Added to which there should be a systematic following up of patients to encourage the delinquents, and also to ensure the early detection of any recurrent lesions.

In conclusion, I beg to point out that an admirable organization for the treatment of venereal disease already exists under the aegis of the Ministry of Health. That movement rescued this branch of medicine from the realms of chaos, and has proved of great service to the community. It seems justifiable, therefore, to ask that equal facilities should be given to a class of patients who are at least equally worthy of consideration.

DIFFERENT PREPARATIONS OF BISMUTH IN SYPHILIS THERAPY:

RATE OF ABSORPTION AS A GUIDE TO THEIR EMPLOYMENT.*

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BISMUTH is already adopted, only eight years after its introduction into syphilis therapy, by practically all syphilologists throughout the world as a substitute superior to mercury. It is obviously both more efficient and less toxic than this old remedy. Still there remain a few exceptions to this rule. Bismuth can be administered by intramuscular injection alone, as it is absorbed to a very small extent only through the skin and through the intestine. For these methods of administration resort must still be had to mercury. This rapid development of bismuth therapy has brought many hundreds of preparations on the market; it is therefore not easy for the doctor to make a right choice.

The following investigation is not intended to be an examination of a series of factory preparations, but merely a general outline, according to which the proper choice can be made.

Very little is known with regard to the characteristics of bismuth in its effects on a syphilitic organism and the syphilitic infection itself. The blood contains only very small quantities of bismuth (Levaditi et alii,^{1 2} Sei and Weise,¹⁸ Lomholt,^{4 7 8 9} Biro Istvan,¹⁰ Levy and Selter,¹¹ Grulhitz and Sultzberger,¹³ Leonard^{14 15 16}), probably so small that we can disregard a possible direct effect on the spirochaetes similar to that generally produced by disinfecting solutions of heavy metals *in vitro*. Levaditi^{1 2} has tried to give a specific explanation of this strong effect on the spirochaetes. He suspects the formation of a special compound of bismuth and the protein substances of the organism ("bismoxy"). He thinks that this compound possesses a particularly strong effect on the spirochaetes.

Though nothing definite is known about the characteristics of bismuth in its effects on the syphilitic infection, it is a well-established fact—obtained from clinical experience as well as from experiments on rabbits with syphilis—that a complete cure is attained only after a prolonged course of bismuth therapy. The best effect is obtained when large quantities of bismuth are introduced, creating a strong bismuth concentration in the organism. Of course, the concentration should never reach the point of intoxication, as this would only weaken the organism. Consequently the aim of the bismuth treatment must be to introduce into the organism the largest possible quantities without intoxication, maintaining thereby a strong saturation over a long period. Under bismuth treatment proper attention should be given to the fact that elimination of the metal is rather slow; consequently an intensive introduction of bismuth causes a rapid accumulation of the metal in the organism, and if continued for a long period will result in an intoxication.

Intensive bismuth treatment should not be continued very long. It may be borne well in the beginning, especially if the remedy used is one of slow absorption, but after some time the organism will be oversaturated and an

intoxication will appear. This fact is to be taken into account in planning the scheme of treatment. The old scheme of intermittent treatment (Fournier) permits the use of larger doses than does the continuous method without interruption, proposed by some modern authors. The intermittent scheme has given undeniably excellent results, and its rhythmic character may be considered to agree well with the rhythm of vital processes. The essential thing in all bismuth treatment must be to secure a uniform and regular absorption. Otherwise a sudden strong absorption may bring a dangerous intoxication; or, on the contrary, a lack of absorption may cause a deficiency of the therapeutic effect. For this very reason the internal and percutaneous administration of bismuth must be left out of the question. Ointments may give an absorption of bismuth, but this is always weak and very irregular (Klauder,¹⁹ Oelze,²⁰ Giemsa,²¹ Engelhardt²⁶). Applied on injured skin bismuth may be absorbed to quite a large extent—a fact well known since ancient times from the treatment of extensive burns with bismuth ointments. Even fatal accidents have occurred. Internal administration produces also a very weak absorption (Engelhardt²⁶), probably due to the fact that insoluble BiOCl is formed in the stomach, owing to the effect of HCl upon the bismuth compound in question. If no HCl is present, but only organic acids such as lactic acid, complex compounds of bismuth may be formed and absorbed in the same way as the many alkaline bismuth tartrates used in bismuth therapy from its very beginning (Levaditi,¹ Gérard and Daunic,²² Perrin and Ducas²³). Consequently bismuth must be used in the form of injections.

