rosis developed which proved fatal, an end picture equally typical of glomerulo-nephritis.

Kaufmann and Mason[6] are of the opinion that a nephrotic kidney may progress into a secondary contracted type, to be distinguished from the primary contracted kidney of glomerulo-nephritis. They describe a carefully studied case in which the patient passed through a first stage of the typical nephrotic type, and then entered upon a second stage in which such features as hypertension, retinal changes, and nitrogen retention were superadded. Whether such cases and the one recounted above should be regarded as nephrosis progressing to renal insufficiency or as true but atypical glomerulo-nephritis from the beginning is open to question, a question which must still remain unanswered.

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COMPLEMENT IN HEALTH AND IN DISEASE

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HOWEVER complicated immunity problems may be they always furnish interesting subjects for investigation. Also, this wide field happily supplies a mental playground for medical men, for surely no physician is so bound to the routine of his daily work, or so involved in the subtle scientific intricacies of modern medical practice that he neglects to let his thoughts dwell on the broader aspects—the unexplained marvels of immunity phenomena — that come under his daily observation.

The difficulty experienced in discussing a problem in immunity is to confine ourselves to that single problem. The opinions and experiments concerned with each point of view or theory are numerous, complicated and technical. A study of a single factor with all its associated biological phenomena, involves us in a consideration of other problems in the wide question of infection and resistance.

Phagocytosis, the antibacterial action of the body fluids, the bacteriophage, the mechanical and chemical protection provided by certain cells, afford varied factors in the body's resistance to infection; but for the purpose of this discussion we will attempt to limit ourselves to a consideration of a phase of the bactericidal property of the blood serum—namely, the foreign body—antibody—complement reaction.

The response to the invasion of the body tissues by a foreign agent is observed in the formation of an antibody. The action of the antibody on the foreign body is facilitated in some, if not all, instances, by a third substance—complement or alexin. The fluctuation in the power of the latter factor has been the subject of but limited investigation.

This complement may be defined as a substance of unknown nature, present in the blood serum, by means of which the latter is able to take part in certain immunological reactions. Complement is thermolabile in the sense that it is rapidly destroyed at 55° C., and it is, moreover, extremely sensitive to the action of acids and alkalies. Normally, after removal of the blood from the body this immunological power gradually disappears; also, it may be destroyed by shaking; and finally, under certain conditions, it may be reactivated.

Although the nature of this substance is indefinite, yet a fairly accurate estimation of its ability to take part in certain immunological reactions may be demonstrated by the use of the complement fixation test. As is well known,

this test is one of the most striking phenomena concerned in the problem of immunity. It involves and depends upon the interaction of the foreign body (infective agent), the antibody (amboceptor) and the complement (alexin). The practical and valuable application of the principles of variation among these three substances, as may be determined in vitro, is exemplified in the serum test for syphilis and other diseases.

The variations in the three factors, foreign body, antibody and complement within the tissues, and the endless variations in relation to one another give rise largely to the difference in symptoms and results observed in many infectious diseases. The nature of the foreign body may be considered accidental, but the formation and the use of the antibody depend on the body tissues.

With this in mind it was thought that a further study of the variations in the power of the complement in health and in disease would prove of advantage. Investigations were carried out on the blood of 230 normal persons and 280 patients suffering from various diseases. The persons in normal health included children, students, laboratory workers and prisoners. A specimen of blood from a prisoner represented a portion of that which it was necessary to obtain for the routine Wassermann examination. The regular life and diet of the prisoners naturally was conductive to a uniform standard of health.

Technique.—The blood was collected from a vein into a sterile vacuum tube. All specimens were collected at the same hour of the morning in order to obviate, as far as possible, any variations in the complement content that might arise following the ingestion of food. The specimens were placed in the incubator for thirty minutes and were then removed to the icebox where they were left for four hours before the tests were carried out. They were not centrifuged, as centrifuging was found to cause variations in complement content. Some specimens were left in the icebox for twenty-six hours. Variations in the complement titre between those left in the icebox for four hours and those left for twenty-six hours were found to be neglible.

One-half c.c. of each individual serum was withdrawn from its container and sufficient normal saline added to make a dilution of one in fifty. A series of test tubes was set up for each specimen, and to those were added the same amount of sensitized sheep cell mixture, and sufficient saline to make an equal total volume.

Amboceptor for sheep cells of the same titre was used throughout all the tests. Specimens containing an excess of natural sheep cell amboceptor were discarded.

