The Horace Dobell Lecture ON THE MECHANISM OF THE SERUM REACTION.

DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS
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BY H. R. DEAN, M.D., F.R.C.P.,
PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF MANCHESTER.

THE serum reactions are those which take place between an antigen and its homologous antiserum. Of the chemical nature of antigens we have no certain knowledge. Examples are bacteria and their products, red cells and blood serum when injected into an animal of different species. Substances capable of acting as antigens appear to be attached to protein matter, and have not as yet been isolated in a pure state. Attempts have been made to show that antigens are of a lipoid nature. Antigen-containing substances have been extracted with alcohol and ether, and the material obtained after evaporation of the solvent has been injected into animals (Bang and Forssman, 1916 and others). The results obtained have not been conclusive (Ritchie and Miller, 1913). In this connexion it must be remembered that antigens are active in very small amounts, and that an ethereal solution of lipoids, although apparently perfectly clear, may well contain minute fragments of protein matter in suspension. Moreover, substances not usually soluble in fat solvents may be dissolved or taken up as a very fine suspension in the presence of lecithin. A chloroform solution of lecithin can take up or dissolve such substances as cobra venom, trypsin, rennet, and even oxide of iron. In no case, so far as I am aware, has the injection of a pure substance of well defined chemical constitution been followed by the formation of antibodies. Our definition of antigen is a substance the introduction of which into the animal body is followed by the formation of a specific antibody.

It is usually held (Pick, 1902) that the antibodies are for the greater part precipitated with the globulins of the serum, with the pseudoglobulin fraction in the case of the horse, with the euglobulin fraction in the case of the goat. Moreover, an increase in the globulins of the serum during the process of immunization has, on several occasions, been observed. It is, however, probable that euglobulin and pseudoglobulin merely represent different phases of physical aggregation of their constituent particles, and the difference between even albumin and globulin may be of a physical rather than chemical nature. Viewed from this point of view, the fact that the greater part of the antibody in a serum is precipitated with any particular fraction of globulin yields no information as to the chemical nature of the actual antibody. As a matter of fact it was shown by Ledingham (1907) that the ratio of distribution of antitoxin among the various serum proteins, euglobulin, pseudoglobulin, and albumin, differed considerably at different stages of the process of immunization. We may suppose that the process of immunization is accompanied by a disturbance of the physical state of the serum proteins, and the regrouping of protein molecules may lead to an increase in the globulin fraction.

As to the chemical nature of antigen and antibody we are in complete ignorance. When, however, antigen is mixed with antibody a reaction takes place, and the occurrence of this reaction can be shown by certain phenomena known as the serum reactions. These reactions are:

1. *The Precipitation Reaction.*—When a normal serum or a bacterial extract is mixed with its homologous antiserum a precipitate is formed.
2. *The Agglutination Reaction.*—When a suspension of red blood corpuscles, or bacteria, is mixed with homologous antiserum the bacteria or cells are agglutinated to form clumps.
3. *Lysis.*—When red corpuscles or bacteria are mixed with antiserum or complement the cells are dissolved, or, at any rate, some change takes place which leads to the escape of the intracellular contents.
4. *Complement Fixation.*—When antigen is mixed with antiserum and complement, the complement is used up, and if subsequently there be added a mixture of red blood corpuscles

and homologous antiserum, the fixation of the complement can be demonstrated by the absence of haemolysis.

5. *The Oponic Reaction.*—If red cells or bacteria are treated with antiserum the cells or bacteria are so altered that they are more readily ingested by phagocytes. This reaction is more marked in the presence of complement.

Two main theories have been advanced to explain these reactions—the theory of Ehrlich and the theory of Bordet. The former theory assumes a chemical union between the antigen and the antibody; the other interprets the reactions as adsorption phenomena in which the antibody is adsorbed by the antigen. In spite of some opposition the theory of Ehrlich has acquired a dominant position in medical literature, and its general outline is familiar to all who have even the scantiest knowledge of medical sciences.

According to the views of the Ehrlich school each of the serum reactions is due to the existence of a separate and particular antibody. These various and hypothetical antibodies have been arranged in three classes.

