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.

Among the many bismuth preparations which are available, the following have been used: (1) soluble preparations, (2) insoluble preparations suspended in oil, (3) insoluble preparations suspended in glucose or water. Different preparations from each of these groups, and especially from the latter, have been used, and, from practical experience, the preparation which gives the most consistently good results with the least likelihood of upset to the patient is one of insoluble bismuth in a very fine suspension in isotonic glucose solution. It should contain a high percentage of bismuth, and the drug should, in our opinion, be given intramuscularly.

The Action of Bismuth in Destroying the Spirochaeta pallida in vivo.

When a therapeutic dose of bismuth is administered intramuscularly to a patient suffering from a primary chancre or a secondary rash in which the *Spirochaeta pallida* has been demonstrated, the organism is not destroyed so rapidly as it is when a therapeutic dose of one of the arsenobenzols is given either intravenously or intramuscularly. After an arsenobenzol product is administered we can rarely find a living spirochaete in the surface lesion twenty-four hours later; whereas after a potent therapeutic dose of almost any bismuth preparation, spirochaetes can not infrequently be demonstrated for three or four days subsequently. From this we may assume that bismuth does not act so rapidly in reducing the contagion of syphilis. This slowness of action is not due to the slower absorption because the bismuth is administered intramuscularly. We have had the same experience when comparing the effect of an intramuscular injection of sulpharsenol with that of an intramuscular injection of bismuth. We have noted the same slowness of action after the intravenous injection of colloidal bismuth.

The Effect of Bismuth on the Surface Lesions of Syphilis in all Stages.

The continued administration of bismuth intramuscularly causes the primary sore, the surface skin lesions, and the later gummatous manifestations to disappear rapidly, and in this respect bismuth is almost as efficient as the salvarsan preparations. It is much more rapid in its action on these signs of active syphilis than any of the mercurial preparations. In this respect it would seem to be almost the equal of, and occasionally superior to, the arsenical drugs. In three cases which were seen by the author, all of which were in the nature of hypertrophic papular syphilides of a recurrent type, the administration of bismuth rapidly cleared up the eruption when arsenic in one case, and arsenic and mercury in combination in the two others, had previously failed to do so.

The first patient, a case of primary syphilis with a strong positive Wassermann reaction, had been treated by a complete course of novarsenobillon, totalling 4.3 grams in a period of eight weeks. Three weeks later a papular syphilide appeared on the face. A second course of 3.00 grams of novarsenobillon was administered in the succeeding seven weeks, and one month later the papules again recurred. Bismuth was administered intramuscularly, and after three injections of "hypoid" bismuth the papules disappeared and have not recurred since. The bismuth treatment was continued in this case for close on two years and the patient has been under observation for over eighteen months since. There has been no recurrence of any clinical sign of syphilis, and the Wassermann test has been consistently negative for over two years.

In the second case, one of early generalized syphilis, the patient had had a course of injections of neokharsivan and simultaneously mercury was being given by the mouth. The total amount of neokharsivan administered in eight weeks was 4.05 grams. Six weeks subsequent to this course a papular syphilide appeared at the angles of the mouth and nose. Bismuth was administered, and the patient, apart from appropriate intervals of rest, has now been under treatment with bismuth and iodides for two years. There has been no recurrence of the clinical signs; the blood Wassermann after two courses of bismuth became negative and has continued negative up to the present.

The third case is even more striking.

