Let us not be discouraged. The direction of our vision is everything, and after weltering four years in chaos poor stricken humanity still nurses the unconquerable hope of an ideal state "whose citizens are happy . . . absolutely wise, all of them brave, just and self-controlled . . . all at peace and unity, and in the enjoyment of legality, equality, liberty, and all other good things." Lucian's winning picture of this "Universal Happiness" might have been sketched by a Round Table pen or some youthful secretary to the League of Nations. That such hope persists is a witness to the power of ideals to captivate the mind; and the reality may be nearer than any of us dare dream. If survived, a terrible infection, such as confluent small-pox, seems to benefit the general health. Perhaps such an attack through which we have passed may benefit the body cosmic. After discussing the various forms of government, Plato concludes that "States are as the men are, they grow out of human characters" (*Rep.* VIII), and then, as the dream-republic approached completion, he realized that after all the true State is within, of which each one of us is the founder, and patterned on an ideal the existence of which matters not a whit. Is not the need of this individual reconstruction the Greek message to modern democracy? and with it is blended the note of individual service to the community on which Professor Gilbert Murray has so wisely dwelt.

With the hot blasts of hate still on our cheeks, it may seem a mockery to speak of this as the saving asset in our future; but is it not the very marrow of the teaching in which we have been brought up? At last the gospel of the right to live, and the right to live healthy, happy lives, has sunk deep into the hearts of the people; and before the war, so great was the work of science in preventing untimely death that the day of Isaiah seemed at hand "when a man's life should be more precious than fine gold, even a man than the gold of Ophir." There is a sentence in the writings of the Father of Medicine upon which all commentators have lingered, "*ἡν γὰρ παρὶ φιλανθρωπίας, πάρεστι καὶ φιλοτεχνίας*"—the love of humanity associated with the love of his craft!—philanthropia and philotechnia—the joy of working joined in each one to a true love of his brother. Memorable sentence indeed! in which for the first time was coined the magic word *philanthropy*, and conveying the subtle suggestion that perhaps in this combination the longings of humanity may find their solution, and Wisdom—philosophia—at last be justified of her children.

DIAGNOSIS OF TUBERCULOSIS BY THE COMPLEMENT DEVIATION METHOD.

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VARIOUS attempts based on Bordet's phenomenon have been made with a view to determine whether, in tuberculosis, as in syphilis, a diagnosis of the disease could be established by the complement deviation method. First studied by Wassermann, the subject was further investigated by subsequent workers, the technique employed in the test being in fundamental particulars identical with that of the Wassermann reaction. A number of antigens, all being preparations or extracts in some form of the tubercle bacilli, have been used. Among these were the old tuberculin used by Wassermann¹; an emulsion of dry tubercle by Nesfield,² and Emery³; an emulsion of dead tubercle by Dudgeon⁴; and an emulsion of living tubercle by Inman,⁵ McIntosh and Fiddes,⁶ and Fidlar.⁷ The outcome of their investigations in general showed that in a certain proportion of tuberculous cases (60 to 90 per cent.) an antibody could be demonstrated in the blood which, in the presence of a tubercle antigen, was capable of inhibiting complement.

On the other hand, it was also found that not infrequently (5 to 30 per cent.) a similar reaction resulting in the absorption of complement was obtained with a normal, but more often with a luetic, serum. Further, it was shown that where a positive reaction was elicited the amount of complement fixed was usually small. In face of these results, in especial of the large proportion of cases giving a non-specific reaction, it must be conceded that a diagnostic significance cannot be ascribed to any of the various tests. Thus the want of a reliable laboratory test which would not only detect the presence of a tuberculous lesion, but also discriminate an active from a latent lesion, has led us to try to elaborate a technique admitting practical application. As in the test the antigen constitutes a very important factor and one which is probably responsible, in part at least, for the discrepancies in the results arrived at by previous workers, the first step in our study was directed to the question of preparation of this reagent. Our investigation was begun towards the latter part of 1918, and was conducted throughout in the Royal College of Physicians' Laboratory, Edinburgh. After many preliminary trials, which need not be detailed here, both in regard to the antigen preparation and to the technique, we have adopted for the test the following procedure:

Requisites for the Test.

