authorities of a trachoma-ridden country to the disability under which its nationals labour, and to the necessity for remedial measures.

In conclusion, I would venture to reiterate my belief that the best line of attack is through an efficient school service. Through this we can get an oversight of the children such as no other means will secure. The school also tends to inculcate a sense of personal responsibility that is invaluable to the common health. There is no doubt that if we could keep the children of one generation free from the disease trachoma would be extinct.

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SOME IMMUNOLOGICAL PROBLEMS IN SEPTICAEMIA.*

BY

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WHEN pyogenic micro-organisms overcome all defences of the body, travel freely through, and even on occasion multiply in the blood stream, giving rise to symptoms of a general invasion, the condition is recognized as septicaemia. Any definition of the term, however, is apparently subject to modification; for instance, with the extension and perfection of blood culture methods, micro-organisms may be recovered from the blood in many states, such as typhoid and pneumonia, which are not classed as septicaemia. Then, too, disease entities exist in which the evidence suggests that there is a general invasion of an ultra-microscopic organism or virus. The diagnosis of septicaemia, then, rests not alone on laboratory procedures, but depends also on the clinical evidence. For this discussion I will consider the type of case in which the symptoms of a general bacterial invasion overshadow those of local origin, and which is characterized, clinically, by chills, sweats, irregular temperature, and is associated with the finding in the blood stream of the causative micro-organism, generally a pyogenic coccus, most frequently a streptococcus. In the treatment of such cases the physician turns for help to the immunologist.

The origin and outcome of such a condition depend naturally, on the two interdependent variables—the infective agent and the patient's resistance.

THE INFECTIVE AGENT.

Briefly let us consider the invasive power inherent to the micro-organism. What is the influence of numbers? We know that a measured quantity of a certain microbe may at times be required to induce a septicaemia, yet, clearly, it is not the determining factor, for the few streptococci driven into the tissues and the lymph channels by the prick of a needle may initiate a rapid and fatal type of the disease, while on the other hand a massive infection frequently remains localized. That the power of elective

localization of bacteria has an essential bearing on the question has been clearly demonstrated by Rosenow. Even so, in elective localization the variable factor is in evidence, for a meningococcal infection occasionally exists only as a septicaemia, with no clinical or pathological evidence of any particular involvement of the meninges. Again, the *Streptococcus viridans* may invade the heart valves, which indicates that the microbe passed through the blood stream unaffected by the defences of the body, and possibly without giving rise at the time to clinical manifestations of its presence in the blood; subsequently a septicaemia arises from the endocardial focus.

An overwhelming invasion following the inoculation of a few organisms suggests that the circulatory system may be the elective site, for it is not unusual in some cases to find scant evidence that any particular tissue is involved, even though the micro-organisms may be noted in direct blood smears. Besredka, however, emphasizes the importance of tissue immunity at the primary site of elective localization; according to his theory a general invasion of the staphylococcus or streptococcus indicates a previous cutaneous or mucous area of infection.

The capacity to produce powerful toxins, to multiply rapidly, or to resist destruction is peculiar to certain bacteria. Such factors determine aggressiveness; while just as important, evidently, in favouring a continued bacteraemia, is the inability of the causative organism to incite antibody production.

As a rule bacterial association favours a local infection, but that it is, in septicaemia, an important factor receives slight support; however, a simultaneous general invasion of more than one micro-organism may occur. Further, while one grants that septicaemias may be induced experimentally by the inoculation of a single selected strain of an organism, such as a streptococcus, yet the evidence shows that no single strain is responsible for all streptococcal septicaemias. Here, in carrying out agglutination tests with forty-five strains of streptococci recovered from as many cases of septicaemia, we failed to obtain any common agglutinative type.

Virulence as associated directly with the microbe lacks definition. More recent work, such as that of Falk, stresses the theory that the dynamics of the electro-potential differences of the cells underlie some of these problems. For the further elucidation of the term virulence as related to the micro-organism, Holman suggests more intensive physiological studies of the metabolism of bacteria. These factors are bound up with the structure of the microbe; how infinitely complicated this may be one can judge from the fact, as Cameron illustrates, that a comparable unit, such as a red blood cell, contains approximately a million million molecules and ions.

