

THE AGGLUTINATING POWER OF THE BLOOD SERUM OF TUBERCULOUS PATIENTS

SERUM DIAGNOSIS—SERUM PROGNOSIS *

PAUL COURMONT, M.D.

LYONS, FRANCE

The serum diagnosis of tuberculosis is to-day one of the most generally employed and most reliable laboratory methods of diagnosis.

1.—HISTORICAL

It is well known that the ordinary cultures of the bacillus of Koch can not be used for agglutination. Arloing, however, in 1898,¹ obtained a fluid homogeneous culture of the tubercle bacillus and demonstrated its specific agglutinability by the serum of tuberculous human beings or animals, thus rendering possible the serum diagnosis of tuberculosis. Arloing and Paul Courmont² later perfected the method, determining the best manner of producing homogeneous cultures, applying the serum diagnosis to hundreds of patients and studying in these and on animals which had been rendered tuberculous the agglutinating power of the blood. Paul Courmont has further studied³ local serum diagnosis (diagnosis of the nature of pathological serous fluids by their agglutinating power) and the serum prognosis of pleurisies. To-day the Lyonese

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1. Arloing (S.): Sur l'obtention des cultures homogènes du bacille de la tuberculose, *Compt. rend. Acad. d. sc., Paris*, May 19, 1908; Agglutination des bacilles de Koch par le sérum sanguin des tuberculeux, *Cong. franc. de méd., Montpellier*, April 13, 1898; *Acad. d. sc., Paris*, May 16, 1898.

2. Arloing (S.) and Courmont (Paul): De l'obtention des cultures homogènes les plus propices à l'étude du phénomène de l'agglutination par le sérum sanguin des tuberculeux, *Compt. rend. Acad. d. sc., Paris*, Aug. 8, 1898; Recherche et valeur clinique de l'agglutination du bacille de Koch, *Compt. rend. de l'Acad. d. sc., Paris*, Sept. 19, 1898; *Cong. de la tuberc., Paris*, 1898; Séro-diagnostic de la tuberculose, *Cong. de la tuberc., Berlin*, 1899; *Ztschr. f. Tuberk.* 1900, i, No. 1; *Gaz. d. hôp., Paris*, Dec. 1, 1900.

3. Courmont, Paul: Séro-diagnostic des épanchements tuberculeux, *Cong. de la tuberc., Paris*, 1898; *Compt. rend. Soc. de biol.*, 1898; L'agglutination du bacille de Koch par les épanchements tuberculeux; *Arch. de méd., expér.*, November, 1900.

method is employed in all parts of the world and numerous observations have been made on this question.⁴

Among the students who have confirmed this work may be mentioned: In France: Widal and Ravaut, Dieulafoy, Schrapf, Sabareanu and Salomon, pupils of Professor Landouzy, in Paris; Ferre, Mongour and Buard, in Bordeaux; Carrière, in Lille; Hawthorn, in Marseilles; Lagriffoul, in Montpellier; Bard and Humbert, in Geneva, Switzerland; Bendix, Rumpf and Guinard, Romberg, in Germany; Kazarinow, Shakaranin, in Russia; Marzagalli, Caffareno, Marchetti and Stefanelli, Marini, in Italy; Thomescu and Gacesky, in Roumania, etc.

4. Arloing, S., Bayle and Dumarest: Etude sur les rapports entre la séro-agglutination et l'évolution de la tuberculose chez l'homme, Cong. de la tuberc., Paris, 1905.

Arloing, S., and Courmont, Paul: Variations de l'agglutinabilité des bacilles de la tuberculose: deux mémoires, Rev. de la tuberc., 1904.

Bronstein: Soc. de pédiat. de Moscou, Vrach, 1901.

Courmont, Paul: Valeur sémiologique de la réaction agglutinante chez les tuberculeux, Cong. de Lyons de l'Assn., franç. pour l'avancement d. sc., 1906; Tuberculose latente et séro-diagnostic, Bull. Soc. med. d. hôp. de Lyons, 1904.