Tubercle Antigen.—This is essentially the bodies of the tubercle bacilli after their fatty substance has been removed. The process of extracting the fat is, with slight modification, that adopted by one of us (Wang)⁸ in studying the antigenic effect of lipoids *in vivo*. For the preparation a good growth of the bacilli is required. This is obtained by inoculating a 5 per cent. glycerin veal broth (standardized to + 5) with a young egg culture, preferably one of two to three weeks old. The amount of the broth medium used is 200–300 c.cm. contained in a conical litre flask, and the growth is started on the surface. At least two flasks should be sown, one with tubercle bacilli of the human type, the other with bacilli of the bovine type. When, at the tenth week, a well formed scum is seen, such a culture is ripe for use. If a good growth does not occur, as often is the case with primary cultures, subinoculation by transplanting a piece of the surface growth on to fresh broth is necessary. The growth is transferred to a bottle and is now dehydrated by treating with absolute alcohol, which should be repeatedly changed. After the final washing, the alcohol is replaced with ether, in the amount of about 100 c.cm. to 10 grams of the wet bacilli. The bottle is shaken for two hours in a mechanical shaker, at a speed of about 120 strokes per minute, and at the end the fluid is centrifuged at a high speed. The residue is now treated with chloroform in the same amount and shaken as before. Here, before drawing off the fluid for the centrifuge, it is mixed with three volumes of ether, and the shaking continued for another couple of hours. After centrifuging, the process is repeated alternately with fresh ether and chloroform, until five extractions in all have been completed. The residue is then dried and stored in the dark. A fluid antigen is made up for use by grinding 100 mg. of the residue with 3 c.cm. saline in a mechanical mill overnight. The mill may take the form of a circular flask (diameter 10 cm.) a little more than half-filled with glass balls of the size of small peas, and is driven at about twenty revolutions per minute. At the finish the fluid is drawn off and the flask and balls well washed with repeated changes of saline. The washings are pooled and enough saline is added to make 100 c.cm. The antigen is preserved in 0.5 per cent. phenol and kept in the cold.

Syphilitic Antigen.—This is an alcoholic extract of the human heart, with or without the addition of cholesterol. For use, the extract should be allowed to float on the saline for ten minutes before being mixed.

Patient's Serum.—(a) The blood is collected as for a Wassermann test from an arm vein with a needle. After separation, the serum is heated at 55 to 56° C. for two full hours. It is important that the serum should be heated on the day of the test, for, as has been pointed out by Browning and Mackenzie,⁹ a serum may, on standing, develop increased anti-complementary power, whether it had been previously inactivated or not. (b) When, for any reason, the above procedure cannot be practised, sufficient blood for the test (to be carried out by the drop method

* *Œuvres complètes d'Hippocrate*. Par E. Littré, t. ix, 258.

hereafter described) may be obtained from the finger. The thumb, previously bathed in comfortably warm water, is deeply pricked and the blood allowed to flow into either a Wright's capsule or a small tube, till about 0.5 c.cm. or more blood is collected. The separated serum is inactivated as before, but here, to prevent undue loss of fluid during heating, the tube should be closed with a rubber cap.

Blood Suspension.—This is prepared from defibrinated ox blood, which at the final washing should be spun at a fixed speed for a definite time, so that approximately the same thickness of blood is obtained each time. This precaution is important, as unless the strength of the amoceptor is estimated at each day's test the haemolytic titre must vary according to the strength of the suspension and consequently to the thickness of the blood. For this reason it is therefore necessary that the titre of the amoceptor should be determined from time to time against a working dose of the blood of a fixed concentration, in the presence of an excess of complement—namely, 5 minimum haemolytic doses. For use, a 1 per cent. suspension is made up, sensitized at room temperature with 8 to 9 M.H.D. of amoceptor.

