

Pathological.

A CLINICAL STUDY OF PULMONARY TUBERCULOSIS

IN CHILDREN FROM 5 to 14 YEARS OF AGE.

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I N T R O D U C T I O N .

A study of the nature of the present one, is somewhat difficult to approach on sequential lines. There is very little unanimity amongst eminent Authorities as to the attitude which should be taken up concerning pulmonary tuberculosis in children.

The first point that confronts a medical practitioner, when a child is brought to him with some symptom, or a train of symptoms, suggesting pulmonary disease, is to diagnose the nature of the malady, or, at any rate, to give a definite opinion as to the presence or absence of pulmonary tuberculosis. Finding myself in this undesirable position on more than one occasion, I forthwith sought the help of more experienced men.

One boldly asserted that loss of weight with a family history of tubercle was the key to diagnosis; another considered night-sweats with family history disclosed the nature of the disease; a third assured

me that lung signs, in the presence of a positive history of consumption in a relative, was sufficient evidence; still a fourth demanded what amounted to the whole symptom-complex with the assistance of radioscopic examination. It must be obvious from this diversity of opinion on the matter that no very definite basis of diagnosis exists.

It was therefore necessary in the first place to work out a method of examination which would be supported by results.

It was soon evident that diagnosis was unreliable in the absence of a specific test. The specific test ^{which} seemed to me to offer greatest opportunities for extracting information, in a manner not prejudicial to the patient, was the cutaneous reaction. The ordinary cutaneous test appeared to be more amenable to control than some of its modifications or allied tests. Obviously the quantitative reaction as suggested by Ellermann and Erlandsen was the most instructive, but somehow the results did not produce the mathematical exactness that theory would demand.

One's first problem was to decide whether it was necessary to use both types of tuberculin. Again, very little work has been done on the questions pertaining to technique etc. in the performance of the test, so one undertook a fairly complete investigation of all possible factors that might interfere with the final result.

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Having perfected the test to a certain extent one compared its findings with those of ordinary clinical methods of investigation, radioscapy, etc. This led to what appears to be a fairly reliable procedure in the examination of children.

All this matter comes into Part I.

Again, early life is eminently suitable for studying many important factors concerning tubercle in man; one felt justified in accepting the cutaneous tuberculin reaction as a specific foundation, and in association with each type of reaction other ascertainable clinical facts were analysed and arranged to see whether or not one might learn anything regarding:

(1) the frequency of transmission of bovine tuberculosis to human beings, (2) the identity of bovine and human tuberculosis, (3) the possible channels of infection, and other matters which might be suggested.

This investigation is included in Part II.

Thus an attempt is made to render this investigation as complete as possible by trying to ascertain the nature of the tubercular infections in early life; how these agents effect an entrance into the body; and the most reliable simple method of diagnosing their presence in a ^{numbers} ~~manner~~ sufficient to produce disease. In attaining this object the sequence has often to be broken to pursue some point of

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importance, e.g. where experimentally founded theories do not fit in with clinical facts an explanation is essayed, which I am anxious should be interpreted, not so much as a criticism of pathological investigation, as an endeavour to associate or dissociate, as seems justifiable, the fruits of clinical and laboratory research.

THE DIAGNOSIS OF PULMONARY TUBERCULOSIS IN

CHILDREN WITH SPECIAL REFERENCE TO THE

QUANTITATIVE CUTANEOUS REACTION.

There is no more difficult problem in the practice of medicine than the diagnosis of tuberculosis, especially pulmonary, in children. The most immodest observer would hesitate to question either a positive or a negative diagnosis in the first 14 years of life in a large number of cases; and yet it is most important to take up some standpoint on a question so individual and universal.

Comparing phthisis with any other clinical condition it is fairly apparent that differences must exist. One cannot pick out any pathognomonic symptom or train of symptoms. It is only a slight exaggeration to assert that there is no symptom in children which may not attach itself to tuberculosis, and conversely, there is no manifestation of tuberculosis which cannot be initiated by, or associated with, some other disease, physical or social. Night sweats are not peculiar to phthisis, indeed they are often the outcome of imperfect ventilation and over-clothing; or they may arise without apparent cause; similarly loss of weight cannot be regarded as an index of tubercular disease, the rapidity with which tubercular children under proper conditions gain weight is most

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striking, except of course in advanced cases. One would almost be inclined to regard loss of weight in most cases as social and inductive to tuberculosis rather than a special symptom.

Sputum, of course, is very rare in children so it is not possible to find tubercle bacilli for diagnostic purposes. The other possible symptoms, including cough, are too vague to deserve any recognition other than that suggesting the advisability of careful examination.

Similarly it is impossible to support any train of symptoms even if associated with physical signs in the lungs.

Besides, symptomatology and personal history involve the powers of observation, and accurate narrative, on the part of fond parents. I wonder how far dread of the complaint, emphasised by a somewhat tragic family history, tends to obscure the real state of affairs: my experience is that one is sometimes forced to give undue weight to symptoms revealed by the mother, as after events prove. We are here, then, dealing with second-hand information, tintured with the exaggeration born of anxiety, or a tendency to inexactitude with ulterior motives.

The presence of a family history of tubercle is endowed with great weight in making a diagnosis, and rightly too, but about 30% of tuberculous children give a negative family history. Again, about 20% of cases presenting themselves for examination, who are

not phthisical, record a relationship with a consumptive subject. Other symptoms may be very similar in such cases, so it is necessary to demand other resources.

The great majority of medical practitioners put their faith in physical signs when making a diagnosis. Physical signs are exceedingly valuable, especially if associated with family history and suggestive symptoms, but one has been so often led to mistaken conceptions on such a diagnostic basis that recourse to other methods had to be adopted. It is not an unusual experience to find such a case clearing up in a week or two and showing later no tendency to recurrence; obviously in the large majority of these cases such a clinical picture is not induced by the tubercle bacillus. Again, there are many cases which reveal no signs of tuberculosis, and yet there is that about them which renders exclusion of tubercular infection a great responsibility. Of course there may be no disease; on the other hand this elusive quantity masquerading under the dignified title of "Hilus Tuberculosis" may be the hostile influence at work.

Tuberculosis in children regarded on such a basis leaves much to be desired, it would be a minor matter if cases presenting difficulties were rare occurrences. Such is not the case. Cases are often missed which are really phthisical, whereas many children are labelled consumptive whose con-

dition is not produced by the bacillus tuberculosis at all.

When one looks at this state of affairs fairly, one is convinced that other aid is essential if work is to be done on sound lines. It was at once evident that sins of omission and sins of commission could only be ruled out on the strength of some specific test. Such a test too must be within the reach of all, otherwise it scarcely meets the needs of the case. After consideration the quantitative cutaneous reaction seemed to open up the greatest possibilities; it is safe, universally applicable, and, with practice, easily performed. Its great drawback is that very little work has been done on it, and there is no definite technique and no fundamental basis of interpretation.

An attempt is here made to rule out certain fallacies and to bring the test into relationship with clinical work on lines which practice would seem to justify; whether the conclusions are right or wrong, time must determine. This involved an immense amount of work, the record of which may be tedious to the reader, but it appears to me desirable to state exactly the methods of procedure, lest some error may unconsciously arise in my own deductions.

It will be seen that I am accepting the specificity of the tuberculin reaction. I think that has been established beyond doubt by such men as

Von Pirquet, Lord, Von Ruck and others, but it is still necessary to have a clear idea of what constitutes a reaction, what influences affect it, and what interpretation it merits.

As suggested the responses presented many irregularities, so if any degree of success were to be attained, it was necessary to undertake a minute and complete investigation, so I decided on a programme of procedure.

On consideration it appeared to me at least practical to regard a cutaneous reaction as a localized tuberculosis, of which more anon, and in its study one was dealing with three factors, viz:

1. The patient. 2. Non-infective trauma.
3. Infective trauma. Such a design is comprehensive, and though it was quite impossible to deal with each of the three separately, everything was considered on the triple-headed basis for the sake of completeness.

The programme was to determine as far as possible the following:-

1. Whether or not the reaction varied with the type of tuberculin.
2. Technique - its influence in producing variations in the response.
- 2a. Factors in patients' skin and in tuberculin producing variations in the response.
- 2b. Extraneous factors producing variations in the response.
3. Nature of a reaction from clinical standpoint and its interpretations.

4. The prognostic significance.
5. The therapeutic significance if any.
6. The diagnostic value studied comparatively with physical examination, subcutaneous test, ~~X-Ray~~ or radioscopic examination and thermometry, etc.

1. WHETHER OR NOT THE REACTION VARIED WITH THE TYPE OF TUBERCULIN.

Obviously it is impossible to deal with this subject in detail here. In Part II I publish my work in full.

For the present purposes it is enough to state that 302 cases were investigated by the ordinary differential cutaneous reaction. I used .1 T and .1 P.T. with a control of normal saline between with the following results:-

Number of cases with both human and bovine positive	- 87
Number of cases with both human and bovine negative	- 83
Number of cases with only human positive	- 27
" " " " " bovine "	<u>-105</u>
Total	- 302.

I do not propose to discuss these findings or justify them in the light of Gauvain's recent work on this subject or of any other work. The outcome of this preliminary research convinced me that in doing a quanti-reaction it is necessary to use both types of tuberculin if accuracy be aimed at. I may say, too, the experience of later work justified the adoption of

both human and bovine tuberculin in performing the test.

II. TECHNIQUE - ITS INFLUENCE IN PRODUCING VARIATIONS.

Ellermann and Erlandsen introduced a method whereby it is possible to work out the cutaneous sensitiveness of a patient to tuberculin. The test consists in applying tuberculin of varying strengths to the forearm and measuring the resulting papules, and, from the information obtained, calculating the lowest strength of tuberculin that will produce a reaction. It may be argued that it would be less liable to error, were one simply to apply the low strengths and thus obtain direct knowledge. In practice such a procedure is scarcely feasible, besides, it is much more definite to work from real tangible reactions towards the vanishing point, than to wrestle with problematical results, for such they would necessarily be when development is at its minimum. To simplify the calculation in the former case, Erlandsen has produced a table, which has been modified by Morland; by reference to this scale the sensitiveness of any case can be determined in a few moments. Since this section of the work deals with the influence of variations in technique, it is necessary to sketch briefly the procedure.

As I have indicated it is essential to have both types of tuberculin; dilutions were prepared in 64 per cent, 16 per cent, 4 per cent and 1 per cent

strength, one series of T and the other of P.T. using the usual saline and carbolic diluent. It will be noticed that these preparations ascend from 1 to 64% by geometrical progression. The papules resulting from applying these dilutions are supposed to vary in arithmetical progression; such an assumption is supported by experiment and by Weber's law. Each of the 8 bottles is supplied with a sterilized pipette; these pipettes are of the same calibre. Dilutions should be made up fresh for each operation if possible, though I could find little defect in preparations up to 3 days old.

Both forearms were cleaned with ether or spirit. When dry, four scarifications were made roughly in a line down each arm with an intervening space of at least $1\frac{1}{2}$ inches.

The scarifier used was made from a steel knitting needle which was ground to a fine hatchet edge, two small dents were made with a knife file in the edge, thus producing a margin consisting of three flat teeth. About two inches of needle were used. The blunt end was pointed and fixed into a piece of hard, slightly barrel-shaped, wood, $1\frac{1}{2}$ inches long, which fitted into a tube. Either end of the wood wedged in the tube. Before use, in each case, the needle was dipped in spirit and passed through the flame of a spirit lamp. This apparatus could be kept very sharp and smooth-edged; by holding it like a pen and rotating it a few times, it was possible, when the

skin was stretched in the usual way, to make a "clean" abrasion which excited very little traumatic reaction.

Human tuberculin was applied to the right forearm invariably, the strengths ascending from the wrist towards the elbow, thus obviating any interference that the lymph flow might create. Similarly the left arm was treated with the corresponding dilutions of P.T.

The scarifications were as near as possible of equal size, and bleeding was avoided. Approximately equal drops were applied to the different abrasions. At first a control was used but later discarded as it seemed unnecessary.

The latent period preceding the formation of a papule is very variable, some explanations of these variations appear later. Their existence, though, claims the close attention of the observer for 4 days or even more; fortunately, under ordinary circumstances an examination in 24 hours and then again in 48 hours will catch the great majority of cases. Inspection of a positive case reveals a series of papules varying in size from above downwards, and apparently evincing a certain regularity in their diminishing size. When development has reached a certain stage, the papule formation is, as a rule, quite striking and easy of definition; it is set, as it were, in a halo of congestion in most cases. When difficulty is experienced in determining the raised part it will be found very helpful to pass the thumb or forefinger over the reddened

area, as a result of the pressure it is quite easy to distinguish the infiltrated or exudated from the congested area. Once the papule is defined, measure its diameter with dividers, preferably worked with a screw and spring; place the points of the dividers on a steel scale graduated in millimetres in such a way as to determine accurately the diameter of the papule. In the same way, measure the diameter of the scarification, and subtract this from the above result, the remainder is regarded as the size of the papule. The size of each reaction is decided in the same way. Add together the size of the four elevations, and divide by 4, the result is the "average papule size". Again subtract the size of the .01 reaction from that of .64 and divide by 3 and thus obtain the "average papule difference". Having got the size and difference, refer to Erlandsen's table and at once a number is obtained which represents the cutaneous sensitiveness of the patient to tuberculin: e.g., suppose the papule size is 3 and difference 2, the above table shows sensitiveness to be 100; which simply means that the reciprocal of 100, i.e., $1/100$ of .01 is the lowest strength of tuberculin which will produce a reaction. It is usually advisable to measure on two occasions and take the average.

The above is a very cryptic description of the method of performing the test, but will serve to indicate the importance of scrupulous care in technique: as the following experiments show, very small aberrations

tions materially vitiate the final result. If the results of the experiments are tabulated below their headings the significance will be perfectly obvious, thus time and space will be saved.