A patient with a primary sore of ten days' duration and a weak positive Wassermann test was treated during the first three months with neosalvarsan and mercury (grey oil), 4.5 grams of the former intravenously and 7 grains of the latter intramuscularly. Some three to four weeks after this treatment a circinate syphilide appeared on the forehead and palmar and plantar syphilides on the hands and feet. A second intravenous course

consisting of 4 grams of novarsenobillon and an intramuscular course of 8 grains of mercury (grey oil) was administered, but failed to influence the skin eruptions. Intramine and colloidal iodine were then given, the former intramuscularly and the latter intravenously in large doses. This was followed by a course of intramuscular injections of grey oil, the total quantity given being equivalent to 16 grains of metallic mercury. Potassium iodine was also given in large doses (20 grains thrice daily) by the mouth. As this course of treatment failed to influence the syphilides, silver salvarsan was administered in weekly injections to a total of 3 grams in eight weeks. The syphilides disappeared temporarily during this treatment, but recurred six weeks later. Protein therapy was tried, T.A.B. vaccine was injected, and this was followed by a course of neo-silver salvarsan and mercury. There was no sign of syphilis for three months after this, but subsequently the plantar syphilides reappeared and also a recurrent papulo-squamous syphilide on the forehead and on the extensor aspect of one elbow. Bismuth was now exhibited, and four courses, totalling about 15 grams of metallic bismuth, were given in the following year. After the third injection of bismuth in the first course the signs of syphilis on the skin completely disappeared and they have not recurred since. The blood Wassermann reaction became negative after the first course of 4 grams of bismuth and it has remained negative since. This patient has been under observation for close on two years without treatment and has had no recurrence of any sign of syphilis, and the blood Wassermann and cerebro-spinal fluid have remained negative throughout.

While these may be isolated cases they are impressive, and there are undoubtedly certain cases of syphilis in which the surface signs react extremely well to bismuth, and better than they do to salvarsan and its derivatives.

The Effect of Bismuth on the Serological Reactions in all Stages of Syphilis.

If bismuth is administered to any case of syphilis before the Wassermann test has become positive, and if the Wassermann test, taken again seven days subsequent to the first injection, is still negative (sero-negative syphilis), it is our experience that very few of these cases, if the bismuth treatment is persevered with, will ever develop a positive reaction in the blood. One or two of our cases, however, have developed positive reactions when so treated, and Parnell has quoted similar cases. In all the cases in which this has occurred the second test taken within a week after the first treatment showed a weak positive reaction. It is our experience that the development of a positive reaction in a case of sero-negative syphilis treated with the arsenobenzols is extremely rare. Bismuth, therefore, would not seem to be so potent as the arsenobenzols in making certain that a sero-negative case does not become sero-positive.

When comparing the effect of bismuth with that of the arsenobenzols on the reactions of sero-positive syphilis in the primary and early generalization stages, as assessed by the Wassermann test, taken at least one month after a course of treatment, the percentage of negative findings after bismuth is not, in our opinion, so large as with the arsenicals. It is certainly much inferior to that obtained when salvarsan and bismuth or salvarsan and mercury are administered concurrently. In late syphilis and latent syphilis it is difficult to estimate comparatively the effect of bismuth and salvarsan respectively on the Wassermann test. Both are successful in a considerable number of cases, while in others both fail to render it negative. In cases in which we have failed to influence the Wassermann test by combinations of salvarsan and mercury or salvarsan and iodides, bismuth also has failed, and we have not as yet been able to find any drug or combination of drugs which will permanently influence certain cases with resistant Wassermann reactions. It is our experience that bismuth is rather more potent than is the intravenous injection of the arsenicals in altering some of the pathological reactions in the cerebro-spinal fluid in certain types of case.

The Effect of Bismuth on the General Health of the Patient.

When bismuth is given in therapeutic doses it appears to influence the patient's general health beneficially, and especially so if before and during the time of its administration the hygiene of the mouth is attended to. The arsenobenzols also have a tonic action, but it is our experience that old and debilitated patients tolerate bismuth in appropriate doses rather better than they tolerate the arsenobenzols. In cases which have shown

themselves sensitive to the arsenobenzols, bismuth is often well tolerated and greatly benefits the health of the patient. It does not appear to be so depressing in its action as mercury, and there is not the same tendency on the part of the patient to lose weight when under bismuth treatment as when mercury is being administered.

The Toxicity of Bismuth and its Immediate and Remote Side-Effects.

