STUDY OF THE BACTERIOLYTIC SERUM-COMPLEMENTS IN DISEASE: A CONTRIBUTION TO OUR KNOWLEDGE OF TERMINAL AND OTHER INFECTIONS.

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It has long been known that individuals who suffer from such chronic diseases as nephritis and cirrhosis of the liver are very liable to develop an acute infection during the last stages of their illness. These patients rarely die of their chronic ailment. Often in the very last days, or perhaps hours, of the disease pneumonia, a dysentery, an acute endocarditis, or a streptococcus infection sets in, which quickly terminates fatally and must be regarded as the immediate cause of death. So familiar is this course of events that such pneumonias or dysenteries are now known as a fairly definite group of infections, namely, terminal infections. Often they are not recognized before death, but at autopsy their frequency and varying characters have been well shown by Flexner[1] in his statistical and experimental study upon the subject; and though in some cases of terminal septicaemia the portal of entry was not easily found, yet it is important to note how frequently such local infections as leg ulcer or tonsilitis served as a starting point for the general invasion of bacteria. Of still more importance are his observations upon the bactericidal action of the blood of patients who have chronic diseases. The serum from six out of nine such patients showed a distinct decrease in its destructive power toward the *Staphylococcus aureus*, and two of the three patients whose serum did not show a diminished bactericidal action left the hospital improved.

Since these observations, the work of Ehrlich, Morgenroth, and

[1] Flexner. *Journal of Experimental Medicine*, 1896, I. p. 21.

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Bordet has laid bare the mechanism by which the body protects itself against foreign cells; and it is only necessary to state here that the protective substances of the blood consist in two elements—the intermediary or immune body (amboceptor)—a specific substance, stable at a temperature of 58° C.; and the complement, or alexin—a labile substance, present in all normal sera, but easily destroyed at temperatures above 58° C. For the dissolution of any foreign cells, whether bacteria or red blood corpuscle, both these substances must be present in the serum; therefore, if any individual's blood is bacteriolytic or haemolytic, that person's serum must contain both intermediary body and complement for bacteria or red blood corpuscles.

Ehrlich and Morgenroth[1] have found further that the intermediary body and complement are entirely independent of one another, and may exist in the same serum in different amounts. Under certain conditions the intermediary body remains unchanged, while the complement is decreased. Ehrlich cites an experiment where the haemolytic complement was entirely absent in the serum of a rabbit poisoned by phosphorus, and Metalnikoff[2] has observed the loss of spermolytic complement in the serum of an artificially immunized rabbit which had developed an abscess during the process of immunization. The experiments of Abbott and Bergey[3] have proven conclusively that a marked diminution in the haemolytic complement-content of the blood of rabbits results from the alcoholization of these animals, and the authors have furthermore demonstrated the impossibility of immunizing alcoholized rabbits against foreign red blood corpuscles. The latter phenomenon they believe is due to the decrease in complement, which thereby robs the animal of its power to overcome the toxic effects of foreign cells.

Not only may the complement be decreased, but it may by certain artificial means be increased. This increase in the complement has been effected by injections of various substances, as for instance peptone, salt solution, bouillon, or serum (Wassermann,[4] Müller,[5] Nolf[6]). Moro[7] has found besides that the serum of sucklings is more highly bacteriolytic than the serum of weaned infants.

[1] Ehrlich and Morgenroth. *Berliner klin. Wochenschrift*, 1901, XXXI. p. 683.
[2] Metalnikoff. *Ann. de l'Institut Pasteur*, 1900, XIV. p. 580.
[3] Abbott and Bergey. *Univ. of Pennsylvania Med. Bulletin*, 1902, XV. p. 186.
[4] Wassermann. *Zeitschrift f. Hygiene*, 1901, XXXVII. p. 197.
[5] Müller. *Centralbl. f. Bacteriol. u. Parasitenk.*, 1901, XXIX. p. 175.
[6] Nolf. *Ann. de l'Institut Pasteur*, 1900, XIV. p. 297.
[7] Moro. *Jahrb. f. Kinderheilkunde*, 1902, LV. p. 396.

The important part which the complement plays in protecting animals against artificial infections has been beautifully demonstrated by Wassermann[1]. Typhoid bacilli were inoculated into the peritoneal cavity of guinea-pigs. The result was rapid destruction of the typhoid bacilli and complete recovery of the animals. If, however, anti-complement were injected together with the typhoid bacilli, the dose which before had been harmless now became rapidly fatal. Again, in his article on "Infection and Auto-infection," Wassermann[2] suggests that the so-called lowered resistance of certain individuals which renders them so susceptible to infections of various kinds can be explained by a decrease in the complement-content of their blood, and the same hypothesis, he thinks, may account for the development of auto-infections. Supporting this theory are the observations of Neisser and Doering[3], confirmed later by Laquer[4], who found a decrease in the haemolytic action of the blood in uraemia. These authors explain their findings on the assumption that an auto-anti-complement is formed in the blood during uraemia.

Quite recently Hedinger[5] has reported several cases of uraemia in which the blood serum showed a suspension of haemolysis, sometimes only lasting during the period when the symptoms of uraemia were most pronounced.

It is evident, then, that the complement is capable of very great variations from the normal, the intermediary body remaining meanwhile unchanged. The complement represents the more sensitive portion of the serum. It is influenced by a variety of conditions—it may be decreased, it may be increased—but under all these conditions the intermediary body remains a constant quantity. And since the complement is of the most vital importance for the protection of the body against infections, its destruction or even decrease may be attended with the utmost danger to the life of the organism.

At the suggestion of Dr Flexner a series of experiments was made to determine whether in the latter stages of chronic diseases there is a perceptible decrease in the bacteriolytic action of the blood, and, if this is true, to discover what changes take place in the serum to account for the reduction. The serum of seventeen such cases was examined,

[1] *Loc. cit.*

[2] Wassermann. *Deutsche med. Wochenschrift*, 1902, XXVIII. p. 117.

[3] Neisser and Doering. *Berliner klin. Wochenschrift*, 1901, No. 22, p. 593.

[4] Laquer. *Deutsche med. Wochenschrift*, 1901, No. 43, p. 74.

[5] Hedinger. *Deutsches Arch. f. klin. Med.*, 1902, LXXIV. p. 24.

and included uraemia, cirrhosis of the liver, chronic pericarditis, and chronic endocarditis.

