SOME ASPECTS OF THE NATURAL RESISTANCE OF THE BODY TO BACTERIAL DISEASES

BY

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The natural resistance of the body to bacterial infection is a problem of great importance in clinical medicine, and one which has received much attention from bacteriologists. The problem is, however, a very complex one, and involves the consideration of many factors, about most of which we have very little exact knowledge. In the study of preventive medicine, which is now so much to the fore, a quantitative knowledge of the factors concerned in natural immunity would be a very valuable asset, but at present we have not yet even reached the stage of qualitatively estimating them.

MAIN DEFENCES

Phagocytosis is probably the most important defensive mechanism of the body. It is to Metchnikoff that we owe this discovery. He was originally a zoologist, and he was able to demonstrate in the *Daphnia* (a water-flea) various stages in the ingestion of bacteria by certain amoeboid cells, which he termed "phagocytes." Later he was able to demonstrate that similar phagocytizing cells—that is, the leucocytes—were present in the higher animals, and that their activities were of paramount importance as a defence mechanism in combating bacterial invaders. The leucocyte itself, however, is not the only factor in the phagocytizing of organisms. When leucocytes are added to a suspension of staphylococci *in vitro*, very little phagocytosis occurs. Serum must be added to the mixture before any extensive phagocytosis can take place, the serum probably exerting some sensitizing action on the foreign organism. This property of serum is known as "opsonin" (Wright and Douglas, 1903). The substance concerned is heat-labile, being destroyed at temperatures between 56° and 60° C. It has many properties in common with serum complement, but cannot have exactly the same structure, since there are some important differences. For instance, it has been shown that inactivation of complement by dilute ammonia leaves the opsonic function of serum intact. Gordon, Whitehead, and Wormall (1926, B) treated serum with one-quarter of its volume of N/6.5 NH_4OH , and incubated for about one and a half hours. It was neutralized with acid, and then tested for complementary and opsonic power against a control which had been incubated for the same time and diluted to the same extent with normal saline. The treatment with ammonia yielded a serum with no complement activity, due to destruction of the fourth component of complement (to which further reference is made below), but nevertheless this serum appeared to have lost none of its opsonin. The same workers (1929) also showed that adsorption of serum by staphylococcus completely inhibits the opsonic activity of the serum, while a portion of the complement (fourth component) still remained. Further, Gordon (1930) has shown that a serum whose complement has been inactivated by certain concentrations of congo red is still able to exert its opsonic activity. It seems clear, therefore, that in spite of considerable resemblances, there can be no identity between opsonin and complement. The nature of the "sensitization" of the organisms by serum is not understood, although several workers have recently shown that the effect is probably one of interference with the surface

properties and cohesion of the organisms. Wright and his colleagues have shown that in some diseased conditions there is a diminution in the opsonic power of the serum, and also a diminution of the phagocytic power of leucocytes. It is difficult, however, to assess these alterations from the point of view of prognosis.

The phagocytic cells are the polymorphonuclear cells (microphages) and the mononuclear cells (macrophages). Some of the macrophages are wandering cells, whereas others are sessile, and are found in the spleen, liver, lymphatic glands, and other tissues. These sessile cells are found in the reticulo-endothelial system, in the endothelium of liver capillaries (Kupffer cells), spleen sinuses, lymph sinuses, adrenals, pituitary, and in the reticular cells of the spleen, lymphatic glands, and tissues. The spleen probably contains the predominating proportion of these cells. A good deal of experimental work has been done on the effect on natural immunity of splenectomy and of "blockade" of the reticulo-endothelial system by means of various dyes. There is evidence that some infections which are latent become apparent after splenectomy. The best example is that of *Bartonella muris*. Intravenous injections of many dyes, such as trypan blue, etc., have been used, and it has been shown that these dyes "blockade" or put out of action the reticulo-endothelial system; it has been claimed that animals so treated are more susceptible to bacterial infection. Topley (1930), after injecting bacterial antigens in animals, showed that they were rapidly fixed by the spleen. However, an assessment of the results in this field, taken as a whole, is not free from difficulty, and no clear-cut point of view can as yet be put forward, although the evidence generally leaves no doubt as to the importance of the part played by this reticulo-endothelial system of cells in the defence of the body against infection (Ledingham, 1931). Failures to overcome natural immunity by splenectomy and "blockade" may possibly be explained by the fact that a portion of the reticulo-endothelial system may not be affected by these procedures, or that a compensatory mechanism may rapidly become established.

