

OBSERVATIONS ON THE IMMUNE-BODY CONTENT
OF THE BLOOD SERUM IN PULMONARY
TUBERCULOSIS, AS DETERMINED BY MEANS
OF THE COMPLEMENT FIXATION REACTION.

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THE object of this portion of the investigation was to determine

(a) Whether the amount of immune-body present in the sera of cases of pulmonary tuberculosis, bore any constant relation to the stage of the disease and the condition of the patient.

(b) Whether well-marked clinical phenomena, *e.g.* periods of fever, attacks of pleurisy etc., were associated in any definite manner with variations in the amount of immune-body in the serum.

(c) Whether gradual definite and sustained improvement or deterioration in a patient's condition was accompanied by increase or decrease of the specific immune-body in the serum.

The method adopted was repeated examination of the sera of a large number of phthisical people at more or less frequent intervals, extending over a period of some months, with special reference to marked changes in the patient's condition.

In all cases tubercle bacilli were found in the sputum on one or more occasions while the persons were under observation.

A. The relation between the stage of the disease and condition of the patient and the amount of immune-body in the serum.

In this connection only those cases are considered which could easily be included in one of the three following classes :

(1) Cases with physical signs of extensive pulmonary disease, copious sputum, impairment of nutrition and general health, seriously impaired working capacity and an apparently bad prognosis.

(2) Cases of limited disease, not of long standing, without, during the period of observation, serious constitutional symptoms and whose capacity for work was not greatly affected.

(3) Cases of long standing disease, with physical signs of greater or less extent, without serious constitutional symptoms and in whom a diagnosis of "chronic fibroid phthisis" might be fairly made.

For purposes of comparison it is necessary to fix an arbitrary standard. This has been done by saying that any serum which gave a positive reaction in a 1 in 10 dilution, gave a "strong" reaction.

Adopting this standard, out of 102 sera from cases in class (1) ("severe" cases), 65 gave on one or more occasions a "strong" reaction while 37 gave always a weaker reaction or no reaction.

Of 43 sera from cases in class (2) ("slight" cases), 13 gave on one or more occasions a "strong" reaction and 30 gave always a weaker reaction or no reaction.

Of 60 sera from cases in class (3) ("chronic fibroid cases"), 35 gave on one or more occasions a "strong" reaction and 25 gave always a weaker reaction or no reaction.

These figures are vitiated by the fact that the sera from all cases were not examined with equal frequency; in some cases the serum was examined only on two or three occasions, in others on as many as fifteen occasions. Had this source of error been avoided and each serum examined fifteen times, it is probable that a "strong" reaction would have been met with in a somewhat greater proportion of the sera.

It would appear that the greatest amount of immune-body is likely to be found in sera obtained from severe cases or those with extensive lesions, and, as a matter of experience, this has proved to be the case.

It is, however, quite impossible to foretell the presence or absence of demonstrable immune-body or the amount of such immune-body in the serum of any particular person on general or clinical grounds. Two sera from two comparable cases may show widely different properties.

For example, the following two pairs of cases, while very similar from a clinical point of view, gave totally different results on examination of the serum.

In all the following examples abbreviations have been employed for convenience. C. F. R. +, C. F. R. -, mean, respectively, "complement fixation reaction present" and "complement fixation reaction absent."

The strength of the reaction is expressed quantitatively by the terms, "serum dilution .5," ".01," etc., which mean that the highest dilution of the immune serum with which the reaction was obtained was a 1 in 2, 1 in 100, dilution etc. The term "full-strength serum" means that the reaction was obtained with undiluted serum but not with a 1 in 2 dilution. (In a very few of the later observations, where only the special alcoholic antigen was employed, the reaction was always performed with diluted serum.)

As stated above, tubercle bacilli were present in the sputum of all the following examples:

A. Two "chronic fibroid" cases.

1. Male aet. 42, 20 years' history. Signs of fibrosis of lung (not extensive). General condition good. Working capacity not seriously impaired. Scanty sputum. Temperature consistently subnormal.

