18	12	40	28.9	33.1

The significant difference is in the assessment of minimal reactions. The difference led the writer to observe a reactor rate of 29 per cent. and his colleague to observe a reactor rate of 48 per cent. The interpretation of minimal Heaf reactions has always been open to variation and Gillis and Stradling (1957) thought that "considerable doubt must be cast upon the validity of a 'first degree positive' report by one observer....."

It thus seems that some of the rise in 1961 may have been due to experimental error. While it may be argued that the real incidence of tuberculin sensitivity had fallen throughout the period 1955 to 1962 and that this fall had been masked by the intrusion of unrelated factors, it is assumed for the moment that the figures mean what they appear to mean; that is, that a greater proportion of school leavers in Rawtenstall were tuberculin sensitive early in 1962 than in 1955.

Before considering possible explanations it is proposed to consider in more detail the meaning of tuberculin sensitivity.

B. The meaning of tuberculin sensitivity.

1. Consideration of its specificity.

If an individual reacts to theintradermal injection of tuberculin it can only mean that that person has been previously sensitised by an agent capable of causing such sensitisation. The traditional view was that there were only two agents able to act in this way - the human and the bovine tubercle bacilli. In this view, therefore, tuberculin sensitivity meant previous infection by one or other of these organisms and the certainty of this belief enabled Myers (1946) to express the view that tuberculin sensitivity and tuberculous disease were synonymous, and that if the first was present then the second must necessarily also be present. The supposed specificity of the reaction was the basis for its value as a diagnostic test and for the confidence it enjoyed in this respect. Gaisford (1946) called it "the only sure diagnostic test" in primary tuberculosis in childhood. Furcolow, et al. (1941), however, had earlier reported studies which suggested the possibility of non-specific reactions to tuberculin; they had found it possible, by progressively increasing the dose, to elicit a response from almost everyone they tested, including infants without evidence of tuberculous infection or history of contact. Edwards andHardy (1946), in a follow up of tuberculin positive children under two years of age at time of entry, recorded that of those sensitive only to a large dose of tuberculin the majority subsequently reverted to the negative state, none developed radiological or clinical evidence of tuberculosis and none died of it, and that, by contrast, among those reacting strongly to a smaller dose none subsequently reverted, the majority developed evidence of tuberculosis and seven of the 44 children in this group died of the disease. Edwards, Lewis and Palmer (1948), in attempting to relate levels of tuberculin

sensitivity to other objective signsof tuberculous infection among student nurses not reacting to histoplasmin,found a positive correlation between the incidence of pulmonary infiltration on X-ray and the size of the response to a 5 T.U. dose of tuberculin regardless of the degree of sensitivity shown to a 250 T.U. dose. Goddard, Edwards and Palmer (1949) found the incidence of pulmonary calcification to be 10.7 per cent. in those reacting to a 5 T.U. dose of tuberculin, 1.6 per cent. in those reacting only to a 250 T.U. dose and 0.7 per cent. in those not reacting to tuberculin, reactors to histoplasmin being excluded from all three groups. The evidence led them to doubt the specificity of the response to a strong dose of tuberculin. In 1950 Palmer, Ferebee and Petersen established that the geographic distribution of 5 T.U. reactors amongst a large number of student nurses was fairly even throughout the United States whereas the distribution of those reacting only to 250 T.U. was heavily weighted in favour of the South Eastern United States. The localisation of strong dose reactors led the authors to distinguish between the significance of low- and high-grade sensitivity to tuberculin and to postulate that non-specific allergy was a geographically determined factor accounting for the former kind of sensitivity in the absence of tuberculous infection. Bates, Busk and Palmer (1951) demonstrated remarkable differences in the pattern of tuberculin sensitivity amongst a homogeneous population living in close proximity but at different altitudes, the prevalence of tuberculosis apparently being the same throughout the whole area. On the accumulated epidemiological and statistical evidence Edwards and Palmer (1953) postulated that the kind of sensitivity elicited only by a high dose of tuberculin was the result of something other than infection with mammalian Myco.tuberculosis. Confirmation appeared to come from the report by Palmer (1953)

that the frequency of 5 T.U. reactors was related to the degree of contact with tuberculosis whereas the frequency of 250 T.U. reactors, expressed as a percentage of those negative to the 5 T.U. dose, was entirely independent of the degree of contact. Results of work done in widely separated geographical areas were collated and published in 1955 under the auspices of the Tuberculosis Research Office, World Health Organisation (Edwards, Palmer and Edwards, 1955). All the evidence pointed to the existence of two kinds of tuberculin sensitivity, one specific for infection by mammalian Myco. tuberculosis and displayed as fairly large reactions to a weak dose of tuberculin, the other not specific for tuberculous infection and brought out as small reactions to a 5 T.U. dose of tuberculin or as larger reactions only to a stronger dose of tuberculin.

The cause of non-specific reactions was not then known but by analogy with similar problems in veterinary practice it was thought likely to be other mycobacteria.

Crawford, in 1927, had shown that it was possible to differentiate avian from mammalian mycobacteria by the preferential response of an infected guinea-pig to the homologous tuberculin. Comparative testing of this kind had been used to separate cattle into those with specific and those with non-specific tuberculin sensitivity and the method was now transposed to human populations. It appeared (Palmer and Edwards, 1955)that the high-grade sensitivity was better demonstrated by human than by avian tuberculin, the reverse being true for the low-grade sensitivity, and the authors concluded that the latter was due to infection by organisms antigenically closer to the avian than to mammalian Mycobacteria.

Interest subsequently focussed on other acid-fast bacilli whose existence had long been known but whose clinical or

epidemiological significance had largely been overlooked. However, their capacity to confer partial immunity on guinea-pigs later infected by virulent tubercle bacilli was known (Wenkle, Loomis and Jarboe, 1948) and this finding implied some antigen correspondence. A survey initiated in 1954 in the United States of America called for the central reference of cultures from cases of disease supposedly due to these organisms and by 1959 enough was known to permit classification (Runyon, 1959). Many hundreds of strains have since been isolated but Runyon's classification is used here, since, although it has had to be extended (Marks and Richards, 1962: Marks, 1964,a.) there still seems to be no completely satisfactory system and his simple classification into four broad groups serves the present purpose. The following table, based on one from a paper by Bialkin, Pollak and Weil (1961) has been a useful guide to the writer.

Table 8: Classification of atypical Mycobacteria pathogenic for human beings.

Runyon's Classification.	Synonyms or Specific names.	Pathogenicity	Comments
Group I Photochromogens (cream in dark yellow in light)	M. Kansasii "Yellow bacillus".	for adults: rarely for children.	All organisms in this group belong to same species: Should all be called M. Kansasii.
Group II Scotochromogens (Yellow, orange or red unaffected by light)	M.Scrofulaceum "Orange bacillus".	for children: rarely for adults.	Several species: one, M. Scrofulaceum has produced lymphadenopathy in children.
Group III Non-photochromogens (Creamy unaffected by light)	"Battey" strain.	Commonly for adults.	M. avium almost indistinguishable from Battey strain.
Group IV Rapid growers (heavy in 48 hrs: pigmentation varies)	M.fortuitum M.Ulcerans) M.balnei)	rarely Skin lesions	Many strains.

The comments in the first column refer to the colour of the colonies and their reaction on exposure to light.

These organisms have been variously referred to as "atypical" "anonymous" "unclassified" or "chromogenic" mycobacteria. The last is clearly a misnomer, and since many strains have names and are related to identifiable disease processes the second seems likewise inappropriate. Their classification exists - if imperfectly. The collective term "atypical" mycobacteria is therefore used. Many strains are free-living saprophytes (Singer and Rodda, 1961: Kubice, Beam and Palmer, 1963); some have been recovered from healthy children (Singer and Rodda, 1961) and adults (Edwards and Palmer, 1959: Stewart, 1962); members from each of Runyon's groups have been implicated in disease processes both in this country (Young, 1955; Selkon and Mitchison, 1959; Public Health Laboratory Service, 1962; Marks and Birn, 1963) and elsewhere (Runyon, 1959; Bogen, Froman and Will, 1959; Smyth, Kovacs and Harris, 1964) although all are of low pathogenicity. The view that they are drug induced mutants of virulent mammalian forms has been advanced by Tarshis (1958; 1961). Xalabarder (1961) has postulated that free and reversible movement occurs within the genus mycobacterium, circumstances dictating whether an organism is a saprophyte, a commensal or a pathogen. These views are not generally accepted however and the source of atypical mycobacteria able to sensitise, and to cause disease in, man is not known.

Edwards and Krohn (1957) reported that reactions in excess of about 12 mms. of induration to a 5 T.U. dose of human tuberculin were accompanied by clearly smaller reactions to antigens from atypical mycobacteria, but that reactions to 5 T.U. of human tuberculin falling within the range 3 - 12 mms. of induration were accompanied by reactions of equal or greater size to the other

antigens. Comparative skin testing many thousands of U.S. Navy recruits with human tuberculin and with antigens prepared from Group I and Group III atypical mycobacteria demonstrated a geographic association between the frequency of small reactions to human tuberculin and reactions to the Battey antigen (Edwards and Palmer, 1958). The authors suggested that some of the smaller reactions to the human tuberculin were due to cross-sensitisation by the Battey or a closely related organism. Emphasis was given to this notion by Edwards, Edwards and Palmer (1959) who argued that a small reaction to a 5 T.U. dose of human tuberculin had the same significance as the reaction brought out only by a large dose of human tuberculin and that both represented cross-sensitivity to other organisms. Palmer, et al. (1959) infected one group of guinea-pigs with virulent tubercle bacilli, another with the Battey type mycobacterium and left the third uninfected. By combining members from different groups they were able to create populations of any composition and subsequent testing with standard mammalian tuberculin revealed the patterns of sensitivity to be expected from any particular population. The results confirmed the deductions previously made regarding the recognition of non-specific sensitivity, and were similar to those from a parallel study among patients in tuberculosis hospitals with the same infections. Edwards, et al. (1960) in further work on guinea-pigs infected with different strains of atypical mycobacteria found that the frequency distribution of reactions to the homologous antigen, in the several groups of animals, all resembled the normal curve despite the cultural, morphological and antigenic differences between the infecting organisms. They also confirmed the earlier report by Affronti (1959) that cross reactions could occur to any of the antigens used and they therefore concluded that a reaction to a particular antigen did not necessarily mean infection by the

organism from which that antigen had been prepared. Many accounts of comparative testing with antigens prepared from atypical mycobacteria followed. Mellman (1960), struck by the high proportion (60 per cent.) of tuberculin positive children under three years who reverted within the following three years tested with Battey and standard (human) tuberculins. Preliminary results suggested that many had been reacting non-specifically to the initial test. A later recommendation that reactions, at this age, to human P.P.D. should be questioned in the absence of proven contact with active tuberculosis was made in the context of a suggestion by a committee of the American Academy of Pediatrics that all children under four with a positive tuberculin test should be committed to chemoprophylaxis (Mellman and Barness, 1962). Kendig (1961), presented with a similar problem amongst attenders at a "well-baby" clinic, produced evidence to suggest the widespread occurrence of atypical mycobacteria among the children but was more cautious in making practical recommendations. (Kendig, 1962). Hsu and Jenkins (1962) confirmed that low-grade tuberculin sensitivity in school-children was associated with larger reactions to the Battey antigen and that in the Houston area skin sensitivity to Group I and Group III antigens was commoner than to standard (human) tuberculin. Sartwell and Dyke (1960) likewise showed that amongst college students sensitivity to Battey antigen was more common than to human tuberculin.

The evidence has been presented to support the argument that low-grade sensitivity to tuberculin, as demonstrated by small reactions to a small dose or by reactions only to a large dose, is non-specific, that it may be induced by non-mammalian mycobacteria and that the infecting agent can be identified (broadly, if not specifically) by comparative testing since reactions to the homologous antigen usually exceed those to the heterologous antigen.

Much of the early evidence however was open to another interpretation. This was that weak reactions to tuberculin were induced by slight and infrequent infections with mammalian mycobacteria not usually sufficient to cause detectable tissue damage. These two views, presented in an editorial by Long (1951), were not mutually exclusive although the underlying principles were. It always seemed likely that both interpretations were correct. Proponents of the first had recognised that the reactions falling between the two modal points of the commonly observed frequency distribution of tuberculin sensitivity represented an area of "overlap", including both non-specific and weakly specific responses (Palmer, Ferebee and Petersen, 1950). Smith, et al. (1961) thought that a falling reactor rate which was associated with a rise in the incidence of strong-dose reactors could be satisfactorily explained only by applying both views.

A dual interpretation of the immunological evidence that later accumulated from comparative testing was more difficult but Meyer (1960), in submitting the relationship between the type of infection and the skin test results to statistical analysis, was more impressed by the evidence of geographic localisation in the prevalence of low-grade sensitivity.

The observation that, whatever its significance, its distribution is determined by geographic factors had been a constant report from every large scale survey. The recognition that in areas where low-grade sensitivity is prevalent infection by atypical mycobacteria is also prevalent does not necessarily commit one to the belief that all such sensitivity, wherever it is found, is similarly caused.

In this country the specificity of the tuberculin test was not challenged in the Prophit Survey (Daniels, et al., 1948). In the National Tuberculin Survey 1949-1950 (Medical Research Council,1952)

the existence of non-specific reactions was acknowledged but their proportion was not thought so high as to warrant ignoring sensitivity only to doses greater than 10 T.U. This opinion was accepted by Jarman in his tuberculin survey in the Rhondda Fach (Jarman, 1953). Palmer, Nash and Nyboe (1954) had also concluded, from the results of two-dose testing London schoolchildren, that there was evidence of little non-specific sensitivity. In 1959 a large scale survey among R.A.F. recruits was reported (Pollock, Sutherland and Hart, 1959). This challenged the interpretation of evidence from U. S. Student nurses (Palmer, 1953) in which a relationship had been established between the frequency of first dose reactors and history of contact with tuberculosis and in which the frequency of only second dose reactors was shown to be independent of history of contact with tuberculosis. Pollock et al. found this lack of relationship to apply to any group of people tested with a dose of tuberculin stronger than one to which they had shown no response. They concluded that the cause of small tuberculin reactions in the British population was either a weak response to tuberculous infection or the waning of a previously strong response. In a leader article appearing shortly afterwards (Lancet 1959) the opinion was expressed that in Britain non-specific sensitisation was likely to prove infrequent and unimportant. Edwards and Edwards (1960) claimed that the incidence of cross-reactions to tuberculin among schoolchildren in England was between twenty and thirty per cent. but they gave no evidence to support this contention. Nyboe (1960), in a world-wide survey, estimated the incidence of low-grade sensitivity in the ten to fourteen year age group as less than two per cent. in the United Kingdom. In comparative testing young men in the R.A.F. with avian and human O.T. Hart, et al. (1962) found that, in men reacting to a small dose of both, reactions to human tuberculin tended to be larger than those

to avian tuberculin. Those not reacting to either were tested with a large dose of both and the response to the avian tuberculin then tended to be larger than the response to the human in those who had not previously been given B.C.G. vaccine. In those who had previously been vaccinated the reaction to the human tuberculin remained the larger. In patients with active disease reactions to the small dose of human tuberculin were substantially larger than reactions to avian tuberculin. The authors postulated that the responses to the large dose of human tuberculin in the non-B.C.G. group were either mostly caused by organisms other than mammalian tubercle bacilli, or that they represented specific sensitivity which had dwindled in strength because of the interval since infection. Comparison of their findings with those of Pollock, Sutherland and Hart (1959), also amongst young R.A.F. men, showed that in the interval of five to seven years which had elapsed between the two series the incidence of small dose reactors had fallen from 56 to 29 per cent. while the incidence of large dose reactors had risen from 13 to 25 per cent. The change in the pattern of sensitivity seemed to support more easily the second rather than the first of the two possible interpretations. Flynn (1962) suggested that in Ireland much of the low-grade sensitivity amongst rural schoolchildren was due to infection from domestic fowls and he reported that sensitivity to avian tuberculin in rural children was more common than in urban children. His thesis that avian skin sensitivity was due to infection by the avian type of tubercle bacillus was not supported by Embleton (1962). A study of the prevalence of sensitivity to human and to avian tuberculin using simultaneous Heaf tests in nearly 7,000 children aged five to ten years living in six districts of England and Wales was reported in 1963 (British Tuberculosis Association, 1963). The results showed that in unvaccinated children sensitivity to avian tuberculin was

more prevalent throughout the sample than to human tuberculin (23.1 per cent. and 17.2 per cent. respectively) and that the difference was greater in rural than in urban areas. The Heaf technique was similarly used by Griffith, Marks and Richards (1963) while their antigens were derived from a number of atypical mycobacteria. Testing schoolchildren furnished results which indicated some non-specific tuberculin sensitivity but the authors felt that the choice of technique had limited the usefulness of the survey and had hindered their ability to draw conclusions. Stewart (1963) published the findings of comparative skin-testing more than 15,000 children in East Anglia. He also used the Heaf test, and human, bovine and avian antigens. The evidence supported the notion that, in this country as elsewhere, there was a non-tuberculous cause for tuberculin sensitivity. Sutherland, et al. (1964) pursued the problem which they had set in their earlier paper (Hart et al.,1962) relating to the interpretation of their finding that there was a "cross-over" in the prevalence of sensitivity to avian and human tuberculin between small and large dose reactors. By similarly testing a sample of elderly people and finding that they did not demonstrate a "cross-over" in this manner the authors felt able to conclude that the earlier evidence implied sources of tuberculin conversion other than tuberculous infection.

It has been established that the tuberculin test is not specific, that non-specific reactions appear as small responses to small doses of tuberculin or as responses only brought out by large doses of tuberculin, that atypical mycobacteria may be responsible for much non-specific sensitivity, that it exists in this country as elsewhere, and that low-grade sensitivity is also due to waning of previously strong specific sensitivity.

Other agents, altogether, have been incriminated.

Zinsser and Tamiya (1926) sensitised guinea pigs with Brucella

abortus and found them to be subsequently tuberculin positive. Aronson, Taylor and Parr (1940) reported that a large proportion of Indians in Alaska reacted to brucellin despite the fact that they never had fresh milk, and they thought this to be a cross-reaction to tuberculous infection which was common. However, brucellosis is not only, nor even perhaps primarily, a milk-borne infection (Spink, 1964; Boycott, 1964) and on the evidence given one cannot exclude the possibility of infection from other sources. Bothwell (1962:1963) has suggested a cross-immunity between tuberculosis and brucella organisms and has argued that tuberculin and brucellin skin positivity should be negatively correlated. He quotes Angle, et al. (1938) as noting the absence of positive correlation between the two tests.

Singer and Rodda (1963) were able to sensitise guinea-pigs to tuberculin preparations with fungi, such as Aspergillus fumigatus, and some dermatophytes, and to demonstrate, by gel-precipitation, antigens common to fungi and mycobacteria.

Before leaving the question of non-specific tuberculin reactions it should be remembered that a small proportion of subjects probably react not to the tuberculin but to the diluent. Griep and Bleiker (1957) found that in testing 235 persons with physiological saline 1.8 per cent. gave reactions with a diameter of induration greater than four millimetres. Edwards, Edwards and Palmer (1959) reported that 0.5 per cent. of reactions to a buffered diluent exceeded six millimetres diameter induration and Nyboe (1960) recorded twelve of 170 reactions to buffered diluent greater than six millimetres diameter induration.

2. Consideration of its stability.

The other attribute of tuberculin sensitivity to be understood, so that the reactor rate may be properly interpreted, is its stability.

Rich (1951) quoted the common assumption "that only in exceptional circumstances will the test be negative in healthy persons who have been previously infected ....." but rebutted this belief with his own, and other, evidence. He concluded that in circumstances of decreasing opportunity for re-infection hypersensitivity may decline to a point at which it could no longer be detected by routine tests.

Dahlstrom (1940) observed the behaviour of tuberculin sensitivity over a five to fifteen year period and related its persistence to its initial strength; he noted that it was unusual for a person strongly sensitive to tuberculin later to become tuberculin negative but that of those weakly sensitive seventy per cent. subsequently failed to react. The reaction was also stable in circumstances of continuing exposure to infection but in families with no history of tuberculosis almost one quarter of the family members became negative. There was a significant correlation with age, the great majority of the unstable reactors being children.

That the persistence of sensitivity was dependant upon continuing exposure to infection was also demonstrated by Madsen, Holm and Jensen (1942). In their studies among Danish children the reversion rate was found to be highest in districts having the lowest infection rate. Puffer, et al. (1946) related a falling reactor rate in schoolchildren, and a loss of tuberculin sensitivity in schoolchildren given serial tests, to a declining tuberculosis death rate in the community. The loss of sensitivity was frequent among weak reactors to 0.1 mgm. of tuberculin but unusual amongst those reacting to 0.01 mgm. In this country the authors of the Prophit Survey (Daniels, et al., 1948) noted a similar association with the degree of exposure to infection and the original degree of sensitivity. They recorded reversion rates of 1.5 per cent. in one year for contacts and of between five and six per cent. for the

control group. Jarman (1955) recorded a reversion rate of 13.4 per cent. following intensive efforts to eliminate tuberculous infection in the community, as opposed to a reversion rate of 2.2 per cent. in a neighbouring community where no such efforts had been made. Kunofsky and Katz (1958) serially retested the inmates of a closed community over a period of ten years and observed that there was a close negative correlation between the annual infection rate and the annual reversion rate.

The relationship between the degree of sensitivity and its duration was observed by Edwards and Hardy (1946). Of 163 children under two years of age, 34 were sensitive to a minimum dose of 1.0 mgm. of tuberculin, 26 to a minimum dose of 0.1 mgm. and 103 to a minimum dose of 0.01 mgm. of tuberculin. Thirty of the first group, eleven of the second and ten of the third group subsequently became tuberculin negative. Marks, Tokuyama and Peterson (1958) estimated a reversion rate in schoolchildren of 26.4 per cent. in one year if 6 mms. was accepted as the positive criterion and of 12.4 per cent. in one year if 8 mms. was accepted as the positive criterion. Adams, et al. (1959) plotted reversion rates against degrees of skin reactivity. The resultant curve fell from a rate of 76 per cent. for those weakly sensitive to 17 per cent. (one reversion amongst six subjects) for those strongly sensitive.

England, Muir and Reynard (1957) tuberculin tested male industrial workers aged between forty and forty-five years. In a series of three annual tests, of 388 positive on first testing sixteen were negative at the second test, and of 362 positive at both, one was negative at the third test. Amongst the 116 negative at the first test 43 were positive at the second; of these, nine were negative at the third. The authors appreciated the possible influence of experimental error and concluded that some of the changes in sensitivity may have been more apparent than real. These

errors, which have already been discussed, may bear as much on estimates of reversion rates as of conversion rates.