TABLE 1

Test tubes 75mm. 9mm. No.	1	2	3	4	5	6	7	8	9	10
in c.c.	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Sensitized cells	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Normal saline ...	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0

The tubes were incubated for thirty minutes, then removed from the incubator and allowed to stand for one hour at room temperature; readings were then taken. A second method was to place the tubes in the icebox for eighteen hours before the readings were made. No appreciable difference was noted between the results obtained by the two different methods.

The tube containing the least amount of diluted serum which showed complete hæmolysis was taken as the titre of the complement power for that particular specimen. If no hæmolysis was noted in tube 10 the strength of the original serum dilutions was doubled and another series of tests set up. In four instances the use of undiluted serum failed to produce hæmolysis.

Findings in Health.—The reactions on the specimens of blood taken from persons in normal health gave a fairly uniform result. In 224 cases out of 230 examined with the technique adopted, complete hæmolysis took place between tubes 5 to 8.

Variations from these findings were noted in six cases. In these twice the normal amount of serum was required to produce hæmolysis. Investigations showed that one of these persons was recovering from influenza, one from diphtheria, while two proved to have nephritis and one developed into a definite case of endocarditis. The serum from one person who had no definite demonstrable pathological condition though he was of a sallow type and complained of fatigue on exertion, gave a complement titre of but 65 per cent normal.

Investigations were made on the blood of three persons in normal health to determine whether there was any variation depending

on the time of day the specimen was taken, or if there existed a variation in relation to meals. If, in the titration of such blood, hæmolysis took place in tube 6 in the morning specimen the rule was for the complement power to be increased by evening when complete hæmolysis might be noted in tube 5. There was never more than a one tube variation. However, the complement power of these persons frequently showed a weekly difference as wide as that found between persons in normal health; that is, while the blood of such a person gave complete hæmolysis in tube 5 one day, it might not give complete hæmolysis up to tube 8 a week later, or vice versa. The age of a person apparently made no appreciable difference in the complement power of the blood serum; the average age of those in normal health was twenty-five years.

Findings in Disease.—There seems to be no absolute rule for the variations found in the complement of patients' blood during disease. However, the investigations carried out on 280 patients indicated the existence of a fairly uniform reaction throughout the course of an acute infection. Commonly there was a slight increase of complement at the onset of the symptoms of disease, followed by a steady decline as the symptoms subsided, and during convalescence the complement gradually returned to normal. Similarly too, there was an increase of complement coincident with the onset of complications. Many fatal cases, however, showed a steady decrease in complement, and in some no reaction indicating its presence could be obtained.

While throughout the course of an illness fluctuations in the amount of complement may follow a general rule, the investigations of the substance in certain diseases showed that there was a wide and striking variation depending on the nature and location of the infection. In septicemia, endocarditis and nephritis the decrease was, as a rule, distinct, while in syphilis, chronic tuberculosis and chronic arthritis the loss was slight. Serum from patients with uncomplicated malignant disease, pernicious anæmia, goitre and diabetes gave but a slight change in alexin content.

The investigations of sixteen cases of septicemia showed that there was a loss of complement ranging from half normal to total absence. Twelve of these cases proved fatal. Specimens of blood from twenty-one patients with diseased hearts were examined. Valvular lesions, without evidence of existing infection, gave results which were normal, or close to normal; on the other hand, in eight cases diagnosed as subacute bacterial endocarditis a decided decrease in complement was noted progressive with the course of the disease, and in each fatal case there occurred, eventually, a decrease of from 50 to 100 per cent. Three cases diagnosed as bacterial endocarditis gave a normal complement titre, these three patients recovered. In none of the three was a positive blood culture ever obtained. A complement titre of half normal was found in two cases of auricular fibrillation, and in one case of myocarditis following diphtheria.

A loss of complement of 50 per cent or more was also noted in some cases of pneumonia, peritonitis, cellulitis, acute rheumatism and other severe infections. On the other hand, many cases were examined in which there was the usual slight variation in complement during the course of the disease, but which showed no evidence of a progressive decrease. Also, in five cases of severe illness the blood gave a normal complement titre even when taken a few hours before a fatal termination to such an illness. This is in agreement with a finding of Gunn[1] in his comprehensive study of the variations of complement in diphtheria, scarlet fever and typhoid.

