THE COMPLEMENT FIXATION REACTION IN TUBERCULOSIS.

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In a previous paper (*Lancet*, 4. I. 1913), we published a preliminary report on this subject and are now able to give further particulars of our results and to discuss in detail certain points arising from them.

We have examined the blood from 234 cases of pulmonary tuberculosis (in all of which tubercle bacilli had been found in the sputum). Many of these were examined on several occasions.

Of these 234 cases, 209, or 89·3 %, gave a positive reaction; 194 on the first examination, while of the 15 which were negative on the first examination, 11 were positive on a second and 4 on a third.

In 25 cases a positive reaction was not obtained; of these 25, 11 were examined once only, 11 twice, 2 three times and 1 four times.

Out of 33 cases of "surgical" tuberculosis a positive reaction was obtained in 20 and a negative in 13.

A certain number of observations upon the sera of cases diagnosed clinically as tuberculous but without bacteriological proof and a few upon sera obtained from the post mortem room are disregarded as the numbers are too limited to allow any conclusion of value to be drawn.

The Technique. As our object has been largely to determine the quantity of immune-body present in different sera or in serum from the same case upon different occasions, careful standardisation of all

reagents has been necessary in order to render the "immune serum" the one unknown factor in the mixture.

The question of standardisation and of the antigens employed are dealt with in full by one of us (L. S. D.) in the preceding paper (this *Journal*, pp. 52–71).

To detect variations in the amount of immune-body present in the sera we have employed the method of diluting the sera with normal saline.

Any serum which gave a positive reaction when undiluted was further investigated in increasing dilutions until a point was reached at which no reaction was obtained.

The dilutions of serum commonly employed were 1 in 2, 1 in 10, 1 in 20, 1 in 100 and if necessary 1 in 200 and 1 in 1000, etc.

In a few of the cases a full series of intermediate dilutions was employed with results of considerable interest, as instanced by the results obtained with the sera of cases to whom nuclein had been given. (See Table.)

The adoption of this procedure in every instance would have necessitated the investigation of a much smaller number of cases and our primary object has been the detection of marked changes in the strength of the reaction.

In about half of the cases investigated a parallel series of tests were made using various dilutions of the antigen. As we met with no instance in which a serum or dilution of serum gave a positive reaction with dilute antigen after failing to do so with antigen of full strength, this procedure was abandoned.

In quite a considerable number of cases a positive reaction was obtained with a serum dilution of 1 in 100, while in a few instances the reaction was still positive with a serum dilution of 1 in 1000. No human serum we have yet examined has given a positive result in a greater dilution than this.

While in many cases the amount of immune-body as estimated by titration remains remarkably constant over long periods, in others, striking variations occur. For instance, a serum which, on a certain date, gave a positive reaction in a dilution of 1 in 1000, was found a fortnight later to give a negative reaction in a dilution of 1 in 2. Another serum which on one day only gave a positive reaction when undiluted, was found, on the following day, to give a reaction in a dilution of 1 in 10 while three days later it was again positive only when undiluted.

Table to show the effect of the administration of nuclein upon the "complement fixation reaction."

In this Table under the headings of the various dilutions of the sera, "no trace of haemolysis" (or a positive reaction), is designated by a − sign, "complete haemolysis" (or a negative reaction), by the letters C.H.

	Case	Date	Hour	Number of leuco-cytes per c.mm.	Percentage of poly-morphonuclear neutrophiles	Percentage of lymphocytes	Complement fixation reaction	Full strength serum	Serum dilution .9	Serum dilution .8	Serum dilution .7	Serum dilution .6	Serum dilution .5	Serum dilution .4	Serum dilution .3	Serum dilution .2	Serum dilution .1	Serum dilution .09	Serum dilution .08	Serum dilution .07	Serum dilution .06	Serum dilution .05	Serum dilution .04	Serum dilution .03	
(A)	Male.	28 Sept.	9.0 p.m.	6·980	56·5	34·25	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	C.H.
	Chronic fibroid disease (extensive)	29 Sept.	6.30 a.m.	(Nuclein 3 i).																				
		29 Sept.	11.30 a.m.	(Nuclein 3 i).																				
		29 Sept.	6.0 p.m.	9·540	66·5	25·5	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	C.H.
		30 Sept.	9.0 a.m.	9·440	72·0	21·0	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	C.H.
(B)	Male.	20 Aug.	5.30 p.m.	4·200	59·5	34·0	+	−	−	−	−	−	−	−	−	−	C.H.								
	Extensive chronic disease	21 Aug.	6.30 a.m.	(Nuclein 3 i).																				
		21 Aug.	12.30 p.m.	6·560	66·5	26·0	+	−	−	−	−	−	−	−	−	−	C.H.							
		22 Aug.	9.0 a.m.	11·260	66·5	18·5	+	−	−	−	−	−	−	−	−	−	C.H.							

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Since in all the cases of pulmonary tuberculosis considered in this report, tubercle bacilli were present in the sputum, we are not in a position to speak with authority on the value of the reaction in the diagnosis of this condition. To be of value in this respect the reaction must be shown to be present in individual cases before bacteriological proof is available.

It is quite certain that the absence of a reaction on one occasion is of little value in diagnosis for, as is shown by some of the examples quoted in the second portion of this paper, the serum of undoubted cases of phthisis may fail to give a reaction for protracted periods.

We have met with no positive reaction among our control sera obtained from presumably healthy individuals of the middle class.

The effect of nuclein solution upon the reaction.

In several cases a solution of nuclein was administered by mouth or hypodermically to phthisical persons with the object of noting any subsequent change in the amount of immune-body demonstrable in the blood serum.

In no case could any variation be detected.

The observations on two of these cases are shown in the foregoing table.

In two cases where demonstrable "immune-body" had disappeared from the blood serum after previously being present, the administration of nuclein solution brought about no return of the "immune-body."

The effect of therapeutic doses of tubercle bacillary emulsion upon the reaction.

Since our preliminary report was written we have had opportunity of examining sera from a considerable number of phthisical people who were receiving continued small therapeutic doses of bacillary emulsion $\left(\frac{1}{500,000}\text{ to }\frac{1}{300}\text{ mgm.}\right)$. The variations in the strength of the reactions observed with the sera of these patients have not convinced us that small doses of this emulsion have any constant or marked effect upon the amount of immune-body in the serum.

In several instances marked improvement in the condition of the patient with diminution in the amount of immune-body or its complete disappearance from the serum has coincided with or followed gradually increasing doses of the drug.