Receptors of First Order.—To this class belong the antitoxins, which possess a haptophore group, a grouping of atoms capable of satisfying the affinities of the corresponding grouping in the haptophore molecule of the homologous toxin. The toxin molecule is thus rendered harmless, for it is no longer able to combine with the cells of the body.

Receptors of the Second Order.—These have, in addition to the haptophore group, a second group, the ergophore group, which by virtue of its chemical constitution is able to bring about the change peculiar to the particular type of antibody. To this class belong the precipitins and agglutinins. The haptophore group of the agglutinin combines with the bacterium, and subsequently the ergophore group proceeds to produce agglutination.

Receptors of the Third Order.—In addition to the haptophore group, the antibodies possess a complementophile group, which combines with a substance called complement, which is necessary to complete the lysis of a corpuscle or bacterium. The antibodies concerned in the complement fixation reaction are held by many to constitute a separate class of amboceptor, and the opsonins or bacteriotropins are also considered to belong to this group.

It is assumed, then, that each serum reaction is an entirely separate and distinct phenomenon, the result of the action of a highly specialized chemical substance expressly manufactured for the purpose. A precipitin is a body which combines with homologous antigen, and then, by virtue of a special chemical formula, proceeds to precipitate it. It is entirely distinct from the complement-binding amboceptor, which is structurally adapted to perform the specific function of complement fixation. It is manifest that the side-chain theory affords no explanation whatever of the mechanism of the serum reactions. It may, as a matter of mere terminology, be convenient to say that any serum contains an agglutinin for *B. typhosus*, but the process of agglutination is in no way explained by saying that the agglutinin possesses two groups, the one a haptophore which combines with the bacillus, the other an ergophore which produces agglutination. We already know that clumping occurs and that the reaction is specific.

Ignorance, however aptly veiled in attractive terminology, remains ignorance. With each addition to the store of experimental fact, new substances have been imagined and endowed with the appropriate functions. To difficulties in the interpretation of the reaction between toxin and antitoxin we owe the coining of such words as proto-toxoid, syntoxoid, and epitoxoid. The observation that bacteriolysis does not occur in the presence of a great relative excess of antiserum led Neisser and Wechsberg (1901) to elaborate the hypothetical conception of complement deviation† (*Komplement Ablenkung*). The experimental facts are explained in this case by supposing that free amboceptors have a greater affinity for complement than those which have effected union with the receptors of the bacillus. Ferrata's experiments (1907) showed, by precipitating the euglobulin of fresh serum, that two substances appeared to be necessary for complement action. The names "midpiece" and "endpiece" fraction of the complement were accordingly coined, and the

* Certain tables and charts by which the lecture was illustrated have not been reproduced.

† Complement deviation (*ablenkung*) should not be confused with the more familiar complement fixation (*Bindung*).

diagrams which accompany Brand's article (1907) are examples of the attempt to make new experimental data conform to the limits of a ruling hypothesis.

A theory, right or wrong, is of value as long as it tends to progress and further investigation; and it is notorious that the researches of Ehrlich and his school have yielded results of high theoretical interest and great practical value in the realms alike of diagnosis and therapeutics. Nevertheless the outstanding genius of Ehrlich and the greatness of his discoveries have tended to give to the theory associated with his name a position comparable to that of a well-known law of physical or biological science. New observations have been held to be explained if they were shown to be consistent with the side-chain hypothesis. But agglutinins, precipitins, amboceptors are mere words, and a passive belief in the existence of such bodies tends to impede rather than advance our understanding of what is actually taking place. In our present state of ignorance of the nature of the reaction it seems undesirable to use a terminology which implies a knowledge which we do not possess.

We know that when substances containing antigens are mixed with substances containing antibodies a change takes place, and we can obtain indirect evidence of this change by observing certain phenomena, such as precipitation, agglutination, or lysis. It seems to me probable that these phenomena are the result of one fundamental reaction which takes place between antigen and antibody. The so-called serum reactions, precipitation, agglutination, lysis, complement fixation, and the opsonic reaction constitute different methods for the indirect observation of one reaction which underlies and is essential to them all.* They are, in fact, accessory phenomena, and their demonstration is dependent on accessory characteristics in the reagents which we employ. For all the reactions which can be demonstrated in a test tube it is only necessary to postulate one kind of antibody.

Precipitation.