Complement.—The complement used is that of guinea-pig serum of from four to eighteen hours old. After the animal has been bled an examination of its organs should be made, and if, to the naked eye, evidence of disease, in particular tuberculosis, is found, the serum ought to be rejected.

Technique.

First Stage.—Preliminary to the test the M.H.D. of complement is ascertained as follows: With a graduated 1 c.cm. pipette 0.1 c.cm. complement is accurately measured into 2.9 c.cm. saline (dilution 1 in 30). To a row of tubes the following doses of this solution are added: 0.05, 0.10, 0.15, 0.20, 0.25, 0.30 c.cm. Saline is added to equal bulk. Titration is made against 1 c.cm. of a 1 per cent. suspension of blood previously sensitized, as already stated, with 8 to 9 M.H.D. amoceptor. The tubes are incubated at 37° C. for an hour, and the M.H.D. is then noted.

Final Stage.—The titre of the complement being known, the neat guinea-pig serum is now diluted thus:

If M.H.D. complement (dilution 1 in 30) is—

- 0.10 c.cm., 1 vol. serum is mixed with 29 vol. saline (dilution 1 in 30);
- 0.15 c.cm., 1 vol. serum is mixed with 19 vol. saline (dilution 1 in 20);
- 0.20 c.cm., 1 vol. serum is mixed with 14 vol. saline (dilution 1 in 15);
- 0.25 c.cm., 1 vol. serum is mixed with 11 vol. saline (dilution 1 in 12);
- 0.30 c.cm., 1 vol. serum is mixed with 9 vol. saline (dilution 1 in 10).

A serum giving weaker complement value than the last should not be used. It will be seen that 0.10 c.cm. of each of the above dilutions contains one M.H.D. of complement. For each serum three tubes are put up in the manner as shown in Table I.

TABLE I.—Routine Method.

	Tube 1.	Tube 2.	Tube 3.
Complement	0.20 c.cm. (2 M.H.D.)	0.40 c.cm. (4 M.H.D.)	0.40 c.cm. (4 M.H.D.)
Saline about	2 c.cm.	2 c.cm.	2 c.cm.
Syphilitic antigen	—	1 dose	—
Tubercle antigen	—	—	0.20 c.cm.
Patient's serum	0.20 c.cm.	0.20 c.cm.	0.20 c.cm.
*Incubation.			
1 per cent. blood sensitized with 8 to 9 M.H.D. amoceptor	1 c.cm.	1 c.cm.	1 c.cm.

* Quarter of an hour at room temperature, then half an hour at 37° C., followed by a quarter of an hour at room temperature.

After the blood has been added the tubes are again incubated at 37° C., and a result is taken when once the first control tube shows complete haemolysis, generally ten to fifteen minutes.

The satisfactory results which have attended Donald's drop method¹⁰ for the Wassermann test, practised by Harrison on a large scale and by one of us when the amount of serum available is insufficient for the test to be conducted in the usual way, has suggested to us that it might be applied here.

By this drop method we have tested over thirty specimens of serum in parallel with the first method, and have invariably found the two results agreed. However, this method should not be adopted as a routine and should only be practised when the first method is inapplicable. In the actual test the fluid is measured, instead of with an ordinary graduated pipette, in drops delivered from a vertically held Wright's pipette fitted with a teat, at a uniform rate and pressure. Except when a series of pipettes gauged to a standard is available, the same pipette should be used throughout the test, though it must be remembered that there is here a slight variation in the size of the drops between the different reagents. The pipette is cleansed between each reagent and between succeeding serums by filling and emptying several times with saline. In the preliminary stage of the technique the complement is titrated as in the first method and diluted to a constant strength—that is, 0.10 c.cm. 1 M.H.D.

The final stage is conducted as shown in Table II.

TABLE II.—Drop Method.

(The figures in the table indicate the number in drops.)