As a rule there was noted a decrease of complement in cases of nephritis. The decrease varied from 5 per cent below normal to complete absence. This refers to cases of nephritis of unknown origin and also to those following infectious diseases. In acute nephritis the complement rapidly returned to normal on subsidence of the symptoms, but in chronic nephritis it remained deficient, eventually becoming almost or entirely absent in those cases that progressed to a fatal termination. Rockwood and Beeler[2], however, noted that patients with severe uremia showed no significant variation in the complement content of the serum.

It was thought that it would prove of interest to investigate the complement power of patients' blood before and after transfusions of small amounts of blood serum. Examinations were made on five such patients who were known to be deficient in complement, and in three the increase in this substance after transfusion

varied from 10 to 40 per cent. There was no response in two patients who were in a moribund condition from septicemia. An increase of 40 per cent was obtained in one case by the transfusion of but 20 c.c. of fresh serum. This latter patient, severely ill with a streptococcus hæmolyticus septicemia and with almost entire loss of complement, was treated with repeated transfusions of fresh human serum, together with inoculations of rabbit serum containing an amboceptor which had been prepared by the use of the specific streptococcus. There was a striking beneficial response to the treatment and the patient recovered.

Two specimens of blood out of 510 examined were found to be anticomplementary when tested against guinea pig complement. One of these serums was obtained from a patient suffering from a bacterial endocarditis, and one from a patient with a severe nephritis with uremic symptoms. High dilutions of these serums did not bring about hæmolysis, and microscopic examination of the sediment showed that the cells were not destroyed.

Attempts were made, in vitro, to reactivate the complement in four serums from patients when these serums had shown almost a complete absence of complement power. Reactivation, showing an increase of alexin over that of the original specimen, and varying from 10 to 30 per cent was obtained by the addition of fresh serum in three instances.

Discussion.—The findings for normal persons indicate that in health the complement content of the blood is fairly constant. Any decrease of more than 25 per cent under the normal suggests a careful scrutiny of that person's condition. I think it justifiable to consider a high complement power as a beneficial factor in immunity.

While the complement titre of the blood shows, as a rule, definite fluctuations at certain periods in the course of a disease that is due to infection, and also wide variations depending on the severity, character and location of the infection, yet there are exceptions which make it impossible to draw aboslute conclusions. *A slight fall of complement that coincides with an improvement in the patient's condition indicates that immune bodies are being formed with a subsequent binding of complement. Such a variation in complement was noted in patients in whom there was a favourable outcome. However, the decided and progressive loss of this substance, more especially during those diseases that terminate fatally, would suggest that the finding of a persistent low complement power in disease is to be considered of grave significance, and the finding of a steady and progressive loss of this power is a bad prognostic sign.* Such an extreme loss was occasionally noted in patients who were apparently doing well, but who afterwards did badly. In such cases, and the findings most frequently occurred in endocarditis, the investigations may prove of value as an aid to diagnosis. Finally, since complement is so much concerned in body immunity, it would seem justifiable, when so required, to treat the patient with a view to either stimulating the production of, or to replacing this substance.

The question arises: Is alexin essential to life? Two cases of disease in which a complete absence extending over months was noted, proved fatal. Yet one of the normal cases investigated —a girl who had recovered from an attack of diphtheria—showed almost complete absence of complement for months, and still the girl appeared to be in good health. Also, two patients with chronic nephritis and one with endocarditis showed a severe loss of complement extending over a period of three years, and, while the outcome was fatal, during that time these patients gave no evidence of disease other than would be expected from the essential condition. One apparently normal case showed a diminution of complement power of over 25 per cent.

In this connection it is well to note that there has been discovered a race of guinea pigs in the blood of which active alexin was found to be greatly diminished.[3] They were reported, however, to lack the vitality of the average stock. Apparently, then, life itself is possible in the absence or decrease of complement as may be determined by the examination of the blood serum.

Now, the reason for the diminution of complement in disease is not established. Is there a failure of the tissues to produce it? Is it bound in the body-antibody reaction, or is it destroyed or inactivated? These are questions that have been the subject of extensive investigation and to decide which will require considerably more experimental evidence than is at present avail-

able. Evidently, during the course of a disease, there is some relation between antibody content of the blood, and complement. A slight diminution of complement is to be noted coincident with the formation of immune bodies, otherwise this relation is not definite. Evidently, too, the complement power does not vary directly with the blood cell count. In pernicious anæmia the average was nearly normal; moreover patients with a low red cell count frequently gave a high complement titre. Patients were also noted who, with a leucocyte count of 20,000 or more, showed an extreme loss of complement, while again, other patients with the same count showed an increase over normal in the alexin titre.

