These particles were now collected and ingested by the sessile phagocytes of the ellipsoids, which thereafter migrated into the splenic parenchyma, just as the phagocytes of the lymphatic glands travelled when the empty ellipsoids underwent a regenerative process accompanied by hypertrophy. As Dr. E. S. Mills had shown, this process might lie at the root of splenomegaly. In answer to a criticism by Sir Almoth Wright, who objected to a division of the tissues into haemorrhagic and anaemorrhagic, on the ground that the blood coagulating principles were soluble rather than cellular, he stated that no tissue extract was active unless it contained cellular debris. He referred to recent work by Dr. Cleland and himself on the nervous machinery controlling rhythmic contraction.

THE KINETICS OF THE VARIOUS HAEMOLYTIC SYSTEMS.*

BY

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THE object of an opening paper should admittedly be to arrange and to condense the subject so that it can be easily grasped even by those who are unfamiliar with it. In the case of the subject of haemolysis, with its many and diverse investigations, this is impossible; I propose, therefore, to fix at the very beginning the point upon which all these investigations must ultimately converge, and to deal with the subject by describing certain successive steps which lead up to the final problems; for the solution of these final problems, concerned as they are with the reactions occurring in complement-antibody systems, forms the principal justification for the labour spent on the study of simpler haemolytic phenomena. This treatment can only result in the presentation of the subject from a restricted point of view; it will, however, make the connexion between the simple and the complex forms of haemolysis as plain as is possible.

Before considering the action of even the simplest haemolysin it will be as well to be quite clear about the structure of the cell upon which it acts. All the recent investigations lead us to the conclusion that the red cell of mammals is a balloon-like structure possessed of an envelope of considerable strength. One of the clearest proofs of this is the fact that the changes of shape and size which the cell undergoes, both in hypotonic solutions and in solutions containing haemolysins, are those of a balloon-like body and not those of a sponge-like structure;¹ if more direct evidence is required, Seifriz² has actually microdissected the human red cell, stretched its envelope, and observed the escape of fluid containing haemoglobin. There is considerable evidence, from investigations on quite different lines, that the envelope is composed principally of protein and not of lipid, as was once thought; in this connexion may be mentioned the work of Oliver and Barnard³ on cell agglutination, of Seifriz on microdissection, as well as the results of the recent work on the haemolysins. The best conception of the structure of the envelope is probably one similar to Bechold's—a protein framework, in the interstices of which lipid is contained. Several proteins probably enter into the composition of the framework.

The action of the haemolysins must therefore be principally on this complex envelope, its continuity being destroyed, with the result that the fluid contents are liberated into the surrounding fluid.

1. Simple Haemolytic Systems.

Setting aside the instances of lysis by mechanical means, which tell us very little, the simplest cases of haemolysis are to be found in systems which contain one lysin of known constitution and in known quantity, acting on washed red cells, and acting in the absence of any substances which accelerate or inhibit the reaction. As an

example we may take the case of saponin acting on washed mammalian red cells at a constant temperature.

In such a case it is easy to satisfy oneself that the reaction which results in lysis is accompanied by a using up of saponin, and by a combination of the lysin with some component of the red cell envelope. This component is certainly protein in nature. The amount of saponin used up in producing lysis of any given number of cells can be very exactly measured, and the rate at which the using up proceeds gives us the rate of the reaction between the lysin and the protein component of the envelope with which it combines. This reaction we call the "fundamental" reaction. The factors upon which its velocity depends have been exactly determined, and it is known that the amount of saponin, x , used in producing lysis in time t , is given by the expression (1):

$$\kappa t = \log \frac{c}{c-x}$$

where c is the initial concentration of saponin present in the system, and where κ is a constant which varies with the surface presented by the cells, the temperature, and other factors. The fundamental reaction, which is described by this expression with great accuracy, is therefore a reaction of the first order, and its velocity at any moment dependent on the concentration of free lysin present at that moment.

Expression (1) thus gives the quantity of saponin combined with the cells at the end of any given time, but it does not, as it stands, give the amount of lysis which results from this combination. The reason for this is that the cells offer different resistances to the lysin, so that the least resistant cells haemolyse when only a small amount of their protein component is united with the saponin, whereas the more resistant cells require large quantities of the protein component to unite with the lysin before haemolysis takes place. On theoretical grounds we should expect that the cells, if grouped according to their resistance, would give a frequency distribution of a symmetrical type, the resistance of a few cells being small, the resistance of a few cells being great, and the resistance of the majority being intermediate. This is in fact the case, and the particular distribution, for human cells at least, is of the type shown in expression (2):

$$n = y_0 \left(1 - \frac{x}{a}\right)^m$$

Here n is the number of cells, expressed as a percentage of the whole for convenience, in any group of resistance x ; y_0 is the number of cells of mean resistance, and a and m are constants.