The observations that weak tuberculin reactions are unstable and that they are also often non-specific have been linked by Mellman (1960) who suggested, on evidence from comparative skin testing children under three years, that those who reverted had been infected by the Battey organism and that its antigenic activity had been insufficient to maintain the cross reactivity to typical human tuberculin.

It is well known that tuberculin sensitivity may be temporarily diminished or lost during the course of certain infectious fevers and under the influence of certain drugs. It is equally well known that it declines, or disappears, in old age. However, those are not circumstances which have any bearing on the present problem.

C. Factors affecting the reliability of the reactor rate as an index of community tuberculosis.

Essentially, the problem in Rawtenstall arose only because of an observed disparity between different indices in the same community. There would have been no problem in interpretation had the trend of tuberculosis notifications and deaths in Rawtenstall risen over the last two decades. The situation challenged the validity of the reactor, notification and mortality rates as indices of the prevalence of community tuberculosis.

The fidelity with which the reactor rate reflects the prevalence of community tuberculosis will depend on a number of factors, some of which have already been considered in some detail.

1. Experimental error.

The reliability of the figures diminishes as the experimental error increases.

The statistics which could be used as possible measures of the tuberculosis problem were reviewed recently (Tubercle, Lond., 1964). After noting the World Health Organisation recommendation that the percentage of tuberculin positive children aged 14 years should be regarded as the most useful, the author commented that although difficulties in standardisation existed these were probably less than variations in the standard of notification. Interest was expressed in the possibility that local reactor rates might be published separately for each local health authority. These rates can be obtained (Ministry of Health , 1963) and are reproduced as Appendix A. Figures are not available for the years before 1959, and all are expressed as a percentage of those tested and read. Assuming that gross changes in reactor rates from year to year in the same age group of the same population in this country are unlikely, then one would expect that those areas showing low levels of tuberculin sensitivity in 1959 would show low levels in 1962, and that those areas showing high levels in 1959

would show high levels in 1962. That is, if the County areas were to be arranged in rank according to their levels of tuberculin sensitivity in 1959 and again according to their levels in 1962 one would not expect to find large differences in placing; the coefficient of rank correlation should then be near to unity. Using the formula $R = 1 - \frac{6\Sigma d^2}{n^3-n}$ (where Σd^2 is the sum of the squares of the rank differences and n is the number of County areas submitting returns for the years 1959 and 1962) the coefficient, for the English County areas, is + 0.447. The greatest difference in placing is shown by East Suffolk, ranked equal 8th in 1959 (with a reactor rate of 11.9 per cent.) and 44th in 1962 (with a reactor rate of 28. 8 per cent.). Stewart (1963,a.) believes this to be due to their adoption in 1960 of comparative skin testing and since this involved a departure from the standard method of using and interpreting the Heaf test it is justifiable to exclude their returns from these calculations. The coefficient then becomes + 0.505 and this is significant at the 0.1 per cent. level (using the formula $t = R\sqrt{\frac{n-2}{1-R^2}}$ with 41 degrees of freedom). Applying the same test (with 67 degrees of freedom) to the figures submitted by the English County Boroughs in 1959 and in 1962 the coefficient of rank correlation is + 0.432 which is also significant at the 0.1 per cent. level.

Allowing the original assumption that the real amount of sensitivity within the same age group and in the same area should not vary much from year to year then this test of rank correlation invites a measure of confidence in the reliability of the recorded rates. Apparent vagaries in particular rates as between one authority and another need not detract from this general view. Such differences are difficult to interpret, particularly those from the County Boroughs. There is no obvious reason, for instance, why the rate should be high in Bournemouth and low in Southend nor why it

should be high in Oldham and low in Rochdale - two towns of similar character six miles apart. Geographic differences of this kind were noted by the Chief Medical Officer of the Ministry of Education (Ministry of Education, 1960) who regarded them as "unaccountable". Their explanation must be sought in terms of one or other of the factors presently being considered.

It may be argued that the assumption made is not a fair one and that the conclusion drawn from the test described is not valid. The test itself is somewhat crude however, the conclusion is tentative and the assumption is made in general terms. The reactor rate represents the cumulative experience of the subjects tested, modified to an extent dictated by the reversion rate. In comparing the level of sensitivity amongst a specific age group of the same population year by year the degree of tuberculous exposure in the previous environment of the subjects tested one year will differ from that of the subjects tested the next year only in respect of the year at either end of the scale. Tuberculous infection within the first year of lifein this country is unusual. Wolman (1952) found no positive reactors among 46 three year old Manchester children. In Newcastle Cammock and Miller (1953) recorded a conversion rate of 1.6 per cent. at one year and in Bournemouth MacDougall, Mikhail and Tattersall (1953) a rate of 0.9 per cent. at three years. The conversion rate in infants under one year in Cardiff was 0.9 per cent. (Griffiths, Bellamy and McFarlane, 1960) and in London 0.02 per cent. (Keeping and Cruikshank, 1960). In these circumstances the general assumption seems warranted.

2. Non-specific reactions.

Belief in the specificity of the reaction allowed great confidence in its use. Harrington, Myers and Levine (1937) had no doubt of its value, regarding it as "the best criterion of the tuberculosis problem in any community", far superior to mortality

rates and more accurate than notification rates. On the other hand, knowledge that it was not always specific introduced doubts. Edwards and Palmer (1953) warned that it may inflate estimates of the prevalence of tuberculosis because of the inclusion of reactions not due to tuberculous infection.

Very little is known of the epidemiology of sensitising infections other than tuberculosis yet their existence has not appeared to undermine the authority formerly given to the reactor rate as an epidemiological tool. Myers (1946) judged the success of a tuberculosis control programme in Minneapolis from the progressive fall in sensitivity among schoolchildren. The same principle was followed in the University of Minnesota (Myers, et al. 1957) where, each year since 1928, entering students had been tuberculin tested. In that year one third reacted to tuberculin but the proportion positive decreased yearly and in 1945 was 6.4 per cent. A sudden rise to 19.3 per cent. in 1946 caused concern but was shown to be due to the entry of World War II veterans who were older than their predecessors. Heimann and Simon (1950) thought an assessment of tuberculin sensitivity among children "the best index of the efficiency of a tuberculosis control programme in any community". In the National Tuberculin Survey samples of children and young people under twenty years of age were tested throughout England and Wales and the results gave a composite picture of the prevalence of tuberculous infection (Medical Research Council, 1952.). The author of this survey compared its results with those of the earlier Prophit Survey and felt able to draw general conclusions from the comparison, thereby demonstrating confidence in their value. In the survey conducted in the Rhondda Fach it was planned to estimate changes in the prevalence of tuberculous infection in the area by tuberculin testing the schoolchildren. (Cochrane, Cox and Jarman, 1952: Jarman, 1953). Griffith (1960) asserted that

the annual conversion rate among children was a "reliable index of the prevailing risk of infection in the community". Keeping and Cruikshank (1960) regarded the tuberculin sensitivity of young children as "an indication of the prevalence of tuberculous infection, both human and bovine, in a given area at a given time".

Stewart (1963) tested more than 15,000 schoolchildren in East Suffolk with human, bovine and avian tuberculins and concluded that sensitivity to human tuberculin was the best guide to the prevalence of tuberculous infection in the community. There was a significant degree of correlation between the incidence of such sensitivity and the notification rates of tuberculosis, all forms, but none between the incidence of sensitivity to avian tuberculin and the notification rates of tuberculosis. There was also a good agreement between the rates for non-respiratory tuberculosis and the incidence of reactions to bovine tuberculin. These relationships were established only after the exclusion of reactions to the bovine and avian P.P.D. tuberculins in the first instance and of reactions to the human and avian P.P.D. tuberculins in the second instance. The distinction between these kinds of sensitivity cannot be made with the material and method ordinarily used in the schools B.C.G. programme however and the reactor rate as commonly expressed includes all tuberculin sensitivity from whatever source.

The writer had already correlated local reactor rates (Appendix A.) with local notification rates of tuberculosis, all forms (Appendix B.), the latter being shown as notifications per 1,000 population. Both statistics were supplied by the Ministry of Health (1963). If the English Administrative County areas are placed in rank according to their reactor rates in 1959 and again according to their notification rates in 1959 and if ranking differences between the two are then calculated, the coefficient of rank correlation, using the same formula as previously, is - 0.502.

This degree of negative correlation, with 42 degrees of freedom, is significant at the 0.1 per cent. level. The same test applied to the two rates for all the English Administrative County areas submitting both returns for the years following again demonstrates a negative correlation, although not to a significant degree. The coefficients are given in Table 9, which also shows those from the English County Boroughs.

Table 9: Coefficients of rank correlation between the reactor rates and the notification rates separately for the English Administrative Counties and the English County Boroughs for the years 1959 - 1962 inclusive.

Local Health Authority	Year			
	1959	1960	1961	1962
English Counties	-0.502	-0.241	-0.03	-0.187
English County Boroughs	+0.031	-0.079	-0.123	-0.165

Since there is no correlation between the two rates, each may give an impression of a local tuberculosis problem at variance with the other. That this occurs may be seen from Table 10 in which both rates from selected County Boroughs in England are shown.

Table 10: Notification rates of tuberculosis, all forms, per 1,000 population, and per cent. reactor rates for selected pairs of English County Boroughs for the years 1959 to 1962 inclusive.

	Paired County Boroughs	Years			
		1959	1960	1961	1962
I	Rochdale N.R.	0.46	0.39	0.27	0.45
	Oldham N.R.	0.49	0.74	0.32	0.40
	Rochdale R.R.	-	4.8	3.6	2.4
	Oldham R.R.	15.3	19.0	12.8	28.7
II	Bournemouth N.R.	0.59	0.51	0.28	0.36
	Southend-on-Sea N.R.	0.60	0.47	0.38	0.42
	Bournemouth R.R.	12.1	13.7	12.5	28.2
	Southend-on-Sea R.R.	5.5	8.2	10.0	2.5
III	Blackburn N.R.	0.59	0.37	0.48	0.34
	Smethwick N.R.	1.60	1.29	1.05	0.86
	Blackburn R.R.	29.1	23.2	21.4	37.5
	Smethwick R.R.	9.5	7.6	7.5	11.0
IV	South Shields N.R.	1.32	1.05	0.80	0.97
	Darlington N.R.	0.52	0.49	0.42	0.37
	South Shields R.R.	13.6	12.5	9.9	12.9
	Darlington R.R.	44.2	35.7	25.4	23.6

N.R. = notification rate
R.R. = reactor rate.

County Boroughs have been chosen to demonstrate the apparent absurdities because they are, by and large, free from the influence of bovine infections. The pairings have been made between County Boroughs of approximately similar character; others could have been used to illustrate the point with almost equal effect.

It is tempting to project the conclusions made by Stewart and to argue that if sensitivity to human tuberculin among children is positively correlated to the known incidence of tuberculosis, all forms, then the absence of correlation apparent in Table 9 must be due, in County Boroughs at least, to the inclusion of non-specific reactions. However, Stewart remarks on the small size of his sample and conjecture of this kind may be unwise. Reference to the other half of the association - the notification rate - is made

later.

If these two tables offer no explanation for the discrepancies they reveal, they do show that Rawtenstall is not exceptional.

While it is clear that non-specific sensitivity is a significant factor in this country, for it to be proposed as the sole, or major contributory, cause of the phenomena under enquiry one would have to postulate its distribution in restricted, geographic, pockets. That this is possible is suggested by the finding, already quoted, of Bates, Busk and Palmer (1951) that the pattern of tuberculin sensitivity may differ radically amongst a homogoneous population living in close proximity, the prevalence of tuberculosis apparently being the same throughout the whole area. Although the evidence was indirect the authors argued that the most plausible explanation was the presence of non-specific sensitivity amongst one section of the population and its absence from the other; the distance between the two sections was less than three miles. However, its distribution is more usually conceived in wider terms. Nyboe (1960) related the incidence of non-specific sensitivity to climatic zones, observing that it increased from temperate to tropical areas. A similar distribution, on an intra-continental scale, had been observed in the United States by Palmer, Ferebee and Petersen (1950) and in Australia by Abrahams and Silverstone (1961). The recent survey conducted to assess the incidence and distribution of non-specific sensitivity in the United Kingdom (British Tuberculosis Association, 1963) recorded its presence in all six of the sample areas and at a frequency greater in rural districts than in towns. The samples were unevenly distributed however and none was from the North-West of England.

The idea that non-specific sensitivity was prevalent in the Rossendale Valley area, and in Rawtenstall at its centre, was one

which, if correct, would have provided a simple explanation for the variance between the different indices, and a practical demonstration of the warning advanced by Edwards and Palmer (1953) to which reference has already been made.

3. Bovine infections.

A comprehensive account of the effect of infection by Mycobacterium tuberculosis var. bovis on the reactor rate has been given by Madsen, Holm and Jensen (1942). These authors showed that the level of tuberculin sensitivity amongst schoolchildren was lowest in those areas of Denmark where tuberculosis eradication schemes in cattle had been most effectively executed. They tuberculin tested children aged between six and fifteen years in a town in which the milk had been safe for the previous nine years and had shown that the greatest fall in the level of sensitivity occurred between children aged nine years and children aged ten years at the time of testing. Tuberculosis in cattle had been practically unknown on the island of Bornholm since 1925 and about seven per cent. of seven year old children were tuberculin positive. This figure was accepted as representing the extent of the spread of infection from tuberculous humans. Tuberculosis was prevalent amongst cattle in Haderslev county on the mainland and 23 per cent. of country children there were tuberculin positive by the age of seven. In Haderslev town itself the figure was 47 per cent. The same infected milk was consumed in the country as in the town but whereas in the former its source was a single herd, or even a single cow, in the latter it was pooled from a number of herds. The livelier intercourse of town life allowed greater spread of human infection and this was believed to be an additional factor to account for the difference between the town and country rates. The infection rate (the percentage of tuberculin negative subjects who converted to give a positive reaction in one year) was about

five times as great in Haderslev County (excluding the town) as in the town of Rønne on Bornholm. On the Island of AErø tuberculosis in cattle had been completely eradicated by 1935 but whereas the southern part had been virtually free since 1930 the northern part still had half its herds infected in that year. Tuberculin testing of schoolchildren in 1935 revealed a significantly greater incidence of positive reactors in the latter.

Similar influences were shown by the results of a tuberculin survey conducted in the Calder Valley area of the West Riding of Yorkshire (Keidan et al., 1952). Almost twenty per cent. of school leavers were positive. The authors noted that at every age there was between 9 and 19 per cent. more reactors in the survey area than in Leeds or Hull where the incidence of respiratory tuberculosis was twice as great. It was estimated that 40 per cent. of cows in the Calder Valley area were positive tuberculin reactors and that 80 per cent. of the milk consumed was raw. Primary abdominal tuberculosis was notified, relatively speaking, between three and six times as often in the Calder Valley as in Leeds or Hull. The explanation for the high reactor rate in the survey area (that a largeproportion of the milk consumed by the children was infected) seemed self-evident.

As a result of tuberculin testing children in Cambridgeshire, Coutts (1947) had earlier reached the same conclusion to explain his finding that in children under 15 years the level of infection was more than 20 per cent. higher in rural areas than in towns.

In the National Tuberculin Survey 1949 - 1950 (Medical Research Council, 1952) - of which the report from the Calder Valley formed a part - it was recorded that the "most striking difference found was that between rural and urban areas". On average, almost twice as many rural as urban children were found to be infected at the age of entry to school, yet the death rate

from pulmonary tuberculosis had been notably less in rural areas than in towns. Whereas at that time much of the milk sold in the country was raw and came from non-attested herds most of the milk retailed in the large cities was pasteurized and the author attributed the high level of tuberculin sensitivity in rural areas to bovine infection.

A similar finding and conclusion was reached by Van Zwanenberg et al. (1956).

Groth - Petersen, Viskum and Wilbeck (1955) showed that reactions to tuberculin were substantially larger, on average, in districts where cattle tuberculosis had been prevalent than in areas where it had been rare. Although the average size of the reactions decreased as the period since eradication increased the total incidence of tuberculin sensitivity did not appear to alter much. While the influence of other factors cannot be ignored the evidence implied that the eradication of cattle tuberculosis was followed by a waning of tuberculin sensitivity - qualitatively if not quantitatively.

It will be recalled that on the basis of the figures in Table 9 the suggestion was tentatively made that in County Boroughs (where the influence of bovine infections can largely be excluded) the disparity between the two rates might be due to the inclusion of non-specific sensitivity. It is as likely that the incongruity in the County figures may be due to the inclusion in their reactor rates of sensitivity to the bovine organism also. In view of the fact that tuberculosis among cattle was not eradicated in this country until 1960 it is notable that the only significant finding in Table 9 is the degree of negative correlation between the two rates for the Counties in 1959 and that the coefficients for the Counties and for the County Boroughs are subsequently the same.

The view was held in Rawtenstall that the high level of

tuberculin sensitivity among local 13 year old schoolchildren since 1958 was due to past bovine infections and that the figures had no present significance. The facts used to support this view were that non-respiratory tuberculosis, especially that affecting the cervical glands, had been common in the valley, that raw milk was widely distributed and consumed in Rawtenstall and that until recently a proportion of it had been infected. The explanation was simple, superficially convincing and worth closer scrutiny.

The annual reports of the Medical Officers of Health from 1894 to 1948 and of the Divisional Medical Officer of Health from that year to the present have been preserved in the Rawtenstall Health Department. In the first thirty years of that period there was scarcely a single issue to which more space was devoted than tuberculosis, and the aspect of tuberculosis control to which attention was most often drawn was the part played by milk borne infection from infected cattle. Successive Medical Officers of Health advised on the gravity of the problem and on the remedies which ought to be taken.

The first account of local conditions for the production and distribution of milk in Rawtenstall appeared in the Medical Officer of Health's annual report for 1906 - "There are no registered milk shops in the Borough, as all the farmers who sell milk do so from carts direct to the consumer. There are 180 farmers registered as dairymen and purveyors of milk in the Borough." The first milk shop, "not being a farmer", was registered in 1909. There was little change by 1920: "All the milk producers are also milk retailers and the milk consequently reaches the user within two or three hours of being taken from the cow". There were "114 registered Dairy Men Cow Keepers" and one milk seller in that year. The place of the small dairy farmer retailing milk has been preserved in Rawtenstall and in 1957 there

were 54 such men delivering in the area, 34 selling T.T. milk and 20 selling raw ungraded milk. In 1962 36 producer-retailers remained.

Tuberculosis in cows was not uncommon. In 1913 it was reported that "Veterinary inspection of tuberculous cattle was commenced in the Spring, and during the year 18 cows have been destroyed". Under the Tuberculosis of Cattle Order, 1925, nineteen of 226 beasts examined by the Veterinary Surgeon in 1927 were slaughtered. In 1930 fifteen were slaughtered of 184 examined and in 1937 three of twenty-five examined. With the decontrol of meat in 1954 six private slaughterhouses were licensed in the area. Results of the inspection of meat for tuberculosis in the years following are shown in Table 11.

Table 11: Results of the inspection of meat for tuberculosis in Rawtenstall 1954 to 1962.

Year	No. of cows killed (1)	No. of whole carcasses condemned on account of T.B. (2)	No. of part carcasses or organs condemned on account of T.B. (3)	(2)+(3) as % of (1)
1954	234	0	91	39
1955	787	3	258	33
1956	611	9	134	23
1957	668	2	179	27
1958	702	1	140	20
1959	560	1	73	13
1960	542	0	24	4
1961	603	0	1	0.17
1962	850	0	0	0

The biological testing of milk samples for infection by Myco. tuberculosis was recorded first in 1936 and Table 12 gives the results in those years up to 1952 for which figures are

available.

Table 12: Results of the biological testing of milk for infection by Myco. tuberculosis in Rawtenstall from 1936 to 1952.

Year	No. of Samples	No. Positive
1936	10	0
1937	22	0
1938	39	1
1939	69	1
1940	18	0
1941	34	2
1942	38	1
1943	52	3
1944	47	1
1947	8	1
1948	46	2
1952	85	0

In 1952 the supervision of milk production became the responsibility of the Ministry of Agriculture, Fisheries and Food, and at least one sample of milk from each retailer of raw milk was taken for biological testing each year. Two years later Rawtenstall Borough Council made overtures to the Ministry that the area become a "specified area" and in 1958 it became illegal in Rawtenstall for any person to sell by retail for human consumption any milk other than designated milk. By the end of 1958 seventeen of the twenty producer-retailers who had previously been selling raw ungraded milk became licensed T.T. producers; the remaining three ceased retail delivery and sold their milk wholesale for pasteurisation. Under the Tuberculosis (Area Eradication) Order, 1950 and with effect from March 1st 1960 the compulsory

eradication of cattle tuberculosis was undertaken. The results of the biological tests on milk samples from 1953 to 1962 are shown in Table 13.

Table 13: Results of the biological testing of milk for infection by Myco. tuberculosis in Rawtenstall from 1953 to 1962.

Year	No. of Samples		No. Positive	
	T.T.	Raw Ungraded	T.T.	Raw Ungraded
1953	28	45	0	2
1954	55	65	2	5
1955	35	35	0	4
1956	26	45	0	3
1957	37	48	1	1
1958	37	7	0	0
1959	44	-	0	-
1960	41	-	0	-
1961	35	-	0	-
1962	37	-	0	-

It is evident that infected, untreated milk was being drunk in Rawtenstall up to and including 1957 and it is possible that it may occasionally have been distributed since. Black and Sutherland (1961) have described the spread of tuberculous infection amongst schoolchildren drinking untreated milk from an attestedherd. All the animals had been negative reactors from 1951 up to and including June 1959. In December, 1959 there were thirtyfive positive reactors and in January 1960 evidence of tuberculous infection was found to be widespread in the village children consuming the untreated milk from this herd. The Ministry of Education (1960) recorded the diagnosis of three cases of tuberculous adenitis in a primary school in Northern England in October

1959. Samples of the school milk supply, from a tuberculin tested herd, were found to contain tubercle bacilli and on investigation about a quarter of the herd were found to be positive tuberculin reactors. MacRae (1962) estimated that the incidence of reactors among cattle tested in Great Britain during 1961 was 0.15%. He thought there was good evidence that bovine strain infection was being reintroduced into several herds by tuberculous owners or attendants.

These observations represent exceptional circumstances and in general the possibility of milk acting as a source of tuberculous infection in Rawtenstall after 1957 need not be seriously entertained. That infected cows were being slaughtered locally up to and including 1961 may be of little significance. It is thought that the bulk of the animals came from farms outside the area and the proportion infected had, in any event, diminished rapidly since 1958. The few condemned in the last three years probably represented positive tuberculin reactors culled from herds as part of the tuberculosis eradication campaign.

While it is easy to demonstrate that a local source of bovine infection had existed until recently it is hard to assess its present impact upon the children in the community.