Dieulafoy. Semaine méd., 1903; Clin. méd. de l'Hôtel-Dieu de Paris.

Froment: Séro-diagnostic de la tuberculose chez le vieillard, Compt. rend. Soc. de biol., 1903.

Hawthorn: Séro-réaction tuberculeuse. Compt. rend. Soc. de biol., June 6, 1902; Jour. de physiol. et path. gén., 1903, No. 1.

Humbert: Diagnostic de la granulie par la séro-réaction. Rev. de la tuberc., 1904, No. 4.

Il Vento: Sull' agglutinabilità del bacille tuberculare e sua importanza diagnostica, Riforma med., 1902, 266.

Kazarinov: Contribution a l'étude de séro-diagnostic tuberculeux, Nevrologicheskii, 1901, 849.

Lagriffoul and Verges: Compt. rend. Soc. de biol., 1903.

Landis: Studies in agglutination in tuberculosis, Jour. Med. Research, 1908.

Marchetti and Steffanelli: Sulla séro-reazione tuberculose. Riv. crit. di med. clin., 1903.

Marzagalli and Caffareno: Sur l'agglutination du bacille tuberculeux. XII Cong. Soc. ital. de méd. int., Rome, October, 1902.

Mongour and Buard: Compt. rend. Soc. de biol., 1899.

Neisser, J.: Valeur pronostique de la séro-réaction, Cong. ital. di med. int., Genoa, 1905, 920.

Ravenel and Landis: Agglutination studies in tuberculosis, Med. News, 1907.

Rodet and Lagriffoul: La séro-réaction tuberculeuse. Jour. de physiol. et path. gén., 1902.

Rumpf and Guinard: Recherches sur la séro-réaction tuberculeuse, Presse méd., 1902, No. 24; Deutsch. med. Wchneschr., 1902, No. 8.

Schrapf: Diagnostic de la tuberculose par la séro-agglutination. Arch. de méd. mil., February, 1902.

Widal and Ravaut: Agglutination du bacille de Koch dans 24 cas de pleurésies tuberculeuses, Cong. de la tuberc., London, 1901.

If, on the contrary, some authors have contested the importance and value of serodiagnosis, their attitude, I and my associates believe, arises from their not having avoided the following causes of error.

2.—CAUSES OF ERROR

I. TECHNIC

First, one must possess a good agglutinable bacillus. We have shown that agglutinability is a property not common to all bacilli of Koch. Our bacillus A (human tuberculosis, Arloing) fulfils the conditions of facility of culture and agglutinability. This organism we have sent to all who have sought cultures, and most of the results obtained in different parts of the world depend on investigations made with this bacillus. The liquid homogeneous culture must be developed and employed under the conditions which we have explained at length elsewhere. The cultures, which should be four to eight weeks old, must be diluted with a 0.7 per cent. salt solution and tested with the standard serum, and mixed with the serum to be tested in suitable proportion; it is necessary to take into account only those reactions visible to the naked eye. These steps are easy to follow in a well-appointed laboratory; we can, moreover, furnish tubes of homogeneous cultures ready to be employed, just as one provides tuberculin, dry or liquid, for tuberculin reactions.

But it is evident that technical modifications in the preparation of the cultures, in their age, their dilution, etc., modify their agglutinability so that it becomes impossible to compare the results obtained with these cultures with those obtained by ourselves and by those who have strictly followed our instructions.

II. APPRECIATION AND VALUE OF THE DEGREE OF AGGLUTINATION

It is advised that in the case of an adult the serum and the culture be mixed in three small test-tubes in the following proportions: (1) one part of serum to five of culture; (2) one to ten; (3) one to fifteen. Under these conditions the serum of a man free from all evident or latent tuberculosis should not agglutinate ordinarily at 1 to 5, whereas the serum of the tuberculous will agglutinate in dilutions varying between 1 to 5 and 1 to 15 or 20, and rarely in higher dilutions.