Now as the fundamental reaction proceeds according to expression (1), quantities of lysin x_1, x_2, x_3 , etc., combine with the cells in times t_1, t_2, t_3 , etc. The cells whose resistance corresponds to x_1 haemolyse when x_1 is formed, and, if we want to determine their number, we can do so by means of expression (2). When x_2 is formed, the cells whose resistance corresponds to x_2 haemolyse; this number is again given by expression (2). And so on for x_3 , and for all other values of x . The number of cells which are haemolysed at any moment from the beginning of the reaction until the stage of complete haemolysis is accordingly not to be found from any one expression, but from the simultaneous solution of expressions (1) and (2).

The result of this simultaneous solution is an S-shaped curve which gives the number of cells haemolysed at any stage of the experiment, and, as the fundamental reaction is steadily slowing down, the S-shaped curve is always asymmetrical. Recently several methods have been introduced for the study of such curves, by far the best being that which depends on the use of selenium as a means of measuring the intensity of the light transmitted by the cell suspension. By this method, which we owe to Mellanby, it can be shown that the S-shaped curves obtained from experiment agree exactly with those calculated from expressions of the form of expressions (1) and (2).⁴ The conclusion must be that the fundamental reaction between the protein of the envelope and the lysin is of the first order, and that the resistances of the cells is expressed by a frequency distribution of Pearson's Type II. That some explanation such as this is the probable one was suggested by Brooks⁵ in a theoretical

* A paper read in opening a discussion on haemolysis in the Section of Physiology and Biochemistry at the Annual Meeting of the British Medical Association, Edinburgh, 1927. Sir Edward Sharpey-Schafer, M.D., F.R.S., President of the Section, was in the chair.

paper of outstanding importance some six years ago; all the investigations since that time, both theoretical and experimental, have placed this hypothesis in an unassailable position.

From the foregoing we should expect there to be a relation between the quantity of protein in any particular type of red cell and the resistance of that cell to saponin. This relation certainly exists, for if we arrange the cells of different species in order of their resistance to saponin, we find them arranged very nearly in order of their protein content. Unfortunately for simplicity, however, this relation does not appear to hold for other haemolysins. Kofler and Lazar⁶ have shown that the protein content does not determine the resistance to digitonin, senegin, and other glucosides, and McLachlan and I have shown the same absence of the relation in the case of the haemolysins of bacterial origin.⁷ Such observations certainly give rise to some little difficulty, but it is to be remembered that the affinity of the protein of the cell for the lysin, as well as the absolute amount of the protein in the cell, has to be taken into account. In the case of saponin, the affinities of the proteins of the cells of the ox, sheep, rabbit, etc., for the lysins are much the same, with the result that the absolute quantity of the protein is the only factor influencing the resistance; in the case of other lysins the affinities may be quite different, perhaps owing to slight differences in grouping within the protein molecule, and thus the effect of the absolute quantity of protein present in the cell envelope may well become of secondary importance. The matter can be decided by a careful evaluation of the constant κ in expression (1), but this is a matter of great difficulty.

By methods identical with those used for the investigation of the haemolytic properties of saponin it can be shown that sodium taurocholate, and also sodium glycocholate in certain concentrations, form compounds with the proteins of the cell envelope; the process of formation of this compound is, as in the case of saponin, a reaction of the first order, and is described by an expression of the form of expression (1). The complete solution of the kinetics of the haemolytic reaction involves two expressions just as in the case of saponin, the first relating to the velocity of the fundamental reaction, and the second giving the distribution of the cell resistances. The frequently made statement that the bile salts act as solvents of the lipoids of the red cell envelope and thus produce lysis will not bear even the most superficial examination; it is, for example, quite incompatible with the fact that sodium glycocholate in concentrations of about 1 in 100 is much less haemolytic than the same salt in concentrations of 1 in 1,000.