The amount of disease caused by the bovine organism has been associated loosely with the incidence of non-respiratory tuberculosis. Wilson, Blacklock and Reilly (1952) analysed data from the examination of specimens collected throughout Great Britain in the period 1943 to 1945. In that part of their report relating to England and Wales bovine organisms were isolated from approximately one quarter of the specimens from extra pulmonary sites. The proportions varied, according to the site of disease, from about one tenth of all specimens from genito-urinary and bone and joint disease, about one quarter from cases of meningitis and one third

from abdominal disease to about one half of all specimens from cervical glandular disease. Only in the case of specimens from cervical glandular disease and from abdominal disease were bovine organisms isolated more frequently than human organisms (Eleven and six respectively in the latter and 119 and 88 respectively in the former). The authors divided England into eight regions and estimated the ratio of observed to expected cases of bovine infection according to region and site of disease, the expected incidence being the number of cases of disease at each site which would have been due to bovine infection had the regional incidence been the same as the national incidence. The observed overall incidence in the North-West was higher than the expected incidence (ratio 1. 330) and in this respect was second only to the North Midland region (ratio 1.511). The ratio for genito-urinary disease was the highest (2.646) recorded at any site in any region. The ratio for tuberculous meningitis (1.657) was higher than the same ratio in any other region. The ratio for cervical glandular disease was near to unity (1.061). An analysis of the frequency at different ages showed that the maximum proportion of bovine-type infections was in the 5 - 9 years age group. The authors attributed this to the gradual replacement of raw by dried, boiled or pasteurised milk for infant feeding and to the introduction of the milk-in-schools scheme.

While these findings relate to the incidence of disease, it is interesting to note that Stewart and Carpenter (1955) concluded from the results of comparative skin testing children in two E. Suffolk towns that bovine infection occurred mainly before entry into school. However, a later survey in the same area seemed to confirm the fact that the 5 - 9 year age group was the most likely to be infected (Van Zwanenberg, et al., 1956). Madsen, Holm and Jensen (1942), in Denmark, typed the mycobacteria demonstrated in

diagnostic specimens in the period 1931-1935 and also found the maximum proportion of bovine infections in the school age period. Analysis by geographical distribution demonstrated a higher proportion of bovine isolates from rural districts than from urban districts at all ages and from all sites. Specimens from diseased cervical glands were associated with the bovine organism more often than specimens from other extra-pulmonary sites. Tables 14 and 15 are constructed from data supplied by these authors.

Table 14: The age distribution of cases from which human and bovine isolates were made in Denmark in the period 1931-1935 according to the source of materials.

Source of Specimen	Age in Years														
	0 - 5			5 - 15			15 - 30			> 30			All ages		
	H	B	%B	H	B	%B	H	B	%B	H	B	%B	H	B	%B
Surgical T.B. Cervical Glands C.S.F.	143	87	38	151	131	46	561	176	24	476	62	12	1331	456	26
Sputum	408	32	7	370	29	7	1916	116	6	806	21	3	3500	198	5

Table 15: The age distribution of cases of tuberculous cervical adenitis from which human and bovine isolates were made in Denmark in the period 1931- 1935.

Source of Specimen	Age in Years														
	0 - 5			5 - 15			15 - 30			> 30			All ages		
	H	B	%B	H	B	%B	H	B	%B	H	B	%B	H	B	%B
Cervical glands	8	22	73	12	66	85	72	62	46	100	16	14	192	166	46

In both tables H = number of isolations of M. tuberc. var. hominis.

B = number of isolations of M. tuberc. var. bovis.

(Percentages estimated to nearest whole number.)

In only one other instance (C.S.F. in the 0 - 5 year age group) were more bovine isolates made than human.

These findings are similar to those of Wilson, Blacklock and Reilly and lead to the conclusion that the incidence of tuberculous cervical adenitis in those under fifteen years is a fair indication of the prevalence of bovine infection. However, Marsden and Hyde (1962) suggested that a proportion of cervical adenitis in children is due to infection by atypical mycobacteria and they isolated scotochromogens as the causal organism from four of five positive cultures in 18 cases in one year. Such an association had been noted before and is suggested in the synonym (M. Scrofulaceum) given to the organism (Prissick and Masson, 1956). Davis and Comstock (1961) had reached similar conclusions but relied more on the results of comparative skin testing than on bacteriological evidence and in some of their cases the Battey organism had been incriminated. Smith, Kovacs and Harris (1964) reported that, in Western Australia, Battey mycobacteria recently had been isolated more frequently than M. tuberculosis from children with cervical adenitis. This alternate aetiology suggests that the condition may be less reliable as an index of bovine infection than has been supposed.

The incidence of all non-respiratory tuberculous disease is a less certain guide since only about one quarter has been found to be due to infection by the bovine organism. In small communities, where the number of notified cases at all ages and sites is likely to be small, divisions and subdivisions yield less and less information. The total of all non-respiratory cases must then be

accepted as the only available index and discretion used in its interpretation.

The compulsory notification of pulmonary tuberculosis was introduced in 1912 and of non-pulmonary tuberculosis in 1913. The number of each notified annually in Rawtenstall from 1913 to 1962 and the average number of each notified annually in quinquennia over the same period are represented in Appendix C. It is apparent that the overall reduction in the incidence of tuberculous disease has been due more to a fall in the number of non-pulmonary cases notified, and that, relatively speaking, the biggest reduction has been during the period 1958 to 1962.

The total number of cases of tuberculous cervical glandular disease notified in Rawtenstall quinquennially since 1942 has been as follows :

1942 - 1946 :	10
1947 - 1951 :	11
1952 - 1956 :	10
1957 - 1961 :	6

Five cases were notified during 1957 and 1958.

There has thus been a diminishing amount of disease attributable to bovine infection since 1958.

No records relating to the distribution of untreated milk in Rawtenstall (other than the number of licenced retailers) are available. It is known that only pasteurised milk has been distributed to schools for many years.

The only inferences that can be drawn from this evidence are that infected milk had been consumed in Rawtenstall up to and including 1957, that this source of infection had probably led to disease, in decreasing amount, up to 1957 and possibly, but not certainly, thereafter, and that it could be held to account for the relatively high reactor rate in the early years of the period

1955 - 1962.

The writer can see no justification for assuming, on the evidence available and without further enquiry, that it had also caused the level of tuberculin sensitivity among thirteen year old children to increase from 1955 to early 1962.

4. Reversions.

The reactor rate in any community at any time is the balance struck between the conversion rate and the reversion rate. Evidence previously quoted demonstrates that the stability of the tuberculin test is directly related to the degree of continuing exposure to infection, and that in an environment affording a decreasing opportunity for re-infection the reactor rate will fall not only because there are fewer conversions but also because there are more reversions.

Without a programme of serial retesting the reversion rate cannot be known, nor is there any guidance from the literature which would enable a prediction to be made, except in general terms, as to the probable effect on the reversion rate of the removal of infected milk as a source of infection. In the work of Madsen, Holm and Jensen (1942) already referred to, the reactor rates among schoolchildren in the parishes of the island of AErþ were related to the percentages of dairy herds found to be "impure" in the corresponding dairy districts. The findings were expressed as figures for a single year and they failed to show the dynamic relationship between the two over a period of time. Elsewhere the authors clearly demonstrated that the reversion rate among children was highest in those areas having the lowest incidence of cattle tuberculosis but this observation did no more than establish the relationship without revealing the influence of the time factor.

It may be assumed that, other things being equal, the eradication of cattle tuberculosis will be followed by an increase in the

reversion rate and a fall in the reactor rate and that the change will be most evident among children. Changes in the kind of milk supplied may exert a greater influence on the tuberculin sensitivity of children thanchanges in the incidence of respiratory tuberculosis among the population at large.

These assumptions lead the writer to doubt whether bovine infection can be held responsible for the significant rise in the rate in 1961 in Rawtenstall.

5. The sample tested.

The reliability of the reactor rate as an index of the prevalence of tubercular infection in the community will depend on the size and nature of the sample tested. "Tuberculin testing of an adequate sample of the population, especially of children, will readily give an indication of the extent of infection in the community". (Fletcher and Springett, 1959). Where the "sample" is the whole, or almost the whole, of the population and when in addition sampling is repeated at regular intervals, as was described by Gedde-Dahl (1952), then the rate will give a reliable and comprehensive account of the situation. More often the sampling is restricted or the testing is confined to a single occasion. From practical necessity restricted sampling has to be used where the population is large and the reliability of the results will then depend on the sampling technique and on the efficiency with which it is executed.

(a) the size of the sample.

The routine tuberculin testing of school "leavers" as usually practised in this country is fitted to the needs of the B.C.G. vaccination programme and in this sense the sample is virtually complete since it is deficient only in respect of those few Local Authorities not participating and of those parents not consenting to the testing of their children. It is questionable, however,

whether the results should be used for other purposes and it is not surprising that they should fail to measure up to the demand when used to indicate the prevalence of tuberculosis in the whole community.

Some Local Authorities have extended the tuberculin testing of children so as to serve a particular purpose. Cardiff, for example, instituted a four year serial testing programme among local children over the age of one year with the intention of using the information so gained to trace sources of infection in the population at large. (Griffith, Bellamy and McFarlane, 1960: Griffith, Bellamy and Davey, 1963). In Newcastle children are tuberculin tested at each of the three routine school medical inspections undertaken during a child's school life. (Miller,Seal and Taylor, 1963). The Chief Medical Officer of the Ministry of Education (1960) reported that "Many authorities offer tuberculin testing to school entrants as a routine and have a high acceptance rate."

Schemes such as these yield considerably more information than the single test done at thirteen years, not only because more children are tested each year but also because each child is tested more than once and because the younger the child found "positive" the more recently is conversion likely to have occurred.

The size of the sample may be reduced by parental selection. The B.C.G. vaccination programme in this country is voluntary. If the proportion of parents giving consent for their children to be included were to show large changes from one year to another or from one area to another then it might be possible for the reactor rate to be influenced by such changes. The acceptance rates for Rawtenstall and for Lancashire County are given in Table 16.

Table 16: Acceptance rates for B.C.G. vaccination in Rawtenstall and in Lancashire County for the years 1955 to 1962 (from data supplied by the Divisional Health Office, Health Division No. 12, Lancashire County, and from the Annual Reports of the Principal School Medical Officer, Lancashire County).

Year	Rawtenstall	Lancashire County
1955	66.8%	71.3%
1956	66.9%	67.3%
1957	-	69.1%
1958	61.7%	69.0%
1959	71.6%	73.3%
1960	70.3%	71.8%
1961	65.3%	73.4%
1962	64.3%	72.6%

The differences are small and cannot be held responsible for any apparent inconsistencies in tuberculin sensitivity.

(b) the nature of the sample.

The age group of the children tested is not the only factor determining the nature of the sample.

In County authorities, schools draw pupils from a relatively wide area. While the notifications of tuberculosis relate to cases living within the area of a particular sanitary authority the reactor rate measures the tuberculin sensitivity of children who may well live outside the same area. Both statistics are recorded in a way that suggests only local significance and the record thus implies a relationship which need not necessarily exist.

Rawtenstall secondary schools admit children mainly from three

boroughs - Rawtenstall itself, Haslingden, and Bacup. Similarly some children who live in Rawtenstall attend Haslingden Schools and a few attend Bacup schools. The number of such transfers, either way, is not known nor can it be assessed retrospectively; however there is reason to believe that the influx to Rawtenstall is the greater. Bacup has no grammar school and secondary school children living there, other than Roman Catholics, who are able to benefit from this education attend the grammar school in Rawtenstall. The only Roman Catholic secondary modern school within the three boroughs is also maintained in Rawtenstall. This division of educational facilities introduces the possibility of selection on socio-economic grounds - on the assumptions that Roman Catholic families tend to be larger than the families of other religious denominations, that intelligence is related to size of family and that both are related to social background. Even if these assumptions were true the relevance of this sort of selection can be refuted by noting that the reactor rate among children attending the Roman Catholic secondary modern school is not different from the rate among children attending the other secondary schools.

Table 17: Per cent. reactor rate, to nearest whole number, of children attending Rawtenstall secondary schools, 1955 - 1962, separately for each school.

Year	School					
	Grammar	Sec.Mod. 1	Sec.Mod. 2	Sec.Mod. 3	R.C.Sec. Mod. 1	R.C.Sec. Mod. 2
1955	38	30	36	25	14	-
1956	35	30	42	37	23	-
1958	21	46	32	40	33	-
1959	36	50	28	24	15	-
1960	28	28	18	35	50	-
1961	39	69	26	-	-	42
1962 March	-	56	48	-	-	38
1962 December	66.6*	26	37	-	-	34

No pre-vaccination tuberculin testing was done in 1957.

Secondary Modern 3 school closed in 1960.

R.C. Secondary Modern 1 school closed in 1960, the pupils being transferred to the newly built R.C. Secondary Modern 2 School.

* Only three pupils were tested.

Each borough maintains its own register of notified cases of tuberculosis: the rates/1000 population are given in Table 18.

Table 18: Notification rates of tuberculosis, all forms, /1000 population, separately for the Boroughs of Rawtenstall, Haslingden, and Bacup for the years 1955 - 1962.

Year	Rawtenstall	Haslingden	Bacup
1955	0.64	0.35	0.59
1956	0.61	1.36	1.0
1957	1.06	0.71	1.35
1958	0.87	0.21	0.76
1959	0.25	0.29	0.82
19601	0.96	0.50	0.53
1961	0.59	0.14	0.41
1962	0.25	0.35	0.18

It may be that fluctuations in the incidence of tuberculosis in Haslingden and in Bacup bear on the recorded reactor rates of children attending Rawtenstall schools. Table 19 has been constructed to show the pooled reactor and notification rates for the three boroughs.

Table 19: Pooled reactor rates and notification rates of tuberculosis, all forms,/1000 population of the Boroughs of Haslingden, Rawtenstall and Bacup, 1955 - 1963, together with the Rawtenstall reactor rate for the same period.

Year	Pooled Reactor rate	Pooled Notification rate	Rawtenstall Reactor rate
1955	34	0.56	31
1956	38	0.93	34
1957	/	1.09	/
1958	37	0.67	33
1959	31	0.44	33
1960	24	0.71	29
1961	32	0.42	41
1962	44	0.24	40
1963	27	0.36	22

The two rates still appear to be unrelated. Pooling of the statistics in this way does not explain the fluctuations apparent in the Rawtenstall reactor rate.

It is likely that some thirteen year old children will either have had tuberculosis or will have been tuberculin tested as contacts of a case. In the latter event they will have been vaccinated with B.C.G. if found to be negative. The reactor rate of school leavers will be influenced by whether such children are included in the B.C.G. vaccination programme or not. No guidance is given to those whose responsibility it is to administer or execute the scheme, and policy may therefore differ from one area to another. Various hypothetical situations can be envisaged. An area in which the incidence of tuberculosis is relatively high may exclude from its B.C.G. vaccination programme all children known to be tuberculin positive whereas another, having a somewhat lower incidence of tuberculosis, may tuberculin test all thirteen year old children irrespective of their previous experience. The second area may then record the higher reactor rate. Such changes in policy may destroy any relationship that would otherwise exist between local reactor and notification rates, and may discriminate

not only between one area and another but also in the same area from one year to another since the policy, and therefore the nature of the sample tested, may fluctuate with successive tester-readers.

Two further factors bear on the subject. First, whatever the views of the individual responsible for the selection of children to be tested the wishes of the parents are honoured. It is the writer's impression that the parents of thirteen year old children known to be tuberculin positive, from whatever cause, are less likely to consent to the further testing of their children than are the parents of children who have not been tested previously. If this is the case (and no direct evidence is known either to support or to refute the impression) then clearly the reactor rate will increasingly fail to reflect the prevalence of community tuberculosis as this rises. Second, it has been customary for some years in certain centres for B.C.G. vaccination to be offered routinely to neonates. This introduces problems of selection at thirteen years and may influence parents against the need for further testing.

The nature of the sample tested may be affected by changes in the composition of the population.

The immigration of Commonwealth citizens in significant numbers is a recent development known to have increased the prevalence of tuberculosis in certain areas. Springett et al.(1958) reported that there were between four and six times as many notifications in Birmingham from Asian born persons as would have been expected from the population figures. A further report (Springett, 1964) assessed the annual notification rate in Birmingham of U.K. born males as 0.68 per thousand. For other birth place groups the rates per thousand for males were : British Caribbean area - 1.3

India - 4.5

Pakistan -18.2

The author was able to estimate these rates from the 1961 Census which provided information as to place of birth of the population enumerated. Stevenson (1962) reported that in Bradford the estimated annual rate of incidence of tuberculosis among Pakistanis was at least twenty per thousand, or thirty times greater than the incidence in the British population in Bradford. The number of cases notified among non-Pakistani males fell from 177 in 1955 to 110 in 1961. The number notified among Pakistani males rose from 20 to 124 in the same period. Edgar (1964), reporting from the same city, gave the figures for 1963 as 94 and 198 respectively. In Wolverhampton, Aspin (1962) recorded that in 1960 "over four times as many new cases of pulmonary tuberculosis were recognized among Indian immigrants as might have been expected among a similar number of local inhabitants" and that the proportion of Indians among locally diagnosed adult cases of pulmonary tuberculosis rose from 0.8 per cent. in 1954 to 11.0 per cent. in 1961.

Evidently the selective immigration of Pakistani nationals to localized areas results in a rise in the notifications of tuberculosis. Unless there is a parallel rise in the reactor rate population changes of this kind will distort the relationship between the two rates, as appears to have happened in Bradford:

	1959	1960	1961	1962
Notification rate/1000	0.88	0.76	0.90	1.08
Reactor rate	13.9	14.1	13.3	13.5

The reason for this dissociation may lie in the immigration patterns and social habits of Pakistani nationals, described by Stevenson (1962) and by Edgar (1964). In contrast to immigrants from from the British Caribbean area, among whom immigration is viewed as a permanent, family change, these authors recorded that Pakistani males came to this country alone with the intention of returning to

their families after a relatively short time, and that while in this country they tended to live and work together.

The 1961 Census enumerated the residents in Rawtenstall born outside England and Wales and classified them broadly according to citizenship (General Register Office, 1964). There can have been few Pakistanis at that time since the number of those in the total classification was 33 per 1000 residents. It is the writer's impression that the number has increased since and it is a notable fact that two of the six notifications of tuberculosis in Rawtenstall in 1963 were of Pakistanis and that two of the ten notifications in 1964 were also of Pakistanis. None were notified as suffering from tuberculosis before 1963.

The phenomenon of large scale Commonwealth immigration has been quoted as a factor likely to affect the validity of the reactor rate as an index of community tuberculosis. It is not propounded as an explanation for the actual circumstances under review since it is clearly inappropriate to them.

Emmigration from Ireland to this country differs in almost every respect from that just discussed, including the problems they separately create in the epidemiology of tuberculosis.

The notification rate amongst Irish immigrants is high. Hess and MacDonald (1954) interviewed almost 300 patients with pulmonary tuberculosis in five hospitals in the N. W. Metropolitan Region and found that the ratio of Irish patients to Londoners was at least three times that expected on the basis of the relative numbers in the general population. Springett et al. (1958) reported that in Birmingham the notifications of Irish born persons were about twice as numerous as would be expected from the population figures. Brett (1958), from an analysis of the records of a single mass radiography unit, assessed the incidence of active tuberculosis in U.K. born residents as 5.7 per thousand examined and of Irish born

residents as 42 per thousand examined. These reports also suggested that infection occurred after entry into this country; a previous finding of the Prophit Survey in this country (Daniels et al. 1948) and of Flynn and Joyce (1954) in Ireland that Irish country dwellers had a low incidence of tuberculin sensitivity strengthened this belief. On the other hand most reports have suggested that the notification rate among Pakistanis in this country is high because many were infected before arrival. Edgar (1964) tuberculin tested 2,859 Pakistanis in Bradford and found that only 13 per cent. were negative.

There are many first generation Irish families in the Rossendale Valley area of Lancashire. Whatever the theoretical complexities of their influence on the local epidemiology of tuberculosis, and in particular on the level of tuberculin sensitivity among the children, the practical point may be repeated that, in Rawtenstall, the reactor rate of the Roman Catholic children has not differed from that of the Protestant children (Table 17).

6. Tuberculosis in schools.

It might be thought that the occurrence of an infectious case of tuberculosis within a school would lead to widespread dissemination of infection without necessarily causing much active disease. If this were the case then the reactor rate would rise to an extent not matched by any change in the notification rate and it would then give an exaggerated account of the prevalence of community tuberculosis.

Hyge (1947) described the explosive spread of infection from a teacher later found to have an active pulmonary lesion but subsequent morbidity among the child contacts was also high. Roe and Dick (1949) recommended that a "thorough search for a possible infector should be carried out" wherever "a tuberculin survey of scholars reveals a higher percentage of positive reactors than that considered normal". The authors described how an infector within

the school caused an increase both in the amount of tuberculin sensitivity and in the number of active lesions diagnosed radiologically. Bevan, Bray and Hanly (1951) recounted how the reactor rate of a class rose when under the charge of a teacher with pulmonary tuberculosis. Morbidity was again high. In the three episodes described the source of infection had been traced to a teacher. Anderson and Grenville-Mathers (1952) investigated nine day schools in which sporadic cases of tuberculosis in children had occurred. The results of tuberculin testing were unexceptional and no further cases of tuberculosis were discovered. In one school, however, where a teacher had the disease, two other cases of pulmonary tuberculosis and one case of pleural effusion occurred. The authors concluded that a pupil with open pulmonary tuberculosis was not responsible for gross dissemination of infection in day schools but that the position was different if a school teacher had a pulmonary lesion. Silver (1958), however, failed to find any significant spread of infection as judged by skin test results in two schools in which adult members of the staff were known to have sputum positive disease, while Stronge and Balmer (1961) reported that a pupil with a progressive pulmonary lesion caused extensive tuberculin skin conversion and twenty three cases of tuberculosis in the school. The Ministry of Education (1960) quoted reports from three areas which had experienced school infections within the previous two years and in none was there any evidence of the spread of infection. In 1962 (Ministry of Education, 1962) further episodes were described. In four areas no spread of infection occurred either from an infected pupil or from an infected teacher but in a fifth a pupil was the source case for eight children subsequently found to be suffering from tuberculous disease.

From these accounts it appears that the assumption made is untenable and that tuberculosis in schools may lead to substantial

spread of infection, or to none, and to widespread disease, or to none: or that it may not do either.

Respiratory tuberculosis has been diagnosed either in pupils attending, or in members of the staff of, Rawtenstall schools on a number of occasions since 1955.

Table 20: Cases of respiratory tuberculosis notified among pupils or staff of Rawtenstall schools during the period 1955 - 1963.

Year	Case No.	Pupil	Staff	School
1956	1	Schoolgirl	/	Grammar School
1958	2	Schoolgirl	/	R.C. Sec. Mod. 1
1958	3	Schoolboy	/	Sec. Mod. 1
1959	4	Schoolboy	/	R.C. Sec. Mod. 1
1960	5	/	School meals helper	C.E. County Primary
1961	6	/	Schoolmaster	Grammar School
1963	7	Schoolboy	/	Sec. Mod. 2

No records remain of any investigation undertaken at the time of the first four episodes.