The next problem for consideration is that normal serum alone, and free from all phagocytizing cells, has a marked bactericidal effect on various organisms, particularly the Gram-negative group. Organisms such as *V. cholerae*, *B. dysenteriae* Shiga, *B. dysenteriae* Flexner, *B. enteritidis* Gaertner, *B. typhosus*, and various members of this group, are rapidly killed if added to serum at body temperature. The factors involved in this bactericidal power of serum are complement, and some other non-specific portion of serum which is heat-stable. In view of the fact that complement plays such an important part in the defence mechanism of the body, it is of interest at this stage to consider briefly its nature and structure.

NATURE OF COMPLEMENT

Complement may be defined as that property or constituent of normal serum which causes lysis in a system of immune body plus cells (for example, sensitized bacteria or red blood corpuscles). As its name implies, complement alone cannot effect the lysis, which takes place only when cells are subjected to the combined action of both complement and immune body.

The close study of complement that has been carried out during the past forty years has not so far led to any adequate or clear conception of its nature or mode of action, though a vast number of facts of varying importance have been established. Some of the most important of these are as follows.

1. *Complement is thermolabile.*—Serum heated for a short time to 55°–56° C. loses its property of lysing sensitized cells.

2. *Complement is complex.*—Methods for the fractionation of serum proteins into albumins and globulins result in a fractionation of complement. Browning and Mackie have been notable workers in this field. Protein fractions are obtained which singly do not possess the properties of complement, but which, when reunited, are almost as effective as the original serum from which they were prepared. Four components of complement are now generally recognized: *mid-piece*, associated chiefly with the serum globulins; *end-piece*, associated with the albumins (Ferrata, 1907; Sachs and Altmann, 1909; Liefmann, 1909; Brand, 1907); a third component which is removed by yeast (von Dungern, 1900) or zymine (Whitehead, Gordon, and Wormald, 1925); and a *fourth component*, which is destroyed by small quantities of ammonia (Gordon, Whitehead, and Wormald, 1926, A). The third and fourth components of complement are interesting in that they are both heat-stable—that is, in the case of the third component, treatment with yeast or a zymine preparation inactivates complement, but a serum so treated can have its complement activity renewed by the addition of serum which has been heated at 56° C. for half an hour. The fourth component of complement can be demonstrated by adding small amounts of ammonia to a serum, incubating for about one and a half hours, and then neutralizing. This treatment destroys the complement activity, which, as in the case of the third component, can nevertheless be restored by the addition of heated serum. It is important to notice that this action of ammonia is specific, and is not due simply to its alkalinity. The fourth component is not identical with the third component, the former occurring mainly in the end-piece, the latter mainly in the mid-piece. It has also been shown (Gordon, Whitehead, and Wormald, 1926) that a serum inactivated with ammonia can be reactivated on adding serum which has been deprived of all its third component by treatment with zymine. This inactivation of complement by ammonia does not appear to be associated with any interference with the albumin-globulin ratio or with the phosphorus partition of the serum—that is, the total organic phosphorus, the lipid phosphorus, and the inorganic phosphorus (Gordon and Marshall, 1929). These components, however, should not be looked upon as necessarily mutually exclusive, nor may we assume that there are no other components still to be found.

3. *Complement is very sensitive* to a variety of physical and chemical agencies other than those just mentioned. (a) Reaction. Acids and alkalis have inactivating effects, which are at least partly reversible if the treatment has not been drastic. (b) "Adsorption." Many substances in the finely divided or colloidal state are able to remove complement from serum—for example, casein, kieselsol, kaolin, and living and dead bacteria (Landsteiner and Stankovic, 1906). (c) A number of dyes, both electro-positive and electro-negative, when dissolved in salt solution, combine with complement and render it inactive (Klopstock, 1924). Gordon (1930) showed that congo red and similar dyes inhibited complement activity, and that the effect of the dye is increased by the addition of magnesium sulphate. Complete inactivation was produced by treating 1 c.cm. of guinea-pig serum with 0.2 c.cm. of a 2 per cent. congo red solution, but the inactivation was reversible, activity being restored by adding adsorbing agents, such as charcoal, heated serum, serum albumin, or serum globulin. The conclusion was drawn that the congo red was first adsorbed by the complement—that is, on the serum protein, and then removed by another adsorbing agent. It is interesting to note that this occurs not only with haemolytic complement, but also with streptococcal haemolysis (Gordon, 1931). (d) Complement does not act at 0° C. (e) Violent shaking causes destruction of complement (Jacoby and Schutze, 1910). (f) Inorganic salts in hypertonic concentrations cause more or less reversible inhibition of complement. (g) Complement is destroyed by trypsin—that is, a proteolytic enzyme (Michaelis and Skwirsky, 1910; Wormald, Whitehead, and Gordon, 1925). (h) The addition to serum of 10 per cent. sodium chloride inhibits complement activity, but allows the complement to pass through a Berkefeld candle. After filtration complement action can be restored by diluting to normal salt content (Muir and Browning, 1909). (i) Ultra-violet rays have a destructive effect on the heat-labile protein components of complement (Gordon and Wormald, 1928).