Oct. 11.	C.F.R. +.	Serum dilution .1.
Nov. 1.	C.F.R. +.	Serum dilution .1.
Nov. 25.	C.F.R. +.	Serum dilution .05.
Dec. 16.	C.F.R. +.	Serum dilution .05.
Jan. 1.	C.F.R. +.	Serum dilution .01.
Jan. 28.	C.F.R. +.	Serum dilution .05.
Feb. 11.	C.F.R. +.	Serum dilution .05.

2. Male aet. 23, 8 years' history. Fibrosis of upper lobes. Scanty sputum. General condition good. Working capacity not impaired. Temperature consistently subnormal.

Nov. 8.	C.F.R. -.
Nov. 26.	C.F.R. -.
Dec. 18.	C.F.R. -.
Jan. 21.	C.F.R. -.

B. Two moribund cases.

3. Male. Very extensive disease. Great emaciation. Bedridden for some months before death. No serious complications.

Nov. 8.	C.F.R. +.	Serum dilution .1.
Nov. 13.	C.F.R. +.	Serum dilution .1.
Nov. 21.	C.F.R. +.	Serum dilution .5.
Dec. 3.	C.F.R. +.	Serum dilution .5.
Dec. 16.	C.F.R. +.	Serum dilution .01.
Jan. 6.	C.F.R. +.	Serum dilution .5.
Jan. 14.	C.F.R. +.	Serum dilution .01.
Feb. 5.	C.F.R. +.	Serum dilution .5.
Feb. 19.	C.F.R. +.	Serum dilution .01.
Mar. 5.	C.F.R. +.	Serum dilution .01.
Mar. 28.	Death.	

4. Female. Uncomplicated pulmonary tuberculosis.

May 26.	C.F.R. -.
June 9.	C.F.R. -.
June 26.	Death.

B. The relationship between variations in the amount of immune-body in the serum in pulmonary tuberculosis and exacerbations of the disease, *e.g.* periods of fever, acute pleurisy, extending lesions, etc.

Repeated examinations of the sera from a number of cases over extended periods show widely varying results. Periods of fever, with or without definite signs of extension of the tubercular process in the lungs or attacks of acute pleurisy, may occur without any marked change in the amount of immune-body, or they may be accompanied by a considerable increase or decrease of this substance.

On the other hand, profound changes in the strength of the reaction occur from time to time in tuberculous subjects without any accompanying change in the clinical condition.

This being so, it seems advisable to cite some of the more interesting examples met with without further comment.

5. Reaction appearing shortly after an attack of acute pleurisy.

Male. Extensive disease. Serious constitutional and pulmonary symptoms. Afebrile.

On May 29th, acute pleurisy with effusion, with fever which lasted till June 11th.	May 19. C.F.R. - .	
	June 6. C.F.R. - .	
	June 11. C.F.R. - .	
Between June 11th and 15th the effusion was rapidly absorbed. The temperature fell below 98·4 on June 11th and remained subnormal subsequently.	June 18. C.F.R. + .	Serum dilution ·5.
	June 25. C.F.R. + .	Serum dilution ·5.
The patient slowly convalesced from the attack of pleurisy but the original severe symptoms persisted.	July 14. C.F.R. - .	
	Aug. 14. C.F.R. - .	
	Aug. 28. C.F.R. - .	
	Sept. 18. C.F.R. - .	

6. Variations in the reaction during an attack of acute pleurisy.

Male. Extensive disease. Severe constitutional and pulmonary symptoms. Afebrile.

	Feb. 19. C.F.R. + .	Full strength serum.
May 5th. Acute pleurisy with effusion. Fever with marked oscillations of temperature. Gradual defervescence to a normal temperature on June 4th.	May 14. T.° 101·8 C.F.R. + .	Serum dilution ·1.
	May 20. A.M. T.° 98·6 C.F.R. + .	Full strength serum.
	May 20. P.M. T.° 101·6 C.F.R. + .	Full strength serum.
	May 21. A.M. T.° 99·2 C.F.R. + .	Full strength serum.
	May 21. P.M. T.° 100·8 C.F.R. - .	
	May 29. T.° 99·4 C.F.R. + .	Full strength serum.
From June 5th the temperature remained subnormal, the effusion was slowly absorbed and the patient very slowly regained his former condition.	June 5. C.F.R. - .	
	June 11. C.F.R. + .	Serum dilution ·5.
	June 18. C.F.R. + .	Full strength serum.
	July 14. C.F.R. - .	
	Aug. 28. C.F.R. - .	