In 1960 a school meals assistant in a Church of England County Primary School was found to have respiratory tuberculosis. The remainder of the staff was X-rayed and the children were tuberculin tested, positive reactors being referred for X-ray. No radiological evidence of further active disease came to light. Twenty-four of the 320 children tested were positive. Retesting of 115 of these children has subsequently been completed under the B.C.G. vaccination programme. There have been no reversions andten of those originally negative have since become tuberculin sensitive.

In 1961 a member of the teaching staff at the Grammar School was admitted to hospital with a pleural effusion and was notified

as suffering from tuberculosis. All the children in the classes taught by this master were tuberculin tested, positive reactors being referred for X-ray. No further case was discovered. It may be thought that the incidence of positive reactors (39 per cent.) was rather high in relation to the previous experience of the school, particularly in view of the fact that the children tested were aged from eleven to thirteen years.

In December 1962 the annual pre-vaccination tuberculin testing of thirteen year old children was performed. Among the positive reactors referred for X-ray a pupil attending Secondary Modern 2 school was found to have bilateral post-primary disease. He was asymptomatic and Myco: tuberculosis were not cultured from gastric washings. The staff of the school were X-rayed and none showed evidence of disease. The following term the six children who had been in the same class in December and who had then shown a Grade 1 or 2 reaction to the Heaf test were retested. Three gave similar reactions, two had reverted to negative and one showed a marked increase in sensitivity. This last child was twice X-rayed at six monthly intervals without showing any radiological abnormality. Tuberculin testing at the beginning and at the end of the year showed a drop in the frequency of sensitivity in this school (Table 18).

It seems that these episodes of tuberculous infection in the schools had remained isolated and that they did not lead to further disease.

Episodes 2, 3 and 6 were associated with an increase in tuberculin sensitivity in the schools affected and it may be that the reactor rate in 1958 would have been lower had the first two not occurred. The steep rise in the reactor rate in 1961 was clearly due more to the high incidence of sensitivity in Secondary Modern 1 school, in which no tuberculous disease was suspected,

than to the lower incidence in the Grammar school in which a case of tuberculous disease had been diagnosed.

It cannot be claimed, therefore, on the facts as they are known, that the occurrence of tuberculous disease in schools has dictated, or has significantly contributed to, the pattern of tuberculin sensitivity in Rawtenstall children. The suspicion remains, however, that the experience of Secondary Modern 1 School should have prompted investigation, as was advised by the Joint Tuberculosis Council in their memorandum on the control of tuberculosis (1962) whenever "the incidence of positive reactors found in school entrants or leavers" was "substantially above the national average".

7. Expression of the results of tuberculin testing.

Tuberculin testing as a preliminary to vaccination is used as a qualitative test, its purpose being to define those children who would benefit from vaccination. It is doubtful whether even for this use it should beregarded in such an unsophisticated manner and certainly if the information derived from the test is to be directed to other purposes then it is not enough to express results qualitatively since the strength of the response may beas relevant as the fact of the response.

Unfortunately there is no requirement that the results of pre-vaccination tuberculin testing in schools in this country be expressed in any way other than as numbers "positive" and numbers "negative". It is thus impossible to judge from the published figures quantitative changes in tuberculin sensitivity over a period of time.

Smith et al. (1961) showed the changes in kind which accompanied a decline in the amount of sensitivity over a thirty year period among students attending a medical school in the United States of America. The reduction was due to a fall in the

numbers of first, or small, dose reactors; large dose reactors progressively increased in number over the same period. A similar pattern of changes was recorded in this country by Hart et al.(1962) who compared their results of tuberculin testing R.A.F. personnel with those obtained by Pollock, Sutherland and Hart (1959) some six years earlier, the age of the population studied being similar in both series. The proportion positive to 1/3000 O.T. had fallen from 56 per cent. to 29 per cent. in that time, but the proportion positive only to 1/100 had almost doubled.

These observations are of more than academic interest. Griffith, Marks and Richards (1963) were unable to relate low grade sensitivity among children to infection by virulent tubercle bacilli, a finding previously suggested by Hsu and Jenkins (1962). Van Zwanenberg (1964) found evidence of contact with disease in thirty per cent. of children with high grade sensitivity but in only seven per cent. of children with low grade sensitivity, and evidence of tuberculous disease in twenty two per cent. of children with high grade sensitivity but in none of the children with low grade sensitivity.

These findings lead to the conclusion that small reactions to tuberculin, whatever their significance, are not a reliable index to the prevalence of tuberculosis. Not only are they of doubtful significance but, being most open to reader error, their recognition is unreliable also. It seems logical that the frequency of only large reactions should be used in assessing the prevalence of tuberculosis.

If the results of pre-vaccination tuberculin tests on schoolchildren in this country were required to be submitted to the Ministry of Health in quantitative terms much of value would result.

II. The Notification Rate.

The notification of cases of tuberculosis was voluntary up to 1908. The Public Health (Tuberculosis) Regulations of that year compelled the medical officer of a Poor Law Institution to notify cases of pulmonary tuberculosis diagnosed among inmates of the institution and The Public Health (Tuberculosis in Hospitals) Regulations 1911 caused the compulsory notification of cases of pulmonary tuberculosis occurring in non-rate aided hospitals. The Public Health (Tuberculosis) Regulations 1911 extended the compulsory notification of pulmonary tuberculosis so that it applied generally and The Public Health (Tuberculosis) Regulations 1912, which came into operation on the first day of February 1913, laid down that (subject to certain provisions) ".. every Medical Practitioner .. attending on or called to visit any person .. shall, within forty eight hours after first becoming aware that such person is suffering from Tuberculosis, make and sign a notification of the case .. and shall transmit the notification to the Medical Officer of Health .. ". The main difference between this and the previous Regulation was that compulsory notification was now required of non-pulmonary as well as of pulmonary cases of the disease. Article VIII of these Regulations stated that ".. a Medical Practitioner shall be deemed to have become aware that a person is suffering from tuberculosis when he has arrived at this conclusion from evidence other than that derived solely from tuberculin tests applied to that person". Subsequent amendments made in the Regulations of 1921, 1924 and 1936 were directed mainly to the form of register kept by the medical officer of health and to the requirements regarding the quarterly returns of cases notified.

The Public Health (Tuberculosis) Regulations 1952 are those currently in force. They direct that every medical practitioner

"who forms the opinion from evidence other than evidence derived solely from tuberculin tests that a person is suffering from tuberculosis shall, as soon as he forms that opinion, send to the medical officer of health of the district in which the person is living at the time a certificate .. ".

The number of notifications made over a period may be regarded as a measure of the amount of tuberculosis in the community and the number per unit of population as a comparative index, but neither has enjoyed much confidence in this respect. Myers (1946) considered that morbidity and mortality rates under-estimated the true incidence of tuberculosis and said that they occasioned "a false sense of security". In the Prophit Survey (Daniels et al., 1948) the notification rate was described as "notoriously unreliable". Bentley, Grzybowski and Benjamin (1954) wrote that "notifications have been a deficient measure of the prevalence of disease". Cochrane, Cox and Jarman (1955) thought it improbable that the notification rate would ever be satisfactory as an index, and MacLeod (1960) called it an unsatisfactory criterion.

Factors affecting the reliability of the notification rate as an index of community tuberculosis.

1. Interpretations of the regulations.

The regulations of 1912 and 1952 distinguish between tuberculous infection and tuberculous disease and clearly state that only the latter need be notified. The distinction is not always clinically evident however and, as pointed out by MacLeod (1961), since it may be impossible to decide where the one ends and the other begins, especially in children, the interpretation of this requirement may then vary from centre to centre and, within the same centre, from doctor to doctor. The author further points out that the word "suffering" may have little meaning in these days of asymptomatic diagnosis.

The general certificate of notification of infectious

diseases (the form used for the notification of cases of tuberculosis) bears a note on the front cover referring to this problem. It reads ".. A person who should be notified as 'suffering from tuberculosis', therefore, is a person who, because of tuberculosis infection, may infect others: or a person who is suffering from an active tuberculous lesion which calls for medical treatment or for some modification of the patient's normal course of living".

The infectivity of tuberculous disease applies mainly to the pulmonary form and is a relative characteristic. Shaw and Wynn Williams (1954) investigated the problem by tuberculin testing all children aged fourteen years or less who were contacts of cases of pulmonary tuberculosis, a group of children within the same age range who were not contacts being tested as controls. The source cases were separated into those with sputum which was positive on direct smear, those with positive cultures (either from sputum, laryngeal swabs or gastric washings) and those from whom no organisms had been recovered. The results showed that the per centage of tuberculin sensitive contacts was 65.2, 26.8 and 17.6 respectively and that the per centage of tuberculin sensitive no-contact controls was 22.1. The age distribution of the controls was weighted in favour of older children who normally would be expected to have a higher incidence of tuberculin sensitivity than those in the younger age groups. If this bias is corrected so that the age distribution of the no-contact controls is the same as the age distribution of the child contacts of cases of pulmonary tuberculosis from whom no organisms had been recovered, then the incidence of sensitivity in these two groups becomes 19.7 per cent. and 17.6 per cent. respectively. The incidence of tuberculous disease among the child contacts showed even greater variation, the three types of source cases described causing disease in 14.4

per cent., 2.6 per cent. and 0.9 per cent. of the child contacts respectively. Van Zwanenberg (1955) obtained rather different results although the evidence was not all direct. The rate of tuberculin sensitivity in the general child population was estimated to be 24.3 per cent. Source cases were classified in the manner described by Shaw and Wynn Williams. The per centage of tuberculin sensitive contacts of the three groups was 72.9, 45.8 and 38.4 respectively. The source cases caused disease in 16.4 per cent., 1.04 per cent. and 3.03 per cent. of the child contacts respectively. In a subsequent paper (Van Zwanenberg, 1960) the same author described how 65.6 per cent. of child contacts of index cases with direct positive sputum were tuberculin sensitive as against 25.7 per cent. of child contacts of index cases with sputum positive on culture only and 21 per cent. of child contacts of sputum negative index cases. The incidence of disease among the three groups of child contacts was 23 per cent., 1.5 per cent. and 2.4 per cent. respectively. Hertzberg (1957), in a comprehensive study, found that pre-school child contacts of source cases without demonstrable tubercle bacilli had an incidence of tuberculin sensitivity 3½ times as great as children of the same age living in homes free from tuberculosis. The incidence of tuberculin sensitivity among pre-school child contacts of source cases without demonstrable organisms and without cough or sputum was 2½ times as great.

It thus seems to be the case, despite the evidence of Shaw and Wynn Williams, that any person with active pulmonary disease may infect others and the guidance that a person should be notified as suffering from tuberculosis if able to infect others does not solve the clinical difficulty of diagnosing activity in the absence of bacteriological evidence.

The need for treatment or for some modification of the patient's normal course of living depends on the judgement of the clinician and, in this context, on his assessment of the activity of the lesion. Those persons thought suitable for chemoprophylaxis are, by definition, excluded from notification since the absence of active disease is assumed.

Except in this last instance the note referred to thus offers no practical help to those upon whom the onus is placed of distinguishing between infection and disease. The sole criterion of notification remains that an active tuberculous lesion shall be deemed to exist and on this issue a large measure of error must inevitably exist.

The confusion thus caused detracts from the reliability of the notification rate as a comparative index, although in a particular centre where a stable policy has been pursued over a period of time it may act as a reasonable guide to changes in incidence.

2. Diagnosis.

In addition to the diagnostic difficulties mentioned others are involved in which, although disease is clearly present, it's nature is uncertain. Most morbidity records are affected in this way.

With the recognition of disease caused by atypical mycobacteria another diagnostic pitfall has been introduced. Although the amount of all forms of disease caused by these organisms in this country has probably been very small they may have played a numerically significant role in the aetiology of cervical adenitis. Disease caused by them is not notifiable, since it is not tuberculous, but, because clinical differentiation between the two may be impossible and since bacteriological evidence may be lacking, errors in notification must necessarily result.

3. Late notification.

It may happen that notification is not made until after death. The number of such notifications is published in each annual report of the Chief Medical Officer of the Ministry of Health. In the annual report for 1950 (Ministry of Health, 1950) the opinion is expressed that "in most cases failure to notify is due to inadequate regard for the statutory requirement".

Late notifications may relate either to persons known before death to have tuberculosis in whom notification had been omitted either by oversight or by death occurring so soon after diagnosis that there had been not time for formal notification, or to persons previously notified whose names had been removed from the register on "cure", or they may relate to persons not known before death to have tuberculosis in whom its presence had been established only by post-mortem examination. In this last instance the corollary is that its presence may be overlooked altogether.

Of the four circumstances leading to notification after death the first two do not entail any diminution in the total number notified since the cause of death, being known, is entered on the death certificate and notification will be made subsequently through the registrar. The fourth does imply this possibility however. If it is assumed that those known before death to have had tuberculosis will have been treated and that those not known before death to have had tuberculosis will not have been treated, then it is possible to draw tentative conclusions from the published statistics as to which category the persons so notified will have predeominantly occupied.

Table 21: Notifications of tuberculosis, all forms, deaths from tuberculosis, all forms, and deaths of tuberculous persons not notified before death, in England and Wales for the years 1945 - 1962,

together with an estimate of their relationships.

Year	Notifications (1)	Deaths (2)	Post-Mortem Notifications (3)	(3) as % of (1)	(3) as % of (2)
1945	52,110	23,959	3,603	6.9	15.0
1946	51,289	22,850	3,580	6.9	15.7
1947	51,725	23,551	3,682	7.1	15.6
1948	52,576	21,993	3,551	6.8	16.1
1949	52,041	19,908	3,282	6.3	16.5
1950	49,358	15,969	2,704	5.4	16.9
1951	49,440	13,806	2,606	5.2	18.9
1952	48,093	10,585	2,239	4.7	21.1
1953	46,546	8,902	2,286	4.9	25.7
1954	42,348	7,897	1,627	3.8	20.6
1955	38,134	6,492	1,495	3.9	23.0
1956	35,504	5,375	1,465	4.1	27.3
1957	32,659	4,784	1,474	4.5	30.8
1958	29,838	4,480	1,335	4.5	29.8
1959	27,100	3,854	1,171	4.3	30.4
1960	23,605	3,435	952	4.0	27.7
1961	21,747	3,334	1,036	4.8	31.1
1962	20,519	3,088	1,016	5.0	32.9

It is apparent that over this period an increasing proportion of deaths have been among those not notified before death and since the increase coincides with the introduction of specific drug treatment in the early 1950's and with its effective development during the middle and latter half of that decade it seems legitimate to presume that most notifications of tuberculosis after death are not made in respect of persons who were known before death to have the disease and who were therefore

treated for it. It may be the case, however, that many of them relate to the death of persons previously notified and "cured" who died of some condition other than tuberculosis, this diagnosis appearing in Part II of the certificate.

Although the conclusion reached here is at variance with the opinion expressed by the Chief Medical Officer of the Ministry of Health (already quoted) it receives qualified support from Smith (1962) who investigated all cases where tuberculosis was noted on the death certificates of people dying in Birmingham in 1961 and who concluded that "Deaths still occurring from tuberculosis seem mainly to be due to failure of diagnosis .....".

In successive annual reports the County Medical Officer of Health for Lancashire County had referred to the problem of post-mortem notifications of tuberculosis with concern and in 1964 an enquiry was made into the circumstances of such notifications which had occurred within the administrative area in 1963. The results (Lancashire County Council, 1965) suggested that of the total of 41 non-notified fatal cases of tuberculosis only ten had active pulmonary disease at the time of death and that of these only three were receiving appropriate treatment at the time of death. Further reference to the results of this survey will be made in the discussion on mortality rates since post-mortem notifications cannot be interpreted fully without regard to the system of death certification.

4. Double notifications.

Local Authorities are instructed, in making their returns of tuberculosis notifications, to exclude from them those notifications registered in respect of tuberculous persons who have moved into the area, notification having been made previously in another area. It is possible that through misunderstanding or error the notific-

ations of these persons may be included in the returns from both areas. In that event the estimate of the amount of tuberculosis in the whole country would be inflated and the estimate in the receiving area would be inflated by comparison with those areas in which exclusion of the number of "transfers-in" was rigorously pursued.

However, in relating the notification rate to the reactor rate in any given area it may be that the number of all known tuberculous persons resident in the area might form a better basis for comparison than the one usually adopted. The number of "transfers-in" registered in Rawtenstall can be computed and Table 22 compares the reactor rate among Rawtenstall schoolchildren with the number of notifications as normally expressed and with the number of notifications plus the number of "transfers-in".

Table 22: The percent. reactor rate among thirteen year old children, the number of notifications of tuberculosis, all forms, and the number of notifications of tuberculosis, all forms, plus the number of "transfers-in", in Rawtenstall for the years, 1955 - 1962.

Year	% Reactor rate	Number of notifications	Number of notifications plus "transfers-in"
1955	31	16	20
1956	34	15	16
1957	-	26	32
1958	33	21	23
1959	33	6	6
1960	29	23	26
1961	41	14	17
1962	40	5	8

There still does not appear to be any relationship between the incidence of tuberculin sensitivity and the amount of notified disease.

It has already been shown that it is not usual in England for such a relationship to exist despite the theoretical expectation that it should do so, and reasons for the lack have emerged in what has so far been written. While the real incidence of tuberculosis may not be accurately portrayed by either measurement consideration must be given to the possibility that one or other of the indices is true and that its partner is false. The problem of tuberculosis in this country has been so generally regarded, and for so many years, as one of declining importance that doubt is almost intuitively cast on any measurement purporting to reveal an increasing incidence. In these circumstances a natural reaction would be to accept the validity of the notification rate (since its trend shows a fall) and to reject the validity of the reactor rate (since its trend shows a rise). Without compromising this view the opposite should be considered and the question asked whether the rise in the reactor rate does not reveal an increase in the local prevalence of tuberculosis not recognized by other means. Although the possibility was advanced it did not meet with the acceptance needed to initiate action and the writer knew, in 1962, of no answer to this question nor of any way of arriving directly at an answer that did not involve a policy decision resting on other authority.

III. The Mortality Rate.

Mortality rates are subject to the same kind of errors as are morbidity rates except that causes of death are open to verification. Relative or absolute failures in diagnosis leading to fallacious morbidity rates may create false mortality rates also. Few deaths are investigated by post-mortem examination and there is no reason why mortality rates should be accorded greater reliability than morbidity rates.

If the mortality rate is to be used as a measure of the number of persons killed by tuberculosis then only those deaths certified in Part I of the death certificate to be due to tuberculosis should be counted. If, on the other hand, it is to be used as a measure of the prevalence of tuberculosis then all death certificates should be counted on which the word "tuberculosis" appears no matter what significance has been given to the diagnosis. However, it is in these circumstances that it loses contemporary value since the entry may relate to disease acquired long before death. Cohort studies made in America (Frost, 1939) and in this country (Springett, 1952) confirm that deaths from tuberculosis in later life are seldom the result of recently acquired disease.

The published statistics relate to the death of persons who were considered to have had, or to have at the time of death, tuberculous disease. This need not necessarily have been the primary, nor even a contributory, cause of death; the difficulty of allocating a role to one of many factors leading to death is well known.

These factors lead to the anomaly that among the number of post-mortem notifications of tuberculosis may be counted deaths of persons who had been notified and "cured" andwho had not died from tuberculosis. In the Lancashire Survey already referred to,

although full information on all of the deaths considered was lacking, sufficient was available to show that six of the total of 21 deaths from pulmonary tuberculosis fell within this category.

The introduction of specific anti-tuberculous drugs and the fall in the number of deaths due to tuberculosis has further robbed the mortality rate of much of its former value.

Its fallibility as an index has been judged by a number of investigators. Of 56 deaths over a two year period in Leicester reported as due to pulmonary tuberculosis no post-mortem evidence of tuberculous disease was found in four. In 26 others tuberculosis was deemed not to be the primary cause of death (Anderson, 1959). Of 170 deaths in a single year in Birmingham where tuberculosis was noted on the death certificates, the diagnosis appeared to be mistaken and tuberculosis was absent in twelve. In 63 others death was due to some condition unconnected with tuberculosis. In only 46 was death due solely to tuberculosis (Smith, 1962). In a review of 87 persons dying in hospital over a five year period whose death certificate included the words "pulmonary tuberculosis" no evidence of tuberculosis was found in four. Fifty of the deaths had been certified in Part I of the certificate as due to tuberculosis; the reviewer considered that in twenty of these tuberculosis had not been a contributory factory. In the remaining 37 deaths the term"pulmonary tuberculosis" appeared in Part II of the certificate; the reviewer considered that in eight of these tuberculosis had been a contributory factor (Simmonds, 1963). In the Lancashire Survey (Lancashire County Council, 1964) at least one of the 21 deaths certified as due to pulmonary tuberculosis was found not to be so caused at post-mortem.

Summary to Part I.

1. It has been suggested (Ministry of Education, 1962) that the incidence of tuberculin sensitivity among thirteen year old schoolchildren may be used as an index of the prevalence of tuberculous infection in the community.

2. The variables in measuring tuberculin sensitivity have been considered. They derive from the possible differences in the method of testing, in the test materials and in the manner of testing and reading.

3. The meaning of tuberculin sensitivity has been examined and the traditional acceptance of its stability has been questioned. A review of the literature supports the notions that it is neither necessarily specific nor stable.

4. The assumption that the reactor rate, as defined, among schoolchildren constitutes a guide to the incidence of community infection is weakened further by variables in the selection of the sample tested, by the occurrence of tuberculosis in schools and by the expression of the results of testing in qualitative terms.

5. It has been shown that, in this country, local reactor rates among schoolchildren and local notification rates are not positively correlated. It is suggested that this is so because of the operation of all or of some of the factors mentioned.

6. Problems of interpretation therefore arise and these are illustrated by reference to local circumstances in a small Lancashire community in which the incidence of tuberculin sensitivity among thirteen year old children had remained constant from 1955 to 1960 and had thereafter increased. The

tuberculosis morbidity and mortality rates implied a decreasing incidence of the disease over the same period.

7. The problem has been approached in terms of the factors already considered.

8. The rise in the reactor rate in 1961 was associated with a change in the method of tuberculin testing from the 10 T.U. Mantoux intradermal test to the Heaf multiple puncture test.

9. Appreciation of the fact that tuberculin sensitivity is not specific and that it may be caused by infection with organisms other than mammalian Mycobacteria Tuberculosis makes it possible to suggest infection by atypical mycobacteria as a factor in maintaining the local level of tuberculin sensitivity.

10. Since it is thought that small reactions to the Heaf test are not characteristic of tuberculous infection it is possible to advance the view that the use of a stronger dose of tuberculin involved in the change of testing method brought to light a reservoir of non-specific sensitivity not previously revealed.