Methods. The blood was drawn from one of the arm veins, usually by means of a large syringe or by an apparatus devised by Dr Crampton, of the Ayer Laboratory. This apparatus consists of a small glass flask provided with a straight nozzle, 2 cm. in length, which extends out from the side of the flask just below the mouth. Over the nozzle fits a short, stout rubber tube supplied with a needle at the free end. The mouth of the flask was plugged with cotton, and the flask, rubber tube, and needle sterilized. When it was desired to draw the blood, a long rubber tube was fitted over the mouth of the flask and a large aspirating syringe attached to the other end. The needle was then put into a vein, and, by the action of the exhaust syringe, blood was drawn directly from the vein into the sterile flask, where it was allowed to remain for from twelve to eighteen hours until the serum separated from the clot. In every case the skin of the arm was carefully cleansed before the operation. When venesection was thought necessary the blood was caught in a sterile flask as it spouted from the vein.

For the experiments 25 to 150 c.c. of blood was used, the serum being allowed to separate out in the ice-box, and in from eighteen to twenty hours after the blood was taken the clear supernatant fluid was drawn off by means of sterile pipettes. Control cultures were always made from this serum, but in no instance was a growth of bacteria obtained. The bacteriolytic action of the serum was then tested upon two organisms—*B. coli* and *B. typhosus*—the same strain of both organisms being used throughout the experiments. Emulsions from eighteen-hour agar slants were made in normal salt solution, and one loopful (a standard platinum loop) from each salt suspension plated for control. Six loopfuls of each salt suspension were then added to 1 c.c. of unheated complement-containing serum, and three loopfuls of this mixture plated immediately. The mixture was at once put in a thermostat at 36·5° C., and at intervals of one, five, and twenty-four hours, three loopfuls were again plated. The Petri dishes were kept at 36·5° C. for at least twenty-four hours, when the number of colonies on each plate was estimated by means of a piece of plate glass, ruled into small squares, the colonies if numerous being counted under the No. 3 ocular. In spite of certain difficulties, such as the formation of a single colony by agglutinated bacilli, the method proved surprisingly accurate when as controls two or three sets of plates were made from the same tube of serum.

To estimate the reactivating power of a given serum, several cubic centimetres of serum were heated for one hour at 56° to 58° C., and to each cubic centimetre of heated serum containing intermediary body but no complement varying amounts of unheated or fresh serum containing complement were added. The remaining technical procedures were the same as above. By using from 1/20 to 8/10 c.c. of unheated serum containing complement the smallest quantity was determined which sufficed to reactivate 1 c.c. of heated serum (amboceptor)—that is, give sterile plates in twenty-four hours.

The first experiments were made with the serum of normal individuals. Seven different healthy sera were tested; but as might be expected, the results from all the cases were not absolutely in accordance. In every instance, however, 1 c.c. of unheated active serum gave complete bacteriolysis with both organisms in twenty-four hours, and often with typhoid bacilli in five hours. The most noticeable variations occurred in the reactivating power of different sera or in the complement-content but even this variation was not marked, provided the person was in good health. Usually when 1/20 c.c. of unheated serum was added to 1 c.c. of heated serum, reactivation was complete for typhoid bacilli in twenty-four hours, and this mixture would become as destructive as 1 c.c. of fresh unheated serum. *B. coli*, on the other hand, proved much more resistant, so that it required 6/10 c.c. of fresh unheated serum to reactivate 1 c.c. of heated serum (Table I.).

TABLE I.[1]

Observation I. W. T. L., aged 25 years. No typhoid. Healthy.
Blood drawn June 11, 4 p.m. Serum used June 12, 3.30 p.m.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. of unheated serum + B. coli	38,000	6,820	3,180	2	Sterile
1 c.c. ,, ,, + B. typhi	45,000	10,000	5,350	15	,,
1 c.c. of heated serum + 1/20 c.c. unheated serum + B. typhi	45,000	9,950	5,180	270	,,
1 c.c. of heated serum + 6/10 c.c. unheated serum + B. coli	38,000	4,900	2,600	3	,,

Observation II. M. G., aged 23 years. No typhoid. Healthy.
Blood drawn June 18, 5 p.m. Serum used June 19, 3.30 p.m.

1 c.c. unheated serum + B. coli	36,000	5,500	3,200	4	Sterile
1 c.c. ,, ,, + B. typhi	24,000	5,520	1,150	Sterile	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	24,000	4,740	2,920	110	,,
1 c.c. heated serum + 6/10 c.c. unheated serum + B. coli	36,000	4,140	3,000	3	,,

[1] For brevity's sake *B. typhosus* is styled *B. typhi* in the tables.

It sometimes happened that when blood was used from an individual whose health was not up to the standard, bacteriolysis was not so rapid as in the above cases. This slight difference was well brought out in one instance where two observations were made upon the blood of the same person—the first one during the spring months, the second after a month's vacation. The first examination is shown in Observation I. In the second examination bacteriolysis was much more rapid than in the first, and when 1/20 c.c. of fresh serum was added to 1 c.c. of heated serum, great numbers of typhoid bacilli were completely destroyed in five hours (Table II.).

TABLE II.

Observation III. W. T. L.

Blood drawn September 21, 2.30 p.m. Serum used September 22, 12 m.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	Innumerable	10,000	3,200	Sterile	Sterile
1 c.c. heated serum + 6/10 c.c. unheated serum + B. coli	10,000	3,100	1,480	46	,,

In still another case—a middle-aged man who used alcohol in excess—the reactivating power of the blood was much below the normal average. This observation is directly in accord with the work of Abbott and Bergey. These slight differences in the reactivating power of normal sera, are, of course, dependent upon the complement-content of the blood. If an individual's health is slightly impaired the complement-content of his serum falls only a little below normal; but if an actual injury is done to his tissues, as in the constant use of alcohol, the decrease would seem to be more pronounced.

Finally, the interactivating power of different normal sera was tried; that is, the complement[1] of one normal serum was added to the intermediary body of another. In several cases it appeared to make little or no difference whether complement A was added to intermediary body B or complement A to intermediary body A. Table III.

[1] The designation "complement" is not wholly accurate, as the full normal serum was employed. The quantity used is, however, active through its complements wholly or in large part.

TABLE III.

Observation IV. *A.* Healthy male. *B.* Healthy male.
Serum A. Blood drawn May 15, 6 p.m.
Serum B. Blood drawn May 23, 4 p.m. Serum used May 24, 1 p.m.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. *A*'s heated serum + 1/20 c.c. *B*'s unheated serum + B. typhi	50,000	9,800	5,080	8	Sterile
1 c.c. *A*'s heated serum + 7/10 c.c. *B*'s unheated serum + B. coli	39,000	2,600	1,300	Sterile	,,

From the results of the examination of normal sera it is evident that for the two strains of bacteria used 1 c.c. of unheated serum will destroy large numbers of both colon and typhoid bacilli in twenty-four hours, the reduction in numbers being more rapid with typhoid than with colon bacilli; and that 6/10 c.c. of unheated serum will reactivate 1 c.c. of heated serum for *B. coli*, while 1/20 c.c. of unheated serum will reactivate 1 c.c. of heated serum for *B. typhosus*. With these figures as a standard for the complement-content of healthy normal serum, the following experiments were made upon the bacteriolytic power of the blood of 17 different individuals suffering from nephritis, heart disease, and other chronic affections.