As for reactivation: in vitro, such reactivation as we could obtain by the addition of fresh serum to a serum of a patient which was deficient in complement averaged 20 per cent. In vivo, alexin may be reactivated, or its production is stimulated by the transfusion of even small amounts of serum high in complement power.

The source of complement is unknown. The frequent findings of a diminution in conditions affecting the heart and kidneys, as indicated in these studies, offers a problem for further investigation.

Therapeutic value of Complement.—The discussion of the therapeutic value of the complement calls for a study of the exceptions noted in these investigations, and again, to a consideration of the body-antibody-complement reaction. Occasionally it was observed that during the course of a severe illness, and even up to a fatal termination, the complement power of the patient's blood was practically normal. *If the complement power is high and the patient is not doing well, it is probable that the antibody content of the blood to the specific organism is low.* Such was found to be so in six cases of this character investigated in order to determine the antibody content of the blood. Also, this offers one explanation for the chronic character of certain diseases, even though a high complement power may be present; that is, sufficient antibodies may not exist in the blood to unite with the alexin in order to destroy the infective agent.

Conversely, it was noted that some patients with a definite infection had a high antibody content in the blood and a persistently low complement power. If the complement power were raised would those patients improve, and what construction may be placed on such findings as to make them of value in the treatment of the case?

The resources of medicine are directed towards the elimination of the foreign body and towards aiding the development of resistance on the part of the patient. This resistance, as concerned with known infection, may be considered, in part, as due to the development of a specific antibody and to the formation and use of complement.

Scientific medicine has occasionally endeavoured to supply the antibody but what of the complement? Also, has sufficient consideration been given to the specific nature of the antibodies and their definite quantitative relation with the complement.

For instance, let us consider the case of antistreptococcus serum, a float thrown without enthusiasm by the physician to the sinking patient with a streptococcus infection. Wherein does it lack its sustaining power? First, there are many strains of streptococci, and usually the serum is minus the specific antibody to the essential strain, a possibility that is generally recognized. Second, but not so generally recognized, if we are fortunate enough to obtain a serum containing a specific antibody, the patient may lack the complement necessary to make the specific reaction possible. The active complement in such stock streptococcic serums has long since disappeared.

It was noted before that in some cases, by means of transfusions or inoculations of even small amounts of fresh serum the complement titre of the patient's blood may be raised. Such a procedure would appear to be logical when indicated by the finding of a low complement power in the patient's blood. Again, if the complement power is high and the antibody content of the patient's blood is low, the natural indication is for the therapeutic use of specific antibodies. The use of such antibodies depends upon the determination of the infective agent and the preparation of a serum containing the specific antibody, at present our most difficult problem.

The method adopted for the therapeutic use of serum containing antibodies or complement is one for serious consideration. It would appear safer to give a serum containing only anti-

bodies, by the subcutaneous method. *Such a serum, containing powerful amboceptors, if given intravenously, may cause too sudden and too great a liberation of bacterial endotoxins.* Also, since complement is required to complete the reaction, it may make a sudden and severe demand on the complement reserves of the body. When a titration of a patient's serum indicates that the complement power is low, one should proceed cautiously in the use of a therapeutic agent that makes further demands on the exhausted complement reserves.

The relative value of the different methods, subcutaneous, intramuscular or intravenous, for the therapeutic use of serum containing complement, remains to be determined. The intravenous method, at present, appears the best although success has been obtained by the subcutaneous inoculation of fresh serum.

Transfusions of whole blood have been used frequently in the treatment of severe infections, and the giving of small repeated transfusions, as reported by Polak[4] and others, appears to have been of value. The favourable results obtained have been considered to be either, because of an increase in the blood cells, or of a foreign body reaction, or of the action of the antibodies that were contained in the blood used for the transfusion. It is probable, however, that some of the fortunate, though unexplained, beneficial results occasionally obtained by such transfusions of blood in septic cases may have been due to the action of the complement. On the other hand, many observers are critical of the value to be derived from blood transfusions in septic cases. Baldwin[5], in an extensive survey of the subject, comes to the conclusion that such transfusions are of no value in acute sepsis.