This is a reaction which is usually demonstrated by mixing antiserum with an antigen-containing fluid. According to the side-chain hypothesis the antiserum contains an active substance, the precipitin which precipitates the antigen, called in this reaction "the precipitinogen." That any person who had carried out many precipitation reactions should continue to hold this view is not a little surprising. In practice relatively large amounts of antiserum are invariably employed, while the antigen-containing serum may be employed in quantities of 0.0001 c.cm., 0.00001 c.cm., or in exceptional cases still smaller amounts. That a fairly abundant and easily visible precipitate could be derived from such a minute quantity of antigen is scarcely conceivable. It is to Welsh and Chapman (1906 to 1910) that we owe a most important observation on this subject. These workers showed by gravimetric methods that, under the usual experimental conditions, the greater part if not all of the precipitate was derived from the antiserum. A paper in the *Proceedings of the Royal Society* (1907) by Welsh and Chapman illustrates this point. On the other hand, the weight of the precipitate is directly proportional to the amount of antiserum, provided that the mixture contains sufficient antigen to precipitate all the precipitable matter in the antiserum.

If, however, the mixture contains an insufficient quantity of antigen precipitation is incomplete and a smaller precipitate is obtained. The proof given by Welsh and Chapman that, under the usual experimental conditions, it is the antiserum which is precipitated by the antigen, is of far-reaching importance. It casts an entirely fresh light not merely on the precipitation reaction but on the other serum reactions as well.

Before leaving the subject of precipitation it is necessary to refer to the importance of the relative proportions of antigen and antiserum in the mixture.

The relative proportions of antigen and antibody constitutes a factor which is present in all the serum reactions. This influence of relative proportions suggests an analogy with the precipitate which is formed when an electro-positive is mixed with an electro-negative colloid. In this case, if the proportions are optimal, both colloids

are completely precipitated. If either constituent is present in relative excess, precipitation is incomplete. Moreschi (1906) concluded, as the result of a series of experiments, that precipitin and precipitinogen unite in variable proportions to form a series of precipitates. This result is at variance with the conclusions of Welsh and Chapman. The matter is one which merits further investigation.

If, then, antigen is mixed with antibody there follows an aggregation of particles with the formation in all probability of an adsorption compound. This aggregation is an essential part of the mechanism of all the serum reactions, not merely of the precipitin reaction, but also of agglutination, lysis, complement fixation, and in all probability the opsonic reaction. If sufficient antiserum is used, and if the proportions of antigen and antibody are correctly adjusted, there is formed a bulky and flocculent precipitate. If the mixture contains a relative excess of either antigen or antibody, the aggregation process is less complete.

It may be here observed that the ordinary method of performing the test in which a few cubic centimetres of the mixture are placed in an ordinary test tube is not an ideal method of observing a finely divided precipitate. A mixture of antigen and antiserum, which looks as clear as water in an ordinary test tube, may appear opalescent or even turbid if viewed through the length of a polarimeter tube.

The Relation between the Formation of a Precipitate and the Fixation of Complement.

Complement fixation, which since the introduction of the Wassermann reaction has become comparatively familiar, was first observed by Bordet and Gengou in 1901. Interest in the subject was revived by Neisser and Sachs (1906), who elaborated a practical method for the identification of the blood of different kinds of animals. As to the explanation of the phenomenon considerable controversy has taken place. Gay (1905) came to the conclusion that the formation of a precipitate was the essential cause of the disappearance of complement. Neisser and Sachs, on the other hand, found that the amount of the precipitate and the amount of complement fixed stood in no direct proportions. They were able to observe marked fixation of complement in mixtures in which no precipitate could be recognized. They considered that the complement united with the complementophile group of an amboceptor in strict accordance with the theories of Ehrlich. The view was, accordingly, propounded that precipitation and complement fixation were separate and independent phenomena. Muir and Martin (1906) found that the fixation of complement was as a rule closely associated with the formation of a precipitate, but were not convinced that precipitation formed a complete explanation of complement fixation. They cited as an instance a rabbit *v.* guinea-pig serum which produced, when mixed with its homologous antigen, a faint cloudiness but no definite precipitate. The capacity for fixing complement, however, was possessed by this serum to a very high degree. In other experiments they found that, if the antigen was greatly diluted, no precipitate was formed, but nevertheless the mixture was able to bind complement efficiently.