11. The publication of results of tuberculin testing in qualitative terms prevents satisfactory confirmation of this possibility.

12. In December, 1962, a quantitative comparison of the results from the Heaf test by two tester-readers was made. Differences occurred at the level of minimal reactions to the Heaf test. According to the significance attached to these reactions the level of tuberculin sensitivity was found to conform to the constant level measured by the 10 T.U. Mantoux test up to 1960 or to the increased level measured by the Heaf test since 1961.

13. The available evidence suggested a significant source of bovine infection up to, but not later than, 1957.

14. In view of the known propensity of tuberculin sensitivity to disappear on removal of the infecting source it is argued that bovine infection cannot be held responsible for the increase in the rate in 1961.

15. Insufficient evidence was available to allow the part played by tuberculous contacts in school to be judged.

16. The possibility that the real incidence of tuberculosis had increased and that this rise had been recognised by the reactor, but not by the notification, rate is considered. No direct method of providing an answer could be followed.

17. In the light of this evidence it was proposed to test the assumption that a significant amount of tuberculin sensitivity among local schoolchildren was non-specific.

18. In view of local prejudice in favour of the significance of bovine infection itwas decided to attempt themeasurement of its present importance.

Part II. An account of comparative tuberculin testing surveys conducted locally.

Tuberculin sensitivity may be derived from three sources - human, bovine or non-mammalian infection. It is the purpose of the writer now to describe the methods used in the attempt to fractionate the total amount of sensitivity found among thirteen year old Rawtenstall schoolchildren into component parts depending upon the source of infection.

There are many published reports to suggest that this may be achieved by simultaneous, comparative skin testing with tuberculins prepared from different mycobacteria. What seemed to the writer to be the important evidence in this respect has already been summarised in Part I under the heading "The meaning of tuberculin sensitivity" and it is not intended to make further reference to it. It is accepted as valid and the method described has been adopted.

A number of factors led to a decision that the investigation should be spread over more than one survey.

Survey I.

The object of the first Survey was to assess the extent of non-specific sensitivity by simultaneous comparative skin tests with human and non-mammalian antigens.

A. Material and Methods.

1. Test sample.

Since the problem questioned the significance of tuberculin sensitivity in schoolchildren, only they were suitable material. It might have been possible to have included all school-children but there were objections to this. The writer was unfamiliar with the method of comparative skin testing and it seemed a mistake to try to achieve too much at the outset. The work had to be fitted to the practice of a small local authority health and welfare clinic in which the nursing and clerical staff were fully occupied in normal duties. No other medical personnel than the writer was available and no undue disruption of routine work was considered legitimate. It was appreciated that the younger the children tested the less sensitivity, from whatever source, would be found and it was thought an unwarrantable assault to submit a large number of very young schoolchildren to multiple tests in the knowledge that few would react. Consideration for the staff in schools implied a wish to create as little disturbance as possible and to justify that which was inevitable. For these reasons it was decided to restrict testing to children in secondary schools and, initially, to test only thosein their thirteenth year. These children would have been offered B.C.G. vaccination and would have required a tuberculin test in any event; all that was now contemplated was the substitution of a single Heaf test by a number of simultaneous tests, vaccination following in the usual manner.

The size of the sample was thus reduced and it was largely for

this reason that the objectives were limited and that the decision to spread the investigation over more than one survey was taken.

2. Antigens.

Published work on investigations into non-specific sensitivity by comparative testing suggested that the choice of tuberculins used had either been from representatives of one or more of Runyon's four groups of atypical mycobacteria or from Mycobacterium tuberculosis var. avium. At the time the writer began planning the present Survey only two published accounts were known of similar work among humans in the United Kingdom (Hart et al.,1962: Embleton, 1962); in the first the choice had fallen on avian tuberculin because of its close antigenic links with some atypical mycobacteria. Flynn (1962) had reported from Ireland on the use of avian tuberculin; since his interests included the association between tuberculin sensitivity among children and contact with fowls his selection of this tuberculin seemed obvious. Most of the references to work conducted elsewhere described the use of tuberculins prepared from atypical mycobacteria, although Palmer and Edwards (1955) in India and Kuper (1958) in South Africa had used avian P.P.D.

The success of comparative skin testing rests on two conditions: the closer the antigenic relationship between the infecting organism and a tuberculin used the larger will the skin reaction to that tuberculin be, and the more dissimilar the other tuberculins used the more easily will the antigenic differences be detectable on skin testing. Two obvious practical difficulties arise: first, the identity of the infecting organism is not usually known (if it were, comparative testing would be unnecessary) and secondly, all mycobacteria are antigenically related. The choice of antigens therefore rests on an appreciation of the

differences between tuberculins and on the recognition of the more likely infecting organisms.

Disease caused by avian and by atypical mycobacteria is relatively uncommon. Bradbury and Young (1946) reported the first case of human tuberculosis due to the avian type tubercle bacillus in this country and suggested that infection had been derived from raw eggs which the patient had consumed daily. Dragstedt (1949) recorded that up to three per cent. of market eggs were infected but that the pathogenicity of the avian tubercle bacillus for man was slight and that only six cases had been found in Denmark in the previous fourteen years. Selkon and Mitchison (1959) described a survey of positive cultures from more than one thousand untreated patients with pulmonary tuberculosis from which only one strain of Mycobacterium var. avium had been isolated.

Accounts of disease caused by atypical mycobacteria in this country are as infrequent. Young (1955) described one case and Nassau and Hamilton (1957) added seventeen others; they referred to many reports of this type of infection, mostly from the United States where it was evidently more common. In the survey reported by Selkon and Mitchison (1959) five photochromogenic (Runyon Group I) strains were isolated from more than one thousand specimens, as was one strain of scotochromogen (Runyon Group II) although the pathogenic significance of the latter organism was not established. More recently the Public Health Laboratory Service (1962) recorded an incidence of 1.4 per cent. of clinically significant atypical strains among nearly 3000 strains of mycobacteria isolated from the sputum of patients.

Only one strain of an atypical mycobacterium, identified as a photochromogen, had been recovered from a patient with chronic pulmonary disease known to the local chest service, although

another (a scotochromogen) had been isolated from a child who had attended the Paediatric department of a local hospital suffering from cervical lymphadenitis. No local record of an avian mycobacterium isolate existed. Further reference must be made to the work of Marsden and Hyde (1962) because their demonstration of a link between scotochromogen infection and cervical glandular disease had been based on specimens from patients admitted to the Royal Manchester Children's Hospital, and because the senior author had suggested to the writer that such an association might be more frequent in the North-West of England than elsewhere.

There was thus little evidence to point to any particular non-mammalian mycobacterium as being responsible for non-specific sensitivity, although what there was suggested that atypical, rather than avian, organisms were the more likely.

That tuberculin prepared from the avian mycobacterium was able to identify non-specific sensitivity in this country was implied by Hart et al. (1962). Although the authors were unable to exclude another explanation they considered that the "natural interpretation" of their findings was that low-grade sensitivity "indicated infection with avian tubercle bacilli, or with some other antigenically related organism". Their rider is one which must be added to all work of this kind since cross-reactions are common, as was shown by Affronti (1959) and by Edwards et al. (1960): the infecting organism cannot be assumed to be identical to the organism from which the preferred tuberculin was prepared; it can be said only that the relationship is closer to the preferred tuberculin than to the others. Some knowledge of the antigenic properties of mycobacteria is therefore required.

Studies have been of two kinds. The first has involved the comparative skin testing of subjects with a bacteriologically identified infection and the second has relied on laboratory

techniques of varying complexity.

Edwards and Palmer (1958) carried out comparative tests on patients with pulmonary disease in whom the infecting organism had been proven. They were unable to discriminate between disease caused by typical tubercle bacilli and disease caused by photochromogens because specific and cross reactions to tuberculins prepared from those two organisms were of comparable intensity; they concluded that they were antigenically alike. Patients infected with the Battey organism, however, could be identified because the distribution of specific and cross reactions was dissimilar, and the authors concluded that these two organisms were antigenically quite different. Martosh, Eslami and Atwell (1962) produced somewhat similar evidence by skin testing patients with typical pulmonary tuberculosis, using antigens derived from a photochromogen, the Battey organism and M. Fortuitum amongst others. Of the 104 patients tested, 69 reacted to the first, 39 to the second and 10 to the last, while 100 reacted to the specific tuberculin. The average diameter of the reaction to the specific antigen was approximately 21 mms., and to the photochromogen antigen approximately 13 mms., so that the findings, in this respect, differed from those of Edwards and Palmer. Nevertheless they did imply a closer relationship between M. tuberculosis and the photochromogen than between M. tuberculosis and either the Battey organism or M. Fortuitum. Smith et al. (1961) closely linked the avian and Battey organisms on the basis of skin test results both on patients and on medical students.

Laboratory animals have more commonly been used in these investigations. Comparative skin testing of animals previously infected with known organisms had been undertaken by Crawford (1927), Seibert and Morley (1933), Jensen and Lind (1943) and Johnson et al.

(1949). All had concluded that there were demonstrable antigenic differences between avian and mammalian mycobacteria. This was later confirmed by Magnusson (1961) who also showed that antigens prepared from certain Runyon Group IV atypical mycobacteria differed from both, and that there were recognisable differences on comparative testing between all these antigens and the antigens of Runyon Groups I and III organisms which were themselves dissimilar (Magnusson, Engbaek and Weis Bentzen, 1961).

A different approach had been used by a number of workers who studied the immunising effect of various mycobacteria on laboratory animals later challenged with infections by virulent tubercle bacilli. Wenkle, Loomis and Jarboe (1948) reported that "chromogen-vaccinated" guinea pigs developed rather less disease than did controls, the amount of protection being inverse to the size of the infecting dose of virulent organisms. Fenner (1957) found that prior infection with Runyon Group IV organisms failed to prolong the survival time of mice challenged by virulent tubercle bacilli although it was prolonged by both B.C.G. and M. avium. Youmans, Parlett and Youmans (1961), using the same technique, were able to rank various mycobacteria in order of immunising potency and they concluded that M. kansasii (Runyon Group I) was the most effective in this respect, followed by M. avium, the Battey organism (Runyon Group III), a scotochromogen (Runyon Group I) and a rapid grower (Runyon Group IV) in that order. The last appeared to offer no protection, the mice "immunised" with this organism faring rather worse than did the un-immunised controls. Klugh and Pratt (1962) immunised guinea-pigs either with B.C.G. or with photochromogens and found that both provided protection against later infection with virulent organisms although the former was the more consistently effective. Siebenmann and Barbara (1964) found

that a photochromogenic, Group I strain equalled or surpassed B.C.G. in the protection it afforded mice.

Attempts to identify antigens more specifically had been made. Agar diffusion precipitin techniques were employed by Parlett and Youmans (1956) who established that saprophytes produced a group of antigens quite different from those of human, bovine and avian strains. Nassau, Schwabacher and Hamilton (1958), using the Middlebrook-Dubos haemolytic test, concluded that photochromogens shared common antigens with virulent human organisms but that they had additional antigens specific to themselves.

The relationship between Battey (Runyon Group III) and avian organisms warrants special mention since reports have differed on the nature of the links between them. Runyon (1959) implied that these two organisms were closely related and suggested that the former might be modified strains of the latter. In animal pathogenicity studies Durr, Smith and Altmann (1959) could not support this view, feeling that if Runyon Group III organisms were related to avian mycobacteria, they were "most certainly very attenuated avian strains". However, Bojalil and Cerbon (1960) thought the two organisms inseparable and Takeya et al. (1960) that their tuberculin specificities were almost identical and that they were therefore closely related. (It may be added that these authors, in common with others already mentioned, placed photochromogens somewhere between these two and the human strain of M. tuberculosis in terms of tuberculin specificity). Scammon et al. (1963) thought them to be indistinguishable.

There seemed to be general agreement among those who had investigated these problems that mycobacteria differed antigenically and that the differences could usually be detected by comparative testing. On the basis of their findings it is possible to rank the

organisms in order of antigenic affinity, beginning with photochromogens (Runyon Group I) which are evidently more closely related to mammalian (either human or bovine) mycobacteria than are the avian and Battey (Runyon Group III) organisms. Scotochromogens (Runyon Group II) are further removed whilst the members of Runyon's Group IV seem to have little, if any, antigenic resemblance to mammalian organisms.

In selecting the tuberculins to be used in this survey the writer rejected those prepared from Group I and Group IV organisms - the first because of the practical difficulty of distinguishing between specific and cross reactions to it and to tuberculins prepared from human mycobacteria, and the second because most members of this group had been described as saprophytes and because they had never been incriminated as the cause of non-specific sensitivity. In view of the experience reported by Marsden and Hyde the writer felt that a scotochromogen antigen should be used and it remained to be decided whether an avian or a Battey antigen should be added. It seemed wise to use one or the other but unnecessary to use both.

By the courtesy of Professor W. F. Gaisford, Professor of Child Health, University of Manchester, and of Dr. H. B. Marsden, Royal Manchester Children's Hospital, supplies of two P.P.D. antigens were made available, one from the Battey organism and the other from a strain of scotochromogen which had been isolated from the neck glands of a child subject of the article already referred to (Marsden and Hyde, 1962). Both had been prepared in the Central Veterinary Laboratory of the Ministry of Agriculture, Fisheries and Food. The former contained 2.0 mgms. of tuberculoprotein per ml., the latter 0.5 mgms. of tuberculoprotein per ml. The human P.P.D. tuberculin was supplied by Dr. P. W. Muggleton of Glaxo Laboratories, Ltd., and contained 2.0 mgms. of tuberculoprotein

per ml.

After these decisions had been made, and while the survey was still being planned, two further reports appeared which strengthened the belief that it would not have been profitable to employ either Group I or Group IV antigens. Larson and Wicht (1963) recorded that Group I organisms were as effective as attenuated strains of human tubercle bacilli in conferring resistance against subsequent infection by virulent tubercle bacilli in mice. Griffith, Marks and Richards (1963) in describing the comparative skin testing of children in Cardiff, found the evidence in respect of the photochromogen antigen ambiguous since it exhibited strong cross reactions to mammalian tuberculin; they also felt able to exonerate Group IV organisms as "important causes of non-specific sensitivity".

At the same time a further account of comparative testing in England and Wales appeared (British Tuberculosis Association, 1963). In this, human and avian P.P.D. tuberculins had been used and the results suggested a greater prevalence of sensitivity to the latter. This was no reason, however, for the writer to alter the decision to employ a Battey antigen.

3. Means of testing.

The Mantoux intradermal test and the Heaf multiple puncture test each have advantages and disadvantages in routine use which are accentuated in comparative testing. Since the method calls for the quantitative comparison of reactions one with another it might be thought that the Heaf test, being largely qualitative, could be dismissed as inappropriate. However, in view of the large experimental error inherent in Mantoux testing, to which reference has already been made, it may be asked whether the Mantoux test with a large error is really more advantageous than the cruder Heaf test with an appreciably smaller error. Hart et al. (1962) assessed the

standard deviation of the difference between repeat Mantoux tests with human tuberculin as 4.2 mms. and with avian tuberculin as 4.4 mms. In other words, the measured diameters of two reactions would have to differ by more than 8 mms. if one was confidently to be recorded greater than the other. The quantitative precision of the Mantoux test is thus partly an illusion and serious thought was given to the advantages of the Heaf test.

Intradermal injections are undoubtedly uncomfortable and may well be regarded as painful by some. The Heaf test causes neither discomfort nor pain. It is quicker and easier to perform and is quicker to read since no linear measurement is involved. These factors are especially desirable in simultaneous multiple testing in children and in surveys conducted with limited resources of time.

However, the writer was influenced by the experience of Griffith, Marks and Richards (1963) who implied that their use of the Heaf test had limited their ability to draw conclusions from the results of comparative skin testing since "the range of sensitivity within any grade" was "quite considerable" and since the standard method of recording Heaf test reactions in Grades did not permit the sub-classification of reactions within the same grade.

A method of recording results to the Heaf test in terms of the diameter of the area of total induration had been devised by Stewart (1963a) which seemed to overcome the difficulties described.

It was determined that the Mantoux test should be used in the first survey and that experience should be gained in the measurement of Heaf reactions by this method with a possible view to its full use in subsequent surveys.

4. Dose.

In a historical account of the tuberculin test Edwards and

Edwards (1960) described the process by which the 5 T.U. test became standard for the recognition of tuberculous disease. It was considered to be of sufficient strength to stimulate a specific response but not of sufficient strength to cause cross reactions.

In comparative testing the type of infection is not generally known and the specificity of the tuberculins used is therefore not assured. It can be assumed in this country that some, perhaps most, tuberculin sensitive persons have been infected by mammalian mycobacteria and in them the mammalian P.P.D. will be specific; a 5 T.U. dose can then be accepted as appropriate for their recognition. A proportion, however, may have been infected only by a non-mammalian organism; unless, by chance, a tuberculin is used that has been derived from that particular organism the most that can be hoped for is a cross reaction to what would be a non-specific tuberculin. Since cross reactions are, in general, of lesser intensity than specific reactions it might be argued that the dose of non-mammalian P.P.D. should be greater than the dose of mammalian P.P.D. On the other hand this arrangement would act with bias were the non-mammalian tuberculin fortuitously specific.

Such arguments are conjectural and since no answer can be given an arbitrary decision has to be made. It has been the practice, without exception in the published literature to the writer's knowledge, to follow the principle of using equivalent doses of all tuberculins.

Unfortunately it is not known what constitutes an equivalent dose. Tuberculins which contain the same weight of tuberculoprotein per unit of volume can be prepared but whether these represent equivalent doses in terms of specific antibody stimulating capacity is another matter. It has become the convention to assume that they do. The work of Edwards and Palmer (1958), already

referred to, showed that the distribution curve of specific reactions was the same in patients infected either with typical tubercle bacilli, the Battey organisms or a photochromogen, when the dose of each tuberculin was the same in terms of weight of specific tuberculo-protein. Later work on guinea-pigs, using a wider range of organisms, again demonstrated that the frequency distributions of specific reactions to all the tuberculins resembled the normal probability curve, equivalent doses in terms of weight of tuberculo-protein being used (Edwards et al. 1960). The assumption made is thus based on some experimental evidence.

In terms of Tuberculin Units the most commonly favoured dose has been 5 T.U. for all tuberculins. Magnusson, Bleiker and Griep (1962) had used 1 T.U. doses while Hart et al. (1962) had used an initial dose of 3 T.U. There seemed nothing to commend these smaller doses and the writer determined to follow the standard practice and inject 5 T.U. doses of human, scotochromogen and Battey antigens intradermally.

5. Diluent.

The keeping quality of dilute tuberculin has already been discussed and its dependence on the diluent has been mentioned. The evidence of Magnusson et al. (1958) showed that saline was not suitable and that loss of potency due to adsorption was best prevented by a phosphate buffered saline containing a five per cent. solution of the synthetic surface active agent Tween 80. However, Wijsmuller (1961) found that the addition of Tween 80 to human tuberculin influenced specific and cross reactions differently and he deduced that there were at least two fractions in P.P.D. tuberculin, one of high adsorbability (the more specific fraction) and one of low adsorbability (the non-specific fraction): he further argued that in the study of non-specific sensitivity with human

tuberculin the addition of Tween 80 would be a disadvantage since it would give bias to the specific fraction. Although these remarks were extended to include some non-mammalian tuberculins it was not clear whether the strictures covered their use in comparative testing. Since cross reactions are then unwanted, anything which reduced their frequency or intensity might be accepted as an advantage. As has been said already, however, the specificity of the non-mammalian tuberculins cannot be assured and the writer was advised not to use Tween 80 (Lesslie, 1963).

The dilution of the two non-mammalian antigens was undertaken in a pharmacy in which saline had always been used as a diluent. Reluctance to change could not be overcome. The writer accepted that saline should be used again and the suppliers of the human P.P.D. (Messrs. Glaxo, Ltd.) agreed to use saline also, in order to maintain conformity, although this was contrary to their normal practice.

6. Elimination of bias.

The results of comparative testing depend on the injection of equal volumes of different tuberculins and on the linear measurement of reactions to them. It is essential to avoid prejudice at both stages. The identity of the separate tuberculins should be concealed from the tester, and the reader should be ignorant of the source of any response. In this survey a scheme of colour coding was devised that effectively achieved both.

Supplies of human P.P.D. (diluted to contain 0.0001 mg. per ml.), dispensed in clear glass phials, together with a supply of identical empty phials were received each week in the pharmacy undertaking the preparation of the non-mammalian P.P.D. tuberculins. When diluted to contain 0.0001 mg. per ml. each of these was similarly dispensed. All three, colourless, antigens were now in identical

phials and each was labelled in the pharmacy by a strip of either red, green or blue selotape secured to the phials before issue to the writer. The key to the colour code was held in the pharmacy, was changed each week and was not broken until after the completion of the survey. A supply of new, unused Mantoux syringes was secured having either a red, green or blue barrel. Each tuberculin was injected only with its matching syringe. Since the colour code was changed each week with a new delivery of freshly diluted tuberculins the syringes were discarded weekly also, the principle of colour matching being continued with new syringes. Disposable intradermal needles were used, no needle being used more than once. By these means the writer never knew which tuberculin was being injected but the possibility of different tuberculins being injected with the same syringe or needle was eliminated. Care was taken to sterilise syringes separately between the testing sessions in one week.

Each "colour" was injected at a pre-determined site which remained constant throughout and positive reactions, read by the writer, were recorded against the appropriate site-colour on the subject's individual card.

7. Criteria of positivity.

If tuberculin sensitivity is a continuous variable then its expression at all levels should be recorded and no arbitrary division should be made between what is to be regarded as a significant response and what is to be dismissed as an insignificant response. This view neither ignores the fact that minimal responses may be stimulated by factors other than the tuberculin nor does it condemn the application of "criteria of positivity" when occasion demands that this be done. In the present circumstances there was no need; moreover to have done so would have

introduced unnecessary difficulties. Suppose that only reactions having a diameter of induration of five or more mms. were to be recorded and that reactions having a smaller diameter were to be ignored and suppose that in a particular child the reactions to the three antigens were found to have measured diameters of four, four and five mms. respectively. A binding commitment to accept only the last would be absurd in view of what is known about experimental error.

The same knowledge demanded that a decision be made to allow for experimental error in assessing the significance of one reaction in relation to another, and it was arbitrarily decided that reactions having measured diameters within two mms. of each other should be regarded as equal.