EXPERIMENTS.

It is worth recording, that reactions near to wrist are slightly smaller than those near elbow when the same tuberculin dilution is used; probably the denser tissues tend to limit the exciting force of the toxin. This observation was supported by experiments performed on the somewhat loose structure of the back, here, the papule was larger even than on the fleshy part of the forearm, other corroborative tests seemed to me to warrant the assumption that the less dense the cutaneous and subcutaneous structure, the more extensive is the resulting papule. This is the first note of warning in regard to hasty interpretations of so-called "strong reactions" and "very strong reactions" as adopted by Wolff-Eisner.

Except for the above investigations, it is now permissible to disregard, once and for all, cutaneous reactions on any part of the body save the forearm. Later, I shall have to refer in greater detail to another aspect of the problem concerning the size of the reaction, but in what follows attention was entirely directed to experiments on the forearms. This part has no disadvantage that can be excluded elsewhere; and being eminently convenient, I feel justified

in directing all my energies to the study of quantitative reactions performed on the anterior aspect of the forearms.

(a) Experiments to determine influence of wide and narrow scarification.

As far as possible depth was the same, and also size of drop, and, of course, strength of tuberculin.

	<u>Narrow scar with size of papule.</u>	<u>Wide scar with size of papule.</u>
W.G.	5.5 m.m.	5.5 m.m.
L.P.	7 "	7 "
A.R.	2 "	1.5 "
J.D.	7 "	5 "
I.C.	6.5 "	5.5 "
B.F.	5.5 "	5 "

In performing these experiments scars were made at corresponding points of the arms. It will be noticed that the wide scar tends to give a smaller papule. When it is pointed out that the drops were allowed to dry on the scarification, it is to some extent what might be expected, for absorption into the general system does take place. Control experiments on similar lines with equal sized abrasions, or as nearly equal as possible, showed a reasonable uniformity; slight differences e.g., .5 m.m. occurring indiscriminately.

(b) This question of absorption being raised, one next investigated the effect of depth. Here the vascular layer of the skin was freely opened. One

wondered if this were purely a question of absorption into the system, or if the blood played any part. To decide these points tests were simultaneously performed e.g., on right arm 2 non-bleeding, equal scars, 2" apart; on left arm one scar as on right, and 2" below, deep bleeding scar of same size; blood was borrowed from the latter and just applied to the former. To the proximal abrasions 64% tuberculin was applied and to the distal two 16% with the following results in papule size:-

	<u>Right.</u>	<u>Left.</u>
N.B.	6 m m. 4.5 "	2 m m. X (not measurable)
C.B.	6.5 " 5.5 "	3 " 2.5 m m.
I.C.	8 " 6 "	4 " 1.5 "
L.P.	8 " 7 "	5.5 " 3 "
A.R.	4 " 2 "	2.5 " ? "
F.S.	6 " 5.5 "	5 " X

These results are very striking and seem to demonstrate forcibly the necessity for non-bleeding scars. The upper scar on the left arm was just touched with blood so that a thin film covered the abrasion, still, the effect is pronounced. It should be mentioned that a slight oozing of blood after the application of the toxin has not a marked influence, but any rotating of the scarifier after blood appears exercises a decided effect on the size of the resulting X equals positive.

papule. The thin smear of blood would seem to act as a protector. In the deep scarification probably some toxin is borne away. As in the former case equal drops were used and allowed to dry in. It should be noted that the drops on the left arm took longer to disappear than their correspondents on the right arm; Of the two on the left side, the deep bleeding was the more delayed as a rule, this would seem to suggest that absorption into the general system is not very marked, yet, it scarcely rules it out.

(c) In interpreting the marked diminution where the scar is deep, one wondered if the greater hyperaemia induced by the somewhat extensive trauma played any part. It was first attempted to produce hyperaemia around the scar by miniature cupping, this proved an unsuitable method. One decided then to paint lightly a zone, adjacent to the site scarified, with liquor epispasticus. This was done in some cases before the abrasion was made, and in others after tuberculin had dried in. In addition, slight scarification of surrounding skin was tried on other cases. These experiments, in the nature of things, could not be very conclusive or applicable, still, on the whole the impression conveyed was that congestion did not accelerate or delay reaction but to some extent lessened development.

(d) To decide the effect of a large drop and a small drop: these experiments as in those preceding had all other factors the same i.e., as to scar, site,

etc. It will be sufficient to record the results of four consecutive tests. The drops were allowed to dry in.

	Papule size with <u>small drop.</u>	Papule size with <u>large drop.</u>
W.	6.5 mm.	8 mm.
X	4 "	6.5 "
Y	5.5 "	6 "
Z	X (not measure- able.)	5 "

Note particularly this last case. The above result was not obtained until the third day, though the case was strictly watched. It seems to have some relation to the nature of a reaction. It will be obvious to any observer that the size of the drop has a definite bearing on the size of the papule when complete absorption is allowed to take place. Now this naturally raised another question, viz:- If all other factors, regarding the size and depth of scarification, etc., be the same, and after a certain time the excess tuberculin be removed with a pledget of cotton wool, does one thus ensure corresponding stimulation at each site?

(e) Unfortunately the problem is not so simple, for, by meeting the difficulty so, one is unconsciously assuming a uniform power of absorption by all cutaneous surfaces, under all circumstances and at the same time ignoring any influence that tuberculin content might have. It will be seen that the sub-headings

2a. and 2b. are involved here.

2a. Factors in patient's skin and in tuberculin producing variations in the response.

The time taken by the dose to disappear raises two questions: (1) that of absorption, (2) evaporation. Those who watch the four equal applications drying without interference, must have noticed in practically every case that 1 per cent strength at the wrist took longer to disappear than 64 per cent strength at the elbow. It will be noticed that the glycerine content of 64 per cent tuberculin is much higher than that of 1 per cent. To determine whether the glycerine were the deciding factor the order of application was reversed, with the result that 1 per cent was dry the earlier. It thus appeared again a question of tissue density, for, when application of the same dilution of tuberculin was made above and below the latter was again delayed. Still, given similar points of application one expected glycerine to play some part by delaying evaporation as suggested by Riviere:² 64% and 1%, equal doses were put on corresponding points of both arms; they were dry practically together. It would seem then that the tuberculin constituents play little, if any, part in the disappearance of the dose, it is apparently more a question of absorption than evaporation; the time occupied by the former depending on the density of the cutaneous structure. It was found in practice and experiment that using the same dose and same strengths

of tuberculin, some skins absorb the application in half, or even quarter, the time that others take, e.g., taking a well-nourished and ill-nourished boy, the former absorbed the dose in half the time taken by the latter. The same tendency was shown in girls. Girls generally absorb the drop more quickly than boys, which seems to me corroborative evidence regarding the influence of soft and tough tissues.

With reference to the amount of glycerine in the dilutions, it was considered possible that it played some part despite the facts recorded above, which showed that 64% and 1% dried in practically the same time. It was credible that the glycerine did help absorption of 64% strength and this was equalized by evaporation of 1% strength. At any rate in practice it was noticed that the arithmetical progression of the papule sizes showed greater distortion between the 16% and 4% papule. The most obvious explanation of this phenomenon seemed to be that 4% contained too little glycerine to be very helpful in absorption. To determine the accuracy of such a conclusion the following experiments were carried out: One arm was treated with the ordinary dilutions of 4% and 1%; the other arm was treated with the same strengths of tuberculin, but the diluent used in their making contained 40% glycerine. As previously, all other factors were the same. The appended results were obtained:-

-See over-

	<u>Papule size with ordinary 4% and 1%</u>		<u>Papule size with 4% and 1% containing about 40% glycerine.</u>	
M.H.	4% 1%	X ?	X X	
L.C.	"	6 mm. 4.5 "	6.5 mm. 5.5 "	
M.F.	"	3 " 2 "	4.5 " 3.5 "	
G.W.	"	5 " 4.5 "	7 " 6.5 "	
E.S.	"	3 " 2 "	4.5 " 3.5 "	

It would appear from the above that glycerine extends the range of the tuberculin offensive. One never succeeded in producing a reaction with 40% glycerine and .5 carbolic acid in saline.

2b. Extraneous factors producing variations in the response.

It was found that atmospheric temperature played an important part, and this not only in delaying absorption but also in reducing the reaction. Some of the very cold days in winter were chosen to elucidate this point; it is difficult to bring forth mathematical evidence, however, general impressions have some significance. A batch of cases was chosen, a certain number of whom were recently admitted and still in bed; the others were about. After performing the test, the bed patients were put in a bathroom which was heated, whilst the others were put on rest chairs on the verandah with arms uncovered - after a short stay in Sanatorium patients can bear extreme cold without much discomfort. The applications were allowed to dry in and

other pertinent facts were equal as previously. When dry, bed patients returned to their warm beds, whilst verandah cases remained exposed. The general outcome of this experiment was; that the bed patients developed papules earlier and more marked, though, as far as it is possible to judge, the patients chosen were similar. It was not found possible to induce a patient in bed to leave one arm exposed whilst the other remained under the bed clothes and thus perform the two experiments in the same case. The investigation was conducted on several days, and despite the crudeness of the attempts one felt convinced that atmospheric temperature played a large part in reactivity; possibly due to the tendency which cold has to constrict superficial vessels and thus create a dense tissue difficult to permeate, besides, it seems reasonable to assume a lower vitality and hence the lessened and delayed response in exposed patients. Whether the lack of blood plays any part, or its absence is counteracted by impermeability and low vitality, it is impossible to say.

The conclusion which seems justifiable from research on the influence of the glycerine content of tuberculin, factors in patient's skin, and extraneous factors, is, with reference to the time taken by the dose to disappear, that glycerine apparently plays little part, the nature of the skin a pronounced part, as also the atmospheric temperature.

In the light of facts produced under (e), which involves sub-headings 2a and 2b, one can assert

that the method of removing excess tuberculin after a definite time does not ensure corresponding stimulation at each site, and therefore should not be adopted where accurate results are aimed at. Again, one may be permitted to dissent from, or at least question, Bordman's view that little further absorption occurs after 10 minutes. The time occupied in absorption varies in different cases as well as in different sites in the same patient.

(f) To decide the question raised in the closing sentences above, experiments were undertaken in which, other factors being the same, the applications on one arm were allowed to dry in, whilst those on the other had the excess tuberculin removed after 10 minutes.

	<u>Size of papule excess wiped off in 10 minutes.</u>	<u>Size of papule - dried in.</u>
J.M.	2 mm.	3.5 mm.
P.H.	-	3 "
G.K.	-	4 "
M.J.	X faintly.	4 "

A.B. Complete quanti-reactions were done on both arms with same tuberculin, one had excess wiped off in 10 minutes and the other was allowed to dry.

4 mm.	7.5 mm.
2 "	6.5 "
? "	5 "
-	4 "

Obviously for general application of the

tests, it is essential to allow each to dry in, otherwise, the dosage would be entirely incomparable.

Somewhat irrelevant experiments.

Experiments to test the nerve influence in papule formation: We have already noticed the effect of tissue density, and though these tests are scarcely pertinent here it seems reasonable to introduce them since here the patient is being discussed. Crowe³ performed some tests with eucaine dissolved in tuberculin and was convinced that the nerve end plays some part in the reaction. Other factors being identical, some tuberculin was diluted with diluent containing about 2% eucaine and corresponding strength with ordinary saline and carbolic. Corresponding parts of the arms were used with the following results:-

	<u>Size of papule</u> <u>P.T. without eucaine.</u>		<u>Size of papule</u> <u>P.T. with 2% eucaine.</u>	
W.K.	6	mm.	No papule - redness.	
J.E.	8	"	5 mm.	
L.H.	9	"	4 "	
F.B.	4	"	No papule - redness.	
M.M. 24 hrs.	4	"	negative	
48 "	X		Redness marked.	
M.B.	X		Negative.	
B.M. 24 hrs.	3	"	Negative.	
72 "	-		X	

Those giving only one measurement presented nothing of interest. The results would suggest that either eucaine harms the tuberculin, or else nerve in-

fluence plays a definite role in papule formation; where sensitiveness - decided by Q.R. and not size of papule - is not very high, suspension of nerve action obliterates or at least reduces and delays the response, the delay apparently representing the destruction of the eucaine. As indicated previously, the interpretation is vague. One proposes, when opportunity offers, to perform the reaction on a case with a suitable nerve lesion, though there will also be a fallacy here.

Some experiments were done with reference to the effect of salt concentration: hyper - iso - and hypo-tonic solutions were used, the results seemed too irregular to be arranged with apparent significance.

Before leaving the question of technique it should be strongly emphasized that in those children where the sensitiveness does not reach a certain standard - roughly 100 - the test should be repeated in about 4 days. If on the second attempt the above standard is not reached, further investigation is not necessary, as will be seen later.

A dressing is not required, but it is necessary to see that the child does not wash his or her arms for 2 days.

In conclusion, it is scarcely necessary to labour the obvious character of the facts dealt with under technique, perhaps it should be remarked that it is advisable to keep the scarifications as near the elbow as possible. The question of glycerine content need hardly be considered, since the difference in

ordinary practice is much less than in the above experiments, except in cases where the skin is hard and dense, then it seems justifiable to balance the results by adding .5 mm to the size of the less favoured papules representing 4% and 1% tuberculin. I do not think it likely that a greater glycerine content content would ever convert a negative into a positive reaction.