I have touched only on some of the principal characteristics of the micro-organism which are believed to determine its invasive powers, for aside from preventive measures, the nature of the microbe which infects the patient and produces a septicaemia is the accidental factor over which the physician has no control. The attenuation of the virulence of an infective agent by world-wide measures such as universal vaccine therapy is a problem not yet solved. In Winnipeg the incidence of septicaemia caused by the haemolytic streptococcus shows periodic waves, suggesting the prevalence at intervals of a type or types of this streptococcus favouring such an infection.

THE PATIENT'S RESISTANCE.

The rapid spread of an infection from a small focus indicates primarily an inability of the phagocytes, either leucocytes or clasmotocytes, to cope with the infective agent. A determination of the opsonic index in such cases frequently shows that the blood is deficient in natural opsonins. These opsonins when present facilitate phagocytosis until such time as the body responds with the production of specific antibodies, including the thermostable opsonins, for the bacteria and their products responsible for the infection.

This weakness in the defence, which allows the extended invasion of some bacteria, particularly the pyogenic cocci, the haematopoietic tissues may attempt to offset by an overproduction of leucocytes. It was characteristic of the cases

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of septicaemia in the series we investigated that an increasing leucocytosis paralleled a low opsonic index and a fall in complement. The frequent failure, however, of such a leucocytosis to overcome the infection suggests a more intensive effort on that ever-recurring problem—the early transference of specific immune bodies to such patients.

The production in the individual of specific antibodies to the infective organism requires time; the formation of such antibodies for the endotoxins and the bacterial substance postulates a previous dissolution of the bacterial cell. A haemolytic streptococcus or a staphylococcus invasion may progress with such rapidity that death occurs before the lysis of a sufficient number of bacteria takes place that would stimulate the production of the necessary antibodies. Such an argument, of course, does not take into account the elaboration of antitoxins for those exotoxins that the microbe may produce. Even so, the development of such antitoxins frequently requires more time than the urgency of the patient's condition allows. A *Streptococcus viridans* infection, on the other hand, will persist in the heart valves for months, with just enough production of antibacterial substances to limit the subsequent general invasion to an intermittent bacteraemia.

Should a sufficient interval of time elapse for the development of a leucocytosis and the elaboration of antitoxins, and of agglutinins, precipitins, opsonins, and lysins, without evidence that the patient is overcoming the infection, then, two factors in resistance, based on current concepts of immunity, may be especially considered. First, that there may be a possible failure in antibody production, and second, that, even if such are elaborated, the body cells and fluids may fail to utilize them for the destruction of the micro-organism or the neutralization of the toxins. The failure in bacteriolytic action may result, in part, from a deficiency in complement, that property of the blood serum which the fundamental researches of Ehrlich and Bordet showed was essential to complete the lysis or death of bacteria in the presence of the immune body.

In this discussion I wish to dwell particularly on the influence of complement in septicaemia, a discussion which at once involves us in a consideration of the relation of complement to health and disease.

Complement in Health.

Complement, as a substance or state of the blood serum, exists, so far as we know, in all normal individuals. I have found but slight variation in the titre of complement in the serum of the blood taken from 500 persons in normal health, and under normal conditions. This power of complement was determined by its action against sensitized sheep cells. However, a slight diurnal variation was noted; approximately a 10 per cent. increase occurred in the titre of the specimens of blood taken in the evening compared with those taken in the morning. The finding of a low complement power in a supposedly healthy person suggested disease or the results of disease; subsequent careful clinical examination of these persons proved this assumption to be correct. The results obtained indicate that complement is an attribute of health; further support of this statement is supplied by Huntenueller, who, following investigations on Olympic athletes, states that a fall in complement titre of the blood serum occurred in overtrained competitors, but such did not occur in those who were in perfect condition, even after sustained exertion.