	Tube 1.	Tube 2.	Tube 3.
Complement (0.1 c.cm. = 1 M.H.D.)	1 dose	2 doses	2 doses
Saline	7	5	5
*Syphilitic antigen	—	1	—
Tubercle antigen	—	—	1
Patient's serum	1	1	1
Incubate as in first method.			
1 per cent. blood, sensitized with 8 to 9 M.H.D. amoceptor	5	5	5

* This should be made up to the strength so that 0.2 c.cm. is equivalent to a dose in the Wassermann test.

After the final incubation the tubes are read as in the first method.

Interpretations of Results.

A negative serum is indicated by a complete haemolysis in the third tube (one containing the tubercle antigen), where the first control tube is clear.

A positive serum is denoted, where haemolysis is complete in the first and second tube, by absence of or only partial haemolysis in the third tube. The strength of the reaction may be judged by the degree of haemolysis in this differential tube. Thus:

- A strong positive (+++) is signified by complete absence of haemolysis.
- A moderately strong positive (++) by partial but slight haemolysis.
- A weak positive (+) by partial but considerable haemolysis.
- A doubtful positive (?) by an almost complete haemolysis.

When, as will be shown below, an inhibition of complement by a serum is observed in both the antigen tubes (second and third) it is necessary that here the serum should be further tested in order to eliminate a possible false positive. It is known that a tuberculous but otherwise normal serum may, though rarely, give a positive Wassermann reaction, and, conversely, we have found that a strong luetic serum may yield a reaction with a tubercle antigen. Hence to distinguish one reaction from the other means have to be found whereby the disturbing factor, whatever it may be, can be eliminated. There are various ways by which the Wassermann reaction can be abolished, but these, we have noticed, will also remove the greater part, if not all, of the tubercle antibody. Thus, while heating at 62° C. for half an hour will, according to Sach, annul the reacting substance in a Wassermann serum—a statement, in our experience, not invariably true—heating also has a marked inimical effect on the tubercle antibody, and is therefore inapplicable as a differential test. To detect this cross fixation we have accordingly devised the following method, which has proved itself reliable. The suspected serum, whether previously inactivated or not, is mixed with an equal part of saline in a tube, and to each centimetre of the mixture two or three drops of chloroform are added. The tube is vigorously shaken for ten to fifteen seconds, and thereafter placed in a water-bath at 55° to 56° C. for fifteen minutes. For use, the supernatant fluid is drawn off and the test proceeded with as described above, only here the quantity representing one dose is 0.4 c.cm. (that is, 0.2 c.cm. neat

serum). From ten to twenty minutes after the sensitized corpuscles have been added the results are read. Where less haemolysis is observed in the tubercle antigen tube than in the syphilitic antigen one the serum is tuberculous, in addition to being luetic. If, on the other hand, the reverse is the state of haemolysis, the probability is that the serum is only specific, and not tuberculous.

Results of Investigation.

Our investigation deals with the examination of serums from 104 tuberculous subjects, and 220 controls. Of the tuberculous, in 57 cases tubercle bacilli were found in the sputum, and in 47 they were absent. Altogether 49 of the cases had received tuberculin treatment at one time or another of the disease. The controls consist of 100 positive and 100 negative Wassermann serums, and of 20 serums taken from persons clinically known to be free from tuberculosis. Consideration of space has induced us to give, in lieu of a protocol *in extenso*, merely a summary of the results arrived at, as set forth in the accompanying tables (III, IV, and V).

TABLE III.—Summary of the General Results.

Classification.	Total	T.B. in Sputum.		Injection of Tuberculin.		Results.						
		+	—	Yes.	No.	+++	++	+	—	—	—	—
T.B. Pulmonary ...	97	57		18		6	7	2	3			
					39	26	4	4	5*			
		40		25		5	7	8	5*			
					15	4	3	6	2			
T.B. Adenitis...	4	—	4	4	—	3	1	1	—			
T.B. Abdomen ...	1	—	1	1	—	—	1	—	—			
Lupus ...	1	—	1	1	—	1	—	—	—			
T.B. Dactylitis ...	1	—	1	—	1	—	—	1	—			
Normal serum ...	20	—	—	—	—	—	—	—	20			
Negative Wassermann serum	100	—	—	—	—	—	—	—	100†			
Positive Wassermann serum	100	—	—	—	—	7	10	24	59			

* Including 1 doubtful each. † Including 3 doubtfuls.