The 17 patients can be summarized as follows: 11 cases of uraemia, with nine deaths; two cases of cirrhosis of the liver, with one death; one fatal case of pericarditis; one fatal case of aortic aneurism; one case of chronic endocarditis, living; and one case of diabetes mellitus, which has been lost sight of. Autopsies were made in four of the 12 fatal cases. Blood cultures were also made in four instances, and in several cases at least two observations were made upon the patient's serum. All these cases can be roughly divided into three groups:

Group I. Bacteriolytic action of the serum much diminished; reactivation difficult; 10 cases, seven deaths.

Group II. Bacteriolytic action of serum very slightly reduced; reactivation fairly good; five cases, two deaths.

Group III. No reduction in bacteriolytic power of serum; reactivation complete; two cases, two deaths.

GROUP I.

In Group I. there are six cases of uraemia, all but one of which died; one fatal case of cirrhosis of the liver; one fatal case of aortic aneurism; one case of diabetes mellitus and one case of chronic endocarditis, both living. Autopsies were obtained in four of the seven fatal cases. With the exception of the case of cirrhosis of the liver, the blood was usually drawn two to four days before death; and when there were two examinations of the blood they were made at intervals of two to three days, the last a few hours before the patient died.

If the bacteriolytic power of the serum from the above chronic cases is compared with the action of normal serum, the most striking difference is immediately apparent. Whereas a rapid reduction in the number of colon and typhoid bacilli, with total destruction of all bacteria took place with 1 c.c. of unheated normal serum in twenty-four hours, 1 c.c. of unheated serum from these cases produced little or no effect upon the colon bacilli, and sometimes did not even suffice to destroy typhoid bacilli in twenty-four hours. *B. coli* is fairly resistant even to the action of normal serum, so that it affords a very delicate test for the detection of slight reductions in bacteriolysis; but since heated abnormal[1] serum would almost never be successfully reactivated against this organism, it offers no means by which an estimation of the actual reduction in bacteriolysis could be measured. Fortunately, the typhoid bacillus is so easily destroyed that it was exceedingly rare to find serum of a case in which 1 c.c. did not produce a fairly marked bacteriolytic effect upon it. Moreover, reactivation could usually be accomplished, and thus by comparing with normal serum the amount of unheated abnormal serum required to reactivate 1 c.c. of heated serum a definite ratio between the two and scale of measure could be readily obtained. By this means it was estimated that reactivation was three to six times as difficult with the serum from this group of chronic cases as with normal serum; in other words instead of requiring 1/20 c.c. of fresh serum, 1/10, 2/10, or even 3/10 were necessary for complete bacteriolysis in twenty-four hours (Table IV.).

After it was found that a great reduction in the reactivating properties of these chronic sera existed, the question arose as to the exact cause of this change. Three possibilities immediately present themselves: first, that there is a reduction in the intermediary body of

[1] This term will be used to designate the serum obtained from the diseased individuals.

TABLE IV.

Observation V. J. C., male, aged 64 years? Uraemia. Death May 10, one day after blood was drawn.

Blood drawn May 2, 3 p.m. Serum used May 10, 2 p.m. Autopsy: Chronic nephritis; general Streptococcus infection.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. unheated serum + B. coli	39,000	10,740	8,040	2,100	Innumerable
1 c.c. ,, ,, + B. typhi	50,000	12,400	1,760	15	Sterile
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	50,000	16,000	15,000	14,080	Innumerable
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	50,000	10,120	10,920	6,740	,,
1 c.c. heated serum + 2/10 c.c. unheated serum + B. typhi	50,000	14,000	11,400	960	42
1 c.c. heated serum + 8/10 c.c. unheated serum + B. coli	39,000	5,860	4,860	3,130	Innumerable

Observation VI. M., male, aged 60 years. Uraemia; death April 18. No autopsy.

A. Blood drawn April 17, 5 p.m. Serum used 3.30 p.m. April 18 = Serum A. Healthy serum = serum B.

1 c.c. unheated serum A + B. coli	44,750	7,240	7,580	29	2
1 c.c. ,, ,, A + B. typhi	50,000	13,300	7,120	6,450	120
1 c.c. heated serum A + 1/20 c.c. unheated serum A + B. typhi	50,000	11,325	8,000	10,000	Innumerable
1 c.c. heated serum A + 1/10 c.c. unheated serum A + B. typhi	50,000	11,460	7,150	7,900	,,
1 c.c. heated serum B + 1/10 c.c. unheated serum A + B. typhi	50,000	12,250	7,080	11,450	,,
1 c.c. heated serum B + 2/10 c.c. unheated serum A + B. typhi	50,000	10,000	7,340	6,120	,,
1 c.c. heated serum A + 8/10 c.c. unheated serum A + B. coli	44,750	6,480	3,380	620	,,

Observation VII. M. C., female, aged 62 years. Chronic alcoholism; uraemia; recovery.

Blood drawn April 9, 4.30 p.m. Serum used April 10, 1 p.m. = Serum C. Normal serum = serum B.

1 c.c. unheated serum C + B. coli	Innumerable	16,800	4,460	4	Sterile
1 c.c. ,, ,, C + B. typhi	,,	30,700	8,980	17	,,
1 c.c. heated serum C + 1/10 c.c. unheated serum C + B. typhi	,,	10,900	6,440	16,500	Innumerable
1 c.c. heated serum B + 1/10 c.c. unheated serum C + B. typhi	,,	14,000	7,440	1,010	,,
1 c.c. heated serum B + 2/10 c.c. unheated serum C + B. typhi	,,	13,200	13,600	584	,,
1 c.c. heated serum C + 7/10 c.c. unheated serum C + B. coli	,,	18,500	13,600	9,700	,,

Observation VIII. D. P., male, aged 45 years. Clinical diagnosis: Aneurism.

Blood drawn January 8, 8 p.m. Serum used January 9, 11 a.m. Blood cultures. Four c.c. of blood in three bouillon flasks of 250 c.c. Cultures sterile.