If, however, one change the conditions the results are materially different. For instance, if one should employ cultures which were not agglutinable, the results would be wholly negative. If, on the contrary, one employs cultures which are too agglutinable, one obtains, with a given serum, much higher degrees of agglutination than are obtainable with cultures prepared strictly according to the above directions, and

such results can no longer be compared with ours. This, for example, is what happened in the observations of Kinghorn, who obtained agglutinations at much higher dilutions than we did. It is well known that every normal serum possesses a certain normal agglutinating power; the specificity of the agglutinating reactions is, therefore, relative, quantitative and not qualitative. It is only within certain limits that the agglutinating reaction with a given bacillus has a specific and diagnostic importance, and these limits vary according to the different animal species. For instance, the serum of a healthy dog agglutinates our homogeneous culture at a dilution of 1 to 30; the serum of an adult non-tuberculous cow agglutinates it ordinarily at 1 to 5. Moreover, the agglutinability of the serum of a given animal species varies in degree according to age. Arloing has shown that the serum of the calf does not agglutinate at 1 to 5, whereas the serum of a healthy cow does agglutinate at this dilution. Consequently, for a given animal species, the agglutination of a bacillus is specific only when it is above the ordinary degree of agglutination of the normal serum of this species for this bacillus. Moreover, the age must likewise be taken into consideration. To summarize: A serum agglutination has diagnostic value for a given subject only when it surpasses the agglutinating power of the serum of normal subjects of the same species and the same age.

For human beings it is not easy to fix this limit. It is always difficult to prove that the subject is healthy and has not a latent tuberculous lesion. Nevertheless, for an adult subject, under the exact conditions of our technic, the limit of pathological agglutination seems to begin at a dilution of 1 to 5. We shall see, further on, that this limit is lower in children. But it is evident that if one employs cultures which are much more agglutinable than ours, this limit will be raised above 1 to 5, because under these conditions the normal agglutinating power of the serum of healthy subjects would surpass this limit. One must, then, consider as specific only such serum reactions as are much more intense. It is certainly through their not having taken these considerations into account that some authors, and especially Kinghorn, have considered as specific certain serum reactions due to the normal agglutinating power and have found as many positive reactions in healthy people as in those who are tuberculous. Kinghorn finds, in fact, many reactions at dilutions of 1 to 75 and 1 to 100, degrees of agglutinability which have hardly ever obtained in a tuberculous man. His cultures, therefore, must be regarded as much more agglutinable than ours, so that the nor-

mal human serum, which for us agglutinates only at dilutions below 1 to 5, agglutinates for Kinghorn much more readily. such agglutinations being considered by him as specific reactions.

III. CLINICAL INTERPRETATION

One must take care not to regard the serum reaction as an infallible sign, promising a diagnosis with mathematical precision. Like every pathological sign, like the ocular reaction or like that following the injection of tuberculin, this reaction must be interpreted and discussed in comparison with the other symptoms furnished by the study of the case. The serum diagnosis is valuable only in cases in which a clinical examination has already been made, "in the case of a suspected subject," as we have already insisted with Arloing as long ago as 1898. Applied to healthy subjects not suspected of tuberculosis it has of itself but slight value.

One must remember also that general serum diagnosis (with blood serum) does not point out the localization of the lesions, but only the existence of tuberculosis; it is for the clinician to apply to a local lesion the results of his serum diagnosis. We repeat that all these directions apply not only to serum diagnosis, but to all methods based on the employment of tuberculin (subcutaneous injection, ocular reaction) which are, moreover, open to many other objections.

3.—PROOF OF THE VALUE OF SERUM DIAGNOSIS

The best proofs of the value of this method are the good practical results which serum diagnosis has given to a great number of authors, but there are two kinds of proofs which are especially conclusive.