In therapeutic doses bismuth gives rise to remarkably few toxic symptoms if the technique of its administration is good. There is practically no pain subsequent to its administration such as there is subsequent to the intramuscular administration of mercury, and there is certainly less discomfort than there is with the intramuscular administration of arsenicals such as sulpharsenol or khar-sulphan. The main toxic condition to which it gives rise is stomatitis. This can be obviated by careful cleansing of the mouth and care of the teeth. When it does arise it is not so severe as is the stomatitis set up by mercury. It can be rapidly controlled and ameliorated by the administration of sodium thiosulphate and by oral hygiene. Other toxic effects of bismuth are albuminuria, urticarial eruptions, mild erythematata, and loss of weight. If ordinary care is exercised in the administration of the drug, and if appropriate intervals are allowed between successive doses, these complications are rare when metallic bismuth is used. Bismuth, in fact, can be given with advantage to many cases of nephritis and to many debilitated patients who would not tolerate the arsenobenzols. In general, it is a much less toxic drug than the arsenobenzols and less toxic than mercury. If care is taken that none of the drug is introduced into a vein there are practically no immediate side-effects in the great majority of cases. It does not seem to damage the liver to the same extent as do the arsenobenzols, nor the kidneys to the same extent as mercury, and rarely if ever is an injection of it followed by a Herxheimer reaction.

Permanence of the Results of Bismuth Treatment.

We have referred to the fact that cases of sero-negative syphilis may not always remain so while under treatment with bismuth alone, but there are undoubtedly other cases of established syphilis which have been cured both clinically and serologically by bismuth alone, and have remained so over periods up to three years. The period during which treatment by bismuth alone has been observed in most cases is as yet too short to enable us to state definitely that its results are permanent, and, in addition, there is up to now no general agreement as to what is the requisite amount of the drug to administer so as to ensure permanent negative serological tests and a complete cure.

The therapeutic power of bismuth compounds in comparison with that of the salvarsan group of drugs when each is used alone may be recapitulated as follows:

Bismuth does not so rapidly kill spirochaetes in the early contagious stages of syphilis, and therefore does not so rapidly reduce contagion.

Bismuth has almost as rapid an effect as the salvarsan derivatives in clearing up the surface manifestations of syphilis in all stages of the disease.

Bismuth is less likely to cause intolerance and side-effects, especially in devitalized patients, and in general its intramuscular administration is followed by less constitutional upset than is the intravenous or intramuscular administration of the arsenicals.

Bismuth does not so certainly control the Wassermann and flocculation tests as do the arsenicals, although there are cases in which it very favourably influences these serological tests when other drugs have failed to do so.

When we compare the effect of bismuth with that of mercury, when each is administered alone, the evidence is undoubtedly strong that, of the two, bismuth is the more potent drug in syphilis, both in its effect on the surface lesions and on the serological tests. Bismuth kills the surface spirochaetes and heals up the skin manifestations more rapidly than mercury; there is less pain after its intramuscular administration, and it is followed by fewer signs of intolerance; it also has a more rapid action than mercury on the blood Wassermann and other tests. In

therapeutic efficiency bismuth seems to approximate much more closely to the arsenobenzols than mercury when these drugs are exhibited alone in any given case of syphilis.

The Use of Bismuth in Combination with other Drugs.