The case for the separate identity of precipitins and complement-binding antibodies rests on the following evidence:

1. Mixtures of antigen and antiserum in which a definite precipitate formed were shown to have little or no power to fix complement.
2. Mixtures containing very small quantities of either antigen or antiserum may appear perfectly clear, and yet be shown to be very efficient for complement fixation.
3. Certain antisera give excellent results in complement fixation experiments, but yield very small precipitates.
4. If during the process of immunization daily samples of serum are examined, complement fixation can as a rule be demonstrated at an earlier stage than precipitation.
5. If either the antiserum or the normal serum (antigen) be heated, the capacity for forming precipitate may be lost, while the capacity for fixing complement may be retained. Bacterial extract kept for a time loses its power of forming a precipitate with homologous antiserum, but is still useful for the complement fixation test.

* The reaction which takes place between toxin and anti-toxin is not accompanied by any change which can be demonstrated *in vitro*, and appears to be of a somewhat different nature from that which takes place in the serum reactions which are here considered.

If a series of mixtures are prepared by adding various quantities of antigen to a constant quantity of a good antiserum, it is possible to compare the amount and state of division of the precipitate with the amount of complement fixed, and it becomes evident that the proportions of antigen and antibody which produce the largest quantity of precipitate are not those which effect the greatest fixation of complement. Similar results were obtained by mixing a variety of antigens with the homologous antisera. When antigen and antibody are mixed in the proportions most favourable to precipitation the aggregation process takes place energetically, and large flocculi are rapidly separated. But if the mixture contains a relatively smaller amount of antigen, precipitation is slower and less complete. These are the conditions favourable to complement fixation. Under these conditions the individual particles which form the precipitate are extremely small, but present in the aggregate an enormously larger surface area than the flocculi of a coarser precipitate. It seems probable that there is a direct relation between the surface area of the particles of the precipitate and the amount of complement fixed.

By taking any one antigen and any one antiserum, and by varying the relative proportions of these two ingredients, it is possible to prepare mixtures which demonstrate either precipitation without complement fixation or complement fixation without visible precipitation. The amount of complement fixed is conditioned by two factors: (1) The amount of precipitate formed, and (2) the rate of precipitate formation. Complement is fixed during the very earliest stages of the aggregation process which forms the precipitate. Indeed, after the process has advanced to a visible turbidity, very little complement is taken up. The relative proportions of antigen and antibody which favour rapid and complete precipitation are positively unfavourable to complement fixation.

If a constant amount of antiserum be taken, it will be found, as a rule, that the quantity of antigen which will produce the best complement fixation is many times less than the amount necessary to produce the largest precipitate. The reason why the two reactions do not run a parallel course is not that they are caused by two different sets of antibodies, precipitins, and amboceptors, but because they represent two phases or two stages of the same reaction, and it may not be possible to demonstrate both stages under the same conditions. A flocculent precipitate represents the complete and final stage of a change which can be recognized in its earliest and incomplete stage by means of the complement fixation method. On the other hand, if the mixture contains a very small amount of the antigen, the aggregation process is extremely slow, and may never proceed to the point at which even opalescence is produced. Such a condition is, however, very favourable to complement fixation.

The conditions which we have considered are those in which a relatively small amount of antigen is allowed to interact with a relatively large amount of antiserum. In these cases, although no visible precipitate is formed, the early stages of aggregation afford exactly the physical conditions which favour complement fixation. We must now consider the conditions which obtain in mixtures containing very small amounts of antiserum, and in complement fixation tests a good antiserum can always be used in a dilution of 1 in 100, often 1 in 500, or even 1 in 1,000. If, however, a cubic centimetre of 1 in 500 dilution of antiserum be mixed with an equal quantity of a suitable dilution of the homologous antigen, not even a trace of a precipitate can as a rule be detected, for such a mixture contains far too little of the precipitable protein of the antiserum. What is the mechanism of complement fixation under these conditions? In a series of experiments (Dean, 1912) it was shown that if to a mixture of antigen and antiserum which fixes complement, but produces little or no precipitate, there be added fresh guinea-pig serum, a very definite and flocculent precipitate is produced, although a comparatively long time (up to twenty-four hours) may elapse before precipitation is complete.