1. *Bovine Statistics*.—In cows statistics may be obtained in which the serum reaction is controlled by autopsy. Under these conditions Arloing has determined that serum diagnosis is always negative when a cow is non-tuberculous and positive in 98 per cent. of cases in which there are tuberculous lesions.⁵

2. *Statistics with Pleurisy in Man*.—In pleurisies in the human being one can obtain evidence as to the tuberculous or non-tuberculous nature of the malady by the consideration of clinical observations, together with inoculations and cytology. In such conditions, in statistics of 112 cases, we have never had a positive reaction with the pleural fluid when, by all other criteria, the pleurisy was non-tuberculous; on the contrary, we have had 76 per cent. of positive reactions in cases in which the pleurisy was

5. Arloing (S.): Séro-diagnostic de la tuberculose chez les bovidés. Jour. de méd. vét. de Lyon, September, 1900.

regarded as tuberculous.³ If the results of agglutination with the blood serum of human beings (tuberculous or not) are apparently less easy to interpret, this depends on the variations of the agglutinating power according to the nature, the gravity, the stage of healing or curability of the lesions, as well as according to the age of the subject. These considerations may be summarized as follows:

4.—THE AGGLUTINATIVE REACTION IN PRACTICE. SERUM DIAGNOSIS

According to our own personal statistics (Arloing and Courmont), covering more than 1,200 cases, we have obtained positive serum reactions: I, in tuberculous patients (90 per cent.); II, in hospital cases, apparently non-tuberculous (40 per cent.); III, in apparently healthy subjects (30 per cent.).

I. TUBERCULOUS PATIENTS

The agglutination here varies in frequency and in intensity, according to the following conditions:

The Localization of the Lesions.—The serum of patients with localized tuberculosis (so-called “surgical”⁶ cases) is often less agglutinating (75 per cent. in cases of tuberculosis of bone, of skin, of lupus⁷). The serum of patients with tuberculosis of viscera, lung, pleura and other serous membranes, as well as intestine, agglutinates in a higher degree.

2. *The Gravity of the Lesions.*—The most serious cases of tuberculosis, those with widespread lesions, rapid consumption (consumptive subjects attacked by tuberculous pneumonia, meningitis, acute miliary tuberculosis), nearly all give negative serum reactions. On the other hand, the serum of curable patients, such as those with fibroid tuberculosis, gives the largest proportion of positive reactions (pleurisy *a frigore*, fibroid pulmonary tuberculosis, chronic bronchitis or emphysema with slight tuberculous lesions, curable adenitis, etc.). Similar conditions are observed with animals which have been rendered tuberculous experimentally. Two conclusions may be drawn from these observations: From the point of view of diagnosis, the method will not give such good results in the grave and rapid forms of the disease, but it will reveal latent cases which advance slowly and in which cures are possible; that is, those cases in which the diagnosis is both most difficult and most useful. As to serum prognosis, I shall speak later.

6. Courmont, (Paul): Le séro-diagnostic des tuberculoses dites chirurgicales, Thèse de Clément, Lyons, 1900.

7. Courmont, (Paul), and Nicolas: Séro-diagnostic tuberculeux chez les lupiques, Soc. méd. d. hôp. de Lyon, 1907.

3. *Healed Lesions.*—The serum of tuberculous patients who are convalescent agglutinates very well. One must realize that the agglutinating power of the blood persists long after the anatomical cure of the lesions, and thus it comes to pass that serum agglutination may allow a retrospective diagnosis in cases of cured tuberculosis (for instance, in a past adenitis or pleurisy).

On the other hand, one must always remember the possibility of such a condition when one attempts to interpret the serum reaction in a subject who has clinically no sign of tuberculosis. The reaction here might be due to a persistent power of agglutination remaining in the blood after the cure of an old tuberculosis which has healed without leaving any trace. This difficulty, moreover, is not inherent in serum diagnosis alone; we have seen positive ocular reactions in old subjects, whereas the autopsy and inoculation of the organs showed no trace of tuberculosis in evolution or the presence of any bacilli of Koch. This merely shows that laboratory procedures of diagnosis must be considered in each particular case in their relation to the clinical observation.