7. Persistent increase in strength of the reaction following acute pleurisy with effusion.

Male. Extensive disease. Severe constitutional symptoms. Much sputum. Afebrile.

Jan. 24th. Temperature rose to 103. Pleurisy developed followed by effusion. Temperature gradually fell and reached normal on Feb. 10th.	Jan. 20. C.F.R. +.	Serum dilution ·5.
	Feb. 5. C.F.R. +.	Serum dilution ·5.
Feb. 10th onwards. Afebrile. Slow convalescence. The effusion was slowly absorbed.	Feb. 19. C.F.R. +.	Serum dilution ·01.
	Mar. 5. C.F.R. +.	Serum dilution ·1.
	April 22. C.F.R. +.	Serum dilution ·05.
	June 11. C.F.R. +.	Serum dilution ·1.
	Sept. 4. C.F.R. +.	Serum dilution ·1.

8. Rapid change in the reaction during a febrile period due to acute pleurisy.

Male. Extensive disease. Ill. Much sputum. Afebrile.

March 26th. Acute pleurisy. The temperature rose to 102. No signs of effusion.	March 31. C.F.R. +.	Full strength serum.
The temperature fell to normal on April 8th and remained so.	April 1. C.F.R. +.	Serum dilution ·1.
	April 5. C.F.R. +.	Full strength serum.
	April 11. C.F.R. +.	Full strength serum.

9. Persistent disappearance of the reaction following haemoptysis and extension of the disease.

Male. Old standing unilateral disease. Ill. Much sputum. Afebrile.

Nov. 24. Severe haemoptysis with fever. Temperature 102. Severe haemoptysis repeated almost daily for 8 days. The temperature fell on Dec. 3rd and remained subnormal. Patient very ill.	Nov. 13. C.F.R. +.	Full strength serum.
On Dec. 21st the temperature rose to 103·8 and remained elevated for 10 days. Physical signs of extensive dissemination of the pulmonary disease.	Dec. 12. C.F.R. - .	
The temperature became normal again on Jan. 3rd and remained so. The patient very slowly rallied and improved to a considerable extent.	Dec. 17. C.F.R. - .	
	Dec. 30. C.F.R. - .	
	Jan. 7. C.F.R. - .	
	Jan. 22. C.F.R. - .	
	Feb. 5. C.F.R. - .	
	Feb. 19. C.F.R. - .	
	Apr. 29. C.F.R. - .	

10. Febrile attacks with little or no variation in the strength of the reaction.

Male. Limited disease. General condition good. Slight cough, and sputum. Afebrile.

March—April. Progress uneventful.	Feb. 27. C.F.R. +.	Full strength serum.
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April 30th. The temperature rose suddenly to 102 with expectoration of much caseous matter containing many tubercle bacilli.	April 30. T.° 102·0 C.F.R. +.	Serum dilution ·5.
	May 1. T.° 101·0 C.F.R. +.	Full strength serum.
	May 3. T.° 99·6 C.F.R. +.	Serum dilution ·5.
May 5th—June 11th. Afebrile. Progress uneventful. Little sputum.	May 5. T.° 98·0 C.F.R. +.	Serum dilution ·5.
	May 8. C.F.R. +.	Serum dilution ·5.
	May 20. C.F.R. +.	Full strength serum.
June 11th. The temperature rose to 100. Sputum again abundant.	June 12. C.F.R. +.	Serum dilution ·5.
July 16th. Afebrile. Progress since June 15th uneventful.	June 18. C.F.R. +.	Serum dilution ·5.

11. Reaction persisting until shortly before death.

Female. Uncomplicated case, 9 months' pyrexia, Jan. to Oct.

Oct. 18. T.° 101·8 C.F.R. +.	Serum dilution ·1.
Oct. 26. T.° 100·0 C.F.R. +.	Serum dilution ·5.
Oct. 30. T.° 100·0 C.F.R. +.	Serum dilution ·5.
Nov. 13. T.° 100·8 C.F.R. +.	Serum dilution ·5.
Nov. 25. T.° 100·6 C.F.R. +.	Serum dilution ·5.
Dec. 2. Death.	
12. Reaction becoming less marked before death.