PROTEIN DISPERSION

The above facts point definitely to a very close association of the complement function with the protein constituents of normal serum. A protein complex could very well show all the properties described above if it be assumed that the complement function is only exhibited by the complex when in a particular state of aggregation—that is, if dispersion on the one hand, or further aggregation on the other, cause inhibition of the function.

One of the mildest means of effecting an increase in the dispersion of proteins is by the action of strictly neutral salts, such as sodium chloride or bromide. The action of such salts is more likely to be free from confusing side-effects than any of the agencies so far described, and has in consequence been made the subject of recent work (Gordon and Thompson, 1933). The salts used were the sulphates, chlorides, bromides, iodides, and nitrates of sodium and potassium—that is, salts of strong bases and strong acids, and therefore incapable of affecting the reaction of the serum. Further, the action of these salts was studied on a basis of equivalence (or normality) so as to eliminate any possible valency effect of the divalent sulphate ion. The experiments showed that the order of effectiveness in inhibiting complement activity is as follows:

—that is, the exact order for the effect on the swelling of gelatin at similar concentrations of salts. This series is, of course, part of the well-known Hofmeister or lyotropic series. Work by Stiasny, Das Gupta, and Tresser in Germany, and Northrop and Kunitz in the United States, has shown that the above series is one of increasing dispersive power on gelatin. Their work proves that at concentrations such as were used in the experiments on complement these salts definitely disperse gelatin, as is shown by their effect, not only on swelling, but on osmotic pressure, ultra-filtration, diffusibility, and mutarotation. It may thus be stated that if the action of neutral salts on serum proteins is similar to their action on gelatin, then the inhibition of complement by neutral salts is due to the dispersion or peptization of the serum proteins by these salts.

HAEMOLYTIC AND BACTERICIDAL COMPLEMENT

That the bactericidal power of serum is associated with another factor in addition to complement has been demonstrated in the following way. If to a normal serum which has a marked bactericidal power for an organism like *B. dysenteriae* Flexner suitable amounts of a heated suspension of *B. dysenteriae* Flexner are added and allowed to remain in the ice-chest for two hours at 0° C., centrifuged, and the supernatant fluid tested against a suspension of the live organisms, the serum will then be found to have lost its bactericidal power, whilst still retaining its complement power as tested with sensitized red blood corpuscles. If to this serum, that has been thus treated with dead bacteria, is now added serum that has been heated at 56° C. for half an hour—that is, serum devoid of both complement and bactericidal power—then the bactericidal power of the treated serum is restored. This loss of bactericidal power is attributed to the removal of an immune body present in the serum, and the missing factor can be supplied by serum which has been heated at 56° C. for thirty minutes.

The problem whether the complement functioning in the bactericidal reaction is of the same nature as the complement used in the haemolytic reaction is one of interest. Braun (1911), Liefmann (1911), and Boehncke (1912), using the methods of "splitting" complement into "mid-piece" and "end-piece," showed that the separate

components were inactive in respect of bactericidal and haemolytic power, but that the two combined gave bactericidal power and also haemolytic complement. This similarity in structure between haemolytic complement and bactericidal complement is supported by the weakening of both functions, bactericidal and haemolytic, when the serum is diluted with water and kept at 37° C. for one and a quarter hours (Boehncke, 1912). Gordon and Wormall (1928), in investigating this relation between bactericidal and haemolytic complement, showed that small amounts of ammonia destroy the bactericidal power of normal guinea-pig serum against *B. dysenteriae* Flexner, and that this loss of bactericidal power runs parallel with the destruction of haemolytic complement. The action of ammonia on the bactericidal system and the haemolytic system of this serum is not due to pH effects, nor is any significant action exerted by small amounts of neutral ammonium salts. The conclusion is drawn that haemolytic and bactericidal complement have a similar constitution, and are probably identical. In the experiments with congo red described above, Gordon (1930) showed that this dye inactivated the bactericidal power of normal serum as well as its haemolytic complement, and that this reaction with the bactericidal factor was reversible.