4. *Age.*—The serum of the newly born does not agglutinate (Romberg, Descos⁸); that of tuberculous children agglutinates, but less than that of adults. The degree of agglutinating power rises with the age of the children. It appears, therefore, that the serum reaction has a positive significance in children at a lower degree of agglutination than in adults; this is very important, because of its practical application.³ It is in adults that the serum reaction presents the maximum of frequency and intensity.

In the aged⁹ one finds many weak serum reactions caused by old tuberculous lesions, more or less healed, but strong serum reactions are important in revealing old tuberculosis not yet completely extinct. It is very important to appreciate these variations according to age, for practical application; that is, for the theoretical question of latent tuberculosis. The same degree of agglutination has not the same importance at different ages. On the other hand, the results of serum diagnosis at different ages agree absolutely with those of the necropsy statistics of Naegeli in Germany.

II. REACTIONS IN HOSPITAL CASES APPARENTLY NOT TUBERCULOUS

Here the serum reaction is positive in from 35 to 40 per cent. of the cases; this is not astonishing when one considers the great frequency of

8. Descos: La séro-diagnostic de la tuberculose chez les enfants, Thèse, Lyon, 1902; Jour. de physiol. et path. gén., 1903, No. 1.

9. Descos: Le séro-diagnostic de la tuberculose chez le viellard. Bull. Soc. méd. d. hôp. de Lyons, March 22, 1904.

more or less latent tuberculosis in hospital patients. With tuberculin one arrives at analogous results. Beck, in Berlin, observed 46 per cent. of positive tuberculin reactions in 2,000 patients who were apparently non-tuberculous.

Acute infections do not, as a rule, confer on the serum an agglutinating power for the bacillus of Koch. One must, however, classify typhoid fever separately, for 75 per cent. of typhoid patients agglutinate tubercle bacilli just as if they were tuberculous, whereas autopsy may show no tuberculous lesions. But from a theoretical point of view my experiments, with Arloing, in men and animals, show that there is no relation between the agglutinating power of serum on typhoid bacilli and tubercle bacilli. It is not apparently the same agglutinin which acts on the two bacilli, but two distinct agglutinins. The cause of this double agglutinating power of the typhoid serum is still obscure. It is, perhaps, due to an accidental invasion of Koch's bacilli through the intestinal ulcerations, or to a sort of displacement of tubercle bacilli retained in the organism. At all events, it destroys the value of the application of the tuberculosis serum reaction for the distinction between typhoid fever and tuberculosis.

Serum diagnosis of tuberculosis is less valuable in the acute forms than in the torpid and chronic forms of the disease. The same inconvenience exists with the tuberculin reaction, which can not be applied to febrile cases, and with the ocular reaction, which is positive in most cases of typhoid fever without the coexistence of tuberculosis.¹⁰

REACTION IN APPARENTLY HEALTHY SUBJECTS

The serum reaction is positive in about 30 per cent. of apparently healthy individuals. It also reveals latent tuberculosis, no matter how slight this may be, but, as many cases of latent and slight tuberculosis are compatible with very good health, the serum reaction in such instances has only the value of a *réaction d'attente* (expectant reaction), and without other symptoms the serum reaction has no practical importance—for instance, in soldiers. We may observe, furthermore, that the results of tests with tuberculin, in healthy subjects, confirm those of the serum diagnosis (see the statistics of Beck).