III. NATURE OF REACTIONS FROM CLINICAL STANDPOINT,
AND THEIR INTERPRETATIONS.

One approaches the subject of tuberculin reactions with a justifiable deference. This is scarcely the place to discuss the pros and cons of any theory, except in so far as they are clinically pertinent; for the elucidation of the intricate phenomena which would seem to be involved is essentially the work of the pathologist, besides, any explanation of this phase of tuberculosis is so far more or less hypothetical. Looked at from the clinical standpoint it is a little difficult to explain findings in terms of either a lysin or an antituberculin - of the nature of an amboceptor - theory. There are many advocates for and against both these suggestions, still they represent the great majority of opinions held on the mechanism of reactionary conditions. Von Pirquet attempted to bring his theory with regard to serum disease into the realm of tuberculosis, and thus explain the reaction as the result of the albumen meeting its anti-body in the skin. Wolff-Eisner thinks such a combination would be unlikely to act as an irritant.

A similar objection might be raised to Wassermann and Bruck's ⁴ theory, when they assert that tuberculin associates itself with anti-tuberculin in the foci and fixation of complement results, the complement then seemingly produces "liquefaction of the tubercular tissue". It is difficult to see why this process should not be continuous, and besides, it again

is assuming the satisfaction of chemical affinities as an irritant.

5
Wolff-Eisner's experiments regarding "anti-tuberculin" seemed to discredit that substance as an activator of tuberculin. He preferred to regard antituberculin as a specific lysin which breaks up the tuberculin molecule, into substances of higher toxicity, by a digestive process, otherwise, tuberculin is a fairly harmless toxin. It would, therefore, appear that sensitiveness is bound up in the presence of this tuberculino-lysin. The sensitive organism owes its sensitiveness to the presence of this lytic substance, whilst the non-sensitive is lethargic because of its absence, or presence only in small amount. Riveire and Morland⁶ explain local reactions on this theory as the result of lysin meeting tuberculin at the site of inoculation and thus becoming activated. If the tuberculin be in sufficient quantity the toxin as it circulates becomes lysinized and may produce a general reaction; lysinized tuberculin by irritation, they hold, produces the focal reaction.

On this theory one readily understands how sensitiveness could be a protection in dealing with tubercle bacilli, but when one comes to consider its relation to fragmentary bacilli or tuberculin the case is reversed, the lysins may be useful in "policing" the body and destroying wandering bacilli, but what protection have we against the liberated poison?

Without assuming an ^{*}antitoxin it is difficult
* The term is used in the literal sense.

to explain many of the phenomena relating to cutaneous reactions. Given the lysin a local reaction would seem to be inevitable were there not some anti-body which established tolerance in the tissues. Wolff-⁷Eisner would not seem to favour the presence of an anti-body producing tolerance, for, regarding the interpretation of negative cutaneous reactions he writes - "A negative result indicates that the body is no longer capable of counteracting the toxins of the tubercle bacillus and therefore has to be interpreted unfavourably from a prognostical point of view". Still, he admits that a considerable number of cases giving first a negative result to cutaneous inoculation, on a second attempt will give a positive reaction. In my own cases about 22% gave a reaction above 100 in patients who previously gave a negative response or sensitiveness below 40.

Having made a very short survey of the present attitude towards reactions in general, let us discuss the characteristics of the cutaneous reaction and see whether the above standpoint falls in with the findings.

There is justification for the conception that in tuberculin, and even dialysates of tuberculin, there are ultramicroscopic particles which represent fragments of the bodies of tubercle bacilli, and therefore, qualitatively speaking, there is no essential difference between tubercle toxin and the bacillus itself. This is the standpoint taken up by the majority

of authorities to-day, including Jadassohn and Wolff-Eisner. Hence in tuberculin we are dealing with a tubercular infection which is not capable of a sustained offensive since propagation is impossible.

The outcome of this temporary cutaneous infection is in favourable circumstances, a so-called reaction, which under investigation reveals itself as tubercular disease; this assertion has been doubted by some authors, e.g., Bandler and Kreibich; though they found accumulation of lymphocytes, the giant-cells discovered were not of the Langhans type, hence these investigators referred to the papules as "tuberculosis-like formations". Daels was able to prove the presence of the true Langhan's cells and thus establish the cutaneous papule as a localized tubercular disease. Much discussion centres round the significance of these giant-cells; whether they are a product of a slow bacteriolytic process or not scarcely concerns us here, the point of importance is that tuberculin is a potential infection and its reaction is a localized tuberculosis. Of course there are many degrees of papule formation, and its development presents many variations which will be dealt with later.

An average positive reaction has an incubation period of about 12 to 24 hours. At first, i.e., after the hyperaemia produced by scarification, a reddened area appears with some degree of exudation adjacent to the scar margin, this gradually spreads and becomes more elevated, in its growth it preserves a reasonable regularity and definition, there is usual-

ly a zone of congestion surrounding the papule. When development is fairly complete it is, with a little practice, easy to define the papule. This maturity is, on the average, attained in about 48 hours. The papule margin is mostly circular, sometimes it is irregular. Vesication is rare. When the reaction is not so pronounced some difficulty is experienced in measuring, but usually, it is possible to attain fair accuracy, should confusion arise with regard to traumatic reactions, a control will partly obviate the difficulty - a papule may be a compound tuberculin and traumatic reaction. There is a slight pink tinge about a true reaction which is fairly distinctive.

Many terms are used to describe cases which show variations from the above course. The latent period exceeds 24 hours giving a "late" reaction or may be "torpid". Again some cases develop and disappear in a few hours. ^(Ephemeral) In advanced disease the response is often weak and is interpreted by the sense of touch, colourisation being faint, such are regarded as "cachectic" reactions. Then there is the "scrofulous" reaction which reveals a papule surrounded by small warty nodules. What the true significance of such changes is presents many difficulties in explaining.

The reaction, when its maximum growth is reached, soon starts to decrease, the hyperaemia fades and by degrees passes into an indifferent violet pigmentation which lasts for a very varying time - anything from a few days to three months. Soon after devolution sets in there follows peeling of the epidermis.

Extraordinary differences are exhibited in the life cycle of reactions, some are very shortlived, others are very prolonged, fluctuations are seen in development before the healing process starts, etc. etc.

It must be evident that difficulties will soon arise if an attempt is made to explain these differences of response in different cases on either of the popular theories, e.g., an ephemeral reaction would have to be regarded as a low power on the part of the tissues to defend themselves and therefore of bad prognosis. Clinically the reverse is the case. Incubation period of reactions might be discussed on similar lines (see later). One then asks what is the significance of these variations and is it possible to support any explanation that may be adduced? To answer such a question would seem to demand some fuller interpretation of the nature of a tuberculin reaction. To determine, in some way, how a reaction may be influenced, seems to me to produce applicable evidence of the forces likely to be at work primarily, and thus perhaps reach some explanation which would appear justifiable.

EXPERIMENTS.

The first line of investigation consisted in taking a boy who had been negative to the quanti-reaction. Two weeks after performing the test, the patient was injected subcutaneously with .001 P.T., simultaneously tuberculin was applied in the usual way

to the forearms. After several trials in different cases a definite focal reaction was produced by the injected toxin, practically pari-passu with the reactionary phenomena papules developed on the arms. Papules sometimes developed without focal results. After 4 weeks again, the same case gave no response to cutaneous inoculations. Similar results were obtained in other cases. Cutaneous testing was also performed on the earliest evidence of a general reaction and invariably the incubation period was short. A repetition in 6 days showed a pronounced diminution in sensitiveness, which is contrary to the usual result of subsequent tests in cases untampered with.

Next, cases which presented no sensitiveness on the first investigation were given "sensitizing" doses of P.T. - not enough to produce any response - and re-tested cutaneously. Some were positive and some negative. When it is remembered that $2\frac{1}{2}\%$ of cases untampered with, turn positive on the second trial (see diagnostic use of this test later) it is difficult to put much weight on these experiments unless a large number was done and percentages worked out, which it was quite impossible to do under the circumstances.

It seemed though that the experiment could be turned to more direct account, if, after 3 days no papules presented themselves, a small dose of tuberculin was given and the arms closely watched for any response that might develop. There was no doubt that such administration of tuberculin induced a positive

reaction in many previously negative cases. This influence was signally demonstrated in several of the cases which originally reacted cutaneously, or had failed to react on one investigation, and later treated with tuberculin therapeutically: if a general reaction occurred, in many cases it manifested itself on the arms by initiating a response in those previously non-sensitive, and by re-awakening previous papule formation, amongst the latter one can record a girl of 14 years of age who 7 weeks after the quanti-reaction was performed developed a fairly marked reaction to therapeutic tuberculin and also a renewal of her cutaneous response; papule formation was very vague but there was marked hyperaemia.

It was now a matter of interest to determine whether a negative response could be converted into a positive without the introduction of prepared toxin from without. To this end children, whose arms manifested no change after 3 days, were put to mopping the concrete verandahs; this work was, of course, rather beyond the ability of a child under 14 years of age; they were asked to exert themselves for a considerable period. In several of the children it was possible by this means to induce a positive result, apparently the result of auto-intoxication.

These experiments appear to me to go a long way towards substantiating two points: firstly, that absorption from the skin is incomplete in many cases

for a considerable time, or else there is a histological change in the involved tissues which takes a considerable interval to become neutralized. The second point is that a cutaneous reaction is dependent on something more than lysin, for those cases in above investigation which we shall call positive, demonstrated that it was possible to induce evidence of toxæmia in patients, with a previous negative cutaneous response, if greater demands be made on the patient, i.e., under a greater offensive. It seems justifiable to regard the question of "tolerance" or some anti-mechanism as the deciding factor, it would appear not irrational to consider lysin as a constant in tubercular cases, for the toxic influence would apparently increase with the size of the dose, which in essence is assuming activation, indeed the same may be said of so-called healthy individuals.

If one be allowed to speak of some real anti-body then it will be possible to explain many of the phenomena arising in cutaneous experimentation, e.g., when a second quanti-reaction is positive where originally there was no result, we could argue that the toxin absorbed previously had to some extent neutralized the anti-body and in the midst of such diminished defences it was possible to establish, at the second attempt, a tubercular focus which is a positive reaction. It would also explain how the previous cutaneous inoculations, simultaneously with the second applications, (see necessity for repeating test in a case negative first time) developed corresponding reactions, whose

mensuration revealed usually rather lower sensitiveness than that given by the more recent test. Only in one case did I get a greater response. In a considerable number of cases papule formation was very indefinite at the old scars. On such a basis, it is readily understood how injected tuberculin uses up the body's defences and allows of local reactions.

⁶Wolff-Eisner only found this taking place when a general reaction resulted. He quoted Cohn, however, who observed definite influence after tuberculin injection without reactionary manifestations and this agrees with my own cases.

In this connection it is interesting to note ⁸that Krause asserts, on the basis of animal experimentation, that cutaneous hypersensitiveness is diminished or entirely obliterated during a general tuberculin reaction. In man, where infection is almost universal, one never found the result of general reactions to be anything but the reverse of this statement.

When it is remembered that the toxin is concentrated in cutaneous applications, it is easy to appreciate how a small amount of anti-body brought by body fluids could be overcome in that particular area, especially too, if one considers that neutralisation of defences goes on as a result of absorption from the scarifications. That such absorption does take place is revealed in the occasional occurrence of general reactions associated with quanti-reactions. In one boy the temperature was raised to 102.5^o usually the elevation is not above 100^o. On this line

of argument a late and torpid reaction would suggest either latent disease or disease of low activity where there is a considerable overplus of anti-toxin, "compensation" only breaking down eventually as the result of persistent attack at the spot and the undermining influence of the absorbed tuberculin. (See also the experiments on auto-intoxication) Such an explanation would meet the question of incubation period whether long or short. Whether lysin could be held responsible for this period, certainly for the variations in the period in different cases, is a matter open to doubt.

Such a lysin and "difference theory" would credit the therapeutic administration of tuberculin as a tolerance raising agent. It will explain, too, what no other assumption seems to me to do, viz: why it is that ^{a very favourable} ~~a good~~ case of tuberculosis will often give absolutely no response while a healthy individual will in the majority of cases. In my last 200 cases, 6 patients with very few signs or symptoms, and excellent prognosis, but having tubercle bacilli in the sputum, failed to give any cutaneous response though the test was performed twice as outlined previously. In the healthy it is not conceivable how a large overplus of antitoxin could be maintained and therefore by a fairly high concentration at one spot it is possible temporarily to overcome the comparatively low concentration of antibody and the tissue resistance.

Support for this conception seems to me to be afforded by the investigations of Pickert and

Lowenstein: they mixed the serum of a healthy individual with tuberculin and injected the mixture into that individual with the result that a reaction still occurred. They could not satisfy themselves that any neutralisation had taken place. Similar experiments, however, with favourable cases of tuberculosis, and patients treated by tuberculin revealed evidence of such neutralizing antitoxic substances being present. Reactions in the healthy, then, are the results of overcoming mainly a natural resistance by concentrated attacks over a longer or shorter period according to that resistance, whilst in the tubercular patient a reaction is the result of overcoming mainly an acquired resistance which may be great or small. The fact that reactivity increases with every year of life scarcely proves that the power to react is not innate in man.

On such a basis ephemeral reactions would have a good significance, instead of the reverse, since it indicates a high power in dealing with infection, and clinically this is borne out. The "cachectic" response is obviously an indication of lost resistance both natural and acquired.

Very few scrofulous reactions have been seen, and in these it was not possible to discover any determining factor.

From this discussion it would seem apparent that the phenomena associated with tubercular disease in children is most simply, and accurately, explained by a theory which recognises the existence of a true

antitoxin. Wolff-Eisner's lysin theory and Wassermann and Bruch's Antituberculin theory do not seem to me to afford any satisfactory interpretation for the problems dealt with. For practical purposes, therefore, I propose to accept a difference theory - difference between toxin and anti-toxin - as the most logical hypothesis on which to explain clinical manifestations.

INTERPRETATIONS OF CUTANEOUS REACTIONS.