Gordon and Carter (1932) further investigated the bactericidal reaction, seeking to determine whether this reaction was due to the presence of complement and a series of specific antibodies for these organisms. Normal guinea-pig serum and rabbit serum were adsorbed with a heavy suspension of an organism in 0.85 per cent. sodium chloride, the organism having been heated at 65° C. for one hour, and then washed repeatedly with normal saline. The adsorption took place for two hours at 0° C. The serum was then centrifuged, and the bactericidal power of the supernatant fluid tested against various other organisms. Six c.cm. of serum were adsorbed with suspensions of *B. dysenteriae* Flexner, and this serum tested against (1) *B. dysenteriae* Flexner, (2) *B. typhosus*, (3) *B. dysenteriae* Shiga, (4) *B. enteritidis* Gaertner, (5) *V. cholerae*, and (6) *B. paratyphosus* A. A series of tubes (7 to 12) contained, in addition to the above heated serums, 0.5 c.cm. of serum heated at 55° C. for half an hour and inoculated with the same organism, since the addition of heated serum to an "adsorbed" serum in many cases restores the bactericidal action of the serum. This set of experiments was repeated by adsorbing guinea-pig serum with heated and washed suspensions of each of the six organisms mentioned, and testing the bactericidal power of the adsorbed serum against these six organisms severally. The results showed that a serum adsorbed with *B. dysenteriae* Flexner lost its bactericidal power against *B. dysenteriae* Flexner, *B. typhosus*, and *B. paratyphosus* A, but retained it against *B. dysenteriae* Shiga, *B. enteritidis* Gaertner, and *V. cholerae*. Similarly, adsorption with the suspensions of the other five organisms showed that there was no specific adsorption of the bactericidal power for any particular organism by a suspension of that organism. The organisms used showed a graded sensitiveness to serum, adsorption of serum with emulsions of dead organisms removing first the bactericidal power for the least sensitive organisms, further addition of the adsorbing agent finally destroying entirely the bactericidal power. The conclusion reached is that the bactericidal power of normal serum against various organisms is not due to the presence of specific natural antibodies. The variations in bactericidal power against different organisms are attributed to the varying sensitiveness of these organisms to non-specific factors in the serum (complement plus a heat-stable factor).

LEUKINS, β -LYSINS, AND LYSOZYME

There exist, however, other bactericidal systems of which much less is known than the complement systems just described. Extracts of leucocytes, containing bodies known as leukins, have been studied by a few authors. These extracts are prepared from the leucocytes by obtaining an exudate rich in polymorphs, and treating the exudate by alternate freezing and thawing, supplemented by mechanical means or treatment with weak acids, alkalis, or saline. The leukins are bactericidal towards certain organisms which are not killed by the complement system, and have as a rule a wider bactericidal action, which is effective against organisms such as *B. anthracis*, pneumococcus, streptococcus, and *M. tetragenus*, etc. The leukins are relatively heat-stable, requiring a temperature of 75° C. for half an hour for their destruction, and, unlike complement, are little affected by salt concentration. The action of these leukins on the bacteria is a direct one, and there is no evidence of an immune body system.

β -lysins (so called to distinguish them from α -lysins, a name sometimes used for the complement system) are bactericidal substances present in serum which are rather less heat-stable than the leukins. They have been studied in some detail by Pettersson (1927), who finds that they consist of an "activating" substance which is inactivated by heating at 63° to 65° C. for half an hour, and is therefore more stable than haemolytic complement, and an "activable" substance which is bound to the bacterium on which the activating substance acts. The two systems appear to be very similar—namely:

α -lysins—complement plus immune body.

β -lysins—"activating" substance plus "activable" substance.

The "activable" substance of the β -lysin may therefore be compared to the immune body necessary for the action of haemolytic or bactericidal complement, but, unlike the immune body, it does not attach itself to the bacteria unless the "activating" substance is present at the same time. The "activating" substance is not affected by a reduction in the salt concentration, or by treatment with ether, chloroform, or petroleum ether. The β -lysin content of the serum is not increased by immunization. Pettersson tabulates the bacteria which are affected by the different bactericidal systems, and suggests that there are chemical differences between the cells affected by α -lysins—that is, complement system—and those affected by β -lysins. The organisms susceptible to β -lysins include *B. anthracis*, *B. proteus*, and *B. subtilis*, and also various anaerobes.