1 c.c. unheated serum + B. coli	38,000	5,000	4,980	6	Innumerable
1 c.c. ,, ,, + B. typhi	Innumerable	44,900	3,550	122	,,

Death January 11? Two days before death signs of consolidation at left base. Diagnosis: Pneumonia.

the serum: second, that there is a formation of auto-anticomplement; and third, that there is a true reduction in complement.

The serum from a case which showed decided reduction in bacteriolysis was heated, and to 1 c.c. of this heated abnormal serum small quantities of fresh complement-containing serum from a normal patient were added; reactivation was complete. For typhoid bacilli, 1/20 c.c. of fresh normal serum restored the bacteriolytic property of 1 c.c. of the heated abnormal serum, and 6/10 c.c. of fresh abnormal serum did the same for the colon bacilli (Table V.).

TABLE V.

Observation IX. Serum from Observation I. = serum D. Uraemia; death.

Normal serum = serum E. Healthy male, aged 28 years. Blood drawn May 15, 6 p.m. Serum used May 16, 12 m.

	Control	Immediate	1 hour	5 hours	24 hours	48 hours
1 c.c. heated serum D + 1/10 c.c. unheated serum D + B. typhi	50,000	10,120	10,920	6,740	Innumerable	
1 c.c. heated serum D + 8/10 c.c. unheated serum D + B. coli	39,000	5,860	4,860	3,160	,,	
1 c.c. heated serum D + 1/20 c.c. unheated serum E + B. typhi	23,000	3,580	4,500	1,700	45	Sterile
1 c.c. heated serum D + 6/10 c.c. unheated serum E + B. coli	37,000	4,040	2,180	4	Sterile	,,

TABLE VI.

Observation X. Abnormal serum = serum M. Uraemia; death.

Normal serum = serum N.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. heated serum M + 1/10 c.c. unheated serum M + B. typhi	50,000	11,460	7,150	7,900	Innumerable
1 c.c. heated serum M + 8/10 c.c. unheated serum M + B. coli	44,750	7,420	6,040	2,160	,,
1 c.c. heated serum N + 1/10 c.c. unheated serum M + B. typhi	50,000	12,250	7,080	11,450	,,
1 c.c. heated serum N + 8/10 c.c. unheated serum M + B. coli	44,750	6,480	3,380	620	,,

Observation XI. Abnormal serum = serum O. Uraemia; death.

Healthy serum = serum E. Same as serum E in Observation VIII. Table IV.

1 c.c. heated serum O + 7/10 c.c. unheated serum O + B. coli	60,000	3,720	3,950	2	Innumerable
1 c.c. heated serum E + 7/10 c.c. unheated serum O + B. coli	60,000	4,200	3,700	960	,,

A second experiment was made. Serum from a normal patient was heated, and fresh abnormal serum from cases of uraemia, etc., added in small quantities. There was no reactivation, or rather, fresh abnormal serum M or O did not reactivate heated normal serum N or E any better than its own serum (Table VI.).

Fresh normal serum, then, will reactivate serum which has partially lost its bacteriolytic properties; but this latter abnormal serum will not reactivate heated normal serum. There can be no reduction in the intermediary body, nor can a production of auto-anticomplement account for the entire diminution in bacteriolysis. Anticomplement is stable, and is known to remain uninjured even when heated to 60° C. (London)[1]; it would, therefore, be present in the heated serum, and prevent the action of the complement contained in the added fresh normal serum—that is, if auto-anticomplement existed, the complement of fresh normal serum would probably be neutralized, and hence it would fail to reactivate the heated abnormal serum. There can be only one conclusion: the entire phenomenon is due to an actual decrease in complement. The reduction in bacteriolysis and the imperfection of reactivation are due to a diminution in complement.

The question of the relation of this diminution in complement to the development of terminal infections is important. Do those cases which show the most marked change in the complement really succumb to infection?

In each of the four autopsies a definite infection could be discovered (Table VII.).

TABLE VII.

Observation XII. D. D., male, aged 45 years. Clinical diagnosis; uraemia: pneumonia? Blood drawn February 10, 4.30 p.m. Serum used February 11, 10.30 a.m.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. unheated serum + B. coli	Innumerable	20,300	3,950	—	455
1 c.c. ,, ,, + B. typhi	46,800	14,100	4,900	—	350
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	Innumerable	26,500	12,500	—	19

Death February 10, 11.30 p.m. Autopsy 196.

Anatomical diagnosis: Chronic interstitial nephritis; multiple infarctions of lung.

[1] London. *Centralbl. f. Bakteriol.*, 1902, XXXII. p. 48, p. 147.

Observation XIII. A., female, aged 55 years. Clinical diagnosis: cirrhosis of liver.

Blood drawn February 19, 4.30 p.m. Serum used February 20, 1.30 p.m.

1 c.c. unheated serum + B. coli	43,000	3,750	3,930	820	Innumerable
1 c.c. ,, ,, + B. typhi	50,000	3,840	2,160	870	Sterile
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	50,000	4,890	3,180	3,160	5
1 c.c. heated serum + 4/10 c.c. unheated serum + B. typhi	50,000	3,740	1,920	223	Sterile

Death April 17. Anatomical diagnosis: Atrophic cirrhosis of liver; general infection with *B. coli.*

Observation XIV. D. P., male, aged 30 years. Clinical diagnosis: Uraemia.

Blood drawn March 22, 10 a.m. Serum used March 23, 11 a.m.

1 c.c. unheated serum + B. coli	176	80	29	74	Increase
1 c.c. ,, ,, + B. typhi	9,500	2,820	888	7	Sterile
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	9,500	3,140	1,080	39	,,
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	9,500	2,650	1,060	18	1
1 c.c. heated serum + 2/10 c.c. unheated serum + B. typhi	9,500	2,360	640	12	Sterile
1 c.c. heated serum + 8/10 c.c. unheated serum + B. coli	176	28	21	58	Innumerable

Death March 24. Anatomical diagnosis: Chronic interstitial nephritis, acute bronchopneumonia.

Observation XV. J. C., male, aged 64 years? Uraemia.

Blood drawn May 6, 3.30 p.m. Serum used May 7, 12 m.

1 c.c. unheated serum + B. coli	40,000	59,000	13	380	Innumerable
1 c.c. ,, ,, + B. typhi	50,000	11,780	4,660	11	Sterile
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	50,000	11,780	10,270	2,800	2
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	50,000	13,450	4,020	2	Sterile
1 c.c. heated serum + 8/10 c.c. unheated serum + B. coli	40,000	4,400	3,940	730	Innumerable

May 9. Patient much worse. Blood cultures = Streptococcus pyogenes.