The *intravenous* injection gives decidedly the quickest and most regular absorption, but clinical experience has shown that it is rather dangerous, several cases of death having been reported. Besides, it is not especially efficient. The bismuth injected leaves the blood stream quickly. Sei and Weise³ found in rabbits that after one hour the bismuth content in the blood was reduced from 11.5 mg. per 100 c.cm. to 0.17 mg. Accordingly the elimination was found by most authors (Jeanselme,²⁹ Engelhardt²⁶) to set in and increase quickly, to reach its maximum and fall to a minimum again in rather a short time. In consequence of this rapid passage of bismuth frequent injections are necessary, preferably every day, which makes this treatment rather troublesome. Besides, the treatment gives rise to a particular strong neuralgia in the trigeminal nerve, which occurs immediately after the injection. Intravenous treatment has now been given up even by its original adherents (Pautrier).

Subcutaneous injection cannot be recommended. It causes greater pain than the intramuscular method, and abscesses occur more frequently; also the absorption is slower and more irregular.

Intramuscular injection remains the treatment to be preferred. The single injections should be given in the upper and outer part of the gluteal muscle. The number of preparations made for this purpose is most embarrassing, and it must be admitted that it is possible to obtain quite good results with practically all of them. At a very early date Levaditi¹ pointed out that even quite small quantities of bismuth were able to give a marked antisymphilitic effect. But this is not the same as a maximum effect, and our aim must always be to find just that preparation and that method of treatment which secures the very best result to the patients. The investigation of these problems is simplified by the fact that the antisymphilitic effect is due to the bismuth ion itself—or rather to the bismuthyl ion. As regards the different bismuth preparations, their bismuth metallic content is alone of importance. However, an exception is provided by certain bismuth compounds, in which the bismuth is bound so firmly that the organism is unable to dissociate it (for example, triphenylbismuth, Giemsa²⁶). With these the therapeutic effect will prove to be less than would otherwise be expected. The essential thing must always be to have a preparation with an absolutely regular and uniform absorption rate. These two things depend to a large extent on another quality—that of the rate of absorption.

If a certain quantity of bismuth is injected into a muscle, and if it is not absorbed immediately, the surrounding

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tissue will soon begin to encapsulate it, and from the moment this occurs the rate of absorption will be seen to decrease markedly. Sometimes the bismuth deposit may remain for a long time almost untouched, like a foreign body—that is, if the muscle has had time to produce a sufficiently thick, compact capsule around the deposit. In such a case only an extremely slow absorption will take place, and the therapeutic effect will be accordingly insignificant. In the days immediately following an injection there will as a rule be ample absorption of bismuth from the newly injured surface of the muscular tissue; later the absorption will gradually decrease. Consequently a slow absorption generally means an incomplete absorption, a certain portion of the injected metal remaining encapsulated for an indefinite period. An x-ray photograph of the nates with bismuth deposits will often show a great many shadows due to the encapsulated material. This was confirmed by a large number of authors. (Levy-Bing,²⁷ Kolle,²⁸ Beinhaner and Jacob,²⁹ Sonnenberg,³⁰ Cole, Farmer, and Miskidjan,³¹ Oettinger, Todd, and Sollman³².) Still the x ray is not an ideal method for control in these cases. Small precipitates of chalk often appear around the deposits, the shadow of which may closely resemble that of a bismuth shadow (Müller,³³ Jaffe,³⁴ Gruhzit³⁵).

By experiments on animals, where the injected deposits of bismuth can be excised, one can see still more distinctly how great the differences are, and especially with bismuth in oil suspension (Lomholt^{1, 8, 9}). On the other hand, a single injection is seldom given, but generally a series. By this the irregularity in the rate of absorption in the single deposit will to some extent be compensated.

To the question as to the kind of bismuth preparation which is absorbed most rapidly and regularly after intramuscular injections the answer must be: watery solutions. This emerges clearly from all researches of bismuth elimination after such injections (Lomholt,^{5, 6, 8} Leonard,¹¹ Gruhzit,¹³ Engelhardt³⁶). However, it appears that even small doses cause a certain amount of pain. Consequently it proves necessary to give the injections rather frequently—for example, every other day—to obtain a suitable weekly dose of bismuth, and even then pain cannot be avoided. Gruhzit¹³ attributes a relative absence of pain to thiobismol, a sodiumbismuthoglycolate, a compound first studied by Akamatsu.³⁷ My experience, however, is that this is not quite painless. It must, at any rate, be given three times a week. It is, therefore, impracticable as the intravenous treatment.