Having arrived at a conclusion as to the nature of a cutaneous reaction, it is permissible to discuss the question of interpretation. This can be done under two headings: (1) The significance of negative and positive reactions (2) The significance of the characters of a positive reaction.

The significance of negative and positive reactions.

From the preceding investigation, in conjunction with clinical findings, there seems justification for the following interpretations of a negative response.

1. The case is too advanced to show any power of reaction, the tissues being already poisoned. Natural and acquired resistance have ceased.
2. Tuberculosis present, but the power to react suspended by some intercurrent or associated malady, e.g., measles, whooping cough, mixed infections, etc.
3. Tuberculosis present, but the reaction averted by imperfect technique.
4. Tuberculosis present, but the patients'

defences are so high that it is impossible to establish a tubercular focus in the cutaneous tissues.

5. Negligible tubercular infection and high natural resistance to the tubercular toxin.

On the other hand, a positive reaction should be regarded as an indication of the susceptibility of the organism to the poisonous products of the tubercle bacillus; the sensitiveness in each case being a fair indication of the degree of susceptibility. In our present state of knowledge sensitiveness is founded on preliminary infection. Whether this be ultimately true or not is of little clinical import, the significant point being that reactions to moderate dilutions of tuberculin indicate previous acquaintances with the tubercle bacillus.

Significance of the characters of a positive reaction

It is difficult to classify the forms of reaction under any very comprehensive system. That adopted above, which recognises ordinary, late and torpid (it is only confusing things to separate these), ephemeral, cachectic and scrofulous reactions, though indicating salient features in each case by no means defines or includes all the characters. A late and ordinary response may both be very prolonged, the former usually tends to be slow in disappearing, and the latter occasionally presents a similar tendency. The significance, however, would not appear to be the same in the both cases, for clinically, a late reaction associates itself with conditions apparently not very acute, and where it might be supposed the defensive

mechanism is somewhat obsolete; whereas a prolonged ordinary reaction would seem to suggest that the struggle between the tissues and the infection is rather undecided.

To lend some support to this conception one performed the test on cases who had seemingly done well on tuberculin treatment. In the majority of cases there was a diminution of sensitiveness, but the striking feature about these tests was the short duration of the reaction; some of them had quite gone in 36 hours. On this basis the ephemeral reaction would indicate a high power of dealing with the infection, as suggested above.

Besides this support, those experiments, dealing with the effect of tuberculin injections, auto-intoxication, etc., which showed that the cutaneous papule was markedly influenced by the relationship existing between the diseases and the organism, were pertinent; when the former predominated, e.g., during a general reaction the skin response was intensified or reawakened. Such local change disappeared as soon as the tissues again mastered the general toxæmia.

The question of sensitiveness is best discussed under diagnosis.

9

A recent article on this subject of cutaneous reactions rather tended to repudiate the method of measurement, and urged direct information from the application of high dilutions. The disadvantages of the latter course have been indicated; and it seems to me to have no advantage since experiment confirms,

in a surprising manner almost, the accuracy of the Ellermann and Erlandsen method, i.e., when the method one has worked out is adopted. This was easily done by simultaneously applying, besides the usual dilutions, .008 and .006 etc., and comparing the results of direct and indirect investigations. The same author emphasised the significance of area, colour, elevation, disappearance of cut marks etc.

Area - This factor is often misleading, there is a natural tendency to regard a well-marked exudation or infiltration (it is not possible to differentiate clinically between the two) as evidence of sensitiveness or hypersensitiveness, and therefore of diagnostic value. It has already been shown that the area is greatly influenced by the laxity or density of the tissue inoculated. Apart from this, the quantireaction demonstrates beyond doubt that such an interpretation is unwarranted, e.g., the series of papules may run in either of the following ways: 12, 9, 5.5, 2 or 12, 7.5, 2 m.m. (a true arithmetical progression is not always attained).

Here are two cases whose top papules are large yet the former is well above 100 in sensitiveness (247), while the latter is well below that mark (71). The question of sensitiveness is bound up mainly in the difference between the papules.

Colour - I am afraid I failed to associate any particular clinical picture with the different shades of colour. There was no doubt that the complexion of the patient had an influence. The haemo-

globin percentage of the blood in each case was investigated using a Tallqvist scale - again there was no doubt that the strength of haemoglobin in the blood was a potent factor in determining the colour of the reaction. As far as it was possible analogous cases, from the standpoint of blood and complexion, were compared. In such cases there appeared a strong similarity. There may be other factors at work, but at the moment one is inclined to disregard shades of colouring, except in so far as it may indicate anaemia whose prognostic significance is not a matter for ^{consideration} here. Besides it is really a prognostic point.

The time taken by the scarification to heal is sometimes helpful in deciding an indefinite reaction, delay signifying a positive response.

Elevation always seemed more marked towards the wrist than in the region of the elbow, when the same strengths of tuberculin were used, so here again one felt justified in regarding tissue density as the causative factor: limiting and concentrating the offensive.

IV. THE PROGNOSTIC SIGNIFICANCE - under heading III a good deal has been discussed that pertains to this point. Considering the primary object of the present work one thinks this is best left out.

V. THE THERAPEUTIC SIGNIFICANCE - It is also inappropriate to record the findings on this question

here. The line of work consisted in trying to arrange an initial tuberculin dosage on the basis of sensitiveness and also investigating the result of tuberculin administration firstly on the sensitive and secondly on the relatively insensitive.

VI. THE DIAGNOSTIC VALUE OF THE TEST -

Though the prognostic and therapeutic utility of the quanti-cutaneous reaction is of great value, its usefulness depends principally on its diagnostic application. Most of the points pertaining to the test have been considered. The technique, tuberculin, and patient have been studied, which involved a clinical view of the nature of a reaction and also the interpretations which seemed justifiable from that standpoint.

That a healthy man, in the ordinary sense of the term, may react to cutaneous inoculation is beyond dispute, and therefore for practical use some method of differentiation must be instituted; it is here the question of sensitiveness or hyper-sensitiveness comes in. The healthy man will not react to anything but the higher strengths, whilst in the tubercular patient much greater dilutions will elicit positive results. Among the healthy, Bandler and Kreibich obtained 38 positive results out of 62 cases. An explanation of this fact has been put forward. It now remains to work out some line of demarcation, which will stand clinical testing. Opinions are many and varied, regarding the significance of hypersensitiveness both diagnostically and prognostically. Wolff-Eisner

considers two forms of reaction under the heading of hypersensitiveness - (1) The ephemeral reaction (2) The rapid and strong reaction. From the viewpoint of the quanti-reaction, it is better to regard those cases indicating a reactionary power against very high dilutions as hypersensitive; we have seen that an intense reaction does not necessarily mean hypersensitiveness in this sense. The ephemeral reaction, usually of low intensity, has been dealt with.

This capacity of the body to respond even to very high dilutions seemed to me to be associated with two clinical conditions: (1) A recent case with good general condition (2) An older case with evidence of exacerbation at the time of testing. This is quite in keeping with a difference theory of reaction. In the former case defences have not been established yet, neither have the tissues been materially poisoned. In the latter the interpretation finds justification in the conduct of the organism during a general reaction which is really a temporary exacerbation. Prognosis on this basis is obviously open to refutation; the findings only signify battle, but not victory, and consequently the issue may be defeat, still it does indicate that defeat has not taken place so far.

When it is agreed that battle is taking place it is assuming that the disease is active and hence the obvious diagnostic value of the test. The intermediate degrees of sensitiveness have a relative significance. The decision as regards the point at

which the reaction no longer indicates battle between the body and its infection is essentially somewhat arbitrary, still, it is possible to establish a practical basis. Morland suggests 100¹⁰ and above as indicating active disease. Some American authorities consider it necessary to regard cases as negative, only if their sensitiveness is below 40. This is scarcely a point to quarrel over as will be seen from the cases recorded below - performing the test in the manner outlined above, i.e., repeating every case below 100, very few patients are left in the "no man's land" between 40 and 100. There is no doubt that the reactive capacity of the body is materially altered by a reaction performed not more than 7 - 10 days previously. This change would appear to be a question of degree, and therefore, what interpretation one should give to the amount of alteration as revealed by the second quanti-reaction is difficult to say. Cohn, in his observation on the ophthalmic reaction, inclined to the belief that such an increase of sensibility only occurs in cases of actual tuberculosis. The cutaneous is a more sensitive test, and perhaps variations which do not carry the result to or beyond 100 may be disregarded in dealing with children, unless, there is other evidence to establish the diagnosis, and explain the default of the quanti-reaction.

Before recording results it should be pointed out that over 300 experiments were done to decide the type of tuberculin to use. We have seen the advisability of using both types. A strange feature

about this is, that if I were only to use one type that would be bovine. Contrast this with Paget Lapage, Macneil, etc. The former found bovine positive in only 4% that failed to react to human, whereas 13.5% showed a reverse result; the latter did not have a single case reacting to bovine and not to human.

The next step consisted in performing three or four hundred experiments on technique, nature of reaction, etc.

When it seemed possible to avert many of the discrepancies that tend to arise, about 60 cases were investigated to test the reliability of the experimental findings, and also to perfect the method of working. On such a foundation the following results were obtained:-

Analysis of Cases - after the above preliminaries.

Total number of Cases dealt with	231
Twice ^{Twice} negative or below 40	63
First below 40 and then between 40 and 100.	4.
First below 40 and then 100 or above	19
Cases below 100 and not repeated for various reasons.	34
100 or above first time or on repetition.	130*

*Cases above 100 first time
Cases between 40 and 100 first time
Cases below 40 first time.

It was not considered of any importance to record those cases separately which on the first attempt gave a sensitiveness between 40 and 100, and on the second performance of the test rose to 100 or

above. The only immediate interest of these cases is to ^{Emphasise} ~~urge~~ the necessity of performing the test twice.

Of the 34 cases not repeated the majority were children sent in for two weeks for observation purposes. Most were sent or taken home before I had time to repeat their test.

Comparing the results of those completely investigated the appended tables were obtained. Some cases of course fell out before corroborative evidence was satisfactorily established, and these had to be discarded e.g., developed intercurrent maladies necessitating removal from the Sanatorium etc. Again the excessive pressure of work compelled me to investigate only 50 consecutive positive cases, besides, I could not have obtained many more, for naturally the Sanatorium stay was prolonged and so the state on discharge could not be obtained. Observation was only regarded as complete when the child was voluntarily discharged from the Sanatorium. Some difficulty was experienced in drawing up these tables, still I hope their lucidity will not suffer.

It should be indicated here, that my Chief - Dr. G.B. Dixon - whose encouragement and assistance have been invaluable in investigating these 214 cases, was good enough to bring to my aid his expert clinical knowledge and in many ways make my work more useful. Though already overworked, he undertook the large majority of clinical examinations on discharge, and also of cases presenting difficulties to myself on admis-

sion. Thus any element of bias was removed.

Again to ensure that no influence, conscious or unconscious, should express itself in the records, Dr. A.G. Campbell, my colleague, shared the work of collecting the facts. Every case was studied by him, and in no instance did I override his decision. All problematical points were regarded as negative.

Clinical examination was divided into three headings. It should be emphasised that a large number of the patients dealt with were admitted as observation cases; they all had something pointing to chest involvement, but great difficulty was experienced in deciding the nature of the condition by ordinary exploration. The headings therefore were:

(1) Definite: cases with persistent moisture after cough and evidence of infiltration. (2) Suggestive:- localized affections revealing themselves by rhonchi or occasional rales and not monotonously persistent, but not entirely clearing up with cough; and impaired breath sounds. (3) Indefinite:- any generalised condition with shifting signs, or shifting basal signs both lungs. Also evidence of hilus tuberculosis, or quiescent disease.

With reference to the "state on discharge" active signs mean "definite" as above and also "suggestive" which remained stationary and "indefinite" in those basal cases which persisted throughout. No active signs (N.A.S.) has the usual significance. Indefinite represents intermediate conditions.

A positive quanti-reaction means a case

giving a sensitiveness of 100 or above. A negative means below 40 on repetition of test. Ephemeral has the usual significance.

Each table is worked around one common fact or condition. Though it at first appears complicated an attempt is made to associate facts as obtained and thus one sees how far each method of examination supports or condemns the others. The state on discharge is regarded ^{as} of great value in deciding the nature of the disease present on admission, those clearing up were probably not tubercular.

TABLE I.

48 CASES WITH QUANTI-REACTION NEGATIVE TWICE OR BELOW 40
ON REPETITION.

Clinical Examination on admission.		State on Discharge.		Subcutaneous Test & T.B. +
DEFINITE	11.	No active signs	9	Only 10 questionable cases tested Subcutaneously all were negative as regards focal reaction.
		Indefinite	-	
		Active signs	2. (Bad prognosis)	
SUGGESTIVE.	11	No active signs.	9	On admission two cases had T.B. in sputum
		Indefinite	2	
		Active signs.	-	
INDEFINITE.	26	No active signs	20	Without symptoms or definite signs but regarded as active because T.B. positive.
		Indefinite	4	
		Active signs	2	
TOTALS	48 Cases.	No active signs	38	
		Indefinite	6	
		Active signs	4	
IN PERCENTAGES	80%	of above discharged with no active signs.		
	12%	" " " indefinite "		
	8%	" " " active "		

See foot-note over-leaf.

This is a most instructive Table for it teaches one that observation over a few weeks gives strong support to the value of ordinary physical methods of examination in conjunction with the quantitative reaction performed in the manner I have indicated. Out of 48 patients 4 were established within a week of admission as definite cases from sputum investigation etc. The remainder were never decided as tubercular. 38 were to all intents negative and 6 were vague, no evidence being adduced to establish them as tubercular.