Blood drawn May 9, 3 p.m. Serum used May 10, 2.30 p.m.

1 c.c. unheated serum + B. coli	39,000	10,740	8,040	2,100	Innumerable
1 c.c. ,, ,, + B. typhi	50,000	12,400	1,760	15	Sterile
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	50,000	16,000	15,000	14,080	Innumerable
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	50,000	10,120	10,920	6,740	,,
1 c.c. heated serum + 2/10 c.c. unheated serum + B. typhi	50,000	14,000	11,400	960	42
1 c.c. heated serum + 8/10 c.c. unheated serum + B. coli	39,000	5,860	4,860	3,130	Innumerable

Death May 10. Anatomical diagnosis: General arterial sclerosis, chronic interstitial nephritis, terminal pneumonia, general Streptococcus infection.

Case XV. is of special interest. The first examination showed only a mild complement decrease, but two days later the complement had fallen perceptibly, and *Streptococci* were recovered from the blood. Certainly, the development of the infection is perfectly clear—the gradual reduction of complement with consequent crippling of the protective power of the serum, the onset of an infection, an overwhelming multiplication of bacteria, and then death from general streptococcus infection.

In two other fatal cases of uraemia, which, however, did not come to autopsy, a terminal infection of some kind was suspected from a marked hyperleucocytosis and a rise in temperature; and in a fatal case of aneurism signs of pneumonia were found a few days before death.

The following result obtained in the case of diabetes mellitus needs no comment, since secondary infections in this disease are notoriously common (Table VIII.).

TABLE VIII.

Observation XVI. Philadelphia Hospital. Female, aged 60 years? Clinical diagnosis: diabetes mellitus.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. unheated serum + B. coli	20,900	5,000	2,500	143	Innumerable
1 c.c. ,, ,, + B. typhi	20,200	10,000	5,200	394	4,400
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	20,200	6,300	5,900	184	1,500

Finally, the two cases of uraemia with recovery must be considered. These illustrate the possibility of a decrease in complement, perhaps fleeting, without infection and with subsequent improvement. In these instances the temporary disappearance of the complement, while exposing the individual to infection, may be of short duration, in which event the danger may be accidentally escaped, or infection of light degree occurring, the restitution of complement may suffice to overcome it. But it must be borne in mind that, after all, the use of two organisms which are not the usual ones of terminal infection is only an indirect mode of establishing total bacteriolytic complement-content. Where so many complements are dealt with it might readily happen that the conditions for *Streptococci* and *Staphylococci*, the chief agents of terminal infection, might be quite different. The latter organisms do not, unfortunately, lend themselves minutely to discriminating tests.

The results of examinations from the 10 cases which comprise this group are undoubtedly very suggestive. Every case showed a pronounced decrease in the complement-content of the blood, and the mortality among them was 70 per cent. Of the three patients who did not die, one had diabetes mellitus and one chronic alcoholism. Terminal infection was proven to be the immediate cause of death in five cases, and was suspected to have existed in the other two cases.

GROUP II.

This group includes a series of records much less convincing than those of Group I. Of the five cases only two are known to have died, and neither blood cultures nor autopsies were obtained in any case; one case of uraemia left the hospital improved, and a fourth case was lost sight of; the fifth case, still living, is one of cirrhosis of the liver. In most of the cases bacteriolysis did not take place with normal amounts of reactivating serum; in the rest, bacteriolysis was simply prolonged. Bacteriolysis, however, in every instance was distinctly below normal. The mortality was 40 per cent. (Table IX.).

TABLE IX.

Observation XVII. A. F., male, aged 53 years. Clinical diagnosis: Cirrhosis of liver; patient living.

Blood drawn February 19, 6 p.m. Serum used February 20, 12 m.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. unheated serum + B. coli	43,000	5,300	3,260	8	Sterile
1 c.c. ,, ,, + B. typhi	50,000	5,520	635	1	,,
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	50,000	6,320	4,530	1,900	32
1 c.c. heated serum + 2/10 c.c. unheated serum + B. typhi	50,000	3,660	1,690	310	Sterile

Observation XVIII. Philadelphia Hospital. Male, aged 70 years? Uraemia; unconscious.

Blood drawn February 26, 4.30 p.m. Serum used February 27, 11 a.m.

1 c.c. unheated serum + B. coli	42,100	9,650	11,600	416	Sterile
1 c.c. ,, ,, + B. typhi	Innumerable	15,100	10,200	412	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	,,	13,500	10,500	11,600	424
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	,,	11,425	12,000	5,400	87

Indeed, these records probably represent the usual state of the blood in such maladies as nephritis or cirrhosis of the liver, and suggest

that it is not until the most critical stages of the disease are reached that a great reduction in the complement-content of the blood takes place.

Group III.

Finally, we come to this last group of cases, comparatively small, it is true, but none the less important. In two fatal cases the blood showed no change from the normal as regards its complement-content. One patient died of uraemia; the other, a man, aged thirty years, of pericarditis with effusion. No autopsy is recorded in the second case. The first patient developed symptoms of uraemia after a long attack of chronic nephritis, and remained unconscious for several days. During this time two examinations were made of her blood—the first, three days before death; the second, one day later. At the time of the second examination blood cultures were obtained. No growth developed in any of the bouillon flasks (Table X.).

Table X.

Observation XIX. S. T., female, aged 58 years? Clinical diagnosis: Uraemia.

Blood drawn June 24, 2.30 p.m. Serum used June 25, 10.30 a.m. June 24, leucocytes, 26,150.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. unheated serum + B. coli	20,900	6,800	3,750	7	Sterile
1 c.c. ,, ,, + B. typhi	20,200	6,200	2,300	1	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	20,200	7,300	1,300	5	,,
1 c.c. heated serum + 6/10 c.c. unheated serum + B. coli	20,900	4,600	1,300	6	12,500
1 c.c. heated serum + 8/10 c.c. unheated serum + B. coli	20,900	3,800	1,480	4	Sterile

June 25. Patient about the same. Has had salt infusions. Blood cultures = sterile.

Blood drawn June 25, 3 p.m. Serum used June 26, 2.30 p.m. Leucocytes, 21,900.

1 c.c. unheated serum + B. coli	16,300	3,400	674	10	Sterile
1 c.c. ,, ,, + B. typhi	20,600	5,950	488	Sterile	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	20,600	5,800	4,200	60	,,
1 c.c. heated serum + 6/10 c.c. unheated serum + B. coli	16,300	3,200	936	3	1
1 c.c. heated serum + 8/10 c.c. unheated serum + B. coli	16,300	956	346	46	Sterile

Death, June 27.