8. Selection of children for vaccination.

Since the first survey was planned in the context of the B.C.G. vaccination programme some means had to be devised to identify those children who would benefit from vaccination. All children could have been vaccinated who did not show a response of greater than a determined diameter to any antigen. Alternatively a Heaf multiple-puncture test could have been added using undiluted mammalian P.P.D. tuberculin, vaccination being offered to all children not reacting to it. There were advantages and disadvantages in both. The first kept the number of tests to a minimum but implied the possibility of excluding from vaccination those children reacting only to non-mammalian antigens. If it were known that sensitivity only to, say, the scotochromogen P.P.D. denoted increased resistance to subsequent infection by virulent mammalian organisms then no harm would come by the omission of B.C.G. vaccination. Unfortunately it cannot be claimed with certainty that this would be the case. While Meyer (1956) thought that "the allergenic potency of a vaccine serves as at least a rough guide to

its immunogenic potency" and Youmans, Parlett and Youmans (1961) suggested that infection with atypical mycobacteria non-specifically immunised against infection with Myco. Tuberculosis, cases have been reported in which typical tuberculous disease has been superimposed on disease due to atypical organisms (Runyon, 1959) and Klugh and Pratt (1962) wrote that, in hospital, patients with photochromogenic infections should be isolated from those with virulent human tuberculous infections since they did not have confidence in the immunising powers of the former. If it is conceded that infection with atypical organisms causes low grade tuberculin sensitivity then indirect evidence may be cited to support the view that it confers some degree of non-specific immunity. In the clinical trials conducted by a Medical Research Council Committee investigating the efficacy of B.C.G. and vole bacillus vaccines it was found that the incidence of tuberculosis was lower in those showing low grade tuberculin sensitivity than in those showing high grade sensitivity, although it was higher than in those showing no sensitivity (Medical Research Council, 1956). Griffiths, Bellamy and Davey (1963) likewise reported a greater incidence of disease among high grade reactors than among low. Marfan's Law, that tuberculous cervical lymphadenitis protects against subsequent pulmonary infection, may also be quoted in this context, together with the evidence that some lymph gland disease is due to infection with atypical mycobacteria.

The addition of a Heaf test had the advantage that the normal routine of selecting children for vaccination could be followed. Combined with comparative tests it might also clarify the relationship between non-specific sensitivity and Heaf test responses and thus throw light on the adequacy of the Heaf test as a means of selecting children suitable for B.C.G. vaccination. There was, however, one disadvantage which the writer at first felt to be an absolute contra indication to its use. Rosenthal and Libby (1960)

had recorded that simultaneous tests in the same person interacted and that the response to a 10 T.U. test was significantly reduced by a simultaneous 100 T.U. test. The authors suggested that there was competition for a fixed amount of antibody. Stone (1962) constructed a mathematical model from which it could be predicted that the reduction in size would be dependant upon the total dose of competing antigen. In this event the addition of a Heaf multiple puncture test, using undiluted mammalian tuberculin, to a series of comparative tests could be expected to differentially influence the response to these by diminishing the strength of the reaction to the human antigen. However, the writer was persuaded that this was unlikely to occur and the method was adopted. It may be added that Stewart (1963a.) took the view that the use of three or more concentrated tuberculins simultaneously had a non-specific enhancing effect upon the tuberculin sensitivity of the host. The evidence upon which this belief was based was published after the present survey (Stewart, 1963) but it was clearly a slightly different, and more complex, proposition than that described by Rosenthal and Libby.

The final arrangement, therefore, was that each child was to receive a Heaf multiple puncture test using undiluted mammalian P.P.D. tuberculin (supplied by the Central Veterinary Laboratory, Ministry of Agriculture, Fisheries and Food), and three Mantoux intradermal tests, using human, scotochromogen and Battey P.P.D. tuberculins in doses of 5 T.U. each.

(9) Sites of injection: testing-reading interval.

The conventional site for tuberculin testing is the flexor surface of the forearm and since four tests were to be given it was logical to place two on each forearm. Two further points had to be considered. First, it was important to space the two tests sufficiently to prevent the merging of large reactions, and

secondly it seemed right so to place them that their lymph drainage did not obviously mingle. The two tests on each forearm were therefore performed on contralateral sides of the upper and lower thirds of the flexor surface. The Heaf test was always given on the right upper forearm, the "red antigen" on the right lower forearm, the "green antigen" on the left upper forearm and the "blue antigen" on the left lower forearm. This plan of injection sites was committed to paper as a "map" and was constantly present, and referred to, at all testing and reading sessions.

All tests were read at 72 hours.

10. Questionnaire.

Parental consent for the testing and vaccination of children is sought on a printed, individual, card prescribed for the purpose by Lancashire County Council. It opens with a short account of the rationale and form of the procedure, asks for some factual information about the child (including previous B.C.G. vaccination experience) and ends with a form of consent to be signed by the parent or guardian.

Mention has been made that local opinion favoured milk as the source of much of the tuberculin sensitivity among thirteen year old children. The proportion of raw milk drunk was not known however and the opportunity was taken in this survey to identify the type of milk consumed in each household.

Parents were also asked to give information relating to family history of tuberculosis.

11. Organisation of testing and reading sessions.

Agreement was reached with the head teachers that the work should be undertaken in the local authority clinic rather than in the schools which, for the most part, lacked many of the facilities thought desirable.

All children whose parents consented were tested, and if

necessary vaccinated, irrespective of their previous history. When appropriate, evidence of vaccination was looked for.

If family tuberculosis was admitted the relationship, the degree of contact and the interval since the event was elicited. If these details could not be given, the child was asked to have the information on his return three days later.

Reactions to the Mantoux test were recorded as the average of the greatest and the smallest diameters of induration in mms. Reactions to the Heaf test were recorded in the conventional grades.

(Grade 1: 4 to 6 discrete papules
" 2: a confluent ring of induration
" 3: a plaque of induration
" 4: vesiculation or ulceration)

B. Results.

Three hundred and fifty three children born in 1950 were attending Rawtenstall schools at the time of the survey. Parental consent was obtained for the testing of 250, an acceptance rate of 70.8 per cent. Two hundred and thirty seven were tested and the results read.

Testing began on 7.10.63. and was completed on 28.10.63.

(a) Tuberculin test results.

The reactions are recorded in Table 23.

Table 23: Tuberculin skin test reactions of Rawtenstall schoolchildren, 1963. Survey I.

Reactor	Heaf test (Grade)	Mantoux test (average diameter of induration in mms.)		
		Human P.P.D.	Scotochromogen P.P.D.	Battey P.P.D.
1	1	6	0	0
2	1	4	5	0
3	1	4	0	0
4	1	3	5.5	4
5	1	0	0	0
6	1	9	0	0
7	1	0	0	0
8	1	0	0	0
9	1	0	0	0
10	1	0	0	0
11	2	9	3	4
12	2	4.5	3	2
13	2	7.5	0	0
14	2	6	0	0
15	2	12.5	0	0
16	2	12	0	0
17	2	13	0	0
18	2	8	0	0
19	2	7.5	0	0
20	2	12.5	2	3.5
21	2	11	0	0
22	2	11.5	4.5	3.5
23	2	4	0	0
24	2	4	0	0
25	2	10.5	0	0
26	2	8	0	3
27	2	8	0	2
28	2	4.5	0	3
29	2	8.5	0	0
30	3	22	3	7
31	3	12	0	0
32	3	11	0	5
33	3	10	0	0
34	3	11	0	0
35	3	10	0	0
36	3	12	12	0
37	3	13	8.5	0
38	3	0	11	0
39	3	8	0	0
40	3	16	0	0
41	3	13	5.5	4
42	3	15	0	0
43	3	0	0	5
44	3	7.5	0	0
45	3	18.5	0	2
46	3	10.5	0	4
47	3	13	0	5.5
48	3	11	0	0
49	3	9.5	0	4.5
50	3	9	4	4
51	3	5	0	0
52	3	12	2	2
53	4	14	0	0
54	4	10	6	0
55	4	11	0	0

Fifty-five of the children reacted to the Heaf test - a positivity rate of 23.2 per cent.

Reactors number 31 and 41 had previously been vaccinated with B.C.G., in 1954 and in 1952 respectively.

Reactor number 18 was reputed to have had erythema nodosum twice - once in 1952 and again in 1963.

Reactor number 22 had had a suppurating gland excised from the axilla in 1957, the specimen being found tubercular on pathological examination. No organisms were isolated and treatment with anti-tuberculous drugs was associated with healing and apparent cure.

Reactor number 45 had tuberculous glands excised from the neck in 1957. No organisms were isolated.

The positivity rate in each school was :

Grammar School	-	17.1 per cent.
Secondary Modern 1	-	28.6 per cent.
Secondary Modern 2	-	25.4 per cent.
R. C. Secondary Modern 2	-	20.8 per cent.

Of the 353 children eligible for inclusion in the survey 38.8 per cent. lived outside the boundary of Rawtenstall borough. The acceptance rate for these children was 72.3 per cent. and their positivity rate to the Heaf test was 21.3 per cent.

(b) Questionnaire.

Of the 237 children whose tests were read forty (16.9 per cent.) gave a history of family tuberculosis. This figure included the three children who had themselves had tuberculosis or a probable manifestation of it. Twenty five were Heaf negative (or 13.7 per cent. of all Heaf negative children) and fifteen were Heaf positive (or 27.3 per cent. of all Heaf positive children). Of the twenty five Heaf negative children only six appeared to have had contact with the tuberculous member of the family. Of the twelve Heaf positive children (excluding the two who had themselves had a tuberculous lymphadenitis and the one with a history of erythema

nodosum) eight were known to have had contact with the tuberculous member of the family: only one was known to have had B.C.G. vaccination at the time of contact.

The question relating to milk consumption was answered in respect of 286 children. Table 24 records the answers, the letters P., S. and T. being used to denote pasteurised, sterilised and T.T. milk respectively.

Table 24: The pattern of milk consumption and tuberculin sensitivity among 286 Rawtenstall schoolchildren, 1963. (1)

Milk	Tested				Not Tested	Total
	Heaf -ve		Heaf +ve			
	No.	%	No.	%		
P	20	(83.3)	4	(16.6)	8	32
S	39	(81.3)	9	(18.8)	9	57
T	77	71.3	31	28.7	25	133
P+S	10	(90.9)	1	(9.1)	1	12
P+T	11	(84.6)	2	(15.4)	0	13
S+T	23	(74.2)	8	(25.8)	6	37
P+S+T	2	-	0	-	0	2
Total	182		55		49	286

If the children are separated into those who consume only untreated milk and those who consume only treated milk then the results shown in Table 25 are obtained.

Table 25: The pattern of milk consumption and tuberculin sensitivity among 234 Rawtenstall schoolchildren, 1963 (2).

Milk	Tested				Not tested	Total
	Heaf - ve		Heaf + ve			
	No.	%	No.	%		
Treated	69	83.1	14	16.9	18	101
Untreated	77	71.3	31	28.7	25	133
Total	146		45		43	234

C. Discussion.

It was evident during testing that among those positive to the Heaf test there was a constant reaction to only one dilute antigen each week and it was thought probable that neither the scotochromogen nor the Battey antigen was eliciting much response. Fears were entertained that there had been some error in the preparation or administration of these two antigens because their ability to produce reactions on a comparable, if lesser, scale to those evoked by the human P.P.D. tuberculin had not been doubted. It was decided, therefore, to test the patient living locally who was known to have chronic pulmonary disease due to photochromogen infection and this was undertaken on 8.11.63. The colour code had not been broken by that date and the testing and reading were done in a similar manner to that already described. The resultant reactions had indurations whose diameters were 11, 15.5 and 16 mms. respectively. Since no antigen was specific these results were regarded as confirmation of the potency of the preparations and as partial justification of the technique. When the key to the colour code was supplied and the pattern of sensitivity reactions was interpreted it was assumed, therefore, that specific sensitivity was the only factor of any significance. Some weeks later, however, it was learned that there had been an error in the dilution of the two antigens prepared from the atypical organisms and that these had been supplied at a nominal strength of 3 T.U. Since it was known that the human tuberculin had been used at a nominal strength

of 5 T.U. this error, combined with the use of a saline diluent, was sufficient to rob the results of meaning and they have not been reproduced here in detail.

The survey had not been without value and it provided useful experience in many respects. Those of the results not associated with the comparative testing were valid and some conclusions could be drawn from them.

1. General level of tuberculin sensitivity.

The overall reactor rate of 23.2 per cent. was the lowest ever recorded. If the peak rates of 1961 and March 1962 marked the exposure of a reservoir of non-specific sensitivity by the introduction of the Heaf multiple puncture test then the relatively low rate now recorded must be ascribed either to its disappearance or to a failure to recognise it. The first is unlikely. The second implies "under-reading" of minimal responses and recalls the experience summarised in Table 7. It will be noted that relatively few Grade I reactions were recorded in this survey and that the incidence of tuberculin sensitivity as measured by the Heaf multiple puncture test accorded more with the writer's estimate in December 1962 than with the estimate of the other tester-reader at that time. Since the writer has no compunction in classifying doubtful reactions as negative it seems possible that the present low reactor rate may have been due to "under-reading". The contrary view - that the high rates previously recorded were due to "over-reading" - must also be allowed. The facts that half the present Heaf Grade I reactors showed no response to a 5 T.U. dose of human P.P.D. tuberculin and that the average diameter of induration of the remainder was only 5.2 mms. may be significant. They inclined the writer to the view that caution in accepting minimal responses was justified and that "over-reading" in the past may have been an important factor in the production of spuriously high levels of

tuberculin sensitivity.

2. Response to questionnaire.

The difficulty of obtaining reliable medical information from a questionnaire is well known. Ten of the parents of tuberculin negative children and five of the parents of tuberculin positive children claimed that B.C.G. vaccination had been given previously. There was evidence of it in only one child (reactor 36) and in most it was clear that reference was being made to the tuberculin testing survey in the County primary school in 1960 already described. The parent of reactor 41 claimed that B.C.G. vaccination had not been given previously but the child had a vaccination scar on each upper arm and a record of its administration was available. Fourteen of the 87 parents who withheld consent to the testing of their child and who answered this question claimed that B.C.G. vaccination had been given previously. Since these children were not seen it is not known how accurate this information was, but it may be remarked that they represented 16.1 per cent. of their group and that among the children tested 6.3 per cent. were reputed to have been vaccinated previously.

Information relating to family history of tuberculosis was also known sometimes to be incorrect. Only 39 of the 103 parents not consenting to the testing of their child answered this question. Of the 36 who claimed no family history of tuberculosis the husband of one was known to have died of it. A history of tuberculosis was known to be present in the families of seven of the children tested whose parents claimed no such history.

Because of the poor response to this question from the parents of children not tested it is impossible to judge whether the assumption made (that previous contact with tuberculosis prompts parents to withdraw their children from the B.C.G. vaccination programme) is sound. Even if the question had been answered in all cases the wish of parents to conceal the truth would have made

conclusions invalid.

If the children who consumed only untreated milk are matched against the children who consumed only treated milk then the difference between the number Heaf test positive in either group is large enough to justify the conclusion that the factors are associated ($\chi^2 = 4.371 : P<0.05$) (Table 25). In other words milk is suggested as a source of tuberculin sensitivity in children consuming only untreated milk. It has been shown that such milk has been "safe" since 1958 and the suggestion therefore implies that their higher rate of sensitivity is due either to bovine infection incurred before that time or to some other organism in untreated milk. There is no certainty that the pattern of milk consumption then was the same as now - children who now consume treated milk may then have consumed untreated milk; the reverse seems less likely.

Survey II.

The failure of the first survey required that it be repeated but the experience gained justified extension of the second survey to include an assessment of the amount of bovine infection also.

The object of the second survey therefore was to assess the extent both of non-mammalian sensitivity and of sensitivity to the bovine organism by simultaneous comparative skin testing.

A. Material and Methods.

1. Antigens.

The recognition of bovine infection demanded the use of tuberculins prepared from the human and the bovine organisms. Whether comparative testing with two antigens so closely related would allow discrimination to be made between specific and cross reactions was questionable. In experimental work on cattle and on laboratory animals McIntosh and Konst (1947), Johnson et al. (1949) and Baisden, Larsen and Vandaman (1952) had reported little success in this respect since specific and cross reactions were either identical or the differences were inconsistent. Paterson (1956) considered that differentiation could not readily be made with the corresponding tuberculins. However, the work of Stewart, Embleton and Van Zwanenberg (1961) suggested that differentiation over a series was possible and the method seemed to be worth a trial.

It has already been mentioned that a report published in 1963 described the results of a comparative skin testing survey carried out in the United Kingdom in which human and avian P.P.D. tuberculins had been used (British Tuberculosis Association, 1963). These had been administered by the Heaf multiple puncture test. It occurred to the writer that it would be interesting to compare the results from this method with the results from the use of atypical antigens administered by the Mantoux intradermal test. It was determined that in this survey, therefore, two groups of children should be

selected, one to be tested in the manner described in the first survey and the other to be tested in the manner described by the British Tuberculosis Association.

The antigens used in the former group were the same as those used in the first survey and were obtained from the same sources. The human and avian antigens used for the latter group were supplied by the Central Veterinary Laboratory of the Ministry of Agriculture, Fisheries and Food, as were the human and bovine antigens used for the detection of bovine infection.

2. Test sample.

While the writer was still reluctant to test primary school children it was obvious that the scope of the second survey demanded a larger sample. Since local health authorities are permitted to offer B.C.G. vaccination to children aged from 11 years it was decided to invite the participation of all children attending Rawtenstall Schools who were born in 1951 or in 1952.

Those born in 1952 were submitted to testing with the human and the bovine antigens.

Those born in 1951 were allotted to one of two groups so that in each school half the boys and half the girls born in that year fell into each group. One group was tested with the two atypical antigens previously used, together with human tuberculin, and the other group was tested with human and avian antigens.

3. Means of testing.

Limited experience had been gained in the previous survey in the measurement of Heaf test reactions according to the diameter of the area of total induration. The writer had never been convinced that the quantitative accuracy of the Mantoux test was such as to outweigh its disadvantages. If, as has been suggested, a comparison was to be made between the two methods of assessing the extent of non-mammalian sensitivity, then the avian antigen had to be

administered by the Heaf multiple puncture test since this was the method employed by the British Tuberculosis Association in their survey (B.T.A. 1963). It was decided to test the presence of bovine infection in like manner.

Two of the three groups were therefore given only Heaf multiple puncture tests while the third was given Mantoux intradermal tests, together with a Heaf multiple puncture test, as in the first survey.

4. Dose.

The problem of what dose of dilute tuberculin to use in the Mantoux tests has already been discussed, as have the reasons which led the writer to adopt, in the first survey, a 5 T.U. dose of each antigen as the most suitable. Reference has been made to the fact that before 1961 a 10 T.U. dose of tuberculin had been used in Rawtenstall and the suggestion has been made that at least part of the rise in the level of tuberculin sensitivity recorded in 1961 and in March 1962 had been due to the recognition of a reservoir of non-specific sensitivity not revealed by the 10 T.U. test. The results of the Heaf tests administered in Survey I, together with those administered in December, 1962, have been interpreted as implying a measure of "over-reading" by colleagues or of "under-reading" by the writer. It now seemed appropriate to compare the writer's estimate of the overall reactor rate as measured by the 10 T.U. Mantoux test and by the Heaf multiple puncture test. For this reason the dose of each antigen given by the Mantoux test in the present survey was increased to 10 T.U.

Allusion has been made to the difficulty of knowing what constitutes equivalent doses of antigens in terms of antibody stimulating capacity and to the assumption that equal weights of tuberculo-protein serve the purpose. In a comparative testing survey conducted to measure the amount of bovine infection in a community Stewart, Embleton and Van Zwanenberg (1961) had used a

strength of human tuberculin twice as great as the strength of bovine tuberculin, both being administered by the Heaf test. The authors justified their action by quoting the experience of Green (1946) who found that in guinea-pigs hypersensitised with the human organism it required twice as much human P.P.D. as bovine P.P.D. to elicit the same size of reaction. Seibert and Morley (1933) had earlier found the bovine tubercle bacillus protein more potent than the human in sensitised guinea-pigs. However, this argument did not seem relevant to the problems of comparative testing and the writer could not concede its logic. Moreover, Stewart, Embleton and Van Zwanenberg did not quote another finding in the same report (Green, 1946) that in guinea-pigs sensitised with the bovine organism it required the same weight of human and bovine tuberculo-protein to elicit the same size of reaction. The implication was that if, in comparative testing, the same weights of the two antigens were used then in human sensitised objects cross reactions to the bovine tuberculo-protein would be greater than the specific reactions to the human tuberculo-protein and that if this bias were corrected by halving the weight of bovine tuberculin then in bovine sensitised subjects cross reactions to the human tuberculo-protein would be greater than specific reactions to the bovine tuberculo-protein.

In the early part of a subsequent survey Stewart (1963) tested children with human, bovine and avian P.P.D. tuberculins in dosage ratios of 4 : 2 : 1. Reference to the specificity relationships established by Green shows that the antigenic dissimilarities between human and bovine tuberculo-proteins on the one hand and avian tuberculo-protein on the other hand are so great that differentiation between specific and cross reactions offers no difficulty. The simultaneous use of human and bovine tuberculins, however, poses problems of dosage which are (on Green's evidence)

apparently insoluble. The writer was advised to use equal doses by weight of P.P.D. (Lesslie, 1963) and all three were supplied in the standard strength of 2 mg. per ml.

5. Diluent.

Arrangements were made in this survey for all P.P.D. tuberculins used at a strength of 10 T.U. to be diluted in a buffered borate solution whose composition was as follows :

Boric acid	10.5 gm.
Borax	7.126 gm.
Sodium Chloride	12.375 gm.
Distilled water	2 litres.

The solution was neutralised with hydrochloric acid and autoclaved at fifteen pounds pressure for twenty minutes.

6. Elimination of bias.

The same system of colour coding was applied to the diluted tuberculins as in Survey I.

Because of colour differences in the undiluted tuberculins it was not possible to give them "blind" but they were randomly allocated to the R. or the L. forearm and reading was "blind".

7. Criteria of positivity.

A decision to regard reactions having measured diameters within two mms. of each other as equal was taken before the first survey. It will be recalled that one of the subsidiary aims of the present survey was to compare the results from two methods of assessing the extent of non-mammalian sensitivity. One of the methods was that described in the first survey and the other was that described by the British Tuberculosis Association (1963). In the latter, one reaction was only deemed greater than another if its measured diameter was larger by four or more mms. This standard was therefore adopted in both groups subjected to testing with non-mammalian antigens in the present survey.

8. Selection of children for vaccination.

In the group of children who were to receive three Mantoux tests only reactors to the accompanying Heaf test, using undiluted human tuberculin, were to be excluded from vaccination.

In the group of children who were to receive Heaf tests with undiluted human and bovine tuberculins, any child reacting to one or both tuberculins was to be excluded from vaccination. In the case of single reactors this decision seemed justified on the grounds that it was unlikely for a child to react only to the bovine tuberculin and that even when this occurred it would indicate adequate protection against subsequent infection with virulent human organisms. The protection conferred by vaccination would not be greater since the B.C.G. organism is itself an attenuated strain of the bovine mycobacterium.