For a long time we have held the opinion that, in the treatment of syphilis in all its stages, with the possible exception of cases of pregnancy, it is advisable to administer conjointly both arsenic and mercury in preference to either alone. Since the introduction of bismuth we have come to the same conclusion with regard to it, and we are firmly of opinion that with few exceptions the joint administration of arsenic and bismuth is preferable to that of either alone. The joint administration of these drugs is comparatively safe, it is well tolerated, and the results in the large majority of cases so treated are highly satisfactory. It is impossible to deny that the therapeutic results following the joint administration of arsenic and mercury were very good, and especially so if the mercurial drug was administered intramuscularly, so as to ensure certainty and accuracy of dosage. The joint administration of arsenic and bismuth has, in our experience, given slightly better results. There is, however, the great advantage from this latter combination that there is practically no discomfort or pain following the intramuscular injections of bismuth, and, if due precautions are taken as to the teeth and as to the technique of administration, no intolerance is set up such as occasionally follows the joint arsenic and mercurial treatment. The fact that bismuth is being administered to any given case is not, in our opinion, a reason for lessening the amount of the arsenical drug, and even with the dual therapy there are still some cases of resistant syphilis which are slow to react favourably, although seen and treated intensively at a fairly early period of the infection.

If at any time a rest from either drug is considered advisable, iodides may be substituted, and can be given alike with either arsenic or bismuth.

In several cases we have tried the effect of giving bismuth in combination with mercury, the latter in such cases being given intravenously as mercury cyanide. The two drugs do not, in our opinion, go well together. These two drugs are not dissimilar in their action, and they give rise to toxic effects on the same structures of the body. Their joint administration is apt to lead to depression, loss of weight, neuritic symptoms, and to stomatitis. In any cases which showed a very resistant positive Wassermann test we have not been able to influence it permanently by this combination any more effectually than by other and safer methods of treatment.

Tolerance of the Patient to the Various Drugs when Administered over Long-continued Periods.

With the arsenobenzols great care must be taken to avoid too intensive treatment over long periods, because of the risk of cumulative effect and the possible onset of such conditions as jaundice and exfoliating dermatitis. In long-continued mercurial treatment stomatitis, diarrhoea, and albuminuria are not infrequent, and the discomfort following on intramuscular therapy by mercury is against its long-continued use. Bismuth can be given over long periods without pain and with comparative safety.

In bismuth therapy there is no complication of any importance which cannot be easily counteracted or controlled. So far as safety of administration is concerned, we are of opinion that either alone, or in combination with an arsenical or iodide drug, bismuth can be given over long periods with comparative comfort and safety.

Combination of Drugs and their Influence in Preventing Neurosyphilis.

There is considerable evidence to show, and a general consensus of opinion, that the joint administration of arsenic and mercury is superior to that of an arsenical drug alone, especially in the prevention of the later manifestations of syphilis. So far as the combination of arsenic and bismuth is concerned, it is our opinion that the joint administration of these drugs is superior in its action to that of either alone, especially in early cases of syphilis. It is too early as yet to make a dogmatic statement on the

subject, but we are inclined to the opinion that the two drugs if given together in every case of early syphilis will tend to prevent the later manifestations of syphilis, just as does the joint administration of arsenic and mercury.

As regards the comparative therapeutic efficiency of the two combinations, we are not as yet in a position to judge. In our own cases the end-results are almost similar if viewed from the standpoint of the disappearance of the symptoms and signs of disease. If judged from the standpoint of their effect on the Wassermann reaction there is also very little difference in the results. Where they differ most is in the fact that the combination of arsenic and bismuth is better tolerated by the individual patient, is followed by fewer signs of intolerance, and gives rise to less pain and discomfort.

This latter fact alone is of very considerable importance in hospital work, in that patients more willingly continue under treatment for long periods. There have been very few published statistics of the comparative effect of the two combinations, and those of Smecchula of Hanover published in the *Klinische Wochenschrift* of July 30th, 1925, are interesting. He selected two series of 100 cases, as like each other as possible, and compared the efficacy of neosalvarsan and mercury salicylate with that of neosalvarsan and bismuth. His findings were that neosalvarsan and mercury were superior in their action in secondary syphilis and still more so in their rapidity in changing a positive to a negative Wassermann test in latent cases. He was of opinion, however, that the administration of neosalvarsan and bismuth was followed by fewer relapses than that of neosalvarsan and mercury.