The 9 cases which presented no active signs on discharge, though "definite" on admission, were probably not produced by the tubercle bacillus. At any rate, treatment was not urgently indicated in sanatorium

T A B L E II

50 CASES DIAGNOSED POSITIVELY BY RADIOSCOPIC EXAMINATION.

Clinical Examination on Admission.		Quantitative Reaction.		Subcutaneous Test or T.B.†
DEFINITE	16	Positive Ephemeral Negative	11 0 5	Only 4 cases, negative to the quanti-reaction, were tested subcutaneously - all were negative as regards focal reaction.
SUGGESTIVE	10	Positive Ephemeral Negative	2 3 8	
INDEFINITE	24	Positive Ephemeral Negative	2 2 20	

† No cases with T.B. + in this Table.

TOTALS 50 Cases.

Positive Reaction	21	42% of above were positive to Quanti-reaction
Ephemeral "	2	54% " " negative "
Negative	27	4% " " indefinite (Ephemeral) to Quanti-reaction.
Positive	32%	of above were definite to physical examination.
Ephemeral	20%	" " suggestive "
Negative	48%	" " indefinite "

IN PERCENTAGES.

See foot-note over-leaf.

In this Table I did not record the state on discharge except where it was absolutely necessary. It will be noticed that Clinical Examinations and quanti-reactions associate themselves and the results of prolonged observation support this association, for it was only possible to establish 22 of these cases to be ^{pulmonary} tuberculosis, i.e. 44%, which leaves an error of 56% to radioscopic investigation.

TABLE III.

This is scarcely a Table, and it is not of great value. 10 children, apart from those already referred to, who had given a negative response on two occasions were subjected to the subcutaneous test with the result that 3 reacted positively from the point of view of general and local reactions; 1 case gave a focal. The majority had a general reaction. On discharge one of these 10, viz: that showing a focal response still presented signs. On the theory already discussed, it is quite feasible that the subcutaneous test should react positively where the quanti-cutaneous gave a negative result. The former test is very unreliable in children owing to the difficulty of finding a focal change even if present; certainly general and to a less extent local reactions are unreliable as diagnostic features. Besides, the method is not particularly commendable. The one case which was positive above continued positive to cutan-

eous inoculations; the others relapsed into their previous irresponsive state.

The 4 cases giving sensitiveness between 40 and 100 could have no significance under any circumstances as the number is so small. It was difficult to decide their real conditions as physical signs were vague, and consent for tuberculin injection not obtained.

T A B L E IV.

50 CASES WITH QUANTI-REACTION 100 OR ABOVE.

		State later or on Discharge.		Subcutaneous Test & T.B.								
DEFINITE	29	No active signs. 0 Indefinite 5 Active signs 24	{ Signs cleared up after about 12 wks.	Only one subcutaneous test done, this was positive as regards focal reaction.								
	SUGGESTIVE	8	{ 1 Surgical Tuberculosis 0 1 X-Ray positive. Active Signs 6									
		13	{ 1 Surgical Tuberculosis 3 1 T.B. + Active signs 7 1 Sub-cutaneous test +		4 cases had T.B. in sputum.							
<u>TOTALS</u>	50 Cases.	Active signs on admission or later 42 Indefinite 3 No active signs 5		<table style="margin-left: 20px;"> <tr> <td>1</td> <td>had T.B. in sputum</td> </tr> <tr> <td>2</td> <td>Surgical Tuberculosis</td> </tr> <tr> <td>1</td> <td>X-Ray positive</td> </tr> <tr> <td>1</td> <td>subcutaneous test +</td> </tr> </table>	1	had T.B. in sputum	2	Surgical Tuberculosis	1	X-Ray positive	1	subcutaneous test +
1	had T.B. in sputum											
2	Surgical Tuberculosis											
1	X-Ray positive											
1	subcutaneous test +											

IN PERCENTAGES.

84% of above showed definite signs during observation.
 10% " " accounted for by T.B ; Surgical Tuberculosis, X-Ray, & subcut. Test.
 6% " " remained indefinite - no subcut. Test or Radioscopic Examination done.

See foot-note overleaf.

Here again it will be seen that clinical examination over a prolonged period will establish in the majority of cases the reliability of the quanti-cutaneous reaction.

It must not be argued that since clinical examination and cutaneous reactions run practically parallel there is no need for the latter. The physical examinations were repeated many times and over a considerable period of time, in making a diagnosis such a tardy procedure cannot be acceptable. Hence the great value of the cutaneous test.

At first one intended to arrange a table round definite physical examinations but that would have meant a good deal of over-lapping, which was avoided with one or two exceptions and these exceptions were inevitable. *(the question of definite physical examinations)* Besides, this fact ^{is} involved in above tables.

A close study of these tables will reveal that in children the most accurate guide to diagnosis is the quanti-cutaneous reaction, the dividing line, for the moment, between positive and negative results being 100 since none of my cases proved the contrary.

It will be noted in Table 1, that 3 cases with tubercle bacilli in sputum are included, the resistance in each case was good and symptom^{at}ology slight, and hence the result due to high acquired resistance or tolerance. Of course it is possible despite the

prognosis suggested, that the final issue will be bad, and hence it would really be a case of lost resistance.

It is noteworthy how the signs cleared up, and many of these cases only stopped^a short while in the Sanatorium; contrasting this with the positive cases in Table IV and the persistence of signs over a much longer period lends strong evidence to the reliability of the quanti-reaction.

In Table II it is evident that the cutaneous reaction and physical examination, on the whole, range themselves together, and judged on this basis the X-Ray diagnosis leaves a too considerable margin of error. Subcutaneous tests, where done, corroborated this conclusion. Dr. Lapage¹¹ found closer relationship between X-Ray and cutaneous tests; this may be accounted for by two facts: (1) The association of a clinician and radiographer at the radiosopic examination (2) He did not do quanti-reactions.

Table IV is most instructive and points to the fact that persistent examinations will establish in most cases, the accuracy of the original cutaneous finding. Some of these cases were done twice before they were positive; it would have been too complicated to indulge in further sub-division of the statistics to bring out the differences associated if any. It is scarcely necessary to record that the cutaneous test does not tell what organ or organs is affected, this point can be decided by symptoms and signs as elicited by the physician. The margin of error in

cutaneous tests is so slight that one wonders if there is not justification for extending the confidence established in 94% of cases to the remaining 6%. Without asking so much one feels justified in adopting the conclusions in the summary below.

SUMMARY AND CONCLUSIONS.

- (1) In Birmingham children do not react equally to both types of tuberculin.
- (2) In performing the Quantitative Cutaneous Reaction the following points must be remembered:
 - (a) Use both types of tuberculin.
 - (b) Reactions too near the wrist are handicapped by the density of the cutaneous tissue.
 - (c) Scarifications require to be as near as possible of the same size.
 - (d) Deep-bleeding scars, or superficial where blood is universally distributed over the surface impairs the papule formation.
 - (e) Drops of tuberculin should be about the same size.
 - (f) The low glycerine content of the high dilutions of tuberculin slightly impairs the final result. In practice this point can be ignored as the difference is slight.
 - (g) The power of absorption varies markedly in different cases and in different sites of the same case. Again, atmospheric temperature influences absorption.
 - (h) The only method of ensuring accurate and comparable results is to use a moderately small drop and allow this to dry, in every case.
 - (i) If the first reaction is below 100, repeat the test in about 4 days.

(3) Observing the points indicated above it is surprising how irregularities etc. disappear, the papules show almost a true arithmetical progression.

(4) It is impossible to explain cutaneous reactions, in a manner which is supported clinically, by either Wolff-Eisner or Wassermann and Bruch theories. Experiment would indicate that the reaction depends rather on the patient's tolerance, regarding tolerance as a true antibody. On such a difference theory it is possible to make interpretations which are borne out in clinical practice. Whether a lysin should be recognised or not is impossible to say from this investigation.

(5) On a difference theory the quanti-reaction indicates the relationship existing between the patient and his or her infection. Since infection is so universal it is of great value to have a test which indicates that infection is present to the extent that treatment is demanded.

(6) In making a diagnosis of the cases dealt with, all points were considered, but investigation usually became centred round three methods of exploration viz. Physical Examination, Quanti-cutaneous testing and Radioscopic examinations. Correlation of the different tables, established on the basis of observation etc., proved that our most valuable weapon in diagnosis was the Quanti-cutaneous Reaction. Next came physical examination. Radioscopic investigation

presents too considerable a margin of error to be of great value in forming an opinion - these examinations were done by an expert too.

This order of merit is purely argumentative, for physical examination must be associated with cutaneous reactions in making a diagnosis. When these two are associated and other factors in the history ~~of~~ ^{and} symptoms are considered a standard of diagnosis is reached which will give eminently satisfactory results. Where reliable symptoms of chest involvement are got in conjunction with a positive reaction, even in the absence of signs, the present investigation would support a positive diagnosis of pulmonary tuberculosis being made.

(7) Treatment of children on any basis other than that of specific diagnosis involves a very important economic problem. It will be seen that children presenting definite signs, apart of course from those of overwhelming disease, whose cutaneous response was negative, proved in practically every instance to be non-tubercular. (See Table I).

With a very little judgement it is possible to decide those requiring treatment, a large number could be sent home, the remainder might be dealt with as suggested below. For some time Dr. G.B. Dixon has asserted that a large number of notified children are not consumptive, in the sense that sanatorium treatment is requisite. He suggests that a home should be established under a reliable nursing staff. At appro-

priate intervals an experienced doctor should visit the home and investigate the course taken by the disease present.

Such a course is entirely endorsed by the present work and the cutaneous reaction would be of immense value in alloting cases.

(8) From this lengthy investigation it might be thought that the quanti-reaction is a cumbersome test. As a matter of fact, the reverse is the case. One can perform 34 in the hour. Since for the present 100 is accepted as the limit of active disease .01 strength might be applied as a rough test and so measurement would be avoided. Of course applying .01 alone is not the same thing as doing the whole test and cannot have the same significance. It would take a lower dilution than this to equalise the 100 standard as arrived at by the quanti-reaction for in the latter there is the question of absorption from the stronger dilutions.

(9) What the value of the test would be in adults I cannot say. I should be inclined to regard its application as more limited than is the case with children.

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A CLINICAL STUDY OF PULMONARY TUBERCULOSIS
IN CHILDREN WITH SPECIAL REFERENCE TO BOVINE
AND HUMAN INFECTION.

In approaching the study of this subject from the clinical aspect many difficulties beset one. Firstly, it will be quite impossible to bring forth mathematical proofs for anything but still it has the great advantage of including the living patient and so information gained must be of greater practical value than can ever be drawn from animal experimentation.

To-day the pendulum of opinion swings with undoubted list in the direction of laboratory research, the result has been, with the exception of cardiology, a dwarfing effect on clinical investigation. One of the greatest advances in medicine was achieved when *or rather applied the discovery of,* Lister discovered ^{the} world of microbes; the great enthusiasts of that day were imbued with the idea that at last the secret of disease was revealed, to some extent this was true. Why then have the results been less satisfactory than expectations demanded? It seems to me to be partly accounted for by the attitude taken up towards the other side of the subject: clinical medicine became epitomised into a collection of signs and symptoms which was easy of manipulation, but whose interrelationships were imperfectly understood. To a certain extent research ignores the patient and tries to establish laws from a laboratory stand-point.

Indeed, the matter may be put shortly by asserting that disease can be explained by nothing less than all its history and associations.

The second difficulty arises from the essential complexity of the subject and the lack of agreement amongst pathologists upon the important points under discussion. It would be difficult to discover in any other realm of science such a vast panorama of conflicting evidence on any subject, as that which exists for and against the transmissibility and identity of human and bovine tuberculosis, and also the channels by which infection may reach the lung.

The attitude of Koch himself changed very markedly between 1882, when he discovered the tubercle bacillus, and 1901, when at the Tuberculosis Congress in London he acknowledged his error in previously holding human and bovine tuberculosis to be one and the same thing, and easy of transference between the different hosts. Now he asserted that radical differences existed between the two diseases, and that cattle were not amenable to human infection. Further, he argued that bovine bacilli rarely produced disease in man.

There was much evidence to refute Koch's early view. Virchow and his followers found great difficulty in producing a lesion in cattle by feeding them with material containing human infection, the same animals showed little resistance when the bovine virus supplanted human.

Koch's second assertion, though he had many followers, was on further experimentation deemed inaccurate, certainly as regards transmissibility.

The matter was thus very indefinite since eminent experts were quite opposed. Some, including Baumgarten, Smith, Whittla and others inclined to take a middle course and agree to certain points of similarity.

Unfortunately there is still no consensus of opinion on the frequency of transmission, or on the question of identity or channels of infection. Reference to opposed opinions and clearing the way for a clinical line of argument will involve a good deal of confusion. I hope the reader will be generous, for the task is difficult.

In 1901 the British Commission was appointed to unravel the skein. The investigations established that man was susceptible to both human and bovine infection but especially the former, the latter finding more victims amongst infants and children than in adults, though adults were not immune. Again, cattle, they found, could only be infected with difficulty when microbes were of human origin.

Contemporary and later observers found less difficulty in transmitting human disease to cattle, still, the experiments of Ravenel¹ are eminently pertinent: he found that cattle were highly susceptible to infection, even from a human source if the infection were proved bovine in character.

The results accruing from the clinical ^{section} ~~attribution~~ of the Imperial German commission did not strongly support bovine infectivity in man, for in the results it is reported, amongst other things, that in

151 children who drank uncooked tubercular milk, only two showed tuberculous glands and 14 cases were labeled as suspects.

These clinical findings in Germany are academically disappointing. Much of the work, it would seem, was done by proxy, and perhaps its shortcomings may be discounted on that head.