While it was thought that the blood of all normal animals contained the usual amount of complement characteristic of the individual species, yet there has been reported the existence of a race of guinea-pigs which showed a deficiency of this quality in the blood serum. Moore pointed out that these guinea-pigs were less hardy than the normal animal, and that their opsonic index was about one-half normal. Coca determined that it was the third complement component, the heat-resistant or yeast-absorbed component, which was missing, and Hyde reported the arresting fact that this characteristic of the serums of these guinea-pigs was inherited as a simple recessive Mendelian unit. Pertinent to the discussion is the fact that the deficient serum or plasma could be activated by very small amounts of serum from man or normal guinea-pig, *in vitro* or *in vivo*.

Complement in Disease.

Is it not important to recognize that the complement property of the blood varies widely during disease? In 1914 Gunn noted these changes in cases of typhoid, diphtheria, and scarlet fever. Our investigations, in part previously reported, of over one thousand patients, also showed that this property, as tested by the haemolytic system with sensitized sheep cells, varied from an increase of 20 per cent. over normal to a complete absence, depending upon the nature, location, and stage of the disease. As a rule these fluctuations follow a uniform course; commonly there is a slight increase in complement coincident with the onset of the symptoms of the disease; this is followed by a steady decrease until the infection reaches its maximum; during convalescence complement gradually returns to normal. However, in some cases, the complement property of the serum gradually decreases until no evidence of its presence, unless reactivated, can be observed by the use of the haemolytic system. These latter cases as a rule terminated fatally, but exceptions were noted.

More recently Hadjopoulos and Burbank, in an extensive series of investigations on the blood of persons in health and disease, arrived at similar conclusions, while Goldner stresses the association of a decrease in complement with those infections which interfere with liver function.

We observed that, as a rule, patients with chronic diseases such as tuberculosis, syphilis, chronic arthritis, uncomplicated malignant disease, goitre and diabetes, showed but slight oscillation in the complement titre of the blood serum. However, in a patient with an acute infectious disease, and particularly septicaemia, the fall in complement titre, following the initial rise, was rapid, and in the fatal cases, occasionally a complete absence, as determined by the method of investigation described, was noted.

What component of complement is missing in the serum obtained from the patients with these diseases I have not yet been able fully to determine; but a slight reactivation, 10 per cent., occasionally occurs on the addition of heated normal serum, while an average of 20 per cent. reactivation was obtained by the addition of that inactivated by ammonia. In some instances a slight reactivation was noted following the addition of serum which had been inactivated with a bacterial culture, yet if the blood of a patient with streptococcal septicaemia showed deficient complement, practically no reactivation could be obtained by the addition of normal serum which had been inactivated by previously mixing such serum with the specific streptococcus. Muir and Browning, however, have shown that the removal of the natural bactericidal power of normal serum by treatment with dead bacteria may leave the haemolytic power of complement unaltered.

The recognized necessary part played by complement in the antibacterial action of blood *in vitro* raises the question of the influence of this property in the circulating blood. Long ago Muir emphasized the importance of this factor in immunity, and the dependence on complement of the opsonic action of normal serum. Then, too, that complement exists in the blood plasma in proportional amounts to that noted in the blood serum has been shown by several investigators (Kolmer), and Hyde has demonstrated the action of haemolytic complement for foreign erythrocytes in the circulatory system of the frog.

The dependence on complement of the opsonic action of normal serum suggests that this property exerts some influence on the susceptibility to infection, but to what extent has not been established. However, the necessary part played by complement in bactericidal action in conjunction with antibodies indicates that it is an important factor in determining the limits of an infection. It is logical to infer, if not to state, from the available evidence, that a high complement titre in the blood of a patient with septicaemia aids materially in overcoming the infection.

Complement in Treatment.