Our observations on the comparison of cases so treated do not agree with those of Smecchula. We are of opinion that arsenic and bismuth jointly administered influence secondary lesions rather more rapidly than arsenic and mercury. Arsenic and bismuth in our experience has also produced a negative Wassermann test in latent syphilis more often than arsenic and mercury. We agree with him that there are very few relapses met with if either arsenic and bismuth, or arsenic and mercury are used, but this is more dependent on the long continuity of the treatment than on the combination used. The combination of arsenic and bismuth is, we think, much more efficacious in many cases of neurosyphilis than is that of arsenic and mercury.

In their enthusiasm over bismuth several workers have discarded not only mercury but also the arsenicals in the treatment of syphilis. This is to be deprecated, and especially so in early and contagious syphilis. Arsenical medication is undoubtedly our most efficient method of dealing with syphilis and rendering it rapidly non-contagious, and it cannot be removed from its place of pride by bismuth. Mercury also has still a place in specific medication, but must give way to bismuth for routine use since it is less well tolerated, in that its administration causes rather more discomfort; it is, moreover, slower in its action in killing spirochaetes, in healing the surface lesions, and in its effect on the Wassermann test.

The arguments on which the superiority of bismuth to salvarsan rest are based solely on isolated cases, of which most of us have had experience, and of which I have quoted three. There is no doubt that bismuth is an extremely valuable drug, and that its discovery as an efficient therapeutic agent in syphilis must be regarded as one of the most important developments of therapy during the last few years. We must not, however, allow our enthusiasm over its effects in isolated cases to outrun our discretion and make us lose sight of its deficiencies and of its inferiority to the salvarsan derivatives. What can be said of bismuth is that it is a very valuable addition to the treatment of syphilis, and especially if it is used in combination with the arsenobenzols. It is peculiarly effective and safe in most of the cases which show intolerance to the arsenicals and to mercury. In cases which are proving resistant to arsenic or mercury it not infrequently gives brilliant results in causing the disappearance of the specific lesions. In some cases of neurosyphilis and congenital syphilis it apparently gives better results in clearing up the symptoms and signs of disease than either arsenic or

mercury. It is undoubtedly also a safer method of treatment in some of the devitalized subjects who suffer from syphilis, such as cases of cardio-vascular and visceral syphilitic disease.

It is important, in our view, that in every case of syphilis in its earlier stages a combination of either arsenic and bismuth, or arsenic and mercury, should be given, and that this combination should be continued up to the point of tolerance until both the clinical and the serological manifestations are cleared up. In the subsequent period of treatment we are of opinion that both drugs should still be continued, but the amount of the arsenical drug may then be conveniently lessened with a view to avoiding intolerance. The advent of bismuth may in the course of time enable us to lessen the quantity of the joint therapy which is necessary to control and possibly cure syphilis, but as yet there is far too little evidence of the definite permanency of the results obtained to justify anyone in reducing the time during which any case of syphilis should remain under active treatment and observation.

Bismuth in therapeutic doses can certainly be given over very long periods without in any way inconveniencing the patient to the same extent as mercury does, and this fact alone renders it of very considerable value in the treatment of resistant cases of infection and of old and debilitated patients.

If we were to summarize the present place of bismuth in the therapy of syphilis, we would be justified in coming to the following conclusions:

1. Bismuth is an active antisiphilitic drug and is more rapid in its destructive action on the *Spirochaeta pallida* *in vivo* than mercury; it is not so rapid as the salvarsan group of drugs in this respect.

2. Bismuth influences the surface lesions of syphilis as rapidly as the arsenobenzols, and more rapidly than mercury.

3. Bismuth, with few exceptions, is less active than the arsenobenzols in influencing the Wassermann test, but is more active than mercury in this respect.

4. The combined administration of bismuth and arsenic is more potent than either drug alone and is free from danger if given in therapeutic doses. The same holds good of arsenic and mercury.

5. The administration of metallic bismuth in isotonic glucose solution is remarkably free from pain and side-effects, and in this respect is better tolerated than either arsenic or mercury.