5.—COMPARISON OF SERUM DIAGNOSIS AND TUBERCULIN REACTIONS. ADVANTAGES OF THE SERUM REACTION

If one compares the results given by serum diagnosis and tuberculin reactions (subcutaneous injection or ocular reaction), one sees that these methods give similar results: the serum diagnosis, however, has many

10. Arloing (F.): Ophthalmo-réaction, Jour. de physiol. et path. gén., 1908.

advantages. With all three methods the results are positive in most cases of active tuberculosis; the cases in which no reactions are obtained are often the gravest instances; for example, advanced consumption. With all three methods the results are positive in a fairly large number of cases in which neither the clinical examination nor even, sometimes, the autopsy reveals tuberculosis. The accordance of the results suggests that here there is latent tuberculosis, with very slight lesions, such as are often compatible with good health, lesions which are only revealed by this very delicate laboratory method. It is very remarkable that injections of tuberculin and serum diagnosis give about the same percentage of positive reactions in patients who are evidently non-tuberculous (40 per cent. with the serum diagnosis and 16 per cent. with the tuberculin, according to Beck). It is also curious to see that the ocular reaction is positive in typhoid cases, just as is the serum reaction. At all events, the few objections which one can make to the serum diagnosis (causes of error in feverish cases and in typhoid fever, the great sensitiveness of the method which reveals the slightest tuberculous infections, even those compatible with health) are equally applicable to the injection of tuberculin and the ocular reaction, as we have explained above.

The special advantages of serum diagnosis are the following:

1. *Absolute Harmlessness.*—The taking of a little blood can not give rise to the sometimes serious accidents or inconveniences ascribed, and with reason, to the ocular and other tuberculin reactions.

2. *Facility of Application.*—A few drops of blood suffice, while it is unnecessary to keep the patients under observation for several days, as in the two other methods.

3. *Importance of the Variations of the Agglutinating Power.*—Because of the harmlessness and facility of application of the method, one may repeat the reaction as often as he will, and the variations of the agglutinating power are of great importance, not only for diagnosis, but also for prognosis (see further).

4. *The Possibility of Local Serum Diagnosis.*—This facility does not exist with other methods.

6.—LOCAL SERUM DIAGNOSIS

The serum reaction is ordinarily made with blood serum, in which case it only affords a general serum diagnosis, simply revealing the general specific impregnation of the blood with the products of a given infection, no matter what the lesions may be. But, in our work at Lyons, we established, as long ago as 1898, the possibility and usefulness of local serum diagnosis.³ This is made with local serous effusions, for

instance, in pleurisies. We have pointed out that when a serous membrane is infected by tuberculosis a local reaction is produced and agglutinins are formed locally, independently of what happens in the blood. The search for a serum reaction with pleural fluid furnishes the proof of the existence of local tuberculosis. Our various observations on the subject (more than 200 cases of effusion, of which 115 were tuberculous pleurisies) have been confirmed by Mongour and Buard, Widai and Ravaut, Dieulafoy, Landouzy, Sabareanu and Salomon, Hawthorn in France, Bendix in Germany, Kazarinow in Russia, Marini, Marchetti and Stefanelli in Italy,⁴ and other authors whose statistics are similar to ours. The most conclusive results are given by pleural fluids. The fluid of tuberculous pleurisies agglutinates (at least at 1 to 5) in 76 per cent. of the cases in adults (statistics of 115 cases). Tuberculous pleurisies which give negative results are always of grave character. Non-tuberculous fluids will not agglutinate even at a dilution of 1 to 5 (with the exception of two or three doubtful cases). The agglutinating power of tuberculous fluids is ordinarily less elevated than that of the blood serum, but it may sometimes be more elevated and it may exist only in the pleuritic fluid and not in the blood. It would, therefore, seem that the pleural membrane can produce (*in loco*) agglutinative substances.

In practice: (1) Positive serum reaction at dilutions of 1 to 5 and above is a sign of great value as indicating the tuberculous nature of a pleurisy. The careful comparison of the serum diagnosis with the cytology and the results of inoculation of fluid in guinea-pigs proves the absolute accord of the three methods. The serum diagnosis has the advantage of greater facility and rapidity; one does not have to keep the patient under observation; a few drops of liquid suffice, and this small quantity of fluid can be transported easily to the laboratory for examination.