In the group of children who were to receive Heaf tests with undiluted human and avian tuberculins, all those not reacting to the former were to be vaccinated with B.C.G. It was thought that sensitivity only to avian tuberculin could not be accepted as security against subsequent infection with virulent human organisms. This decision meant that in the case of single reactors the tuberculin causing the reaction would have to be identified immediately after reading. The Health Visitor present at the testing and reading sessions was aware of the site used for either tuberculin and the onus was placed upon her of informing the writer, in these cases, of the identity of the tuberculin responsible.

9. Sites of injection: testing-reading intervals.

For those children subjected to three Mantoux intradermal tests and one Heaf multiple puncture test injections were made at the same sites chosen for the first survey. All tests were read at 72 hours.

For those subjected to two Heaf multiple puncture tests, one was given on the flexor surface of each forearm, the choice of fore-

arm being randomly allocated to one or other of the two tuberculins. The allocation in each child was recorded by the Health Visitor at the time of testing. These tests were read on the 7th day.

10. Questionnaire.

The question regarding family history of tuberculosis was again asked of parents despite the fact that in the previous survey some answers to it were known to be unreliable. Those parents admitting to a previous history gave information which was thought to be of value in assessing the significance of tuberculin sensitivity in their children.

Parents were again asked to nominate the type of milk consumed.

11. Organisation of testing and reading sessions.

Reactions to the Mantoux tests were recorded as the average of the greatest and the smallest diameters of induration in mms. Reactions to the Heaf tests were recorded in the conventional Grades (except that Grades 3 and 4 were combined) but at the same time readings based on the diameter of the area of total induration were also made. For this purpose a transparent plastic gauge imprinted with a series of circles of varying diameter was used.

In other respects the testing and reading sessions were organised along the same lines as in Survey I.

The children were grouped, according to their year of birth and the method of testing, as follows :

Group I constituted all children born in 1952 attending Rawtenstall schools. They were tested with undiluted human P.P.D. tuberculin (P.P.D.-W) on one forearm and undiluted bovine tuberculin on the other, the Heaf multiple puncture test being used.

Group II constituted half the boys and half the girls born in 1951 attending Rawtenstall schools. They were tested with undiluted human P.P.D. tuberculin (P.P.D.-W) on one forearm and undiluted avian P.P.D. tuberculin on the other, the Heaf multiple puncture test being used.

Group III constituted the remainder of the children born in 1951 attending Rawtenstall schools. They were tested with 10 T.U. doses of human P.P.D. tuberculin, P.P.D. from a scotochromogen, and P.P.D. from a non-photochromogen (the Battey organism), the Mantoux intradermal test being used. In addition they received a Heaf multiple puncture test with undiluted human P.P.D. tuberculin (P.P.D.-W).

B. Results.

In all, 638 children were eligible for inclusion in the survey. Parental consent was obtained for the testing of 495, an acceptance rate of 77.6 per cent. There were 32 absentees, eleven from Group I, six from Group II and fifteen from Group III.

Testing began on 21.2.64. and was completed on 22.4.64., being interrupted by school holidays.

Four hundred and sixty three children were tested and had their results read, 199 in Group I, 135 in Group II and 129 in Group III.

Eighty four children reacted to one or more of the tuberculins injected, an overall reactor rate of 18.2 per cent. Seventy eight children reacted to the Heaf multiple puncture test using undiluted human P.P.D. tuberculin, a reactor rate to this test of 16.9 per cent.

The positivity rate in each school was :

Grammar School	- 18.8 per cent.
Secondary Modern 1	- 17.4 per cent.
Secondary Modern 2	- 14.7 per cent.
R. C. Secondary Modern 2	- 16.2 per cent.

Of the 638 children eligible for inclusion in this survey 45.0 per cent. lived outside the boundary of Rawtenstall borough. The acceptance rate for these children was 73.8 per cent. and their reactor rate to the Heaf test using undiluted human tuberculin was 13.4 per cent.

A history of previous B.C.G. vaccination, or family history of tuberculosis, or both, was obtained in 25.2 per cent. of the 119 children whose parents refused testing, but from whom answers to either or both of the relevant questions were obtained. No attempt was made to test the veracity of the answers.

A similar history was obtained in 15.4 per cent. of the 495 children whose parents consented to testing, all of whom answered the questions. Again, no attempt was made to check the accuracy of the answers.

The question relating to milk consumption was answered in respect of 567 children. Table 26 records the answers

Table 26: The pattern of milk consumption and tuberculin sensitivity among 567 Rawtenstall school-children, 1964 (1)

Milk	Tested				Not Tested	Total
	Heaf -ve		Heaf +ve			
	No.	%	No.	%		
P	64	(82.1)	14	(17.9)	13	91
S	68	(87.2)	10	(12.8)	32	110
T	151	77.0	45	23.9	46	242
P+S	14	(82.4)	3	(17.6)	2	19
P+T	26	(83.9)	5	(16.1)	7	38
S+T	39	(88.6)	5	(11.4)	14	58
P+S+T	8	-	0	-	1	9
Total	370		82		115	567

P denotes pasteurised milk

S " sterilised "

T " untreated T. T. milk

If the children are separated into those who consume only untreated milk and those who consume only treated milk then the

results shown in Table 27 are obtained.

Table 27: The pattern of milk consumption and tuberculin sensitivity among 462 Rawtenstall schoolchildren, 1964 (2)

Milk	Tested				Not Tested	Total
	Heaf -ve		Heaf +ve			
	No.	%	No.	%		
Treated	146	84.3	27	15.6	47	220
Untreated	151	77.0	45	23.0	46	242
Total	297		72		93	462

(a) Group I.

The reactions of the children in this group are recorded in Table 28.

Table 28: Tuberculin skin test reactions of Rawtenstall schoolchildren, 1964. Survey II, Group I.

Reactor	Heaf test response			
	Human P.P.D. Tuberculin		Bovine P.P.D. Tuberculin	
	Grade	Diameter of area of total induration in mms.	Grade	Diameter of area of total induration in mms.
1	1	4	1	2
2	1	5	1	2
3	1	5	1	7
4	1	7	1	4
5	1	5	1	4
6	1	4	1	4
7	1	5	1	5
8	1	2	1	7
9	1	4	2	12
10	1	5	2	10
11	1	2	1	4
12	1	4	1	5
13	1	7	1	5
14	1	2	1	2
15	1	4	1	4
16	1	2	1	2
17	1	5	1	5
18	1	7	2	9
19	1	5	1	5
20	1	7	0	0
21	1	7	1	7
22	1	2	1	2
23	1	4	2	8
24	1	2	1	2
25	1	2	1	4
26	1	7	1	4
27	1	7	1	7
28	1	7	1	4
29	2	9	1	6
30	2	10	1	4
31	2	12	1	5
32	2	10	2	12
33	3	14	1	4

The reactor rate in this group was 16.6 per cent. (33/199).

Reactor number 6 had had tuberculous glands excised from the neck in 1958, treatment with antituberculous drugs having failed. No organisms were isolated. The family had had only pasteurised milk since before 1952.

Reactor number 33 had been admitted to hospital in 1957 with the diagnosis of tuberculous mesenteric adenitis. The family took only untreated milk.

Reactor number 11 had been vaccinated with B.C.G. by the multiple puncture method in 1963.

It will be noted that most children reacted to both tuberculins with almost equal intensity. The average size of the reactions to human P.P.D. Tuberculin was 5.6 mms. and to bovine P.P.D. tuberculin was 5.2 mms. One child reacted only to the human tuberculin while three others appeared to give specific reactions to the human tuberculin and cross reactions to the bovine tuberculin. Four children appeared to give specific reactions to the bovine tuberculin and cross reactions to the human tuberculin.

An exactly similar proportion of children in this group (86/198) consumed only untreated milk as in the whole sample tested (196/452).

(b) Group II.

The reactions of the children in this group are recorded in Table 29.

Table 29: Tuberculin skin test reactions of Rawtenstall schoolchildren, 1964. Survey II, Group II.

Reactor	Heaf Test			
	Human P.P. Tuberculin		Avian P.P.D. Tuberculin	
	Grade	Diameter of area of total induration in mms.	Grade	Diameter of area of total induration in mms.
1	0	0	1	2
2	0	0	2	10
3	1	4	1	4
4	1	4	1	2
5	1	2	0	0
6	1	3	0	0
7	1	5	1	2
8	1	5	1	5
9	1	7	1	2
10	1	7	1	4
11	1	4	1	4
12	1	4	1	4
13	1	4	0	0
14	2	10	0	0
15	2	12	1	4
16	2	12	1	6
17	2	11	0	0
18	3	14	1	3
19	3	16	1	5
20	3	10	1	4

The reactor rate in this group was 14.7 per cent (20/135). In terms of reactions to the human tuberculin the reactor rate was 13.3 per cent. (18/135).

Reactors number 2, 19 and 20 had a history of tuberculous cervical adenitis.

Reactor number 5 had been vaccinated with B.C.G. in the neo-natal period.

The average size of reactions to the human P.P.D. tuberculin was 7.4 mms. and to the avian P.P.D. tuberculin was 4.1 mms. Five children reacted only to the former (including the one who had been vaccinated with B.C.G.) and two only to the latter (including one with a history of tuberculous disease). Six children appeared to give specific reactions to the human tuberculin and cross reactions to the avian tuberculin (including two with a history of tuberculous disease).

(c) Group III.

The reactions of the children in this group are recorded in Table 30.

Table 30: Tuberculin skin test reactions in Rawtenstall schoolchildren 1964, Survey II, Group III.

Reactor	Heaf test Grade	10 T. U. Mantoux test: Average diameter of induration in mms.		
		Human P.P.D. Tuberculin	Battey P.P.D. Tuberculin	Scotochromogen P.P.D. Tuberculin
1	0	0	5	0
2	0	0	6	8
3	0	0	4	5
4	0	7	3.5	6
5	1	0	7	0
6	1	3	13	0
7	1	11	13.5	0
8	1	0	7	0
9	1	0	5	0
10	1	0	6	0
11	1	0	4.5	0
12	1	0	0	0
13	1	8	0	4
14	1	14.5	4	8
15	2	16.5	0	7
16	2	12.5	0	0
17	2	14.5	0	0
18	2	8	16.5	0
19	2	13	13	0
20	2	10	0	8
21	2	7	7	8
22	2	19	10	12
23	2	24	6	0
24	3	20	7	8
25	3	14.5	22.5	6
26	3	2	0	6
27	3	14	9	8.5
28	3	25	13.5	11
29	3	15.5	9.5	11
30	3	18	8.5	9.5
31	3	8	15.5	9

The reactor rate in this group was 24.0 per cent. (31/129). In terms of reactions to the undiluted human tuberculin the reactor rate was 20.9 per cent. 27/129).

Reactor number 13 had been vaccinated with B.C.G. in 1960.

Reactor number 21 had been vaccinated with B.C.G. in the neo-natal period.

Reactor number 15 had a history of tuberculous cervical adenitis and reactor number 19 also had a history of previous tuberculous disease.

The average size of reactions to the 10 T.U. dose of human P.P.D. tuberculin was 12.5 mms., to the 10 T.U. dose of Battey P.P.D. tuberculin was 9.0 mms. and to the 10 T.U. dose of Scoto-chromogen P.P.D. tuberculin was 7.9 mms. Twenty-two of the children reacted to the first, twenty-four to the second and only seventeen to the third. Four did not react to the Heaf test and one reacted only to the Heaf test. Twelve children appeared to give specific reactions to one or other of the atypical antigens, either not reacting to the 10 T.U. dose of human tuberculin or appearing to give cross reactions to it.

C. Discussion.

1. General level of tuberculin sensitivity.

Neither this survey nor the last confirmed the presence of the apparently widespread tuberculin sensitivity amongst local schoolchildren experienced in 1961 - 1962. The overall reactor rate to the Heaf multiple puncture test using undiluted human P.P.D. tuberculin was 16.9 per cent. This figure is in line with the progressively decreasing rate measured by the writer since December 1962 and if these are added to the rates recorded before 1961 an apparently sequential series is seen.

1955 - 31 per cent.
1956 - 34 " "
1957 - /
1958 - 33 " "
1959 - 33 " "
1960 - 29 " "
1961 - /
December 1962 - 29 " "
1963 - 23 " "
1964 - 17 " "

Had the last three figures been measures of sensitivity to a

10 T.U. dose of tuberculin, rather than to the Heaf Test, they might reasonably have been expected to be lower. In the Group III children in this survey there were twenty reactors to the first (taking six mms. diameter of induration as the minimum acceptable) and twentyseven to the second, (15.5 and 20.9 per cent. respectively).

The writer therefore again propounds the view that the rates measured in 1961 and in March 1962 were due,in part, to over-reading.

2. Non-specific sensitivity.

A complementary proposition has also been put forward, however, that the excess reactor rates then recorded included a measure of non-specific sensitivity not previously recognised by the 10 T.U. Mantoux Test nor subsequently recognised by the particular reading standard applied to the Heaf test by the writer, and it had been one of the main aims of the present survey to test this proposition.

The result of the Group III tests seem to support it. Twelve of the 31 children in this group reacted apparently by virtue of their sensitivity to non-mammalian tuberculins. Three of the twelve were not identified by the Heaf test. Six of the remainder gave minimal responses to the Heaf test. Only three of the twelve reacted to the 10 T.U. dose of human P.P.D. tuberculin with a diameter of induration greater than 6 mms.

The results of the Group II tests suggest the contrary view, that non-specific sensitivity was an unimportant factor, since in only two of the twenty children in this group was there evidence of specific reactions to the avian tuberculin. This was the more surprising since of the two atypical antigens used in Group III preference was shown more for the Battey than for the Scotochromogen tuberculin and allusion has been made already to the antigenic

links between the avian and the Battey organisms.

There seemed five possible explanations for the disparate results from testing by these two methods.

First, the measurement of Heaf test results in quantitative terms may be false in principle or in the particular experience of the writer. However, the method had been used by Stewart (1963) and by the British Tuberculosis Association (1963) who evidently accepted its reliability. While the writer acknowledged relative inexperience in the use of this method of recording Heaf test results it may be pointed out that only one Heaf test response to the avian tuberculin exceeded conventional Grade 1 in size and that of the eighteen children reacting to the human tuberculin five showed no response to the avian, so that even had the results been interpreted in terms of the conventional grading system the conclusion, that non-specific sensitivity was an insignificant factor, must have been the same.

Secondly, the use of the Heaf multiple puncture test may be inappropriate to comparative testing in some way other than in the measurement of results. This seems an illogical supposition. Indeed, as has been argued previously, its smaller experimental error theoretically makes its use the more apt in this context.

Thirdly, there may have been some error in the preparation, administration or interpretation of the tests. The first is improbable and, since reading was 'blind', the last is also unlikely.

Fourthly, the size of the samples was such that differences of the magnitude recorded in the amount of non-specific sensitivity may have occurred by chance. This seemed, to the writer, a likely explanation.

Lastly, it may be that avian and Battey tuberculins do not, in fact, give comparable results.

3. Bovine sensitivity.

The Group I tests gave equivocal results - a not unexpected outcome in view of the similarity between the two tuberculins used and of the time which had elapsed since exposure to infection with the bovine organism had last been possible. Stewart, Embleton and Van Zwanenberg (1961) had found it possible to assess the extent of bovine infection among schoolchildren by these means even with a dosage ratio of 2 : 1 in favour of the human P.P.D. Although the size of the present sample was small it was not so very much smaller than that in a single section of the population studied by these authors, yet the results are very different :

	Present Survey		Stewart, Embleton and Van Zwanenberg (1961)	
	No.	%	No.	%
Number completing test	199	100	315	100
Tuberculin negative	166	83.4	251	79.6
Reacting to both tuberculins	32	16.1	43	13.6
Reacting to bovine P.P.D. only	0	0	21	6.7
Reacting to human P.P.D. only	1	0.5	0	0
Mean size of reactions in mms.				
to bovine P.P.D.	5.2		9.0	
to human P.P.D.	5.6		6.3	

The results of the present survey do not endorse the view that infection with bovine organisms was widespread.

In the whole sample tested 23 per cent. of children who consumed only untreated milk were tuberculin sensitive as against 15.6 per cent. of children who consumed only treated milk. The difference is not so great as to suggest a causal association between these two factors ($\chi^2 = 3.162$: $P > 0.05$). It will be recalled that in the first survey a significant difference was found between the sensitivity rates of these two groups of children. It was implied that the drinking of untreated milk caused tuberculin sensitivity either because of bovine infection prior to 1958 or

because of infection with some other organism present in untreated milk since then. The fact that the association had now disappeared suggested that the first explanation was the more likely. The level of tuberculin sensitivity caused by drinking infected milk in the past would be expected to decline as the interval since the milk was made "safe" increased. It should also be borne in mind that the Group I children in this survey were two years younger than the children tested in the first survey.

Serious consideration was not given to the possibility that infection by Brucella abortus might have caused the higher rates of tuberculin sensitivity; the transmission of atypical mycobacteria by untreated milk, as suggested by Chapman, Bernard and Speight (1965), seemed worth consideration but the small number of children involved in these surveys made statistical analysis unreliable.

The belief that the consumption of raw milk infected with bovine tubercle bacilli up to 1958 may have influenced the level of tuberculin sensitivity in 1963 but not in 1964 is reasonable, particularly in view of the two year age gap between the children tested. It supports the idea that in the early years of the B.C.G. programme in Rawtenstall much of the tuberculin sensitivity may have been due to infection from this source. It also implies that no part of the increase in the sensitivity recorded in 1961 and in March 1962 can be attributed to infection from this source.

4. <u>Effects of multiple simultaneous tuberculin testing.</u>

Reference has been made to the observation of Rosenthal and Libby (1960) that simultaneous tests in the same person interacted, the response to a single test being reduced by a simultaneous test. The authors reasoned that there was competition for a fixed amount of antibody.

The circumstances of the present survey allowed further examination of this view. In all three groups undiluted human P.P.D.

tuberculin of the same batch was injected in each child by the Heaf multiple puncture gun. In Group I a simultaneous Heaf test using bovine P.P.D. tuberculin and in Group II a simultaneous Heaf test using avian P.P.D. tuberculin was given; all contained 2 mg. tuberculo-protein per ml. In Group III a simultaneous 10 T.U. dose of human tuberculin was given, together with 10 T.U. doses of two non-mammalian tuberculins. In terms of "competition", therefore, the human antigen had decreasing opposition from Group I to Group III. If the theory that there is a fixed amount of antibody is correct, an increasing response to the undiluted human tuberculin would have been expected from Group I to Group III.

Unfortunately the responses to the Heaf test in Group III were not measured in terms of mms. diameter of total area of induration but it will be noted that the average size of the reactions to the undiluted human tuberculin in Group I was 5.6 mms. and that in Group II it was 7.4 mms. It is also evident that the reactions in Group III were larger than either. If all reactions are recorded in terms of the conventional grades then an obvious trend is apparent throughout the three groups.

Table 31: Heaf test responses to undiluted human P.P.D. tuberculin in three groups of children simultaneously tested with various other tuberculins.

Group	Heaf Grades						Total	
	I		II		III			
	No.	%	No.	%	No.	%	No.	%
I	28	84.8	4	12.1	1	3.0	33	42.3
II	11	61.1	4	22.2	3	16.6	18	23.1
III	10	37.0	9	33.3	8	29.6	27	34.6
Total	49	62.8	17	21.8	12	15.4	78	100.0

$\chi^2 = 15.285$ 4 d.f. $P < 0.01$

It seems likely, therefore, that this graded distribution of reactions was caused by the particular tuberculins used in each group and by the dose in which they were used. This supports the observations of Rosenthal and Libby and raises two points of relevance to these surveys.

First, if the strength of the responses shown in Table 31 was influenced by the simultaneous tests then it is reasonable to suppose that in Groups I and II, and particularly in the former, the frequency of responses may have been influenced also. In other words, it may be supposed that the overall reactor rate to undiluted human tuberculin may have been greater than 16.9 per cent. had it been measured by a single Heaf test.

Secondly, these findings strengthen the fear expressed by the writer in the discussion on the selection of children for vaccination in the first survey, that the addition of a Heaf multiple puncture test using undiluted human tuberculin to a series of comparative tests would differentially influence the response to these by diminishing the strength of the reaction to the human antigen. In this view the incidence of sensitivity to the non-mammalian antigens in the group III children has been exaggerated. If that had been so the effect cannot be measured but it is assumed to have been small and not of a magnitude to account for the difference between the findings in the Group II children and in the Group III children. In Rosenthal and Libby's series the addition of a 100 T.U. test to a 10 T.U. test diminished the size of the latter by an average of about one quarter. If all the reactions to the 10 T.U. dose of human tuberculin in Group III children are increased by this amount, no difference occurs in the significance of any of the comparative tests.

Summary to Part II.

1. Two surveys were planned to define the source of tuberculin sensitivity in Rawtenstall schoolchildren.

2. In both, the proportion of children found to be sensitive to the Heaf multiple puncture test using undiluted human P.P.D. tuberculin was within the range 13 to 24 per cent. It is concluded that the proportion found to be sensitive in 1961 (41 per cent.) and in March 1962 (47 per cent.) included some erroneous interpretations of minimal reactions.

3. The identification of children tuberculin sensitive because of infection with the bovine organism was not possible, either because there were none or because specific and cross reactions to human and bovine P.P.D. tuberculins were indistinguishable. An analysis of sensitivity in relation to milk consumption suggested that bovine infection was a decreasing influence which had ceased to be a significant factor in 1964.

4. The identification of 'non-specific' sensitivity (that is, sensitivity to non-mammalian preparations) was pursued by means of avian P.P.D. tuberculin on the one hand and of Battey and a scotochromogen P.P.D. tuberculin on the other. Non-specific sensitivity was demonstrated most frequently with the Battey antigen administered by the Mantoux intradermal test.

5. It is concluded that in Rawtenstall non-specific sensitivity may account for as much as one third of all tuberculin sensitivity recorded.

PART III.

Recapitulation.

If the incidence of tuberculin sensitivity in thirteen year old children is accepted as a reliable guide to the prevalence of tuberculous infection then in a given community the trend it describes over a period of time should be matched by the trend described by other indices of the same phenomenon in the same community. It can be shown that this does not occur in this country and the question arises as to whether tuberculin sensitivity amongst a small sample of children can be accepted as a valid index.

The measurement of tuberculin sensitivity is open to a number of variables and error is likely to be greatest when the method of measurement involves the use of a large dose of tuberculin and when non-specific sensitivity is present.

The problems involved in the interpretation of reactor rates are illustrated by reference to the situation which developed in a small Lancashire town when the level of tuberculin sensitivity among thirteen year old local schoolchildren rose sharply in 1961 without other evidence of increase in the prevalence of tuberculous infection.

Consideration of the theoretical possibilities led to a number of observations and deductions.

It was noted that the increase coincided with a change in the method of testing and it was deduced that a reservoir of previously unrecognised non-specific sensitivity was thereby measured for the first time. However, the size of the increase made it unlikely that this was solely responsible and another observation implied that observer-error was an additional factor.