Instead of watery solutions, solutions of bismuth compounds in oil have been employed—for example, bismuth salts of high atomic fatty acids. They are fairly soluble in vegetable oils. At an early date Merck brought forward "embial." The exact composition of this has never been published. Further, a number of French preparations have lately been recommended by Levaditi³⁸ and his collaborator, L. Fournier³⁹: basic α -carboxethyl- β -methyl-nonoate of bismuth, basic α -methyl-hydrocinnamate of bismuth, camphocarbonate of bismuth, etc. The clinical effect of these preparations is reported as extremely satisfactory and quite painless. I have not been able to confirm this last point, but the pain is certainly not very bad. A considerable amount of material is, however, necessary before the clinical superiority of a particular remedy can be admitted. It would certainly be a great advantage if these oil solutions combined a relative painlessness with an especially great rate of absorption and regularity. Levaditi³⁸ (p. 598) found this, but unfortunately his researches are not extensive. As to "embial," Engelhardt³⁶ (p. 31) found no especially quick absorption. Similar observations were made by Grumach,⁴⁰ who did not find substantial differences between oil solutions and the usual oil suspensions. This fact corresponds fairly well with Levaditi's³⁸ (p. 600) statement that even after twenty-four hours a decomposition of the compound takes place, a definite bismuth deposit being formed in the muscle, which can be traced for a long time. Levaditi thinks that the bismuth is deposited in the form of oxide or oxychloride; but if this is the case there should be little difference between the condition in the muscle whether injected by this compound or by others, suspended in oil. A definite inconvenience with these pre-

parations is the presence of large quantities of vegetable oils and of high atomic fatty acids, which are only with great difficulty absorbed by the tissue.

The form in which bismuth is most commonly used is that of suspensions in vegetable or vaseline oil. Such suspensions are almost painless. The oil covers the small suspended bismuth particles and prevents a rapid reaction between these and the surrounding tissue. How great the difference is was clearly seen from the following experiment with eight patients. A dose of 150 mg. bismuth salicylate suspended in vegetable oil was injected, and another, a week later, in water. The first was borne almost without any pain; the second caused considerable pain in most cases, and, moreover, in three cases a severe stomatitis appeared shortly after the injection. The explanation of this fact was quite clear. It is a well-known fact that the muscular tissue absorbs vegetable oil very slowly—not until after several months—and vaseline oil is not absorbed at all. Before the absorption of bismuth can take place the oil must be separated from the bismuth particles. With bismuth compounds soluble in water or in the tissue fluid a more rapid absorption can take place, but then it always causes pain. It must be said that as a rule it is scarcely possible to have a rapid absorption without a definite pain. This is easily understood. The absorption implies a reaction of the bismuth ion with the tissue. Hereby bismuth albuminates are formed and the tissue is more or less destroyed. If this takes place quickly, pain is inevitable, if slowly, no pain may occur. Even a considerable necrosis of the muscular tissue with abscess may develop without any noticeable pain. More often the tissue forms a capsule of granulation tissue round the injected deposit. The absorption remains imperfect, and will sometimes stop completely, especially with such bismuth compounds as are insoluble in water or in the body fluids.

All bismuth injections injure the muscular tissue in a definite way. The simplest form is a small necrosis, which is gradually replaced by granulation tissue that later on develops into a little scar. In patients who have received long series of bismuth injections it may happen that, in giving an injection, the needle may enter into such highly vascular granulation tissue, and blood will appear; or the needle will meet with strong fibrous resistance—that is, scar tissue. Injections should not be given in either of these cases; in the first, because of the risk of intravascular injection, in the second, because the fibrous scar tissue offers a most resistant barrier to absorption.

As mentioned before, the use of oil for suspension often causes a rather slow and irregular absorption of the contained bismuth. This hampering of the absorption is, however, not a rule without exceptions. In some cases a fair absorption can be seen even in these cases, but it cannot always be expected.

A large number of bismuth compounds have been used in oil suspension. In the composition of these preparations it seems as if the desire to secure an absolutely painless preparation has been the principal aim of both manufacturers and physicians. This seems to me a somewhat narrow point of view. A moderate amount of pain is not a definite drawback. It generally means that a good absorption is about to take place. Still, the pain must not be so great as to prevent the patient from doing his work and perhaps cause him to discontinue treatment.