How may the treatment of septicaemia be influenced by deductions drawn from these observations? Small amounts of normal serum, even at times one-quarter of 1 per cent., will activate blood deficient in complement, both *in vitro* and *in vivo*. I have determined that the addition of small

amounts of normal serum would reactivate serum obtained from a patient's blood which was deficient in cytolytic activity; in patients showing a deficiency of complement resulting from infection, reactivation occurred following transfusions of small amounts of serum derived from the blood of normal persons or animals. This reactivation is immediate, and lasts, as a rule, two to three days, when the serum tends again to show a deficient complement titre, provided the infection which caused the original loss in complement has not abated.

In view of these findings it appeared logical to give repeated transfusions of small amounts of serum from the blood of a normal compatible donor to patients with septicaemia. It may be suggested that transfusions of whole blood would have accomplished the same purpose. Small whole blood transfusions do activate complement *in vivo*, but with this difference—that the decrease in complement titre which frequently again occurs about the third day is considerably more marked than that which follows transfusions of serum.

As regards massive normal blood transfusions for sepsis, I have observed in three patients who received such treatment that subsequently a severe loss of complement occurred by the third day, a greater loss than would be expected as the result of the infection, and within a week the complement titre of their blood serum had dropped 20, 40, and 50 per cent. lower respectively than before such transfusions were made. Consideration must also be given to the problem, as suggested by Wright, that such whole blood transfusions may furnish a pabulum which aids the further multiplication of the infective bacteria.

Antibody and Complement.

We found in patients with sepsis that the relation between antibody and complement followed a general rule—namely, if the patient failed to improve, and the blood showed a high complement titre, then the antibacterial content of the blood for the causative micro-organism was low, and conversely, in such patients, if the antibody content of the blood was high then the complement titre held to low values. The immune content of the blood for the specific infection was determined by the agglutination reaction, and by complement fixation.

Provided the complement is normal or is raised to a normal power, then to complete the destruction of the infective micro-organism by bacteriolytic action, and to facilitate phagocytosis, specific antibodies are deemed essential. Yet the preparation of a specific immune serum for those organisms most frequently connected with septicaemia has always offered a problem of the greatest difficulty.

The frequent failure of the administration of an anti-streptococcal serum to benefit the patient in a case of streptococcal septicaemia is generally held to be the result of an absence in the serum of essential antibodies. The animal from which the serum was derived may have been immunized by a different strain of the micro-organism from the one responsible for the infection in the patient. In an attempt to overcome the latter difficulty we inoculated rabbits with separate vaccines and toxins prepared from over fifty strains of streptococci and staphylococci recovered from as many different patients with septicaemia. On experiment these animals became highly resistant to induced infection.

Further, Gay points out that the evidence indicates that the reservoir for antibody production is in the cells. Again, experiment shows that a specific stimulus, such as the inoculation of a vaccine, causes the appearance in the blood of homologous antibodies, if such are present in the tissues. Then, too, success in the treatment of septicaemia has been reported following transfusions of blood from a donor who had been previously inoculated with the specific organism. Sir Almroth Wright outlined the immunological factors involved in such a procedure, and the method has been further developed by Colebrook and Storer. I have applied these principles in an endeavour to increase the antibody content of an immune animal serum, which was to be used in the treatment of septicaemia. One of the rabbits which had been previously inoculated,

as before described, with some fifty strains of streptococci and staphylococci, was re-inoculated with a broth culture containing the specific strain of the organism obtained from a positive blood culture, and several hours subsequently 8 to 10 c.cm. of blood were withdrawn from the rabbit's heart under aseptic precautions. The serum of such blood frequently gave a high agglutinating titre for the specific micro-organism with which the animal had been inoculated several hours previously. A further procedure was to inoculate rabbits on alternate days with a vaccine and toxin prepared from the microbe isolated from the blood of the patient. If the course of the disease allowed for a sufficient interval of time to elapse for these rabbits to have developed specific antibodies, the serum from the blood of such animals was also used. Cardiac puncture apparently causes the animals no harm.

Treatment with Normal and Immune Serum.