To the substances which fall into this simplest class of haemolysins may be added most of the haemolytic glucosides (digitonin, senegin, smilacin, sapotoxin, helleborin, etc.), the soaps,⁸ and the salts and acids allied to the bile salts. Each of these substances forms loose compounds with protein, and each, when studied quantitatively, will be found to follow the same laws as have been shown to hold for saponin. Sodium glycocholate alone presents peculiarities. Within the last few months McLachlan and I have been able to show that most of the lysins of bacterial origin fall into this class, for the haemolytic substances produced by *B. welchii*, *B. anthracoides*, *B. tetani*, *B. histolyticus*, *B. subtilis*, *B. coli*, *El Tor vibrio*, *Streptococcus pyogenes*, and *Staphylococcus pyogenes*, all act in a manner similar to saponin, and conform to the same quantitative laws. It is of interest to note that two of these lysins—that of *B. histolyticus* and that of *Streptococcus pyogenes*—are definitely known to be proteolytic.

2. Inhibition by Serum.

Since, in the case of all the lysins of the saponin class, the reaction which results in haemolysis appears to be one between the lysin and the protein of the cell envelope, we should expect these lysins to unite with other proteins to form non-haemolytic compounds. This can be readily shown to occur, for, if small quantities of serum or plasma are added to the haemolytic systems, inhibition of haemolysis results. This inhibition was first shown by Bayer⁹ to be dependent on the presence of serum proteins, although

previously it was believed that it was due to the presence of lecithin or cholesterol. Bayer's observations have been repeatedly confirmed. Recently it has become possible to measure the amount of the lysin which unites with these proteins, and the results indicate that the combination takes place according to the formula applicable to adsorption processes¹⁰; we therefore conclude that the lysins of the saponin type, which are all surface active, form with the proteins of serum and plasma non-haemolytic adsorption compounds, as the result of which lysin is removed from the system, so that an inhibition of haemolysis results. These observations have been confirmed by Kennedy¹¹ and by Donnelly and Graeme Mitchell¹²; they are in themselves interesting examples of adsorption occurring in colloidal systems, and their full significance from the point of view of haemolytic reactions will appear when we consider the more complex systems. In the case of sodium taurocholate and of the soaps, the non-haemolytic substance which is formed can actually be seen as a fine opalescence which appears on the addition of the serum.

3. Cell-Serum-Lysin and Cell-Lysin-Serum Systems.

We have now to consider one respect in which haemolytic systems containing sodium taurocholate, sodium glycocholate, or certain of the soaps, differ from systems containing saponin, the glucosides, or the bacterial haemolysins. The serum proteins always inhibit the action of saponin, owing to the formation of a non-haemolytic compound as the result of a combination between the lysin and the proteins; the serum proteins may, on the other hand, either inhibit or accelerate the action of the bile salts, according to the order in which the components of the haemolytic system are mixed together.¹³ As an example, let us take 1 c.cm. of a suspension of washed cells and add first 0.1 c.cm. of serum; one minute afterwards we add 1 c.cm. of 1 in 3,000 sodium taurocholate. The result is an inhibition of lysis by the serum. Now we reverse the process, adding to the same quantity of cells the same quantity of lysin, and adding after the same interval of time 0.1 c.cm. of serum; the components of the system are exactly the same, but the result is not an inhibition, but almost immediate lysis. We have here the interesting case of haemolysis depending not only on the components of the system, but on the order in which these components are brought together. This occurrence introduces into the investigations quite a new type of complexity, and since the two systems which give diametrically opposed results are made up of the same substances in exactly the same quantities, the only way to distinguish between them is to draw attention to the order of the additions, calling the first system, in which there is inhibition, a cell-serum-lysin system, and the second, in which there is acceleration of haemolysis, a cell-lysin-serum system. The order in which the components are written thus indicates the order of addition which is necessary.

The inhibition is easy to explain, for it occurs for the same reason as in cell-saponin-serum systems in which the order of addition is immaterial; the proteins of the serum unite with the lysin to form a non-haemolytic compound, and by the formation of this lysin is removed. The explanation of the acceleration, on the other hand, constitutes a most formidable problem, and, indeed, would probably be impossible to obtain were it not for the fact that an almost identical occurrence takes place in systems in which the lysin is one of the haemolytic dyes. To the consideration of these systems we therefore pass.