That bovine tuberculosis does result in human beings with greater frequency than this would suggest, we have undoubted proof. It seems possible that German statistics were influenced for some time by Koch's later views on the subject, founded, it is said, on the alleged rarity of primary intestinal tuberculosis. This fallacy was exploded by the researches of Fibiger and Jensen. Still the literature does not seem to suggest so marked an incidence of disease from bovine sources as exists in some parts of this country and America, e.g., in Germany, taking the work done in the laboratories of the Gesundheitsamt, Berlin, up to 1907 and Burckhardt (1910) the bovine infection in cervical glands removed by operation from children under 16 years of age only amounted to 35%, the remaining 65% being human.

In England* cases from the R.C.T. and those of A.S. Griffith under 16 years show 64% with bovine infection.

2

A.P. Mitchell of Edinburgh: Out of 72 cases operated on for cervical adenitis 90% proved of bovine origin. These were children under 12 yrs.

*Quoted from Cobbett.

Lewis in America: Out of 15 cases of cervical adenitis 9 showed bovine infection. In this investigation the subjects were much older than those of Mitchell, who were children. It confirms, though, what is more or less established now viz. that bovine bacilli show a marked predilection for young people. In Lewis' work the average age of animal infections was $8\frac{1}{2}$ yrs, whilst those of human infection gave an average age of $17\frac{2}{3}$ years. Taking these figures of Lewis - only those under 16 years and similarly those of Park and Krumwiede we get a bovine infection of cervical glands in 57% of cases. A fair amount of work might be quoted in support of the frequency of bovine tuberculosis in young people, but for present purposes the above is sufficient: The subject is summarised in the report of the Royal Commission 1901 referred to above.

Thus research in different countries has adduced sufficient proof of the intertransmissibility of bovine and human infection, each showing greater virulence in its natural abode; the human strain demonstrating marked ~~reticence~~ ^{reluctance} in adopting a foreign soil.

This question of transference is mainly a matter of Public Health import. Unfortunately transmissibility does not establish the identity of the two diseases, and this seems to me the pivot on which the clinical interest rests. If the sources of error be many in considering mutual infectivity, they would seem to be legion when it is attempted to interpret

identities; of necessity then, conclusions, whether experimentally or clinically founded, must be regarded as to some extent arbitrary.

Tuberculosis varies very considerably in different localities, and how far these variations can be accounted for by dissimilar types of infection would be interesting to determine. Professor Shennan⁴ points out that the death-rate in different towns and cities of Scotland is determined by factors as yet imperfectly understood, and not explicable by density of population, etc. In how far the "soil" i.e. the patient varies one cannot say, this is very unfortunate in that clinical findings cannot reliably be corroborated or refuted. In the pathological side of research this local disparity asserts itself, e.g., note the prevalence of thoracic and abdominal tubercular glands in Edinburgh 62.9 to 48.7 corroborated elsewhere by Still 81 to 59 Rillet and Barthez 79 to 46 &c. On the other hand in Manchester Lapage⁵ found the ratio to be 55 to 71. Again note the marked disparity of results recording the type of infection in cervical glands, in this connection note the predominance of bovine infection in Edinburgh and the low incidence of this type of virus in the German statistics quoted.

It is unfortunate that one cannot collect absolutely analogous statistics, in different districts, on the relationship of bovine to human infection in abdominal and thoracic glands. For the sake of future arguments it might be worth while to record the findings of Eastwood and Griffiths:⁶ 150 post -

mortem examinations of children aged 2 to 10 years, 94 of whom were tuberculous cases, indications suggested that in:

22 cases glands of alimentary tract invaded primarily.

52 cases glands of Respiratory tract invaded primarily,

22 inconclusive.

Those entering by the Alimentary tract showed great predominance of bovine injection, whereas in the respiratory infections only one showed the bovine bacillus. Allowing for the inconclusive cases one can definitely accept the trend of such results as indicating a strong predilection for bovine infection by the Alimentary tract and human infection by the respiratory passages.

Numerous writers, unwilling to accept the prevalence of bovine tuberculosis in this country, point out that the death-rate from tuberculosis in children is greater in those countries where dairy products are not used as food at all, e.g., Sweden, Roumania, Greenland, China, etc. This argument is two-edged and brings out the point which I have hinted at, viz: bovine tuberculosis is a less fatal disease than human. This is supported by many observers and accepted by the Royal Commission above referred to.

The question now arises is this lower virulence simply a difference of degree or of quality?

If one may accept, as many have done, that the difference between human and bovine bacilli is

merely one of degree, then the relative susceptibility exhibited by one animal should be supported by a similar relationship when a new host is chosen, especially, if an animal with moderate resistance to tuberculosis in general be chosen.

Discarding the question of difference between the two infections in the cow, and taking, firstly, the rabbit, which is not a highly resistant animal, it shows a pronounced susceptibility to bovine infection, whereas the resistance to the human type is generally speaking high. The dog, which is endowed with high resistance, shows about an equal sensibility to both types. The cat, again, a resistant animal, is only susceptible to bovine infection. At the other end of the scale animals like monkeys and guinea-pigs, whose powers of resistance are low, are affected about equally with both types. There is no evidence of a relative virulence in the above results.

Again the cultural characters of human and bovine bacilli differ materially.

In the light of present day knowledge, one must dissent from those who regard the two organisms as essentially similar, their characters are quite different.

As previously indicated in Part I, tubercle toxin is essentially the same as the tubercle bacillus, a true ~~Exo~~-toxin not having been established; tuberculin too is simply a suspension of fragments of the organism. This being so, and the bacilli presenting tangible differences of character, it is justifiable to regard the

toxins as dissimilar. Such is a fair deduction from the above reasoning.

METHOD OF RESEARCH: FOREWORD.

When one bears in mind the facts recorded, it appears to me justifiable to at least doubt the identity of bovine and human toxin, and consequently the identity of the two diseases.

It is universally accepted that the cutaneous tuberculin reaction is specific, but it is not established that the different infections only respond to their own type of tuberculin, indeed, for all practical purposes, it is accepted that either infection will react to both bovine and human tuberculin. Such an attitude seems to me to lack foundation.

7

Referring again to Gauvain's work, which suggests that lesions react to both tuberculins, it must be indicated that the test ~~was~~ done on cases with breaking down surgical lesions. Such cases are scarcely analogous to pulmonary tuberculosis in children, where there is seldom evidence of such disintegration. Surgical tuberculosis is, in a general way, regarded by some to be bovine in origin (Raw), the fact of degeneration would suggest the presence of human infection as well. Indeed, in my own cases where such degeneration resulted, e.g., discharging glands, most reacted about equally to both types of tuberculin:

It may be recorded here that Lapage only found 4% that reacted to bovine and failed to respond to human tuberculin, whereas 13.5% showed a reverse

result. Macneill found no cases reacting to bovine that did not react to human. Somewhat similar results have been recorded by others, but the fallacy which appears to account for this is found in the use of too strong dilutions and the lack of proof on a quantitative basis. It is obvious that most individuals have an opportunity for attaining sufficient infection of either type to respond positively to such a sensitive test.

In Birmingham I was struck by the lack of similar response quantitatively to the different types of tuberculin. In the majority of cases children responded to pure or only slightly diluted tuberculin of both types, but the higher dilutions demonstrated a distinct difference. I found that .16 strength was often the limit of reactivity for the less sensitive response. This suggested to me that if I were to take .1 T and .1 P.T., with a control of saline between, I should obtain information that was fairly decisive; because, taking only negative and positive responses, and disregarding size, etc., it was possible to obtain a fair number of cases reacting to bovine alone, and to human alone. Now supposing the case is clinically tubercular, the fact of its reacting only to the bovine type is strong evidence suggesting its origin, - since by using even so strong tuberculin as .1 T. opportunity is given to a human lesion to assert itself. It must be seen then that I used this comparatively high strength so as to be fairly certain

that little chance existed of a double infection, and so results are more valuable. Of course it had the disadvantage of making the absolute diagnosis of cases more difficult.

It remained now to rule out possible sources of error.

The first question that arises is - Are results constant in the same patient? This one decided by applying the quanti-reaction. I was struck by the relative constancy of the results when a sufficient interval elapsed between the performances of the test and, of course, in the absence of tuberculin therapy and making due allowance for hygiene and dietary - all the children were in the Sanatorium.

Secondarily - Are P.T. and T. approximately the same strength? If the results depended on a difference in strength one should find a practically constant margin of difference when tested by the quanti-reaction. This was not so, even when the reactions were performed with tuberculins from the same two bottles and results compared; thus one excluded the possibility of variance from slight differences of standardisation. Again, the question of strength is ruled out by the occurrence of a higher sensitiveness in one case to human and in another to bovine when the identical same dilutions are used.

Part I of this work establishes the fact, with fair decision, that sensitiveness increased with the degree of activity, hence the positive response equals

the active disease.

Some support is lent to the argument that the toxins of both human and bovine tuberculin are different, and react specifically too, by the fact that after prolonged administration of bovine tuberculin, the sensitiveness to P.T. is lowered, whereas the sensitiveness to T. is not so much affected. I only had time to do a few cases on this question so I cannot dogmatise.

An apposite question here is that referring to the stability of type in the animal body, very many "passage" experiments have been undertaken with a view to establishing whether or not the human type, say, gains the characters of bovine bacilli by habitation, in the Cow. The results of these and similar experiments have not established any such change of character, though in some cases an apparent modification takes place. ⁸ Cobbett inclines to regard such instances as due "either to an admixture of two kinds of bacilli in the original virus or to a bovine bacillus creeping in through some accident during the course of the experiments."

If such a transformation took place, in all children above five years human infection would be present, the result of early bovine invasion, and hence one's results would be difficult to support; since it would not seem to take place, the fact that bovine tuberculosis is seldom present in adult life, must mean that the infection by bovine virus easily dies out, as mortality from this source is low. It seems to me just possible that bovine infection is more frequent

in adults than is generally believed. Creighton's suggestion that the lesion showed certain anatomical differences has not been supported by later observation. Cobbett⁸ writes: "Anatomical differences in the tuberculous lesions in man and the ox are not due to differences in the bacilli which imitate them but to differences in the animals which develop them." Pathologically, then, the bovine virus produces a proliferative lesion in cattle, but in man it would seem to take on the degenerative tendency of the human bacillus, evidence on this point is not abundant. The vast amount of proof in favour of adult tuberculosis being due to human infection, is derived from sputum examinations. Such a method of research cannot be representative, since a very considerable number of cases have no sputum; this very fact would suggest some difference in the type of lesion. In Birmingham the relative infrequency of sputum in female adult patients was noteworthy. Associate with this the low female death rate in this City (86, England and Wales - 100). It seems to me justifiable to think that possibly since bovine infection is less virulent in man that the clinical course would be in the majority of cases different, because, progress being slower there would be more time to establish defences, and degeneration and communication with the exterior would be less liable to occur. Another possible explanation will be seen later.

Again, post-mortem investigation of lung tissue cannot be representative because bovine is an admittedly

less fatal infection, consequently few cases come to the post-mortem table.

Indeed, the present attitude, which only allows the bovine tubercle bacillus a very small percentage of all cases of pulmonary tuberculosis may be said to be founded on the following tables for the most part.

※ TUBERCLE BACILLI FROM SPUTUM.

	<u>Total.</u>	<u>Human.</u>	<u>Bovine.</u>	<u>Mixed.</u>
A.S. Griffiths (R.C.T)	29.	27.	2	0.
A.S. Griffiths (London cases)	105.	105	0.	0.
A.S. Griffiths (Edinburgh cases)	43.	42	1	0.
Park & Krumwiede.	296.	296.	0.	0.
Bulloch	23.	23.	0.	0.

※ TUBERCLE BACILLI FROM LUNGS.

<u>Author.</u>	<u>Adults.</u>			<u>Children up to 12 years.</u>	
	<u>Human</u>	<u>Bovine</u>	<u>Mixed</u>	<u>Human</u>	<u>Bovine</u>
Royal Commission	12	0	0	1.	1.
Gesundheitsamt, Berlin.	7.	0.	0.	3.	0.
Eastwood & F. Griffiths.	-	-	-	4.	0
A.S. Griffiths.	-	-	-	3	0.

※ Quoted from Cobbett.

One discusses this question here lest the above tables should be instanced as refutation of my work. It is not applicable for the reasons I have

suggested, besides, it refers to adults mainly.

Thus the fact that pathological findings are said to be similar in both cases, does not necessarily mean that the clinical course is the same, besides research on this subject is not sufficient, it is quite possible that the terminal stages of bovine tuberculosis are effected by human infection. Of course an acute bovine lesion would likely be very similar.

The great point is that Clinical research seems to be necessary before the last word can reasonably be said. Though such research cannot possibly satisfy time-honoured "postulates" it still has in my opinion decided significance.

PROCEEDURE - The material used consisted of 302 cases whose ages varied from 5 to 14 years. All these children were under observation in the City Sanatorium, during the time one was working. Each case had a differential test done as indicated, viz: .1 T. next the elbow and .1 P.T. four or five inches below on forearm, between, was a control of normal saline. In the cases recorded the test was only done once; the results were carefully recorded, interpretations being made in accordance with the usual conceptions.

After completing Part I, there seemed justification for establishing the cutaneous reaction as a constant and specific basis around which to work investigation.

Two main problems presented themselves:-

- I. Was there a reasonable constancy in the Clinical picture associated with reactions to a particular type of tuberculin.
- II. If so, what deductions might logically be drawn from the results?

With these aims in view I drew up a table of investigation which consisted of the following:-

Name, and sex; Cutaneous Reaction; Age; Breast fed, bottle fed or both; Family History; Seat of Disease; General condition; Surgical Tuberculosis; Remarks.