We have treated with serum 56 patients who were suffering from septicaemia; the majority were in an advanced stage of the infection, and with these this method of treatment was adopted as a last resort. Forty-five recovered. Blood cultures showed: in 38 cases a haemolytic streptococcus, in 6 a *Streptococcus viridans*, in 5 a staphylococcus, in 1 an unidentified diplococcus, in 1 a colon bacillus, in 3 both a streptococcus and a staphylococcus, and in 1 a staphylococcus together with the *Bacillus pyocyaneus*. Each case in which blood cultures indicated a double infection proved fatal.

The following method of treatment was adopted. A compatible donor reported at the laboratory. From 60 to 70 c.cm. of blood were withdrawn from a vein in the arm into a large sterile vacuum tube. The blood was allowed to clot at room temperature, then placed in the ice chest. Five to eighteen hours subsequently the serum was drawn into a sterile glass syringe, and then the patient was transfused with this serum. These transfusions were given every second day; four of such treatments constituted the average number given to a patient. On alternate days 2 to 5 c.cm. of immune serum from a rabbit, prepared as previously described, were inoculated subcutaneously. It needs to be pointed out here, however, that the extended therapeutic use of rabbit serum has obvious limitations; the animals are small, comparatively short-lived, and susceptible to certain infections.

This method of treatment does not contraindicate the search for foci, and surgical intervention for the elimination of the same when such a procedure is feasible. Moreover, it is recognized that the nature of septicaemia varies widely, and a patient with apparently an overwhelming bacterial invasion may recover without special therapeutic aid; hence the value of any particular method of treatment, judged by clinical results, is open to discussion. Besides, as suggested by Churchman in a masterful review on the intravenous use of dyes, thought needs to be given to the possibility that attempts at rapid sterilization *in vivo* may defeat their own purpose; serious results do follow the too rapid absorption of freed endotoxins.

OTHER FACTORS.

While one may stress the value of complement and antibacterial substances generally as a part of the defensive mechanism against an extended bacterial invasion, yet the importance of any single factor naturally varies with the individual case, also with the numerous associated processes. So interrelated are these that obvious difficulty arises in confining the scope of this discussion. One would like to consider the absorbing questions of the origin and nature of complement and of the influence of diet and drugs on this property, or of the chemical nature of antibodies and their possible synthetic production. Mention may be made, however, of the work of Mellanby and Green in the treatment of puerperal septicaemia with vitamin A; an evaluation of this work involves consideration of both the physiological and the biochemical relation of vitamins to immune processes. Then, too, the beneficial results occasionally obtained in sepsis, following the use of scarlet fever antistreptococcal serum, touches the live question of the relation of the toxins from the various strains of streptococci to one another. Also of arresting interest are

the observations of Gay, suggesting either the possible mobilization or passive transfer of the tissue macrocytes. In addition, the influence, however uncertain, of the bacteriophage demands attention; in five of our series of cases it was noted that following treatment the specific organisms were undergoing bacteriophagy; recovery occurred in these cases. In four cases with a fatal termination, when it was possible to obtain the organism from a focus, there was no evidence that a bacteriophage for the causative bacteria was present. According to d'Herelle, if a bacteriophage for a micro-organism causing infection is active *in vivo*, then the prognosis becomes more favourable.

It must not be overlooked that some cases of septicaemia offer little hope from the therapeutic standpoint. The destruction of tissue in scattered lesions caused by direct bacterial action is frequently beyond functional repair; especially does this apply to lesions in the brain or heart. Particularly, an infection engrafted on a previously injured heart and giving rise to a septicaemia generally signifies a permanently damaged endocardium resulting in cardiac incompetence that no method of therapy based on immunological studies will rectify. This latter problem suggests some other method of approach, and since a subacute bacterial endocarditis with an associated bacteraemia is prone to develop in an individual with valvular lesions, then the possible prophylactic immunization of a person with a damaged endocardium by means of a polyvalent streptococcus vaccine deserves consideration.