The patient died two days after the last specimen of blood was taken. The anatomical diagnosis at autopsy was chronic interstitial

nephritis, hypertrophy and dilatation of the heart, œdema and congestion of the lungs. Cultures from the heart's blood, spleen, liver, and kidneys gave negative results. On plates from the lungs a few colonies of *Streptococcus pyogenes* were found.

Here, then, is a case without reduction of complement and without demonstrable terminal infection. As far as bacteriological methods go, neither before nor after death was an infection of any kind revealed. Certainly, this case furnishes a supplement for the cases of Group I. We know it is not every case of Bright's disease or heart disease that dies from a terminal infection, nor do all these cases show a reduction in complement; and the mere knowledge of these facts cannot but suggest that there must be some sort of relationship between the two. That in this instance a high complement-content should be associated with the absence of demonstrable terminal infection strongly suggests that one condition is dependent upon the other, and that without complement reduction there is no terminal infection. To support this view still further we can only advance the many positive cases where the complement was reduced and terminal infection did develop.

When the results of this series of experiments are summed up they seem to show that in general during the course of a prolonged chronic disease, such as nephritis, cirrhosis of the liver, and heart disease, the bacteriolytic complement-content of the blood usually falls below normal. If the patient gets seriously worse, the reduction becomes so great that the resistance of the patient is dangerously injured, and the body is no longer protected against the entrance of bacteria. At this time the slightest exposure affords ample opportunity for the entrance of bacteria into the body; and this entrance once effected, an infection is directly set up, which threatens rapidly to terminate fatally. If the necessary exposure is in any way prevented, and the individual tides over this critical period of greatly decreased complement, or has perhaps only a slight decrease in complement, the chances of recovery are good. Just this state of affairs is exemplified in a severe case of cardiac break-down, and such a case is illustrated in Group I.

Finally, a small percentage of cases do not show a diminution in the complement-content of their blood, and it is in all likelihood these cases that escape terminal infection.

The complement may be looked upon as an index to the resistance of the patient. If the complement is decreased, the resistance is lowered; if the complement remains above normal limits, the resistance is

high. But it must not be forgotten that even the normal is not an absolutely fixed quantity; very slight fluctuations are found in comparatively healthy persons, and according to the well-being or ill-being of that person the complement rises or falls.

After the above results were obtained a second series of experiments was undertaken to see whether a decrease in the complement-content of the blood could explain the development of general infections following localized wound infections. It was exceedingly difficult to find suitable cases for this purpose, and the number of observations is, therefore, small. In only one case, moreover, was it possible to prove that a wide-spread infection existed. This was a fatal case of peritonitis. Most of the cases were fairly mild local infections, with rapid recovery. They include nine observations, all of which can be roughly divided into two main groups. In the first the complement was increased, in the second it was decreased.

Group I. comprises:

Cellulitis of arm	1	case.	Recovery.
Appendicitis	1	„	„
Cellulitis of leg	1	„	„
Pyonephrosis	1	„	Death.
Infected scalp wound	1	„	Recovery.
Pelvic abscess	1	„	„
General peritonitis	1	„	Death.

When the blood was drawn for examination the patient's white blood corpuscles were always counted. In every case there was a hyperleucocytosis ranging from 13,000 to 25,000. The serum of every case, even of those that terminated fatally, showed an increase in the complement for *B. coli* and *B. typhosus*. Sometimes with *B. coli* only one-third the normal amount of complement was necessary to reactivate 1 c.c. of heated serum (Table XI.).

The association of the rise in complement with the hyperleucocytosis is noteworthy, and appears to agree with the results of those observers who consider that the complement or alexin takes its origin or at least is present in the bodies of the polymorphonuclear leucocytes. Wassermann[1] has reviewed this subject, and has himself been able to produce an anticomplement for the serum of rabbits by injecting rabbit's washed leucocytes into the peritoneal cavity of guinea-pigs; but anticomplement was obtained in such small quantity that he believes, though the poly-

[1] Wassermann. *Zeitschrift f. Hygiene u. Infektionskrankheiten*, 1901, xxxvii. p. 173.

morphonuclear leucocytes undoubtedly contain a certain amount of complement, they cannot give rise to its total in the body.

TABLE XI.

Observation XX. J. T., male, aged? Clinical diagnosis: Cystitis. July 17, leucocytes, 17,100.

Blood drawn July 17, 8 p.m. Serum used July 18, 1.30 p.m.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. unheated serum + B. coli	14,500	8,900	2,200	Sterile	Sterile
1 c.c. ,, ,, + B. typhi	22,000	16,400	1,300	,,	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	22,000	17,700	2,000	,,	,,
1 c.c. heated serum + 6/10 c.c. unheated serum + B. coli	14,500	2,080	800	,,	,,

Observation XXI. J. C., male, aged 35 years? Appendicitis: operation; general peritonitis.

Blood drawn July 21, 9 p.m. Serum used July 22, 11.30 a.m. July 21, leucocytes, 29,400.

1 c.c. unheated serum + B. coli	Innumerable	12,900	700	Sterile	Sterile
1 c.c. ,, ,, + B. typhi	29,000	7,700	146	,,	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	29,000	8,670	2,800	106	,,
1 c.c. heated serum + 4/10 c.c. unheated serum + B. coli	Innumerable	6,800	2,900	Sterile	,,

Death, July 23. Autopsy. Anatomical diagnosis: acute general fibrinopurulent peritonitis.

Observation XXII. P., male, aged 58 years. Infected scalp wound. June 30, leucocytes, 13,900.

Blood drawn June 30, 12.30 p.m. Serum used June 31, 12.30 p.m. Recovery.

1 c.c. unheated serum + B. coli	Innumerable	4,400	830	Sterile	Sterile
1 c.c. ,, ,, + B. typhi	,,	33,220	4,030	,,	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	,,	22,000	8,200	,,	,,
1 c.c. heated serum + 6/10 c.c. unheated serum + B. coli	,,	4,900	2,800	,,	,,

Group II. In the second group there are only two cases—one of gangrene of the arm and one of carcinoma of the uterus, with operation and intestinal resection, followed by pelvic abscess and death.

The first patient (Table XII.) was exceedingly ill when the blood was taken, but unfortunately the subsequent history was not obtainable, so that the fate of the case is unknown.

Table XII.

Observation XXIII. M. T., male, aged 16 years? Clinical diagnosis: gangrene of arm; amputation.

Blood drawn July 26, 1 p.m. Serum used July 27, 10 a.m.