The rate of absorption of the different bismuth compounds seems to correspond closely with their solubility in water. Most of the bismuth compounds used in syphilis therapy are generally characterized as "insoluble in water." Still, "insolubility" seldom means an absolute insolubility, but in most cases a very slow solubility only. As to the bismuth compounds in question, they are practically all slightly soluble in water, and especially if small quantities of albumin or sodium chloride are added to the water.

It seems practical to divide the various compounds into groups according to their rate of solubility. The carbonate, oxide, and oxychloride of bismuth, and metallic bismuth compose a definite group of very restricted solubility. Also they are absorbed very slowly. Few examinations have been made on this group of compounds, but they all point to a very slow absorption. Thus Biro Istvan⁴¹ found that only 6 per cent. of bismuth was eliminated

in the urine and faeces in thirty days after a series of injections of, in all, 0.2 gram of metallic bismuth in a 10 per cent. suspension in oil ("sorbismol"). I made a few examinations on BiOCl_3 .⁸ In some of these a fairly quick absorption was found, but the reason for this was probably that an exceptionally weak suspension was used, and, moreover, that the doses of bismuth itself were so very small.

The next group comprises the hydroxide, the subnitrate, and the oleate of bismuth. These are not of quite so minimal a solubility as the above-mentioned. The elimination of the hydroxide was studied by me, and it was found that in two cases after fourteen days only 7.53 per cent. and 5.86 per cent. of the injected quantities was eliminated in the urine. Kürthy¹⁷ found with bismuth oleate ("oleo-Bi," Roche) used in a dog that only 10 per cent. was eliminated in the urine during twenty-eight days. Leonard¹⁸ found in rabbits that 5.66 per cent. and 10.60 per cent. was eliminated in fourteen days. Still these preparations are used to a large extent in therapy. Well-known preparations are "muthanol" (French), "casbis" (German), both hydroxides, "oleo-Bi" (Swiss). The dose generally recommended for these preparations seems rather large. The reason for this is obviously their slow absorption. Bruck⁴¹ mentions a case where 1.5 grams of bismuth ("casbis") were given by a mistake instead of 0.15 gram. "In spite of observation for several months, not the slightest untoward consequences of this enormous dosage were shown by the patient." Such observations are rather condemnatory of the therapeutic effect of this sort of preparation. The death reported by Jörgen Munck⁴² was caused by injections of bismuth hydroxide in oil suspension.

The third group comprises certain organic compounds. Bismuth iodoquinatate is absorbed fairly quickly. I found that in two cases 12.85 per cent. and 20 per cent. was eliminated in the urine after fourteen days. Corresponding observations were made by Engelhardt³⁶ with a similar preparation (bismuto-yatren B). He found that 23.7 per cent. was eliminated in the twenty-three days that the treatment lasted, and that this rather strong elimination continued. Bismuth chloride and iodine has, however, a great drawback. It contains only 20 to 24 per cent. of bismuth. Large quantities of the preparation therefore must be injected. Moreover, the high content of quinine and iodine is liable to irritate the tissue. Infiltrations are often seen in the muscle tissue after the use of this remedy. The compound is used under various names: quinby, bijochin, vijochin, bijochinol, biquinyl, rubyl, etc.

Potassium-sodium-bismuth-tartrate was the very first preparation used in therapy by Levaditi under the name of "trépol." Sometimes it is absorbed fairly quickly, but sometimes rather slowly. The first statements of Levaditi are well known. He gave five injections to different rabbits. After one day 30 per cent. of the injected quantity was found to be absorbed, after six days 21 per cent., after thirteen days 23.5 per cent., after twenty days 17.1 per cent., and after twenty-five days 19.3 per cent. The scale of absorption turned out almost the opposite of what might have been expected. I found after two injections that 22.2 per cent. of the injected quantity was eliminated. Biro Istvan¹⁰ found after injection of "bismuluol" (potassium-bismuth-tartrate in oil) that 16 per cent. was eliminated in six days. Leonard and O'Brien found with the same compound 26.30 per cent. and 42.24 per cent. eliminated in the urine during fourteen days.

Gruhitz, Tendick, and Sultzberger found by examination of the deposits in dogs that about 46.7 per cent. of the injected bismuth was absorbed in eight days, and that the figure rose to 90.9 per cent. in three weeks. Still these figures are presumably rather high (see below). Cettingen, Todd, and Sollmann found in a single rabbit a very slow absorption. After 105 days only 30 per cent. was absorbed. The quantity given, 50 mg., was very high for a rabbit, but was tolerated.