6. Bismuth is a very valuable drug in cases of syphilis which are intolerant to treatment by arsenic or mercury.

7. Bismuth is a very valuable drug in the treatment of any patient who has advanced organic disease, whether the latter is due to, or is intercurrent with, the syphilis.

8. The intramuscular injection of an insoluble compound of bismuth gives better therapeutic results with less risk of toxic effects than other methods of administering it, such as the intravenous administration of colloidal bismuth or the intramuscular injection of the salts of bismuth.

9. The addition of bismuth and its salts to the other available methods of treatment does not as yet justify anyone in lessening the length of time over which every case of syphilis should be treated and kept under observation.

10. Apart from cases of intolerance to other drugs, bismuth is only an adjuvant to the treatment of syphilis and should not be used alone, even in the very earliest cases of infection.

DISCUSSION.

Dr. J. C. BUCKLEY (Nottingham) considered the introduction of bismuth second in importance only to that of salvarsan. He expressed optimistic views as to the prognosis in early cases of syphilis, and thought that nearly all could be cured by a properly conducted dual therapy. He had found bismuth particularly useful in patients who were intolerant of arsenic, and only in interstitial keratitis was mercury more valuable than bismuth. It was not justifiable to give bismuth alone in early cases of syphilis, but it should be combined with arsenic. The dose he gave

of bismuth was 0.2 gram daily. He asked whether the blue line on the gums, a common concomitant of bismuth therapy, contraindicated the continuance of the treatment.

Dr. MARY MACNICOL (Edinburgh) said that she had been using bismuth now for three years as an adjuvant of arsenic, and thought it more valuable than mercury. In those cases which, although reacting well clinically to arsenical treatment, persisted in giving a positive Wassermann reaction, bismuth had often succeeded in reducing the reaction. She quoted two cases in illustration of this, and referred to its utility in old tertiary cases of gummata. She had found the drug very useful in cases of intolerance to arsenic; and had not met any case intolerant to bismuth, and only one in which there was stomatitis. In congenital cases she had also been able to obtain negative Wassermann reactions. Lately, however, she had found arsenic and mercury better than arsenic and bismuth in very bad congenital syphilis, but bismuth had the great advantage of being painless. She also found it convenient to give arsenic by the mouth during a course of bismuth; it still acted as a tonic and obviated the continual hypodermic injection which many women disliked.

Dr. E. T. BURKE (Manchester) placed bismuth just second to arsenobenzol as an antisyphilitic, but much higher than mercury; he said it must be realized that bismuth was a reinforcement and not a substitute for arsenobenzol. He was in favour of bismuth being given alternately with arsenobenzol—not concurrently. He thought that the experiments of Lehoff-Wyld to show that the therapeutic action of arsenobenzol was enhanced by the presence of another metal in the blood were very unconvincing. Personally he believed that when two highly treponemicidal drugs were used simultaneously either the tissues of the patient would refuse to react properly or the treponema would become resistant. He thought that the practice of concurrent administration was the cause of many persistent positive Wassermann reactions. He was now able to convert many of these into negative reactions by means of potassium iodide followed by metallic bismuth. Arsenic and bismuth might have an actual neutralizing effect on one another. Cases treated with bistovol—a bismuth and arsenic combination—gave extremely disappointing serological results. If, as Kolle held, bismuth merely kept syphilis latent, the concurrent administration of the two elements might be very harmful. Bismuth was particularly useful in syphilitic lesions of the circulatory mechanism; in cases of coronary and aortic disease it was safest to rely on it, possibly to the exclusion of arsenobenzol. In the newly-born syphilitic child carrying an enormous burden of treponemata he also began always with bismuth. One of its greatest uses was in interstitial keratitis; he only administered arsenic after the eye condition had cleared up. He thought that the best method of administering the drug was in the metallic form suspended in glucose and injected intramuscularly; the intravenous injection of any bismuth salt was dangerous.