	Control	Immediate	1 hour	5 hours	24 hours	48 hours
1 c.c. unheated serum + B. coli	25,500	6,800	800	Sterile	Sterile	Sterile
1 c.c. ,, ,, + B. typhi	34,400	15,200	2,600	132	1	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	34,400	14,400	4,200	12	15	Innumerable
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	34,400	12,500	3,200	6	Sterile	Sterile
1 c.c. heated serum + 6/10 c.c. unheated serum + B. coli	25,500	3,200	294	65	2,600	Innumerable

Table XIII.

Observation XXIV. M. K., female, aged 65 years? Carcinoma of uterus. Operation. Resection of descending colon. July 4, leucocytes 26,600.

Blood drawn July 4, 10 a.m. Serum used July 5, 12 m.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. unheated serum + B. coli	29,700	8,000	2,000	8	Sterile
1 c.c. ,, ,, + B. typhi	19,100	7,700	4	Sterile	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	19,100	6,600	242	2	,,
1 c.c. heated serum + 2/10 c.c. unheated serum + B. coli	29,700	6,500	3,500	1,000	,,

July 11. Patient doing fairly well. Leucocytes 20,300.

Blood drawn July 11, 3.30 p.m. Serum used July 12, 1 p.m.

1 c.c. unheated serum + B. coli	30,150	11,400	1,230	75	Sterile
1 c.c. ,, ,, + B. typhi	38,500	14,600	100	Sterile	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	38,500	13,600	10,300	2,700	3
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	38,500	11,400	3,000	56	2
1 c.c. heated serum + 6/10 c.c. unheated serum + B. coli	30,150	5,900	4,800	1,010	45
1 c.c. heated serum + 8/10 c.c. unheated serum + B. coli	30,150	8,300	2,300	248	Sterile

From this time on the patient was much worse. Death, July 19. No autopsy.

The two observations in the second case (Table XIII.) are instructive, inasmuch as they show that a gradual reduction in the complement-content of the blood took place during the course of the patient's illness, corresponding to which the patient's condition grew worse. We were unable to make a third examination, and no autopsy was permitted, so

that the case remains somewhat incomplete, although the data are still sufficient to throw some light upon the cause of the unfavourable termination.

From this series of cases no very definite conclusions can be drawn other than that hyperleucocytosis has some influence upon the increase in complement for typhoid and colon bacilli. In only one of three fatal cases was there a decrease in complement, and even in this case the reduction must be looked upon as relative rather than real. It must be remembered, however, that with wound infections the danger of general invasion is from *Streptococci* or *Staphylococci*, and not from colon or typhoid bacilli, and the importance of this consideration was very definitely brought out in three or four observations upon the blood of typhoid fever patients.

It has already been shown by Ehrlich and Morgenroth[1], Wechsberg[2], Wendelstadt[3], and Marshall and Morgenroth[4] that haemolytic serum contains several specific haemolytic complements, and Wassermann[5] has succeeded in separating the general group of haemolytic complements from the bacteriolytic complements. The agglutinins, too, are known to be definite specific substances, and Verney[6] has furthermore demonstrated that if a given serum agglutinates both typhoid and colon bacilli, this property is due to the fact that the serum contains a specific agglutinin for *B. typhosus* and another for *B. coli*. Now since the general properties of haemolytic and bacteriolytic sera are so similar, it would not be surprising to find that bacteriolytic sera as well as haemolytic sera possessed not one common complement capable of affecting all bacteria, but a multitude of definite specific complements.

Typhoid fever represents a class of diseases in which the bacteria that cause the affection are widely distributed throughout the body. At one time during the course of the disease bacilli are almost always present in the circulating blood, and it is now fairly certain that typhoid fever is really a general infection characterized by local lesions, and not purely an infection of the intestinal tract.

For this reason it was thought that some interest might be attached to a study of the bacteriolytic properties of the blood of typhoid fever

[1] Ehrlich and Morgenroth. *Berliner klin. Wochenschrift*, 1900, No. 31.
[2] Wechsberg. *Wien. klin. Wochenschrift*, 1901, No. 48.
[3] Wendelstadt. *Centralbl. f. Bakteriol.*, 1902, xxxi. p. 469.
[4] Marshall and Morgenroth. *Centralbl. f. Bakteriol.*, 1902, xxxi. p. 570.
[5] Wassermann. *Op. cit.*
[6] Verney. *Centralbl. f. Bakteriol.*, 1902, xxxii. p. 290.

patients. In this connection the work of Richardson[1] may be cited. He found, using hanging-drop preparations, that typhoid sera were less destructive to typhoid bacilli than normal sera, and that the addition of normal sera to typhoid sera restored bacteriolysis.

Table XIV.

Observation XXV. W. D., male, aged 30 years. Typhoid fever, ninth day of disease. Death, Sept. 2.

Blood drawn Sept. 15, 4 p.m. Widal, negative, Sept. 15.

Serum used Sept. 16, 12 m. Blood cultures, Sept. 15: *B. typhosus*.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. unheated serum + B. coli	40,000	11,000	1,300	27	Sterile
1 c.c. ,, ,, + B. typhi	50,000	16,500	960	3	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	50,000	16,800	4,500	5,500	Innumerable
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	50,000	13,200	3,820	1,620	,,
1 c.c. heated serum + 2/10 c.c. unheated serum + B. typhi	50,000	15,600	2,120	38	36
1 c.c. heated serum + 6/10 c.c. unheated serum + B. coli	40,000	9,000	1,480	220	Sterile

Observation XXVI. W. S., aged 35 years. Typhoid septicaemia, acute endocarditis.

Blood drawn Sept. 23, 3 p.m. Widal, Sept. 23. Positive in 1 : 5000.

Serum used Sept. 24, 1 p.m.

Blood cultures Sept. 6: *B. typhosus*. Blood cultures Sept. 23, negative.

1 c.c. unheated serum + B. coli	60,000	14,800	940	3	Sterile
1 c.c. ,, ,, + B. typhi	50,000	17,800	8,200	33	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	50,000	17,400	19,000	20,000	3,740
1 c.c. heated serum + 1/10 c.c. unheated serum + B. typhi	50,000	15,000	15,800	14,200	1,640
1 c.c. heated serum + 2/10 c.c. unheated serum + B. typhi	50,000	15,900	12,800	2,400	160
1 c.c. heated serum + 4/10 c.c. unheated serum + B. typhi	50,000	17,700	10,200	60	Sterile
1 c.c. heated serum + 6/10 c.c. unheated serum + B. coli	60,000	9,300	3,540	320	120

Observation XXVII. H. R., aged 28 years. Typhoid fever, mild. Widal, positive, Sept. 15.

Blood drawn Sept. 17, 4.30 p.m. Blood cultures, Sept. 17, negative.