Male. Pulmonary tuberculosis and tuberculosis of the intestines.]

May 30. C.F.R. +.	Serum dilution ·1.
June 10. C.F.R. +.	Full strength serum.
June 22. Death.	
June 23. Serum obtained post mortem.	C.F.R. - .
13. Variations in the reaction in an uncomplicated case going steadily downhill.

Female. Prolonged pyrexia.

Oct. 18. Slight pyrexia.	C.F.R. +.	Serum dilution ·1.
Oct. 25. „ „	C.F.R. +.	Serum dilution ·5.
Oct. 30. „ „	C.F.R. +.	Serum dilution ·5.
Nov. 8. „ „	C.F.R. +.	Serum dilution ·1.
Nov. 25. „ „	C.F.R. +.	Serum dilution ·5.
Dec. 12. Marked „	C.F.R. +.	Serum dilution ·05.
Dec. 30. „ „	C.F.R. +.	Serum dilution ·1.

Death a few weeks later.
14. Numerous observations in an advanced case going steadily downhill.

Male. Course mainly afebrile. Occasional slight pyrexia.

Oct. 4. Slight pyrexia.	C.F.R. +.	Serum dilution ·1.
Nov. 1. „ „	C.F.R. +.	Serum dilution ·5.
Nov. 25. Afebrile.	C.F.R. +.	Serum dilution ·1.
Dec. 10. „	C.F.R. +.	Serum dilution ·05.
Jan. 6. „	C.F.R. +.	Serum dilution ·1.
Jan. 28. „	C.F.R. +.	Serum dilution ·05.
Feb. 11. „	C.F.R. +.	Serum dilution ·5.
Mar. 3. Slight pyrexia.	C.F.R. +.	Serum dilution ·1.
April 22. Afebrile.	C.F.R. +.	Serum dilution ·5.
May 20. „	C.F.R. +.	Full strength serum.
June 11. „	C.F.R. +.	Serum dilution ·5.

July 1.	Afebrile.	C.F.R. +.	Serum dilution ·5.
July 2.	„	C.F.R. +.	Serum dilution ·5.
July 3.	„	C.F.R. +.	Serum dilution ·5.

Marked variations in the reaction without any corresponding evident change in the condition or health of the patient.

15. Male. Chronic fibroid disease of one apex. Scanty sputum. General condition excellent. Temperature subnormal.

Dec. 15. C.F.R. +. Serum dilution ·01.

Mar. 3. C.F.R. -.

Mar. 12. C.F.R. +. Serum dilution ·1.

Mar. 25. C.F.R. +. Serum dilution ·5.

16. Male. Fibroid apical disease. General condition excellent. Scanty sputum. Temperature subnormal.

Nov. 1. C.F.R. +. Serum dilution ·5.

Nov. 18. C.F.R. +. Serum dilution ·5.

Jan. 21. C.F.R. +. Full strength serum.

Mar. 11. C.F.R. +. Serum dilution ·1.

C. The relationship between sustained improvement or deterioration in the condition of phthisical patients and the amount of immune-body in their sera.

(a) Patients who had improved.

Only those cases are included which showed a complete loss of all symptoms (including loss of all sputum for some weeks), complete restoration of the general health and restored working capacity together with improvement in the physical signs in the lungs or, at least, no increase in the extent of such signs.

Serum was obtained from the patients on two occasions, when first seen and upon their discharge from a sanatorium. Observations made in the interval are disregarded.

Of 12 such cases, the reaction, as finally observed (compared with the reaction at the first examination), was stronger in 4, weaker in 3, and unaltered in 5.

(b) Patients whose condition was becoming worse.

Serum was obtained from a number of uncomplicated cases who were going steadily downhill, on two occasions, at an interval of some months. In some instances the subject was dying at the time of the second observation.

Of 20 such cases, the reaction at the time of the final observation was stronger in 7, weaker in 7, and unaltered in 6.

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