In one experiment tubes were used the lower portions of which were narrow and calibrated in order that the amount of precipitate formed could be measured. Only one quantity of antigen was employed (3 c.cm. of a 1 in 20 dilution of typhoid extract) and one quantity of the antiserum (3 c.cm. of a 1 in 20 dilution of antityphoid serum). The amount of precipitate

formed by the simple mixture of the antigen and antibody was increased by the addition of guinea-pig serum. In the tubes containing the large quantities of guinea-pig serum the bulk of the precipitate was twice and three times as great as the precipitate produced in the simple mixture of antigen and antibody.

It is difficult to escape the conclusion that the larger precipitates were partly derived from the proteins of the guinea-pig serum.

Similar results were obtained in a large series of experiments in which various antigen-antibody systems were employed. Normal horse and normal sheep serum were shown to be as effective as guinea-pig serum in adding to the bulk of the precipitate. Similar results were obtained if in place of the whole guinea-pig serum a solution of guinea-pig euglobulin was employed. These experiments led to the conclusion that the interaction of antigen and antibody may cause the precipitation of the globulin of normal serum if such is added to the mixture. That this precipitation of the globulin of normal guinea-pig serum is an essential part of the mechanism of complement fixation can hardly be doubted. It will be remembered that if euglobulin is precipitated from fresh guinea-pig serum by distilled water or weak acid, the complement is split in two fractions, the so-called midpiece and the endpiece. The midpiece fraction is carried down with the precipitated euglobulin while the endpiece remains in solution (Ferrata 1907, Brand, 1907, Liefmann 1909, Sachs and Altmann 1909). Moreover, in complement fixation experiments the midpiece is bound to a much greater extent than the endpiece (Skwirsky 1910, Henderson Smith 1910, Sachs and Bolkowska 1910, Amako 1910, and Gengou 1911). It may, however, well be doubted if any such substance as the midpiece fraction of the complement exists. The action of the so-called midpiece may be entirely due to the physical state of the adsorbed particles of euglobulin.

It has already been mentioned that these precipitates, which occurred in mixtures of antigen, antibody, and complement, were often not formed until several hours had elapsed. The tubes were consequently often left overnight in the ice chest. This practice led to the observation that these precipitates are formed most readily at a low temperature, and that if, after the precipitate has formed, the tubes are placed in an incubator at 37° C., the precipitate dissolves and the mixture becomes once more absolutely clear. On replacing the tubes in the ice chest the precipitate reforms. The behaviour of this precipitate, which forms at 0° C. and dissolves at 37° C., strengthens the belief that we are dealing with an adsorption process. At the lower temperature the adsorption of euglobulin by the minute particles of the precipitate is more complete. When the antigen is a cell or bacterium susceptible to lysis, the result of this aggregation of the particles of euglobulin is the concentration of the lytic agent present in the complement (so called endpiece) at the surface of the cell which is to be dissolved. For the subsequent and distinct reaction which causes the solution of the cell envelope a relatively high temperature (37° C.) is necessary, or at any rate desirable. If the fixation of complement is dependent on an adsorption process, we should expect that the reaction would take place with greater facility at a low rather than a high temperature.

Another experiment showed that in a mixture of typhoid extract and antityphoid serum far more complement was fixed at 0° C. than at 37° C. Similar results have been obtained with serum and homologous antiserum and with the Wassermann reaction.

In this experiment duplicate sets of the bacterial extract—the antiserum and the complement—were prepared. Set A was warmed to 37° C., and set B was cooled to 0° C. Antigen, antibody, and complement were then mixed in suitable proportions. Set A was then kept for half an hour at 37° C., and set B for half an hour at 0° C. Both sets were then exposed to room temperature for one hour. Blood and haemolytic serum were then added to each tube, and all tubes were then incubated for two hours at 37° C. The results showed a very marked difference between the two sets.

Moreover, if an experiment be devised to show the rate at which the reaction occurs at the two temperatures, it is possible to demonstrate that although the reaction takes place more rapidly at 37° C., the actual amount of complement fixed is much greater at 0° C.

This result is best explained on the assumption that complement fixation is a process of adsorption.

Agglutination.