Serum used Sept. 18, 11.30 a.m. Recovery.

1 c.c. unheated serum + B. coli	40,000	8,820	2,080	Sterile	Sterile
1 c.c. ,, ,, + B. typhi	50,000	10,840	3,160	44	,,
1 c.c. heated serum + 1/20 c.c. unheated serum + B. typhi	50,000	16,900	9,300	1,350	,,
1 c.c. heated serum + 6/10 c.c. unheated serum + B. coli	40,000	5,200	2,480	Sterile	,,

[1] Richardson. *Journal of Medical Research*, 1901, VI. p. 187.

In the present experiments the blood of three typhoid fever patients was examined. Case I. ended fatally; Case II. was probably a true case of typhoid septicaemia, with symptoms of acute endocarditis; and Case III. ran a mild, short course (Table XIV.).

In the first two cases typhoid bacilli were recovered from the circulating blood; in the third case blood cultures were negative, and the patient's temperature dropped to normal the day after blood was drawn. The significance of the above results, however, lies in the fact that the reactivating power of the serum was greatly diminished for typhoid bacilli and not for colon bacilli. *B. paracoli* (Cushing) and *B. dysenteriae* (Shiga) were next tried, and exactly the same result was obtained. The typhoid serum showed a decrease in reactivating power for typhoid bacilli, but for typhoid bacilli alone (Table XV.).

TABLE XV.

Observation XXVIII. Healthy normal serum from Observation III.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. heated serum + 1/10 c.c. unheated serum + B. dysenteriae	40,000	9,700	2,260	Sterile	Sterile
1 c.c. heated serum + 2/10 c.c. unheated serum + B. paracoli	60,000	9,500	270	,,	,,
Observation XXIX. Typhoid serum from Case XXV.					
1 c.c. heated serum + 1/10 c.c. unheated serum + B. dysenteriae	19,000	4,040	1,840	1,940	Sterile
1 c.c. heated serum + 2/10 c.c. unheated serum + B. paracoli	40,000	11,900	910	113	,,

If normal complement containing serum was now added to these typhoid sera, reactivation was complete (Table XVI.).

TABLE XVI.

Observation XXX. Typhoid serum from Observation XXV. = P. Normal serum from Observation III. = Q.

	Control	Immediate	1 hour	5 hours	24 hours
1 c.c. heated serum P + 1/20 c.c. unheated serum Q + B. typhi	Innumerable	8,800	7,600	2,580	Sterile
1 c.c. heated serum P + 6/10 c.c. unheated serum Q + B. coli	10,000	2,020	500	46	,,

This reduction in the specific bacteriolytic power of typhoid serum, evidenced by the difficulty in reactivating heated serum with unheated

typhoid serum for typhoid bacilli, is due solely to the fact that the complement for typhoid bacilli has been reduced—reduced for this organism, and for it alone[1]. It must be that in typhoid fever the specific typhoid complement is, as it were, picked out from the other bacteriolytic complements, and suffers a change to which *B. coli*, *B. dysenteriae*, and even *B. paracoli* are not subject. This means that we are dealing not with one common bacteriolytic complement, but with a multitude of specific complements, so highly differentiated that organisms as closely related as *B. typhosus* and *B. paracoli* can only be destroyed by the combination of their own peculiar complements with the corresponding intermediary body for that organism. In certain cases of typhoid fever the specific typhoid complement falls, and although the several complements for the other organisms remain unaltered, they can be of no assistance in the destruction of typhoid bacilli, inasmuch as they are unable to unite with the specific intermediary body for that bacillus.

Chronic diseases differ materially from acute diseases. In uraemia or heart disease probably all the complements suffer, though perhaps not in equal proportions; for Flexner[2] has shown that the bacteriolytic power of the blood in these cases is diminished toward the *Staphylococcus aureus*, and Laquer[3], Neisser and Doering[4], and Hedinger[5] have demonstrated a reduction of haemolysis in uraemia. But when *B. coli* and *B. typhosus* are alone used as indicators for the complement-content of serum, accurate results, even in chronic disease, cannot be hoped for in all cases, since it is the pyogenic cocci which are mostly concerned in the production of terminal infections; and in acute wound infections, where, probably as in typhoid fever, only a specific com-

[1] After the completion of this article the important paper by Wright and Windsor (*Journal of Hygiene*, 1902, II. p. 385) appeared. The results given in it in respect to the bacilli of typhoid fever and Asiatic cholera bear directly upon a part, at least, of my studies. The preliminary diminution in bactericidal power of the blood which occurs in anti-typhoid inoculation is of interest in view of the reduction in complement for typhoid bacilli which takes place during the course of typhoid fever. A point in our results upon which we fail to agree entirely, but which a study directed especially to its elucidation might readily clear up, is the evidence in my studies upon normal serum of a difference between the bacteriolytic complements for typhoid and colon bacilli, Wright and Windsor having found that the bacteriolytic body of normal serum is one for both the bacilli of typhoid fever and Asiatic cholera. So far as the individuality of the complement for typhoid bacilli is concerned my results with normal serum are borne out by the tests upon the serum of typhoid patients in whom the complement for the colon bacillus and some other bacilli is unimpaired.

[2] Flexner. *Op. cit.*

[3] Laquer. *Op. cit.*

[4] Neisser and Doering. *Op. cit.*

[5] Hedinger. *Op. cit.*

plement or group of complements is affected, and those for the pyogenic cocci alone, satisfactory experiments cannot be made unless these bacteria are used as indicators for the complement-content of the blood, a procedure not as yet made practicable.

CONCLUSIONS.

1. Normal individuals show slight fluctuations in the bacteriolytic complement-content of their blood.

2. In many prolonged chronic affections, such as nephritis, cirrhosis of the liver, and diabetes mellitus, there is a marked decrease in the bacteriolytic blood complement, which becomes more marked towards the end of the disease.

3. Terminal infection in chronic disease is probably the direct result of the diminished state of the bacteriolytic complement.

4. The blood serum of certain individuals suffering from chronic disease does not show a reduction in complement; these individuals appear to escape terminal infection.

5. Hyperleucocytosis is frequently associated with high complement-content of the blood serum for typhoid and colon bacilli.

6. The blood serum of some typhoid fever patients shows a diminution in the specific complement for the typhoid bacillus.

7. Human blood serum contains a multiplicity of bacteriolytic complements.

I wish to express my great indebtedness to Dr Flexner for his constant supervision and aid in carrying out the experiments, to the Residents of the Pennsylvania Hospital for many courtesies, and to Mr W. H. Mackinney for substantial assistance in the prosecution of this study.