These opinions, for and against, are based on the study of the results obtained from the use of whole blood and a brief consideration of one essential factor is relative to this discussion on complement. There are two classes of cases for which transfusions have been used—those due to deficient cellular elements in the blood, and those due to deficient qualities in the serum. The latter condition is, as a rule, the result of infection. Now, if there are substances, already present in the blood, or added to the blood used in the transfusion, which act as a foreign body, then more strain is thrown on the complement reserve of the patient. Transfusions in a patient with deficient serum qualities might well fail of their purpose or even prove dangerous. This is of surgical interest, for the question of the necessity for a transfusion is often a surgical consideration, and a patient low in complement titre is naturally a poorer surgical risk than one with a normal or high complement power.

Experience has shown that any method of therapeutics which demands blood transfusions should be approached with reserve; there are well known risks connected with the procedure, and inherent dangers in the use of repeated transfusions.

For the intravenous use of complement one of these dangers—that of the patient's reaction to the donor's cells—may be eliminated by allowing the donor's blood to clot and using the serum alone. Moreover, but comparatively small amounts of serum, 30 c.c. or less, have been used with beneficial results.

It is important to note in this connection that human serum is low in complement power compared to that of some animals. Guinea pigs frequently show a complement power of the blood approximately six times as high as that of the human blood. We need not be limited to the use of human blood in order to supply this substance, provided, of course, we are able to use a serum high in complement power, that will not develop anticomplements or anaphylaxis.

In conclusion, I wish to point out that in drawing deductions from these findings one is on the uncertain ground of complicated immunity problems. Three of these problems are particularly concerned with this discussion. First: the power of the complement was estimated only by the hæmolytic method. However, it is known that the agglutinin and bacteriolytic strength of this substance closely parallel the hæmolytic power. Second: there is the much disputed question of the multiplicity of complements—were we dealing with one or with several? It may be noted — whether one or several — the reactions were fairly uniform. Third: while it has been shown by Watanabe[6] and others that complement exists in the blood serum in practically the same amount as in the corresponding blood plasma, yet we can but surmise as to the action and value of the complement in the circulating blood; the deductions were made from findings obtained by the in-

vestigation of blood serums, the theory being that there exists but little variation between the action of the complement found in the blood serum and that of the circulating blood.

I wish to express my appreciation to Dr. C. E. Corrigan for valuable assistance in carrying out the technical work.

Summary

Investigations were made in order to determine the strength of complement in the blood serum of 230 apparently normal persons, and of 280 patients suffering from various illnesses.

The findings indicate that high complement power is a beneficial factor in immunity. In health the complement power of the blood serum varies within narrow limits, while in disease it may vary widely, depending on the nature, location and stage of the disease.

In some cases an estimation of this power is of value in diagnosis and prognosis, and furnishes an indication for a method of treatment.

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X-RAYS AND RADIUM IN THE MANAGEMENT OF BREAST CARCINOMA*

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IT HAS been the custom for a number of years past to make use of both x-rays and radium as adjuncts to surgery during some stage of the treatment of breast cancer. Some surgeons restrict this use to post-operative radiation by x-rays; a few only have have used either x-rays or radium as a pre-operative procedure or preparation for a subsequent operation. Most surgeons will admit that there is some value in this radiation but there are a few who deny any virtue—indeed there are some others who believe the method detrimental.

This diversity of opinion would seem to indicate either that the procedure as carried out by some radiologists is ineffective, or that the type of cases referred by the surgeon is so unsuitable either in its stage of development or in some other important factor as to nullify the benefits possible from the treatment, and it is not remarkable that there should be considerable divergence of opinion, when we consider that the technique of radiation therapy has been going through a period of such rapid development as has been the case during the past years. Much of this work has been entirely empirical, and cannot progress beyond this stage until we are in possession of much more accurate information than we now have as to the exact manner in which x-rays and radium produce the effects, which they undoubtedly do exert upon malignant cells.

The observations which form the starting point for most of our reasoning on this subject centre around the disappearance of superficial epitheliomata of the skin following the application of an erythema skin dose of either x-rays or radium. Such lesions are cured in well over 90 per cent of cases if a proper dose is administered. It was therefore assumed that if a similar dose could be applied to a carcinoma of the breast, a similar result would be obtained, and the great effort of the past ten years has been directed towards perfecting apparatus and a method by which this desired result might be obtained. It may now be said that this is technically quite possible, but hav-

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