Immunity problems of septicaemia naturally concern all the sciences represented in this Section of the Annual Meeting; possibly correlation of the results obtained through the various lines of approach, either clinical or experimental, may furnish some solution. Admittedly, up

to the present, the clearing hewed out of the gloom of immunology by Pasteur, Ehrlich, and their disciples has been well and hopefully tilled, only to produce, in septicaemia, limited therapeutic results. The quickening light afforded by the efforts of those early workers now becomes shaded with the growing clouds of doubt, and some predict barren returns from further efforts in that field. They say we must seek or make new clearings. In advancing some of these problems for discussion to-day it is with the hope that the old furrows retilled, or possibly the turning of a new furrow, may prove the field still fruitful.

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THE PLACE OF PASTEURIZATION IN A SCHEME OF MILK DISTRIBUTION.*

BY

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THE heating of ordinary milk during distribution is generally admitted to be an imperative necessity and is in fact demanded by many city ordinances. In other quarters pasteurization is looked upon as a temporary measure, advisable under present conditions, which it will in time be possible to discard like other methods of preserving milk, and which will cease to be employed in proportion as highly organized and efficient methods of production and distribution become general. Some nutritionists take a more positive view, and think that the sooner this time arrives the better it will be for the consumers, especially children. Some of the evidence on which an opinion may be based is clear enough; in other respects, it is still in an experimental stage.

My experience leads me to adopt the view that milk supplied in bulk for consumption in large urban areas should be submitted to pasteurization by approved methods, the most powerful argument being that the menace of milk-borne infections is thereby largely eliminated, and is restricted to such relatively infrequent incidents as may cause infection during or subsequent to pasteurization. Glasgow is no exception to the general experience that the increasing practice of this procedure has caused a corresponding decline in the capacity of milk to convey specific infection to the consumer. The pasteurizing of milk is now applied to between 80 and 90 per cent. of the city's milk, while about 70 per cent. of the supply is delivered in bottles. The history of milk outbreaks of disease, where the source of infection was at the farm, is entirely concerned with this diminishing portion of unpasteurized milk in the city's general supply.

As regards the history of pasteurization, this process was first practised in Glasgow in the late nineties of last century,

when the "flash" system was introduced by the large distributors, that is, heating to about 160° F., followed by immediate cooling. Prior to this, the scalding or "scadding" of milk (to use a Scotticism) was resorted to by immersing cans of milk in open boilers at temperatures of 160° F. to 180° F., and thereafter cooling in running water. Subsequent to 1900, the rapid growth of the city demanded further supplies from greater distances, and pasteurization became more and more extensively employed to enhance the keeping qualities of the milk. The old flash system has been entirely superseded by modern methods, a change greatly assisted by the educative effect of the Special Designations Order of 1923, the transition to the positive holder type of pasteurizing machine as recommended becoming practically universal. There is a general reluctance to exceed a temperature of 145° F. and the United States standard of 142° F. is sometimes adopted.

Pasteurization grew up and was widely adopted for commercial reasons, as it augmented the keeping quality of milk. It preceded, but did not, as was sometimes feared, prevent the undoubtedly great improvements which have taken place in recent years in the standards of production of raw milk, a large proportion (at least 70 per cent.) of ordinary market milk being now comparable with that of grade "A" quality. "Those who are producing and retailing graded milk have made it clear that, with proper control, it is possible to produce and sell unheated milk successfully, even in the poorer quarters of London." This remark occurs in Research Monograph No. 1 of the Ministry of Agriculture and Fisheries (1929), and might be applied to any city. It is quoted to show the trend of progress in the domain of milk production, and may be taken to mean that the argument of "commercial necessity" in support of pasteurization has lost much of its force, except in relation to the transport of milk over long distances.

There is no doubt that pasteurization of milk has added to the security of cities against the danger of milk-borne infections. This is a matter of great importance, and the following local illustrations may be quoted from experience in Glasgow. All the outbreaks of infectious disease whose source was traceable to farms were associated with supplies delivered direct and untreated from the farm to the consumer, or formed that part of the supply of a particular centre of

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