Most of these headings are of obvious significance except perhaps the last three: "General condition" was recorded because of its influence on the Cutaneous reaction, apparent anomalies might be excluded by such knowledge. "Surgical Tuberculosis" again was recorded because it is obvious that the cutaneous reaction does not localise the site of the lesion, hence if found surgical conditions were tabled. Of course there were few of these; as a rule we only admitted medical cases. Under the heading of "Remarks" was put any fact of importance such as those establishing the diagnosis, etc. These three headings will not be discussed separately they are simply controlling factors which find expression in the results of the other headings.

TABLES OF RESULTS.

Total number of Cases	302.
Number of Boys	163.
Number of Girls	139.

CUTANEOUS REACTIONS: (+ positive; - negative)

Number of cases showing T+ and P.T.+	87.
" " " " T - " P.T. -	83.
" " " " T + " P.T. -	27.
" " " " T - " P.T.+	<u>105.</u>
Total	302.

In view of the question raised with regard to the possible susceptibility of females to bovine infection which, by the way, is derived from a female source, I thought the following table might be of interest.

Of the 27 cases reacting only to human infection we get:-

Boys showing T.+ and P.T. -	15.
Girls " " " "	12.

Of the 105 cases reacting only to bovine infection we get:-

Boys showing T. - and P.T.+	49.
Girls " " " "	56.

AGE.

Average age of children showing T+ and P.T.+	<u>Years.</u> 9.8
" " " " " T + " P.T.-	9.8.
" " " " " T - " P.T.+	9.7

BREAST FED, BOTTLE FED or Both.

This problem presented difficulties. It seemed impossible to obtain anything like accurate information. The points I had in view were really: firstly, what opportunity did the child have of obtaining bovine infection when very young and specially susceptible; and secondly if breast fed by a tubercular mother was there any reason to suspect alimentary infection from human milk on the lines to be discussed later.

One sent a letter to every child's mother requesting an answer to the following questions.

1. Was the child breast fed, and if so how many months?
2. Was the child bottle fed, and if so, how many months?
3. If bottle fed in the first year, did you always boil the milk?
4. From the end of the first year to the end of the fifth, about how much milk did your child get daily, and was this milk boiled?

The answers were not very intelligible always, and some failed to reply, so I do not propose to work out a table as records would require to be greatly reduced to fit into complete answers in this list and hence confusion might arise. The point one does learn is that all children had a fairly ample supply of milk, often uncooked, in 2nd. 3rd. 4th. and 5th. year of life. In the first year it was usually a combination of both, breast predominating. I am reserving the list for reference where these points might be of interest in the future discussion.

FAMILY HISTORY.

If we disregard P.T. results and take all cases reacting to T. we have 114 cases.

Negative Family History	14
Positive Family History.	100.

Of these, 5 gave only a remote history, i.e. an Aunt, Uncle or Cousin, and 8 a history of remote relative and brother or sister or both. Since children seldom give "open tuberculosis" and most of the affected brothers and sisters were also very young, it seems advisable for the sake of accuracy to discard such as potent infective factors. Included as immediate sources of danger are Fathers, Mothers and Grand-parents. Corrections on this basis give the following results:

Negative Family History	27
Positive Family History	87

27 Cases with only T +.

Negative Family History	1
Positive Family History	26.

Subtracting unlikely sources of infection as above gives the following results:

Negative Family History	2
Positive Family History	25.

105 Cases with P.T. + and T -.

Negative Family History	29
Positive Family History	76.

Subtracting unlikely sources of infection as above gives the following results:-

Negative Family History	46.
Positive Family History	59.

It is interesting to record also the family history of the 83 cases giving T - and P.T. -

Negative Family History	40
Positive Family History	43.

After prolonged observation and on ordinary clinical grounds it was possible to establish 10 of these cases as almost definitely tubercular. 7 were very advanced cases, the other 3 would probably have reacted had the test been repeated. Of these 10 cases 5 gave a positive family history and 5 a negative, therefore after making corrections we have 73 non-tubercular cases giving following results:

Negative Family History	35.
Positive Family History	38.

This, of course, cannot be taken as representative, since most of these negative cases were admitted for observation purposes, the suspicion often arising from the existence of a tubercular relative. However, it is a fair guide to control the findings of the 105 bovine cases above.

SEAT OF DISEASE.

Up to this point it will be noticed that discussions really centre round infection rather than clinical disease. It cannot be supposed that a response to .1 T or .1 P.T. necessarily signified manifest tuberculosis. A few original suspects were not sufficiently long under observation to be included in this investigation, so they had to be discarded in collecting the material, otherwise the cases are in no way selected. But after observation, etc., 24 children have to be subtracted as not clinically definite cases of Pulmonary Tuberculosis.

There remains then really 195 cases to discuss under this heading. This is obtained, of course, by subtracting the 83 negative examples plus the 24 clinically negative children just referred to. After consideration the least confusing method of ruling out these 24 seemed to be that in which the corresponding reactions were subtracted in each section.

195 cases have here the site of disease recorded.

Taken as a sum total the lobes involved are as follows:

Right Upper	86.	Left Upper	52.
" Lower	98.	" Lower	111.
" Middle	33.		

It scarcely pertains to the present work to record in table the distribution, where only one lobe is

involved, where 2 are involved, and so on, the tables are sufficiently confusing already. The above is recorded because it is of interest to note the differences which exists between the incidence of disease in the upper lobes, and the similarity of incidence in the lower lobes. Supposing now the 33 cases in the right middle lobe are divided between the right upper and lower lobes, this point is brought out more strongly still.

T+ and P.T. -. 27 cases; 1 clinically negative ,
therefore 26 cases dealt with

Upper lobes involved 22 cases.

" " alone invol-
ved. 15 "

Lower lobes and right
middle lobe involved. 11 cases.

Lower lobes and right
middle lobe alone in-
volved 4 cases.

It is interesting to record that in these four basal cases 2 were breast fed by tubercular mothers. 1 the mother was a tubercular suspect but I have no facts concerning the feeding. The remaining one was breast and bottle fed but only the grandfather was consumptive.

T - and P.T.+ 105 cases, 18 clinically negative, there-
fore 87 cases dealt with

Upper lobes involved. 16 cases.
" " alone involved. 1 case.

Lower lobes and right middle
lobe involved. 76 cases.

" " " "
alone involved. 61 " see over.

The remaining 10 cases are designated as "scattered râles" which are to be interpreted as a type of moist sound which tends to change its position at examination, appearing and disappearing here and there, and lacking ^{the} monotony of character peculiar to the typical crepitation of tuberculosis. All cases of this nature are bovine in reaction.

T.+ and P.T.+ 87 cases, 5 clinically negative, therefore 82 cases dealt with

Upper lobes involved	70 cases.
" " alone involved	9 cases.
Lower lobes and right middle lobe involved	73 cases.
Lower lobes and right middle lobe alone involved	12 cases.

I attempted to work out surgical associations where either upper lobes alone, or lower lobes alone, were involved, small glands in the neck were practically universal, and so of little account. A point which rather struck me was that discharging glands, which were few, came under this section. It was not possible to arrange surgical complications in these cases with any significance. Most indeed were glands.

This table is more or less corroborative evidence to that brought out in the two previous tables, viz. those cases reacting to bovine tuberculin show physical signs in the lower parts of the lungs, whereas cases responding to human tuberculin demonstrate a

marked predilection for the upper parts of the lungs.

Perhaps before leaving this question one should discuss the reliability of the physical examination. My opportunities in this matter were very satisfactory indeed. That examination of children is difficult I am perfectly aware, for this reason it was considered essential to have corroboration of each examination record. The first examination was done at the Tuberculosis Dispensary and notes were made on the child's clinical card. When the patient was admitted to the City Sanatorium another examination was done and records made on the temperature chart. It was fortunate that these examinations were as a rule separated by a few weeks. If these two records were in agreement, that was accepted as definite; but should differences exist, as sometimes was the case, subsequent examinations were referred to, these were always recorded on the clinical card, and in this way it was possible to support or nullify the chart record.

Statistics collected on this basis are as reliable as it is possible to get. Besides most of the work was performed by expert authorities.

SURVEY OF STATISTICS.

The first point that asserts itself is the fact that out of 219 cases reacting to the test indicated, 132 showed a definite response to only one type of tuberculin.

It would appear from the results that children, on the whole, show a preference for bovine reactions

this preference being more marked in the case of girls.

Little of value attaches to the age incidence, since the cases were drawn from a restricted period. Again the information on feeding reveals the fact that milk is extensively used in the food of children in Birmingham and consequently all had an opportunity to gain infection from this source.

Investigation of Family History revealed a pronounced tendency on the part of reactions to human tuberculin to associate themselves with a potentially infective environment. As indicated previously, the occurrence of tuberculosis in a relative was often the factor leading to notification and observation of the child, so that the fact of a high incidence amongst those cases giving a bovine response has little significance. It cannot be logically regarded as an inherent susceptibility to tuberculosis, especially if consideration be accorded to the frequency with which the non-tubercular cases were associated with a tubercular relation.

Expressed relatively 76% of cases responding to T. gave a history of sources of infection which were probably human in type as sputum examination reveals (see previously) Only 56% recorded such a possible source of infection amongst cases reacting to bovine tuberculin; this loses its apparent significance when it is remembered that of the negatively reacting cases 52% gave a positive family history.

Perhaps the most striking fact of all is presented when the seat of disease is investigated in

association with the response to a particular type of tuberculin. Where the response is to T. the upper parts of the lungs are involved in 84.6% of cases, the lower parts being alone affected in 15.4%. while in those reacting only to P.T. the upper parts of the lungs are alone involved in 1.3%, the lower parts being affected in 98.7%. Support for this finding is lent by the table where the patient reacted positively to both types of tuberculin.

Deductions which might be logically drawn from these Results.

There is beyond doubt something more than a chance constancy in the clinical picture existing in connection with positive reactions to human and to bovine tuberculin. The family history is sufficiently distinctive to found a suggestion that infections only react to allied tuberculins. The different site of the lesion in the case of bovine and human response lends strong support to such a suggestion of specificity.

It is stated that either type of tuberculin can produce a focal reaction when administered subcutaneously, this is possibly true up to a point, some cases are much more sensitive to one type than the other, probably the focal reaction is just the result of irritation by a foreign substance and not peculiar to tuberculin, e.g. one has produced what appeared to be focal reactions with creosote by mouth. Some other day one hopes to continue the experiments referred to

in the section on fallacies.

Accepting then that the toxins are different in some characteristics, and that we are dealing with human pulmonary tuberculosis and bovine pulmonary tuberculosis, what facts of apparent value can be drawn from the investigation?

I. Girls are more prone to bovine tuberculosis than boys; the amount of milk consumed by boys and girls would probably be about the same so this fact may be justly interpreted as signifying a greater susceptibility, on the part of girls, to bovine infection. It occurred to me that this might have something to do with the fact that the bovine bacillus in human beings is derived from a female source. Should there be anything in this question of sex it would make distinct differences in experimental inoculations, etc.

II. As regards age, nothing of value can be learned for the reason above given.

III. Family History - It is of interest to note, in view of the point raised above regarding sex, whether in man human tuberculosis shows any sexual preference - it is possible such preference would only exist where a new species of host is chosen or perhaps where the bacillus has from generation to generation a female host such as in cattle for the most part. It is a fact of great clinical interest that connubial associations lead to comparatively few instances of tubercular

infection (G.B. Dixon)⁹.

Of the 114 cases with T.+ , 44 had a tubercular mother, of these 26 were boys and 21 girls; 38 had a tubercular father, of these 18 were boys and 17 girls. In this record there is no evidence of a sexual distinction.

It is not possible to draw any deductions with regard to predisposition from the facts tabled, for the reason already indicated.

IV. It seems a pity to raise again the vexed question of the Channels of Infection in Pulmonary Tuberculosis, but there is far too much difference of opinion yet to regard the matter as settled.

Whether the majority of cases can be readily classified, as to portal of entry, by the state of pathological change existing in say the abdominal or thoracic glands is a big question. It seems reasonable to suppose that the method and intensity of attack would be as potent factors as time in the production of advanced change in glandular substance. Would it be possible that the abdominal glands have greater powers and opportunities of self defence than the thoracic glands? One must remember that the thorax is the home, as it were, of tuberculosis in the human body. Bacilli landing there tend to stop there, so that a cumulative attack, as it were, is bound to result. Apart from this, any spread that may take place from thoracic glands almost certainly invades areas which breed more bacilli, and these in due time bestow more infection on

the glands from whence they originated i.e. thoracic glands are attacked cumulatively, and from front and rear; naturally a stage of advanced caseation could soon result; whereas in abdominal glands, conditions are more favourable for defence, whether they are better trained in this art is a question yet to be proved. Besides, mesenteric glands do not seem to have a marked barrier action - fat droplets etc. are allowed through during digestion - hence it is just possible that their method of functioning is somewhat different from the bronchial glands; a greater permeability would render them less susceptible to massed infection. If such a localisation law can be accepted, then the majority of infections originate in the thorax and are human in type, but the basis of such a line of investigation does not seem to me sufficiently convincing to regard the deductions as absolute.

Be these things as they may, the majority of children in Birmingham show a response to bovine tuberculin, and what significance this can have other than evidence of bovine infection is difficult to see.

The statistics quoted from Eastwood and Griffiths⁶ previously would support the assumption that bovine virus enters mainly by the alimentary tract, which is generally accepted. His finding though of only one case with bovine bacilli in the glands of the respiratory tract is rather against the frequency of infection being bovine in character. But favouring my deduction is the enormous frequency with which Woodhead¹⁰ found fatal Pulmonary phthisis to be associ-

ated with abdominal glands (100 in 127). Numerous experimenters (Calmette, Guerin, Von Behring, Whitla, &c) have proved that it is possible to infect the lung from the alimentary tract. Fallacies, of course, arise in experimental investigation of this point, which make it very difficult to establish on an absolutely mathematical basis the occurrence of such a method of spread, and incidentally the permeability of mesenteric glands.