4. The Haemolytic Dyes.

Browning and Mackie in 1914,¹⁴ and Mackie in 1919,¹⁵ have described a curious phenomenon occurring in systems containing brilliant green, and to a less extent in systems containing other dyes of the triphenyl-methane group. Brilliant green is itself a haemolysin, but only in high concentrations; in lower concentrations it acts by "sensitizing" the cells, so that the subsequent addition of small quantities of serum produces rapid lysis. The "sensitization" is carried out by mixing washed cells with a dilution of brilliant green of about 1 in 50,000. The mixture is allowed to stand for a short time, the cells centrifuged down, and washed till the dye disappears from the super-

natant fluid. The cells are then resuspended in saline. The addition of about 0.1 c.cm. of any normal serum or plasma to these sensitized cells brings about haemolysis in a short time.

The similarity between this phenomenon and that observed when serum is added to cells which have been previously mixed with one of the bile salts will at once be apparent. In each case the lysin, brilliant green, or bile salt must first be brought into contact with the cells, and in each case the subsequent addition of normal serum or plasma brings about rapid haemolysis. The similarity is made even more striking by Mackie's observation that, in the case of brilliant green as in the case of the bile salts, it is the serum proteins which are responsible for the reaction, and that if the components of the system are mixed in the reverse order—that is, cells and serum first with subsequent addition of the dye—no haemolysis results. Expressing this more concisely, in the cell-dye-serum system we get rapid lysis, while in the cell-serum-dye system we get an inhibition of lysis.

The first step in the investigation of this phenomenon is to determine the nature of the "sensitization." To all appearances the sensitized suspension is free from brilliant green, but this appearance is quite deceptive; large quantities of the dye can be extracted from the cells by the addition of acetone or alcohol, and it is therefore plain that the repeated washings remove only such portion of the dye as is not united to the cells. Further, the portion of the dye which is united to the cells must be united very loosely, for merely warming the suspension of sensitized cells causes a considerable quantity of brilliant green to be liberated into the fluid surrounding the cells. This liberated dye does not appear to be altered in any way, and it can be used to sensitize more cells. The "sensitization" thus seems to be nothing more than the formation of a loose compound between the brilliant green and the erythrocytes, so that the dye is present as free lysin in the suspension, adsorbed to the cells, and capable of uniting with added serum proteins. Quantitative determinations of the amount of dye adsorbed show, moreover, that the union is not with the envelopes alone, but also with the contained haemoglobin; within the limits of the experimental range, the dye taken up is nearly proportional to the amount used in order to bring about the sensitization.

In a case such as this there are no doubt several hypotheses which might be advanced in order to account for the facts. Of these we have to select the simplest, and that which is the most in keeping with the explanations which are known to be satisfactory in the case of other haemolytic systems; we therefore assume that the adsorbed dye combines with the serum proteins of the added serum to produce a lysin which is haemolytic for the sensitized cells. That the brilliant green is adsorbed to the cells is certain, and that it is capable of uniting with the serum proteins is equally certain; the only obscure point is why the new lysin is either produced only, or effective only, when the latter combination takes place after the occurrence of the former.

On this hypothesis the whole of the complex phenomena can be accounted for. Suppose, to make the matter clear, that one unit of brilliant green is adsorbed to the cells, and that this one unit can unite with one unit of serum protein to form one unit of the new lysin. In these circumstances, if one unit of protein is added to the system containing the sensitized cells, the whole of the dye and the whole of the added protein will unite to form one unit of new lysin. This new lysin will produce haemolysis of the cells in a time, t , dependent principally on the concentration of new lysin present. Suppose next that only half a unit of protein is added. The whole of the dye will be unable to combine to form new lysin, for there is insufficient protein for the combination; as much dye as possible will unite, and half a unit of the new lysin will be formed. This will take a longer time, t_2 , to bring about lysis, for the concentration of the new lysin is only half of that present in the first case. Similarly, if we add smaller and smaller quantities of serum, smaller and smaller quantities of new lysin will be formed, and these will take longer and longer times t_3 , t_4 , t_5 , etc., to bring

about haemolysis. When very small amounts of protein are added, there may be so little new lysin formed that complete lysis of the cells will never occur; the result is a partial haemolysis, even after long periods of time.