2. A negative reaction constitutes only a presumption against the diagnosis of tuberculosis. One must, in this case, repeat the experiment.

3. A comparison of the agglutinating power of the blood with that of the pleural fluid would give interesting results. One can draw the same conclusions from tests made with other pathological fluids (especially ascites and hydrarthroses), except in cases of meningitis, in which the cerebrospinal fluid is never agglutinative.

7.—SERUM PROGNOSIS

The general idea of the serum prognosis in disease and the significance of the agglutinating reaction in the evolution of infectious diseases was suggested by me for the first time in 1896-7, apropos of ty-

phoid fever.¹¹ I have shown that the degree of the agglutinating power of the blood is more intense when the infection is less grave and the resistance of the subject is greater. This is probably applicable to all infectious diseases running a typical course (self-limited diseases). For tuberculosis the question is more complicated on account of the variability of the form and the duration of the illness. But it would be as important as it is difficult to establish a means of prognosis through the varying agglutinating power in tuberculous patients. Subsequently (Congress of Tuberculosis in Berlin, 1902), with Arloing, I have been able to assert that "the agglutinating power seems to be inverse to the gravity of the tuberculous infection," and in 1900 we arrived at the same conclusions in regard to animals which had been made tuberculous experimentally.¹² The principal arguments on which serum prognosis in tuberculosis is based are the following:

1. *General Statistics.*—The tuberculous in whom the serum is not agglutinating (10 to 15 per cent.) are nearly all very seriously ill; subjects who have advanced consumption, miliary tuberculosis, caseous pneumonia or meningitis have, nearly all, a negative serum reaction.

2. *Experiments in Animals Made Tuberculous Experimentally.*—The agglutinating power is higher when the tuberculosis is less virulent and the animal very resistant, and conversely.¹²

3. *Variations of Intensity of the Agglutinating Power of Tuberculosis.*—These variations appear to be dependent on the prognosis of the disease. Very elevated reactions are found especially in subjects in whom the tuberculosis is slight or in the course of healing (local tuberculosis of the viscera, fibroid tuberculosis of the lungs, primary pleural tuberculosis of Landouzy, etc.). Conversely, weak agglutinations are found especially in patients very seriously ill.

4. *Variations of the Agglutinating Power in the Same Subject.*—If one follows for a considerable period a single tuberculous subject, one sees frequently an elevation of the agglutinating power of his serum if the patient be convalescent, and, on the contrary, a reduction if the disease is progressive, while at times the reaction may even disappear completely. As examples the two following cases may be cited:

11. Courmont (Paul): Signification de la réaction agglutinante chez les typhiques, Thèse de Lyons, 1897, Compt. rend. Soc. de biol., 1897-1898.

12. Arloing (S.) and Courmont (Paul): Des causes qui modifient le pouvoir agglutinant des sujets expérimentalement tuberculeux, Jour. de physiol. et path. gén., January, 1900, No. 1.

CASE 1.—*Tuberculous Pleurisy with Favorable Serum Prognosis.*—Giuseppe, —, aged 18; has benign sero-fibrinous pleurisy without complications, and will recover completely.

AGGLUTINATING POWER OF PLEURITIC FLUID

9th day	+ 5
14th day	+10
21st day	+15

CASE 2.—*Tuberculosis with Unfavorable Serum Prognosis.*—M., —, aged 28; pregnant; double pleurisy with fever; secondary galloping consumption; death in 96 days.

AGGLUTINATING POWER

OF BLOOD		OF PLEURITIC FLUID	
20th day	+10	20th day	+ 5
50th day	+ 5	50th day	0
80th day	0	80th day	0
95th day	0	95th day	0

In the first case the agglutinating power, as may be observed, increased until recovery; in the second it fell and eventually disappeared, remaining absent until death.