The explanation of the agglutination reaction as an adsorption phenomenon has been the thesis of many contributions to the literature of immunity. Bordet (1899) considered that agglutinin is adsorbed by the bacilli as dye is adsorbed by filter paper. The aggregation of the bacilli is then brought about by changes in the molecular attraction between the bacilli and the surrounding medium. The question of agglutination was very thoroughly studied from the adsorption standpoint by Craw (1905). Craw showed that the rate of addition of bacillary suspensions to agglutinating serum is a factor determining the amount of agglutinin fixed by the bacilli. By adding a suspension of bacteria in parts to the antiserum, Craw was able to show that more agglutinin was removed than is the case when the whole amount of bacillary suspension is added at once.

The process of agglutination is probably brought about by an interaction between the antiserum and antigen which has passed out from the bacilli into the medium which immediately surrounds it. The result of this interaction is the aggregation of the particles of the globulin of the antiserum on the surface of the bacillus. In other words, the proteins of the antiserum are adsorbed by the bacillus. For the production of agglutination the presence of precipitable protein is essential. If to a mixture of bacillary emulsion and diluted antiserum there be added a third ingredient—normal serum—the agglutination of the bacteria is rendered more complete. This reinforcement of the proteins of the antiserum by those of a normal serum has been called conglutination. This phenomenon was described independently in 1906 by Muir and Browning and by Bordet and Gay.

The substance present in normal serum which is able to aid the agglutination of red cells or bacteria by the homologous antiserum appears to be the englobulin (Dean, 1911).

That in such a reaction the englobulin is actually precipitated may be shown by experiment.

In discussing the merits of rival theories of the mechanism of the serum reactions it has been frequently observed that Ehrlich's hypothesis alone provides an explanation of the problem of specificity. The value of the side-chain theory as an explanation of specificity may, however, be doubted. To say that antigen unites with antibody as a key fits a lock is no explanation at all. It is merely a diagrammatic representation of the supposed facts. Of the nature of the fundamental reaction between antigen and antibody we have, at the present time, no knowledge. But in all the serum reactions which have been above considered the immediate consequence is an aggregation of globulin particles around the antigen. The degree to which the aggregation or precipitation proceeds depends entirely on the experimental conditions, on the relative proportions of antigen and antibody in the mixture, on the nature of the antigen-containing substance, red corpuscle, bacillus, or normal serum; on the presence of some third factor, a normal serum containing complement or conglutinin. In other words, the various serum reactions are various methods of observing and measuring one single reaction. The simplest of these reactions is the precipitation reaction, for in it the formation of the precipitate is directly observed. In the other reactions the aggregation of particles may be less complete, and the change is measured by indirect methods. The main phenomena are most readily accounted for by Bordet's adsorption theory, and no useful purpose would seem to be served by postulating the existence of a separate kind of antibody for each of these reactions. The reactions are no doubt of a very complex nature, as all reactions which occur in a mixture of colloids must be, and it is to be anticipated that great difficulties must be encountered before any entirely satisfactory explanation is arrived at. Similar difficulties have been met with in the past whenever the attempt has been made to explain physiological phenomena in the light of the laws of chemistry and physics. These difficulties will be met, and with a more perfect knowledge of the mechanism of the serum reactions there will be attained a more perfect knowledge of the laws which govern both natural and acquired immunity.

BIBLIOGRAPHY.

- Amako (1910): *Zeit. f. Immunitätsforschung*, Bd. 8, S. 168.
 Bang and Forssman (1906): *Beiträge z. Chem. Phys. u. Path.*, Bd. 8, S. 238.
 Bordet (1899): *Ann. de l'Institut Pasteur*, T. 13.