Experiment shows that these assumptions are in keeping with the facts. As less serum is added, lysis becomes slower, the observed times, t_1 , t_2 , t_3 , etc., corresponding with times which can be calculated from an expression of the form of expression (1). The new lysin, whose concentration is dependent on the quantity of dye which can unite with the added proteins, according to the law of simple proportions, thus acts as a simple haemolysin, the velocity of whose action depends on the concentration present at the moment. In considering the haemolytic reaction in full, the resistances of the cells have, of course, to be taken into account; this being done, the entire kinetics of the reaction can be solved in terms of expressions similar to (1) and (2), just as in the case of a simple haemolysin.

So far as the reaction between the brilliant green and the cells is concerned, we can recognize at least two distinct stages. In the first the dye is adsorbed to the cell envelopes and their contents, still existing as unaltered brilliant green or as free lysin. In the second, which occurs after a long period of time, a reaction which results in haemolysis occurs between the adsorbed dye and the cell envelopes. It is essential to note that the union of the dye with the serum proteins, and the production of the new lysin which we have been considering, occurs in the first of these two stages. If we replace the brilliant green by sodium taurocholate, we get very similar occurrences taking place; the problem is, however, far more complex, because the reaction which results in haemolysis begins immediately the bile salt is added to the cells. There is thus never a stage of "sensitization" at which the reaction can be stopped short, for the taurocholate, which is haemolytic by itself, is continually attacking the cell envelopes, with the result that the free lysin in the system is continually decreasing. The amount of free lysin at any moment can, however, be calculated quite easily, so that, if at any moment we add serum, we can say just how much free lysin is present in the system to react with the added protein, as well as the amount of taurocholate which has been transformed as the result of the primary haemolytic reaction. In adding serum, we have therefore to be careful that the extent to which this primary reaction has proceeded is allowed for, so that all additions are made under known conditions. Although this involves an elaborate technique, it leads to results which are capable of explanation. They show that the phenomena observed with the bile salt are identical with those observed with brilliant green, the taurocholate replacing the dye as a "sensitizing agent," although it is haemolytic by itself; the sensitization seems to be due to a loose combination of the bile salt with the cells, and the lysis which follows the addition of serum to the formation of a new lysin as a result of the combined taurocholate uniting with the added proteins. Unless care is taken, however, the reaction is influenced by inhibition phenomena; although the nature of the reaction itself is clear, the effect of these secondary reactions still needs investigation.

5. Cell-Complement-Silicic Acid Systems.

These systems have attracted a great deal of attention since the discovery by Landsteiner and Jagic¹⁶ that colloidal silicic acid can replace amboceptor in complement-amboceptor systems. The colloidal silicic acid is best prepared from ethyl silicate, and the complement used should be that contained in guinea-pig serum after removal of the native haemolysins. As there is no specificity attached to the reaction, any type of red cell can be employed.

In one respect at least these systems resemble those already considered, for the velocity of the haemolytic reaction depends on the order in which the components of the system are brought together. The complement should be added to the cells first, and the two allowed to stand for a short time; the subsequent addition of silicic acid then brings about a rapid lysis. The following remarks apply only to systems in which this order of mixing is observed.

The most interesting point in connexion with these systems is the way in which the velocity of the haemolysis

varies with the quantity of complement and of silicic acid.¹⁷ Adding a constant amount of silicic acid, which is non-lytic by itself, to systems containing an increasing amount of complement, we get increasingly rapid lysis until a certain maximum is reached; with greater amounts of complement, however, the lysis becomes slower once more, until finally there is no haemolysis at all. There is thus, for every quantity of silicic acid, one particular quantity of complement which gives a maximum velocity of lysis; quantities greater or less than this give less rapid lysis, or none at all.

These maxima possess a special property which greatly simplifies the kinetics of the systems, for the ratio of complement to silicic acid at any maximum is always constant. For example, if with 0.5 c.cm. of silicic acid we need 0.2 c.cm. of complement to give a maximum, we shall require 0.1 c.cm. of complement with 0.25 c.cm. of silicic acid, or 0.02 c.cm. of complement to give a maximum with 0.05 c.cm. of silicic acid. But the most remarkable point of all is that when complement and silicic acid are added in this ratio which gives the maxima, lysis proceeds as if the lysin were a simple haemolysin. The kinetics of the system become capable of expression in terms of expressions (1) and (2), and all complexity seems to have disappeared. So far as this evidence is concerned, we are therefore justified in assuming that the complement and the silicic acid unite to form a simple haemolysin, provided that they are present in certain proportions.