5. *Mortality from Pleurisy According to the Agglutinating Power of the Pleural Fluids.*—We have studied more than 120 cases of tuberculous pleurisy and followed the patient during eight years. If one compares the mortality of patients in whom the pleural fluids showed an agglutinating power with that of patients whose fluid was not agglutinating one arrives at the following results: 75 per cent. of recoveries in cases with positive reaction, 73 per cent. of deaths in cases with negative reaction.

I published these statistics three years ago¹³ at the Congress of Tuberculosis in Paris, 1905, and in *The Journal of the American Medical Association*. Ravenel arrived at analogous conclusions. Eight years ago Bendix,¹⁴ in Germany, wrote also in favor of serum prognosis.

These facts offer further support to that which I have asserted with regard to typhoid fever, namely, that the agglutinating power is an index of the protective reaction of the system.

CONCLUSIONS

I. The agglutinating power of the humoral fluids in tuberculous patients must be considered as a very important symptom of tuberculous infection. It should be studied in all its variations, according to the age

13. Courmont (Paul): Séro-prognostic des pleurésies, tuberculeuses, Jour. Am. Med. Assn., 1908.

14. Bendix: Ueber Séro-Diagnose der Tuberculose, Deutsch. med. Wehnsch., 1900.

of the patients, to the localization, form and extent of the lesions, and also in relation to other symptoms of infection or protective reactions.

II. In order that the results of such studies may be of value, the serum reaction must be sought for under definite conditions of technic as regards the choice of the culture, the method of its preparation and the technicalities of the reaction.

III. Recognizing the fact that the agglutinating power of the normal serum varies according to age and also with the animal species investigated, the serum reaction is of diagnostic value only when the agglutinating power of the serum is higher than that ordinarily observed in normal individuals of the same age and belonging to the same species.

IV. In serum diagnosis, for practical purposes, the serum reaction must be applied and interpreted with great clinical discrimination; its results must be compared with other symptoms and not interpreted blindly. It would be unwise to regard a patient as clinically tuberculous for the sole reason that his serum agglutinates Koch's bacilli. The reaction can have little or no diagnostic value unless there are other reasons justifying the suspicion of tuberculosis.

In such cases, however, a positive serum reaction is of great value. A negative reaction is of less value, as is generally the case with negative signs.

Diagnostically, the serum reaction may be considered from two different points of view:

1. The general reaction (with blood serum) does not give information as regards the location of the lesions; it indicates only that the system has been or is actually under the influence of tuberculosis. It will be the clinician's task to interpret this information and to derive from it conclusions concerning the location of lesions. The serum diagnosis will be of special use in children, in old people and also in adults suffering from chronic, torpid or latent forms of tuberculosis. Figures pointing to the frequency of latent tuberculosis in adults who clinically do not appear tuberculous are almost the same in the case of the serum reaction as with the tuberculin test (either subcutaneously or in the eye).

2. The local serum reaction depends on the agglutinating power of serous effusions and indicates the location of the lesions. It is particularly useful for the diagnosis of tuberculous pleurisy, and its results are in accordance with those that are given by inoculation or cytodiagnosis.

V. As regards the nature and prognostic value of the serum reaction in tuberculous patients (serum diagnosis), as is the case in many other diseases, the agglutinating power of blood serum and other organic

fluids in tuberculosis, is proportionate to the power of resistance of the patients; furthermore, it is in inverse ratio to the virulence of the infection. The serum reaction is especially likely to be absent in very serious or very advanced cases of tuberculosis. It reaches its maximum height in cases which are in the process of healing. It may diminish or disappear sometimes before death; it can, on the contrary, increase when there is an improvement pointing toward healing or arrest of the disease. The character of the result of the test seems to be an index of the protective reaction of the system.

Practically, a study of the serum reaction and its relations may be of some prognostic value. In tuberculous pleural effusions, for instance, an increasing agglutinating power is of good prognostic import, while the failure of a reaction should prepare one for a fatal evolution sooner or later.