Dr. W. R. SNODGRASS (Glasgow) considered that metallic bismuth in isotonic glucose solution was the most satisfactory preparation. Up to the present the quantity of a standard bismuth preparation necessary to effect and maintain a clinical and serological cure had not been established.

Colonel L. W. HARRISON (London) drew attention to the work of Collard and Evans, who formed a depot of bismuth in a rabbit's ear and then attempted to inoculate it with syphilis. So long as the depot was there no chancre was produced, but as soon as the depot was excised the chancre appeared, showing that the bismuth had only kept the syphilis latent. As regards the effect on the Wassermann reaction he thought there was but little difference between the effect of bismuth in combination with arsenic or mercury in combination with arsenic. He had found bismuth particularly useful in myocarditis, sometimes in conjunction with very small doses of sulfarsenol. The toxic effects of bismuth had not proved very severe, but he had

had occasional complaints of rheumatic aches and pains and also of colitis, and he had known dermatitis to be produced.

Dr. STOPFORD TAYLOR (Liverpool) described a severe case of toxic reaction due to bismuth. The patient had suffered from abdominal pain, sickness, diarrhoea, a measly rash, and gingivitis. He also recommended sulfarsenol in very small doses for cardiac cases.

Mr. LEES, in reply, agreed that bismuth alone should not be used in early cases. He did not regard the appearance of the blue line on the gums as a contraindication to the continuance of bismuth, but merely as an indication for dental attention. The principal contraindication to further treatment was loss of weight. Bismuth was exceedingly well tolerated as a rule; unlike mercury it never produced nodules. It was painless, and very useful in cases of parturient women before starting arsenical treatment. It was also particularly useful in cases which were clinically syphilis but serologically negative. He considered that the inunction and oral administration of bismuth were far inferior to injection. He did not agree that the joint and simultaneous administration of arsenic and bismuth and of arsenic and mercury reduced the bodily resistance of patients, though theoretically it might possibly be expected to do so. Myocardial cases, in his opinion, were the only ones in which bismuth should be used alone; in other cardio-vascular patients it should be combined with sulfarsenol. He found it difficult to explain the cases of dermatitis. Some of the cases of gross intolerance he thought might be due to a slight embolism, a small quantity of the metal finding its way into a vein during injection.

THE EMPLOYMENT OF "POLAR-BODY" DEVELOPING STRAINS OF THE GONOCOCCUS IN TREAT- MENT OF GONOCOCCAL INFECTION.*

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For the last two years, at the Royal Herbert Hospital, Woolwich, we have been endeavouring to elaborate a line of treatment of gonorrhoea in the male by intensive immunizing methods. Preliminary reports of this work have already appeared in the *British Journal of Venereal Diseases* for January, 1927, and in the *R.A.M.C. Journal* for last March. For the present report we cannot claim any degree of finality; our researches are continuing and our methods constantly changing.

The treatment of gonorrhoea at Woolwich aims at: (1) Raising the immunity of the mucosa through which the organism enters the body. (2) Raising the resistance of the particular glands and organs susceptible to attack by the gonococcus. (3) Raising the antibacterial properties of the blood and tissue fluids in order to minimize the risk of systemic spread of the infection. (4) Bringing the patient under certain precise biochemical and colloidal-chemical conditions which have been found to give optimum results as regards defence against the invading organism, and placing the infecting organism under conditions in which it is least able to withstand the defence mechanism of the body. (5) Providing a means of determining whether any local foci of the disease remain or whether the patient is completely freed from the infecting organism—in short, to provide a "test of cure."

These objectives have been sought in the following ways: (1) Thorough drainage of the whole urethra by mild irrigating fluids. (2) The maintenance of the patient's urine reaction at a pH of 7.2 to 7.4. (3) The intraurethral instillation of a product of gonococcus metabolism which may be referred to as "exotoxin." (4) The parenteral

* 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.