TABLE IV.—Showing the Percentage of Positives in Tuberculous Cases treated and not treated with Tuberculin, and in Controls.

	Positive Results.			Negative Results.	Per Cent. Positive.
	+++	++	+		
Tuberculous cases:					
With tuberculin ...	14	16	11	8	84
No tuberculin...	30	7	11	7	87
Normal serum ...	—	—	—	20	0
Negative Wassermann serum	—	—	—	100	0
Positive Wassermann serum...	7	10	24	59	41

All the positive Wassermann serums which were found to give a positive reaction in the test were further tested with the chloroform differential method, and in every instance the serums after treatment became negative. It may be stated here that this differential test has been applied, besides those cases just mentioned, to 30 specimens made up of known luetic and tuberculous serums, and with no exception all the serums remained positive. It is significant to note in the above tables that the results do not afford evidence of an effect which tuberculin, in the small doses as usually administered, has in the production of antibodies in the circulating blood, as judged by the reaction of the test, nor, it may be mentioned here, have we observed any relation between the strength of the reaction and the extent and severity of the disease. Interpreted according to the rules above formulated, arbitrary though they are, the results yielded may be expressed thus:

TABLE V.

Results.	Tuberculous.	Controls.
Strong positive (+++)...	44	—
Moderately strong positive (++) ...	23	—
Weak positive (+) ...	22	—
Negative (—) ...	15	220
Total ...	104	220
Percentage of positives ...	85	0

The findings of the cases investigated therefore furnish 85 per cent. positives out of 104 tuberculous subjects. As none of the controls that have been examined reacted positively to the test, it may be justifiable to regard the test as specific, and where a reaction is provoked a diagnosis may be safely pronounced, not only that the disease is present, but also that the lesion is in an active condition. Here, as in the Wassermann test, a negative finding is significant, though inconclusive.

The non-specific reaction which other observers have found was due, we venture to suggest, to the presence of lipoids in their antigen and, in part, also to the tested serums being insufficiently heated. Even with our delipoidal antigen we have found it necessary, in order to avoid a false reaction, to heat the serums for at least two full hours at 55° C., the usual inactivation for half an hour at this temperature being, in our experience, inadequate for the purpose. Thirty of our positive serums were taken at random for quantitative estimation; in 13 the complement fixed was over 8 M.H.D.; in 7, between 6 and 8 M.H.D.; and in 10 between 4 and 6 M.H.D. The reaction here obtained is, on the whole, more pronounced than has elsewhere been recorded, and this we take to be due to the nature of our antigen, which, being free from lipoids, is more easily emulsified and consequently more favourable to interaction with its antibody.

This investigation is the outcome of the work which one of us is at present conducting on lipoid-free antigens, bacterial and otherwise, *in vivo* and *in vitro*, as means of diagnosis and treatment, and owes its inception primarily to the initiation by Professor James Ritchie of the study of the antigenic properties of lipoids. To him, for this and other valuable suggestions, we wish here to record our indebtedness. We would like also to thank Miss FitzGerald for kindness in supplying us with some of the Wassermann serums.

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WILL THE USE OF SCOPOLAMINE-MORPHINE IN LABOUR HELP TO IMPROVE THE BIRTH-RATE?

BY

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No one will gainsay that the present condition of the birth-rate is largely due to the express intentions of parents to limit their families. Sir Arthur Newsholme says "all the facts point to the conclusion that volitional limitation of the family is the chief and vastly predominant cause of the decline in the birth-rate which is taking place in so many countries."¹ Doubleday's hypothesis as to the influence of increased nutrition is at least so problematical as to be negligible, and Sir A. Newsholme discounts the theory of the inverse relationship between cerebral development and the capacity to procreate. We are mainly concerned, then, with the volitional element, and a rough classification of the grounds on which this is done