The difficulty in understanding the part played as mechanisms of defence by these heat-stable bactericidins is exemplified by the fact that the rabbit is relatively susceptible to anthrax, whilst its heated—that is, complement-free—serum is strongly bactericidal to this organism, while on the other hand the serum of fowls and dogs, which are relatively immune to anthrax, has little bactericidal power.

Mention should finally be made of another system which is possibly allied to the leukins and β -lysins—namely, the bactericidal substance discovered by Fleming (1922) in various secretions of the body (especially in the tears), and called by him "lysozyme." A particular organism known as *M. lysodeikticus* is very sensitive to the dissolving action of lysozyme in extremely low concentrations, but against most pathogenic bacteria it would appear to be inactive. The probability is that various tissues and secretions of the body possess a whole series of bactericidal powers which need extensive investigation.

CONCLUSION

It will be realized that the study of the defence mechanisms of the body has not at present passed very far beyond the descriptive stage. Complete explanation and elucidation are not yet in sight. The haemolytic complement of serum is possibly the simplest of all the factors so far described, and consequently offers the greatest hope of ultimate explanation. Even in this case, however, the usual view that complement is a particular physical state of the serum proteins is not universally accepted as proved, nor can it be until a clearer picture is available of the molecular structure of proteins in solution and the way in which this structure is affected by temperature, reaction, etc. The amphoteric character of proteins—or, in other words, their more or less feeble powers of combining with either acids or bases, or with each other—is without doubt responsible for their power of building up into aggregates of relatively enormous size, but the forces which hold these aggregates together are often so feeble that protein systems in solution are extraordinarily labile and sensitive to relatively mild agencies. On this account a quantitative physical chemistry of proteins is only as yet beginning to emerge, and considerable time must elapse before a theory of complement structure on the lines hinted at above can be either prudently formulated or adequately tested.

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SOME EARLY OCULAR SYMPTOMS OF OVER-INDULGENCE IN SUGAR AND SWEET FARINACEOUS FOOD

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In a series of interesting papers published recently in the *Edinburgh Medical Journal*, Dr. J. Hunter Paton¹ has drawn attention to the great increase in "the national consumption of sugar within recent years in its relation to the occurrence of disease." Glucose is the end-product in the biochemistry of the carbohydrate constituents of the dietary, and it is well known that the capacity to digest and assimilate sugar and starch varies greatly in different individuals. Those whose powers are more than usually restricted in regard to such foods readily suffer from diseases especially associated with disorders of carbohydrate metabolism.

The functional activity of every organ of the body is regulated by the quantity and quality of the blood circulating in its capillaries. Krogh² has demonstrated that the part played by the capillaries is distinct from that of the arteries and of the veins. They are not simply tubes through which blood flows. The cells of the organ have a direct influence upon them. They open up, or close down, in response to the call of the tissues for nourishment, and in the marvellous biological adaptation of structure to function the capillaries play an important part. Much depends upon their size and on the permeability of their walls to colloids.

DISTURBANCES OF VISION AND THE DIET

Visual function depends upon the circulation of the blood in the capillaries of the retina and the choriocapillaris. In proportion to its size the eye is very abundantly supplied with capillaries. Those of the retina and the choriocapillaris are among the most delicate in the body; and in the eye, as elsewhere, "all the secret and intimate business of life is transacted through their walls" (Allbutt). In the structures peculiar to the eye, however, perfect transparency is the primary requisite, and Nature has made provision for this by the relative impermeability of the walls of the ocular capillaries to the passage of colloids (Duke-Elder). The peculiar translucency and the characteristic colour of the normal fundus oculi³ are both due to circulation of the blood in these relatively impermeable capillaries. Dale⁴ has demonstrated that dilatation of the capillaries and increased permeability of their walls to the passage of colloids are brought about very rapidly by the action of metabolic toxins. One of the earliest clinical signs of this form of toxæmia is a diminution in the translucency of the ophthalmoscopic picture—a condition analogous to a muddy complexion. Although this appearance is difficult to describe, it is easy to recognize after attention has been directed to it. Translucency is the most delicate quality of the normal fundus oculi, and any loss of this pristine brilliancy is the first sign of a departure from health.

Among the patients suffering from headache referred to an ophthalmic surgeon is a well-defined group which does not obtain the relief expected from the use of the glasses prescribed.⁵ In these patients the ophthalmoscopic examination of the fundus reveals subtle changes in colour and translucency, which are probably due to interference with the rate of the circulation of the blood in the capillaries of the retina, and to increased permeability of their walls to colloids. The light sense is always more or less disturbed. Patients complain either that they require more light than formerly or that the light must