- Bordet and Gengou (1901): *Ann. de l'Institut Pasteur*, T. 15, p. 289.
 Bordet and Gay (1906): *Ann. de l'Institut Pasteur*, T. 20, p. 467.
 Brand (1907): *Berl. klin. Woch.*, Bd. 44, S. 1075.
 Chapman (1910): *Proc. Roy. Soc.*, B, vol. lxxxii, p. 398.
 Craw (1905): *Journ. of Hygiene*, vol. v, No. 1, p. 495.
 Dean (1911): *Proc. Roy. Soc. Med.*, vol. v (Path. Sect.), p. 62. *Proc. Roy. Soc.*, B, vol. lxxxi, p. 416. (1912): *Journ. of Hygiene*, vol. xii, p. 259.
 Ferrata (1907): *Berl. klin. Woch.*, Bd. 44, S. 366.
 Gay (1905): *Ann. de l'Institut Pasteur*, T. 19, p. 593. *Centralb. f. Bakt.*, Abt. I, Orig., Bd. 39, S. 603.
 Gengou (1911): *Zeit. f. Immunitätsforschung*, Bd. 11, S. 143.
 Henderson Smith (1910): *BRITISH MEDICAL JOURNAL*, vol. ii, p. 1433.
 Ledingham (1907): *Journ. of Hygiene*, vol. vii, p. 65.
 Liefmann (1909): *Muench. med. Woch.*, vol. lvi, S. 2097.
 Moreschi (1906): *Centralb. f. Bakt.*, Abt. I, Ref., Bd. 38, Beiheft, p. 96. *Berl. klin. Woch.*, Bd. 43, S. 100.
 Muir and Martin (1906): *Journ. of Hygiene*, vol. vi, p. 265.
 Muir and Browning (1906): *Journ. of Hygiene*, vol. vi, p. 20.
 Neisser and Wechsberg (1901): *Muench. med. Woch.*, Bd. 48, S. 697.
 Neisser and Sachs (1906): *Berl. klin. Woch.*, Bd. 43, p. 67.
 Pick (1902): *Beiträge z. Chem. Physiol. u. Path.* (Hofmeister).
 Ritchie and Milne (1913): *Journ. of Path. and Bact.*, vol. xvii, p. 429.
 Sachs and Altmann (1909): *Handb. d. Technik u. Methodik d. Immunitätsforschung* (Kraus u. Levaditi), vol. ii, S. 969.
 Sachs and Bolkowska (1910): *Zeit. f. Immunitätsforschung*, Bd. 7, S. 778.
 Skwirsky (1910): *Zeit. f. Immunitätsforschung*, Bd. v, S. 538.
 Welsh and Chapman (1907): *Proc. Roy. Soc.*, B, vol. lxxviii, p. 297.

FIVE CASES OF LABOUR OBSTRUCTED BY A CONTRACTION RING.

By CLIFFORD WHITE, F.R.C.S.ENG.,

SURGEON TO THE SAMARITAN AND METROPOLITAN HOSPITALS;
 OBSTETRICIAN TO IN-PATIENTS, QUEEN CHARLOTTE'S HOSPITAL.

THE importance of a localized contraction of the uterus as a cause of obstruction in labour has been recognized more and more during the last few years. In the *BRITISH MEDICAL JOURNAL* of October 14th, 1916, Mr. H. T. Hicks attempts to describe the type of patient in whom it occurs, and discusses the means of diagnosis and treatment. He states that "in all these cases" the condition is associated with (a) primiparity; (b) some degree of pelvic contraction; (c) thinning of the lower uterine segment; (d) a movable presenting part above the brim, with the fundus continuing to contract, but later passing into a state of "tetany."

In five cases under my observation in which labour has been obstructed by a ring, and therefore probably closely related to his cases, most of the above conditions have been absent. There was not contraction of the pelvis, and tetany of the fundus did not supervene. These five patients had been pregnant 2, 5, 5, 0, and 14 times respectively.

It would appear, therefore, that the condition is one that covers a wider clinical area than Mr. Hicks's account would indicate. My interest in this condition of the uterus was aroused by the detailed examination of a specimen removed during labour by hysterectomy. This specimen showed that the contraction ring formed over a depression in the child's body, and that the part below the ring was not pathologically thinned. Thus, the ring has no connexion with the ring of Bandl, commonly called a retraction ring. It is usually termed a contraction ring, in distinction to the former, and the majority of American writers use this term. In 1912, when describing this specimen, I gave details of three cases, and gave

Left. Right.

Diagram to illustrate, on left, uterus with contraction ring. The lower uterine segment is not thinned, the fundus is frequently relaxed, and the ring forms over a depression in the outline of the fetus. On the right, uterus with retraction ring (of Bandl). The lower segment is thinned, the fundus is contracted, and the ring forms at the junction of the thickened upper and thinned lower uterine segments. It is possible that combinations of these two primary conditions may exist simultaneously.