Too much complement on the one hand, or too much silicic acid on the other, results in a haemolysis slower than at the maximum. In such systems the kinetics have still to be reduced to simple laws; we know, however, that the slower lysis is the result of a reaction very like the inhibition of a simple lysin by serum. Suppose, for instance, that the ratio for the maxima is one unit of complement to one unit of silicic acid. If we add to one unit of complement three units of silicic acid; two of the added units cannot combine to form the lysin, as there is insufficient complement; these two units act as an adsorbent, ready to adsorb and to render inactive the lysin as it is formed. Excess of complement acts in the same way, for the proteins in the complement-containing serum are scarcely inferior to colloidal silicic acid as an adsorbent; only when there is no excess of either component is the newly formed lysin free to act without inhibition.

This completes the account of the problems which connect the simplest haemolytic systems with the most complex, for the next step in order of complexity is the problem of the kinetics of the complement-amboceptor systems themselves. In general, these systems are similar to cell-complement-silicic acid systems; they are, indeed, in some respects even less complex, for the inhibition phenomena are less marked. They can be investigated by the same methods as are applicable to the simpler haemolysins, and their complete elucidation is only a matter of time.

As a review of what is known about haemolysis in general this account is very incomplete. All consideration of haemolysis by hypotonic saline, cobra venom, and ultra-violet light is omitted; no mention has been made of the results of the investigations into the changes of form which the cells undergo during lysis, nor is there any reference to the effects of salts, sugars, and other such substances on the action of the various haemolysins. The necessary degree of compression precludes even the description of the essentials of the technique employed. The paper therefore gives quite an inadequate idea of the weight of the evidence on which the conclusions are based, and accordingly the reader may be left with the impression that some of the explanations offered are rather too simple to be true. It is to be remembered, however, that the almost notorious complexity of most of the less simple haemolytic systems is very largely the result of investigation by methods which are often faulty in themselves and which are never strictly quantitative. It is only when technique is rigidly standardized, and when every variable is subjected to exact measurement, that the apparent complexity disappears.

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DISCUSSION.*

Professor J. MELLANBY discussed the action of enzymes on the red blood corpuscles. He pointed out that the cell envelope could not be acted upon by either trypsin or lipase. Haemoglobin was found to be digested by enzymes, and there was, therefore, evidence that a protective layer or envelope existed which protected the haemoglobin. It was shown that at the end of haemolysis the amboceptor disappeared while the complement was still present in an intact form. The speaker stated that probably in the Wassermann test the complement was precipitated by the syphilitic substance in the presence of the antigen.

Sir E. SHARPEY-SCHAFER questioned the reversal changes described.

Dr. ERIC PONDER, in reply, said that in his opinion there was no fundamental difference between the kinetics of the complement-amboceptor systems and of silicic acid and simple lysins.

THE PLACE OF BISMUTH IN THE TREATMENT OF SYPHILIS.*

BY

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DURING 1921 Sazerac and Levaditi were able to prove that experimental syphilis in rabbits could be treated successfully with a bismuth preparation. In the following year the same workers, and Fournier and Guenot, submitted a series of cases of human syphilis to treatment with a salt of bismuth, and found that the active signs of disease disappeared rapidly, and that this drug appeared to be able to exercise a favourable influence, at least in the earlier cases, on the serological reactions of the blood. Subsequent to the publication of this work in France bismuth and its salts came into general use, and bismuth is now accepted as one of the few drugs which can favourably influence the progress of syphilitic infection.

In considering the place of any drug in the treatment of syphilis it is essential to take into consideration the value of that drug as compared with existing and well known therapeutic remedies, and to review our present knowledge as to—

- The effect of bismuth on the *Spirochaeta pallida* in vivo.
- Its effect on the surface lesions of syphilis in all stages.
- Its effect on the serological reactions in all stages of syphilis.
- Its effect on the general health of the patient.
- The toxicity of bismuth and the immediate or remote side effects to which it may possibly give rise.
- The permanency of the results obtained by its use.

In the limited time available I propose to give a short summary of the observations which it has been possible to make during an extensive clinical experience of the use of this drug in over 6,000 cases of syphilis. The number of injections of bismuth given in this series was over 100,000. In some of the cases bismuth was the only drug used; in others it was used in combination with drugs of the arsenobenzol series and with tryparsamide; in others it was administered with mercury and some form of iodide.

* A paper read in opening a discussion on this subject in the Section of Venereal Diseases at the Annual Meeting of the British Medical Association at Edinburgh. Mr. Lees was President of the Section.