11

Experiments by De Haan on a large ruminant of Java (Karban) are eminently pertinent. He introduced T.B. into its stomach through a fistula. At post-mortem, about $3\frac{1}{2}$ months later, he discovered an extensive pulmonary and pleural lesion, but no trace of tuberculosis, about the alimentary tract - he would not seem to have excluded infection by recourse to inoculation experiments. Calmette¹² produced an analogous result to the above by infecting a goat through an oesophageal tube.

The fact that bovine tuberculosis chooses the lower parts of the lungs, and human tuberculosis the upper parts is strong presumptive evidence that the portal of entry is different.

If such a deduction be accepted one is practically compelled to look to the lymphatic system as the means of spread in bovine tuberculosis, otherwise it is difficult to see how such a location should take place, especially as the apex is generally agreed to be a favourite site of the disease. On the same

grounds too one is compelled to discount the thoracic duct, and the pulmonary arterial system, as a likely means of spread in the sense of producing active disease. It would rather seem to be the case that certain lymphatic glands acquire infection, and these later bestow that infection on the corresponding lung area. According to Most ¹³ a classification of the individual lobes of the lungs into concrete lymphatic areas cannot be supported, but generally speaking the lower and middle parts of the lungs are associated with the inferior tracheo-bronchial glands. These are situated in the angle of the bifurcation of the trachea. Now supposing infection passed from the mesenteric to the retroperitoneal and through the diaphragm to these inferior tracheo-bronchial glands and by a damming back process, which in this case would be aided by gravity and the action of the diaphragm, infection settles in the lung producing disease we would have a logical explanation of the clinical findings. Of course it is possible that bacilli could travel via the thoracic duct and the pulmonary arteries. The blood infection, not being sufficiently concentrated, would be unable to establish a lesion in the lungs, and therefore having no defences, as it were, would be carried to the glands. When sufficiently accumulated it is credible that physical laws would decide in favour of infection selecting the lower parts of the lungs.

It is asserted that the rarity of bovine bacilli in pulmonary tuberculosis is strong evidence that infection seldom takes place by way of the alimentary

tract. We have already seen that most proof for such an assertion, taken on the basis of live cases, is drawn from the results of sputum examination. We shall have reason to believe later that human tuberculosis is aerogenous in its method of infection, and it seems reasonable to suppose that the larger bronchi would be chosen by the invading bacilli, this must mean that bacilli set up a lesion which being in proximity to a communication with the exterior, readily disperses its microbes when breaking down results. Now if bovine be lymphogenous, as suggested above, it cannot have the same ready access to the exterior which the human infection enjoys, and this, together with the argument put forward previously, urging that greater opportunities are afforded the lungs to produce defences since the virus is less virulent, would account for the fact that bovine bacilli are seldom found in the sputum - indeed that sputum may seldom be present as there is not the same direct infection of the bronchial mucosa, and connection with the morbid process in the lung.

So far it has been indicated that there is no more reason to accept the fact, that the primary portal of invasion is manifested by the greater age of the tubercular process in the regional glands of the abdomen or thorax, than exists to support Cornet's localisation law that a primary lesion is produced at the point of entry. To accept the stage of pathological change in different tissues, as indicative of the duration of infection, assumes a relative equality

of attack and defence on the part of the tissues concerned. It has been shown that such an equality cannot be taken for granted so far. One may be permitted then to dissent from those who exclude an alimentary infection on such a basis. Indeed one is compelled to look to such a channel to explain physical findings.

Turning now to the lungs and their associated glands, one wonders if justification exists for accepting the stage of the lesion in the lung and its glands as evidence of the earlier infected tissue, and hence the relation which the gland bears to the lung as an infective organ or otherwise. A lot of work, based, in the main on the fact of the lung lesion being more advanced than that in the corresponding lymphatic glands, would seem to prove that the lung is the seat of the primary focus (Anthon Ghon ¹⁴ E. Albrecht ¹⁵).

Is such an argument supported clinically? If we accept the assertion we must only recognise two methods of infection, viz. Aerogenic and lymph-haemic as of any great importance. The authorities quoted above are strongly in favour of the aerogenic source of infection even in children. It is possible that bovine bacilli could be air borne, but it is much less likely to be so carried than is the case with human bacilli. Supposing it to be so conveyed to the lungs, how would one reconcile its choice of the bases of the lungs, whilst human - admittedly aerogenic in most cases - chooses the apices?

Again, one is justified in believing that the method of infection is different in bovine and human tuberculosis from the clinical fact that lesions at the bases occur with about equal frequency (see previously), whereas apical lesions show a pronounced preference for the right lung.

Another point which struck one was that basal lesions seldom present that localized character which is so often manifest in apical tuberculosis, this to me seems a strong proof in favour of a glandular focus at the root of the lung dispersing persistently its infection to the area it drains without prejudice.

Other clinical facts which support this theory are as follows: In children, who are recognisedly more prone to bovine tuberculosis, basal lesions are much more frequent. Also, in one's own experience, where pulmonary tuberculosis would appear to follow an obvious abdominal lesion, the bases of the lungs are more frequently attacked.

On clinical grounds a haematogenous method of spread does not arise, whether from inoculation or a tuberculous pyaemia as it were. Aerogenic will not meet the clinical findings. One is left with the lymphogenous or lymphæmic.

4

Shennan regards lung infection as possibly secondary to glandular. These glands gain their bacilli by direct spread from other lymphatic glands, and by the thoracic duct pouring its infection into the blood and thence to the pulmonary vessels and tissue, these pass to the glands without producing an

apparent focus in the lungs. Of course by such a lymph-haemic spread the lungs and glands might be simultaneously involved, and besides it would be difficult to explain regional preference on this basis unless it be due to physical laws as suggested. The tubercle bacillus does not seem to appreciate blood to any great extent. In this connection note the type of the lesion, also noteworthy is the infrequency of generalised tuberculosis. It would almost appear that the bacillus avoids the blood except where resistance is very low, only then, apparently, can blood-borne infection produce a lesion. Probably the number of microbes in the blood is small, and unless they are collected at some focus and massed for a considerable attack, disease does not result. Again, it is a rare occurrence to isolate this organism from the blood of an obviously tubercular patient.

Taking everything into account, the fact that disease is mainly basal, the comparative infrequency of infected blood, etc., one would be justified in accepting a purely lymphogenous theory for the great majority of cases of bovine tuberculosis. For those cases where the upper lobes were also involved, it was usually the lower parts of these lobes that were affected, this may be contagion or lymphatic association (see Most's opinion previously). The remainder may be due to spread through the lateral or superior tracheo-bronchial lymphatic glands to the upper parts. Glands on the right and left side are intimately associated. Of course one must remember Cobbett's

experiments, which established that it is possible for bacilli to be aspirated into the lungs from infected material in the process of being swallowed. He used *B. prodigiosus*, but the principle is applicable to tubercle and might possibly account for some of the cases under consideration. Again it is possible that infection through the tonsil or cervical glands could produce an apical lesion.

One discussed the method of bovine infection firstly, because there is so much variance in opinions held regarding the possibility of frequency of phthisis resulting from infection via the alimentary tract and the possible methods of lung invasion, and secondly, by a process of elimination based on the clinical facts recorded, one can deduct with greater exactness the method of invasion chosen by human bacilli. Besides, if bovine virus attacks the lungs, there is only one way, speaking generally, by which ^{infection} ~~it~~ is likely to result, and that is by deglutition and passage through the lymphatics etc. to thorax - Inhalation bovine infection, though possible, is unlikely and therefore this type of tuberculosis merits first clinical attention, because, it is more justifiable to base arguments on than is the case with human infection, which obviously can reach the system by two channels, viz inhalation and ingestion.

It will be noticed that there is a higher percentage of basal lesions in human infections than there is of apical lesion in bovine infections. This

would seem to bear out the possibility of both channels being utilised. At any rate it would suggest, as indicated in the above discussion, that the alimentary pathway is not ignored. This is supported too by the fact that the human bacillus is found in the mesenteric glands. However we cannot account for the majority of human lesion on this ground so it remains to work out the most likely method of invasion.

If deductions so far be correct, it is not possible to account for apical deposits of tubercle bacilli on a deglutition basis, neither is an inoculation or haematogenous infection likely because of the difference shown in its incidence in the two apices (the term apex is used as synonymous with upper lobe because the lesion is practically always near to apex). It is difficult to see how the tonsillar pathway as instanced by Walsham¹⁶ could show such a preference for the right lung. A similar difficulty exists in the case of direct spread from cervical glands - these channels were not discussed in bovine infections because they have never been shown to be of any great significance.

One now concludes that the apical lung focus of human tuberculosis in children must be of inspiratory origin. It remains to be seen whether this is in accord with clinical findings. Baumgarten advocates a gennaeogenetic infection. Such is accepted as a possibility but must be regarded as a rare occurrence.

Much theorising centres round the question of apical involvement in pulmonary tuberculosis. Moore believes that the tubercle bacillus selects the

least oxygenated part of the lungs. Shennan records that the reason for such a choice is not clear, but is probably related to some interference with aeration in this part, and partly to the tendency shown by inspired material to settle in the upper parts of the lungs.

On clinical grounds it appears to me justifiable to regard apical infection as a direct invasion. Cobbett's experiments with *B. prodigiosus* in the air-breathed by guinea-pigs, proved that such direct invasion is possible. The apices were not involved alone but the circumstances are different. In man the erect posture is the more common attitude, now matter before it becomes respirable must be lighter than air, this being so it will tend to rise on the earliest opportunity to the highest part of the organ, offering a reasonable pathway. It must be possible for such infected material to reach the ultimate alveoli without contact with the moist wall of the passages, because in Cobbett's experiment above, such an infection had resulted though some animals were killed within five minutes of exposure to contaminated air.

Another point of importance which occurs to me is that the tubercle bacillus itself is heavier than air, therefore, to become respirable in most cases it would require to ride on a particle of dust making the specific gravity of the floating mass less than that of air, infection from the spray produced by coughing would probably choose such a dusty vehicle. This dust, in association with the virus, would induce a certain amount of trauma which would make the work of the

latter easier of accomplishment, if the subject be not highly resistant.

There is no apparent clinical evidence to support a theory involving defective aeration in the upper parts of the lungs, indeed expansion would seem to be relatively greater, certainly in an upward direction, for the apex is not controlled by a bony wall. Again, defective aeration would mean impaired mobility, this would favour fibrosis and arrest of the disease, and certainly render cavitation an unlikely sequel, but such is not the case. From this standpoint one would be inclined to regard the apices as relatively more mobile than other parts and this favours the development of the morbid process, by causing difficulty in establishing a barrier of defence, and hence the incidence of apical cavitation.

On this theory, assuming the child in the erect posture, infection would choose the right apex because of the arrangement of the bronchial tubes. In the case of a recumbent child, in view of the popular conception that the heart is on the left side, the chances are in favour of the left apex being the highest part of the lung. Apart though from such a theory it is possible for the left lung in a lesser degree to attain infection with the body in the erect attitude.

On this assumption, the clinical fact that the right apex is more frequently attacked than the left &c, can easily be explained and therefore the inhalation theory is in accord with clinical findings.

It must be evident from this somewhat complicated exposition of clinical facts and pathological findings that there is indubitable support for the assertion that human tuberculosis in children chooses mainly the apices or upper parts of the lungs, and is carried thence by an inhalation process, infection in a few cases probably taking place by the alimentary tract and choosing a basal site. Bovine tuberculosis, on the other hand, shows an unmistakable preference for the lower parts of the lungs, and we have seen there is reason to believe ^{this} this is a true lymphogenous spread.

SUMMARY AND CONCLUSIONS of PART 2.

In this part of the work an attempt is made to investigate important points regarding pulmonary tuberculosis in children from the clinical standpoint. It was at once obvious that a purely pathological view of the disease is incomplete, much of the Laboratory evidence brought forth cannot be regarded as absolute and final.

The following facts would seem to be justified from the present clinical investigation.

1. Strong evidence is afforded that each type of lesion only reacts to its allied tuberculin, the clinical picture associated with reactions to either tuberculin alone is too constant to merit any interpretation other than that of specificity.

2. The pathological evidence would not appear sufficiently conclusive to support definite assertions regarding the incidence of bovine tubercle in man or the primary site affected.
3. Accepting that bovine and human tuberculin reveal themselves by reacting to their allied tuberculin one learns that:-
 - (a) The difference between bovine and human toxin is not one of degree but of quality therefore the diseases produced by these two infections cannot be regarded as identical. Hence one is dealing with human tuberculosis and bovine tuberculosis.
 - (b) Bovine tuberculosis is more common than human, amongst children under 14 years of age in Birmingham. In this connection note the low death-rate of children in this City (B. 83. England and Wales - 100).
 - (c) Girls are more susceptible to bovine tuberculosis than boys, suggested possibility of this having something to do with sex.
 - (d) Bovine tuberculosis is admittedly a less virulent disease in man, its incidence could partly account for variations in the death-rate in different localities.
 - (e) Bovine tuberculosis shows a marked preference for the lower parts of the lungs. Infection would appear to be by the alimentary tract and lymphatic connections to the inferior tracheo-bronchial glands and thence to the lungs.
 - (f) Human tuberculosis chooses the upper parts of the lungs. Infection would appear to be by direct inspiration. A certain number selects the lower parts of the lungs, these probably arise by ingestion of infected material.
 - (g) Other methods of infection are probably rare, at any rate it scarcely pertains to the present work to discuss them. The cases can be grouped into the above two classes.
 - (h) Apical lesions explicable on the basis of respirable material being lighter

(h)
(Contd). than air and hence tendency to rise to highest part of lung. Also, trauma and excessive mobility of this part conducive to development of the morbid process.

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