The possibility that in a single school showing an exceptionally high level of tuberculin sensitivity there may have been a

source of infection responsible for some of the increase could neither be confirmed nor excluded in retrospect. The suggestions have been made that such episodes should be immediately investigated and that the results of testing should be recorded in quantitative terms.

Milk was known to have been infected before 1958 and the view that much of the sensitivity was of bovine origin seemed a likely explanation for the fact that the local level of tuberculin sensitivity had been considerably higher than the national and the county averages. However, in view of the known facts regarding skin test reversions, it could hardly account for an increasing level of tuberculin sensitivity three years after the milk supply had been made 'safe', the amount of non-pulmonary tuberculous disease having declined in the same period.

Comparative tuberculin testing surveys were conducted to test the validity of these deductions.

The belief that bovine infection had little to do with the rise in the amount of sensitivity was strengthened by indirect evidence accruing from these surveys.

The fact that the rise coincided with a change in the method of measurement from the Mantoux intradermal to the Heaf multiple puncture test proved not to be a fortuitous association but the main causal factor which operated in two ways.

First, the possible variation in interpreting minimal reactions to the Heaf test is considerable and seems to have been deployed to the full in the early years of its use in the particular community studied. Had the results always been recorded quantitatively this supposition could have been made in stronger terms.

Secondly, by virtue of the fact that a relatively large amount of antigen is injected during Heaf testing an antigen-antibody

reaction is elicited even in the presence of antibodies previously formed in response to related but dissimilar infections. Since these 'non-specific' reactions are usually small they are most open to reader-error. Comparative testing with appropriate antigens demonstrated the presence of non-specific sensitivity among local schoolchildren.

It is suggested that the reactor rates recorded in 1961 and in March 1962 were high because much sensitivity of this nature was included, while the rates recorded since then have fallen because most has been excluded.

These disadvantages of the Heaf multiple puncture test could be circumvented if minimal reactions were, for practical purposes, ignored. Alternatively their incidence should be recorded. Results of Mantoux testing should also be presented in quantitative form.

Until a change of this kind is made in the statistical presentation of the results of tuberculin testing in the schools B.C.G. programme it seems unwise to accept them as a guide to the prevalence of tuberculous infection.

Appendix A.

B.C.G. Vaccination - School Children Scheme. Percentage of children read positive over the total read, 1959 to 1962.

L.H.A.	1959	1960	1961	1962
England and Wales	13.9	15.4	14.3	16.0
Bedfordshire	11.9	9.7	11.5	9.7
Berkshire	12.1	14.1	9.6	15.4
Buckinghamshire	12.8	8.7	9.4	10.7
Cambridgeshire	14.5	21.5	14.2	20.7
Cheshire	19.6	21.4	18.3	21.7
Cornwall	14.3	12.9	14.5	14.5
Cumberland	22.3	17.7	15.7	13.7
Derbyshire	18.6	27.1	20.2	26.0
Devon	15.4	18.5	19.3	16.1
Dorset	11.0	11.0	11.0	6.9
Durham	15.3	22.4	21.2	15.3
Essex	8.9	9.6	7.8	9.8
Gloucestershire	13.9	18.5	17.7	22.9
Hampshire	13.6	11.6	14.0	17.5
Herefordshire	13.1	14.4	16.5	15.9
Hertfordshire	10.2	8.9	7.3	8.5
Huntingdonshire	-	-	14.1	10.6
Isle of Ely	14.7	5.2	6.4	6.1
Isles of Scilly	-	-	-	16.1
Isle of Wight	16.6	15.1	16.8	20.1
Kent	15.3	11.9	11.3	11.1
Lancashire	19.1	19.1	16.1	18.6
Leicestershire	28.0	22.3	17.2	16.9
Lincs. Holland	19.4	19.8	16.4	18.5
" Kesteven	16.2	18.8	14.4	16.3
" Lindsey	12.7	12.2	11.2	10.9
London	8.2	8.6	8.9	8.5
Middlesex	7.1	11.0	10.8	11.1
Norfolk	15.9	15.2	16.5	19.2
Northamptonshire	18.6	24.2	23.1	21.1
Northumberland	17.1	15.9	14.8	9.5
Nottinghamshire	13.0	18.7	16.3	17.8
Oxfordshire	14.6	15.3	18.9	15.6
Peterborough, Soke of	-	-	4.8	6.0
Rutland	-	28.0	41.3	25.9
Salop	18.9	15.2	12.3	11.3

L.H.A.	1959	1960	1961	1962
Somerset	17.3	17.5	11.9	13.7
Staffordshire	15.0	23.3	18.3	13.2
Suffolk, East	11.9	31.4	27.7	28.8
Suffolk, West	-	-	12.9	12.6
Surrey	7.0	5.9	5.8	5.1
Sussex, East	15.8	12.4	10.3	8.5
Sussex, West	22.2	9.4	8.4	10.0
Warwickshire	14.9	23.2	17.3	21.7
Westmorland	15.3	15.6	10.7	7.8
Wiltshire	21.4	24.1	20.1	24.0
Worcestershire	11.8	14.1	9.3	12.1
Yorks, E. Riding	17.8	22.3	20.6	28.5
" N. Riding	-	-	-	-
" W. Riding	21.9	21.7	19.3	19.5
Barnsley	-	9.9	-	-
Barrow-in-Furness	10.0	8.4	9.4	11.9
Bath	-	17.1	29.4	33.0
Birkenhead	33.7	34.6	34.9	18.2
Birmingham	9.4	9.0	7.9	7.5
Blackburn	29.1	23.2	21.4	37.5
Blackpool	13.5	28.2	23.7	24.1
Bolton	18.3	16.2	16.0	16.7
Bootle	23.9	39.8	22.4	-
Bournemouth	12.1	13.7	12.5	28.2
Bradford	13.9	14.1	13.3	13.5
Brighton	18.9	23.7	24.0	12.3
Bristol	8.4	10.9	15.7	13.4
Burnley	11.5	16.7	18.5	14.5
Burton-upon-Trent	-	-	-	-
Bury	18.7	15.3	14.3	25.0
Canterbury	10.9	7.2	4.6	9.5
Carlisle	10.0	13.3	10.0	11.7
Chester	10.8	-	-	7.6
Coventry	17.3	17.1	34.2	14.4
Croydon	7.8	9.8	8.9	9.7
Darlington	44.2	35.7	25.4	23.6
Derby	9.3	18.5	14.0	11.5
Dewsbury	16.8	11.6	10.5	11.2

L.H.A.	1959	1960	1961	1962
Doncaster	-	-	-	-
Dudley	13.0	11.3	12.4	11.6
Eastbourne	9.0	6.4	8.2	6.2
East Ham	15.3	13.3	10.0	9.9
Exeter	13.1	11.0	9.2	13.0
Gateshead	25.0	23.2	15.5	13.2
Gloucester	6.3	14.5	23.5	17.8
Great Yarmouth	11.4	16.3	13.1	20.8
Grimsby	14.2	12.0	13.0	11.5
Halifax	-	26.1	34.1	31.2
Hastings	7.1	13.4	20.1	10.5
Huddersfield	20.0	17.0	12.5	9.7
Ipswich	12.5	15.5	11.1	19.7
Kingston-upon-Hull	17.1	21.2	27.8	21.9
Leeds	-	20.2	14.3	23.0
Leicester	13.5	10.4	8.1	9.2
Lincoln	10.3	12.1	15.4	11.4
Liverpool	17.0	16.1	18.3	18.4
Manchester	13.6	12.1	11.8	13.8
Middlesbrough	-	14.2	11.4	-
Newcastle-upon-Tyne	16.8	19.1	17.8	15.1
Northampton	14.4	15.6	14.3	8.2
Norwich	10.1	17.7	9.5	17.7
Nottingham	12.0	12.9	8.5	13.6
Oldham	15.3	19.0	12.8	28.7
Oxford	9.7	13.1	17.3	13.2
Plymouth	9.3	7.2	6.7	5.7
Portsmouth	10.7	11.4	9.6	11.5
Preston	18.4	17.8	18.4	20.4
Reading	9.1	9.0	6.2	8.1
Rochdale	-	4.8	3.6	2.4
Rotherham	22.5	21.2	22.4	13.1
St. Helens	22.6	26.8	29.8	29.0
Salford	17.0	9.5	10.8	-
Sheffield	10.0	19.8	18.5	29.1
Smethwick	9.5	7.6	7.5	11.0
Southampton	22.6	35.3	24.8	22.8
Southend-on-Sea	5.5	8.2	10.0	2.5
Southport	12.6	17.3	12.4	16.5

L.H.A.	1959	1960	1961	1962
South Shields	13.6	12.5	9.9	12.9
Stockport	13.0	11.4	9.9	10.8
Stoke-on-Trent	14.7	12.5	11.1	7.3
Sunderland	18.7	25.2	31.7	23.4
Tynemouth	11.4	10.1	3.7	7.6
Wakefield	15.3	10.2	17.4	26.1
Wallasey	8.6	7.3	7.2	4.9
Walsall	9.8	10.0	7.4	21.8
Warrington	12.8	9.6	10.1	7.4
West Bromwich	16.6	11.1	8.9	7.3
West Ham	11.3	10.3	29.0	12.3
West Hartlepool	13.2	10.8	19.8	13.3
Wigan	16.9	18.2	10.5	15.7
Wolverhampton	11.8	10.8	13.1	13.9
Worcester	15.4	13.5	13.2	14.8
York	17.2	10.7	11.8	8.0

Appendix B.

Tuberculosis (Respiratory and Non-respiratory)
Notifications per 1,000 population 1959 to 1962.

L.H.A.	1959	1960	1961	1962
England and Wales	.60	.52	.50	.44
Bedfordshire	.60	.73	.45	.57
Berkshire	.50	.38	.37	.33
Buckinghamshire	.41	.42	.35	.32
Cambridgeshire	.32	.46	.27	.23
Cheshire	.29	.27	.29	.28
Cornwall	.62	.53	.42	.38
Cumberland	.65	.63	.47	.45
Derbyshire	.39	.39	.33	.25
Devon	.37	.32	.30	.29
Dorset	.49	.45	.30	.29
Durham	.57	.54	.51	.50
Essex	.39	.41	.37	.35
Gloucestershire	.46	.50	.36	.45
Hampshire	.44	.44	.31	.28
Herefordshire	.40	.42	.33	.26
Hertfordshire	.51	.47	.42	.39
Huntingdonshire	.50	.35	.28	.32
Isle of Ely	.62	.31	.19	.17
Isles of Scilly	.55	.55	-	.56
Isle of Wight	.46	.51	.30	.24
Kent	.56	.46	.39	.39
Lancashire	.52	.39	.38	.38
Leicestershire	.32	.31	.31	.21
Lincs. Holland	.32	.31	.18	.18
" Kesteven	.37	.27	.33	.36
" Lindsey	.43	.34	.35	.33
London	.95	.87	.82	.74
Middlesex	.56	.53	.50	.45
Norfolk	.30	.31	.36	.31
Northamptonshire	.42	.40	.32	.29
Northumberland	.55	.51	.53	.49
Nottinghamshire	.51	.43	.35	.39
Oxfordshire	.52	.45	.49	.33
Peterborough, Soke of	.54	.57	.17	.43
Rutland	.51	.32	.12	.34
Salop	.33	.42	.30	.20

L.H.A.	1959	1960	1961	1962
Somerset	.44	.38	.34	.25
Staffordshire	.48	.43	.39	.34
Suffolk, East	.28	.39	.33	.25
Suffolk, West	.26	.17	.31	.36
Surrey	.44	.35	.40	.34
Sussex, East	.38	.38	.26	.27
Sussex, West	.35	.29	.17	.20
Warwickshire	.55	.43	.35	.36
Westmorland	.50	.35	.31	.19
Wiltshire	.36	.39	.39	.32
Worcestershire	.44	.39	.35	.34
Yorks, E. Riding	.31	.28	.22	.20
Yorks, N. Riding	.36	.28	.35	.27
Yorks, W. Riding	.44	.36	.37	.31
Barnsley	.42	.46	.32	.37
Barrow-in-Furness	.54	.31	.34	.46
Bath	.50	.35	.47	.23
Birkenhead	.74	.60	.61	.50
Birmingham	.73	.80	.73	.68
Blackburn	.59	.37	.48	.34
Blackpool	.31	.33	.48	.39
Bolton	.39	.38	.51	.36
Bootle	1.36	.57	.67	1.03
Bournemouth	.59	.51	.28	.36
Bradford	.88	.76	.90	1.08
Brighton	.51	.52	.47	.33
Bristol	.61	.62	.40	.33
Burnley	.96	.45	.31	.36
Burton-upon-Trent	.55	.38	.28	.30
Bury	.50	.27	.17	.13
Canterbury	.53	.72	.32	.33
Carlisle	.87	.84	.51	.41
Chester	.77	.63	.66	.42
Coventry	.78	.76	.56	.52
Croydon	.59	.56	.75	.46
Darlington	.52	.49	.42	.37
Derby	.52	.54	.47	.47
Dewsbury	.52	.36	.49	.70
Doncaster	.56	.72	.48	.50
Dudley	.72	.66	.79	.58

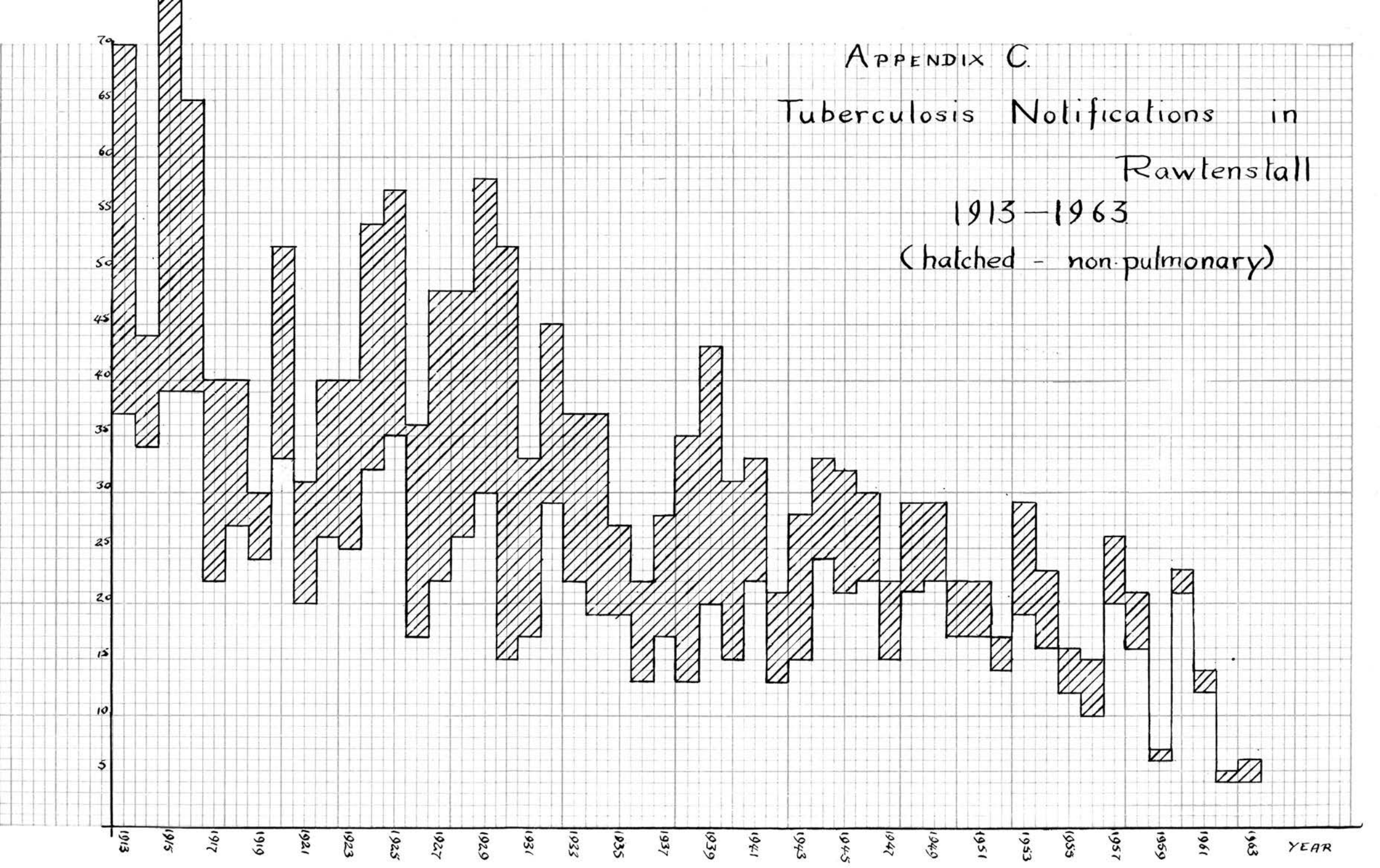
L.H.A.	1959	1960	1961	1962
Eastbourne	.43	.31	.23	.18
East Ham	.88	.49	.74	.79
Exeter	1.03	.57	.47	.48
Gateshead	1.28	1.20	.96	.80
Gloucester	.67	.79	.43	.33
Great Yarmouth	.39	.21	.25	.17
Grimsby	.65	.83	.61	.71
Halifax	.47	.51	.50	.83
Hastings	.47	.63	.42	.59
Huddersfield	.54	.66	.67	.60
Ipswich	.38	.48	.32	.37
Kingston-upon-Hull	.66	.59	.43	.43
Leeds	.74	.70	.70	.63
Leicester	.57	.67	.62	.58
Lincoln	.69	.53	.49	.61
Liverpool	2.22	.64	.62	.65
Manchester	.77	.64	.64	.65
Middlesborough	.76	.67	.68	.61
Newcastle-upon-Tyne	.91	.87	.77	.70
Northampton	.40	.38	.29	.43
Norwich	.39	.31	.36	.38
Nottingham	.89	.65	.67	.66
Oldham	.49	.74	.32	.40
Oxford	.74	.81	.56	.71
Plymouth	.78	.70	.82	.48
Portsmouth	.46	.44	.35	.35
Preston	.45	.38	.50	.45
Reading	.67	.63	.66	.85
Rochdale	.46	.39	.27	.45
Rotherham	.45	.33	.33	.39
St. Helens	.70	.62	.53	.55
Salford	.82	.61	.68	.42
Sheffield	.71	.65	.53	.57
Smethwick	1.60	1.29	1.05	.86
Southampton	.71	.60	.59	.56
Southend-on-Sea	.60	.47	.38	.42
Southport	.32	.20	.22	.37
South Shields	1.32	1.05	.80	.97
Stockport	.46	.30	.40	.46
Stoke-on-Trent	.55	.48	.43	.39

L.H.A.	1959	1960	1961	1962
Sutherland	.84	.66	.73	.58
Tynemouth	.72	.91	.87	.62
Wakefield	.20	.28	.21	.21
Wallasey	.78	.69	.46	.42
Walsall	.63	.63	.70	.60
Warrington	.56	.30	.47	.28
West Bromwich	.77	.70	.70	.90
West Ham	.58	.55	.54	.52
West Hartlepool	.52	.43	.22	.40
Wigan	.80	.64	.46	.34
Wolverhampton	.67	.70	.77	.65
Worcester	.63	.53	.35	.52
York	.16	.27	.22	.30

Appendix C.

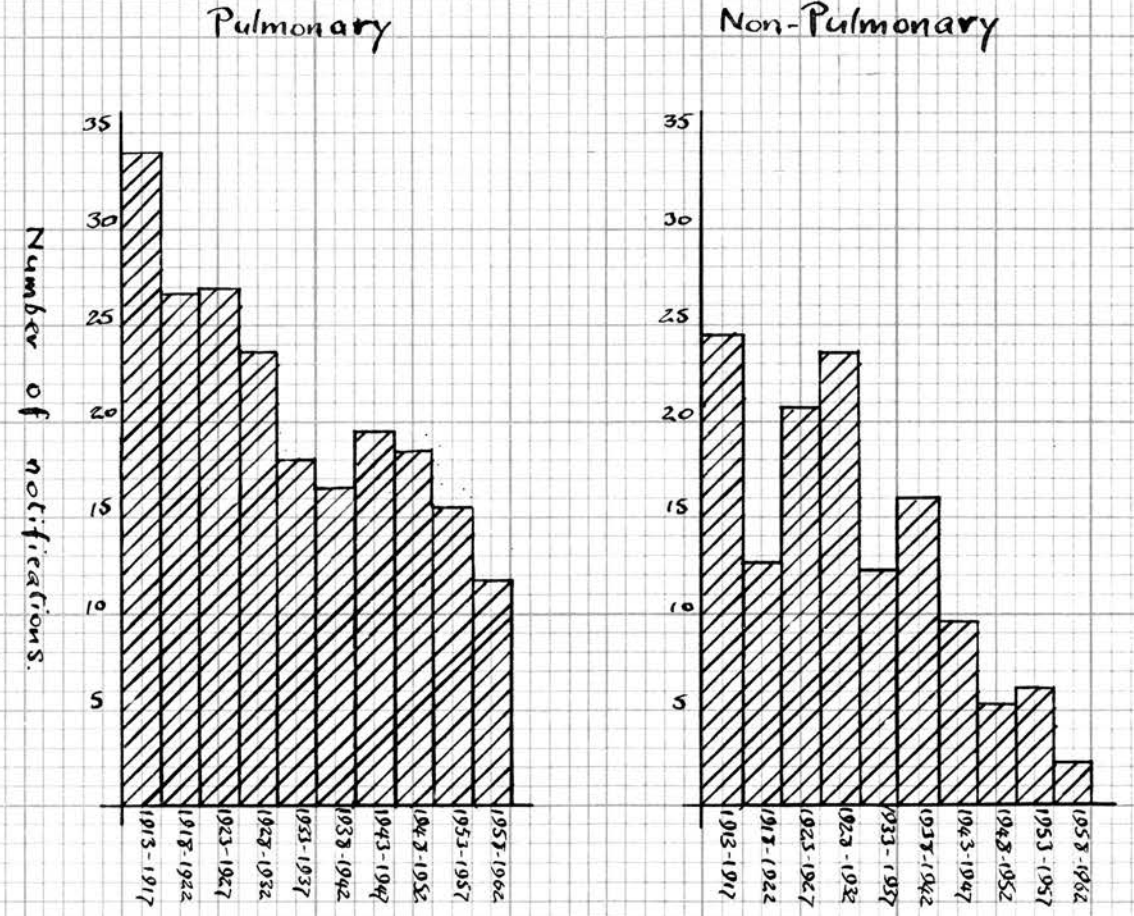
Tuberculosis Notifications in Rawtenstall 1913–1963

(hatched - non-pulmonary)



APPENDIX C

Notifications of pulmonary and non-pulmonary Tuberculosis in Rawtenstall - 5-yearly averages 1913-1962.



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