The conclusion from the above facts must be that this remedy as a rule is absorbed fairly quickly, but that there are numerous exceptions.

Bismuth salicylate is used to a very large extent, especially in America, England, and Germany. Probably it

is the most commonly used of all bismuth compounds in therapy. Gruhitz, Tendick, and Sultzberger have studied its absorption in dogs. The deposits were removed and examined. The average absorption was: 67.4 per cent. in eight days, 57.8 per cent. in fourteen days, and 94.8 per cent. in twenty-one days. The figures of elimination in urine are surprisingly smaller than might be expected from the above; thus in one case only 19.1 per cent. was eliminated during fifty-two days, in another only 13.9 per cent. in fifty-four days, in a third only 22.7 per cent. in twenty-four days, and in a fourth only 9 per cent. in thirty-eight days.

Prater⁴³ mentions a case where an extremely slow absorption of bismuth salicylate was noticed. By mistake a patient received in three days 1.2 grams of bismuth, which is an enormous overdose. After one week a moderate stomatitis appeared and a slight fever, but no serious signs of intoxication.

Summarizing, it may be said that all suspensions of bismuth in oil are absorbed somewhat slowly and irregularly. With the last group, potassium-sodium-bismuth-tartrate, iodoquinatate of bismuth, and bismuth salicylate, this is least pronounced. Because of this fact I think that this last group should be preferred. The tartrate has the drawback of a somewhat varying composition and content of bismuth metal. The iodoquinatate has a rather low bismuth percentage; large doses must therefore be given. Further, it irritates the tissue. The salicylate has no such drawbacks. Consequently I consider this compound to be the most suitable for use in oily suspension.

Still, as often emphasized above, the oil introduces a considerable factor of irregularity. Water, on the contrary, is absorbed immediately, and bismuth particles in watery suspension will therefore at once be brought into direct contact with the muscular tissue, and the best possible condition for a quick and regular suspension is created, especially so as a watery suspension is thin and spreads very easily among the fibrillae of the muscle. The rapid absorption will cause a certain increase of pain (see above under bismuth salicylate).

I made a series of comparative examinations to see what difference a change of suspension fluid would give as to the rate of absorption of two well-known compounds. The results were as follows: bismuth hydroxide in oil gave an elimination of 7.59 per cent. and 5.86 per cent. in fourteen days; bismuth hydroxide in water, 47.4 per cent. and 35.57 per cent.; bismuth iodoquinatate in oil gave an elimination of 10.43 per cent. and 15.57 per cent., against 47.30 per cent. and 48.63 per cent. in water. For metallic bismuth in oil (sorbismol) Biro Istvan found an elimination of 6 per cent. in thirty days; for a watery suspension (néotrépol) Leonard¹⁸ an elimination of 19.20 per cent. in twenty-two days.

It is impossible simply to change from oil to water. This was seen clearly with bismuth salicylate. The pain would be too great, and might even prevent the patient working. A bismuth compound must be found that is less "soluble" and therefore of a slower reaction. The hydroxide proved to be in some ways fairly good, but it had the drawback that it was difficult to obtain a perfectly pure preparation with particles of a definite size. The oxychloride possesses obvious advantages on these two points. It is easy to prepare, is perfectly pure, and has particles of a quite homogeneous size. Moreover, it is less soluble than the hydroxide, and is well tolerated even in a watery suspension. If the particles are very small and the total surface of the bismuth compound correspondingly large, the absorption will be so sudden that it will certainly produce pain. This was the case if the particle had a size of 0.5 to 1 μ .

Experiments were made with particles of different sizes. A size of 3 to 5 μ proved to be suitable. A suspension of these was tolerated well by most patients, and if pains occurred they were mostly slight. The doses of this suspension can be fixed at a lower point than with oily suspensions: 20 cg. (= 170 mg. Bi) is a suitable dose for men; 15 cg. (= 125 mg. Bi) for women, given in series of eight to ten injections at intervals of five to seven days. This means an average dose of about 0.5 mg. per day per kilo of body weight during the course of treatment. After four or five

injections a thin blue line is generally seen along the edge of the gums. But this line is seen with all intensive bismuth treatment. It is simply an inevitable sign of a strong saturation of the organism. The interval between the series should be about six weeks. During this time the blue line will generally weaken, but seldom disappear entirely. The injections must be given in the usual place and manner. Special regard must be paid to the risk of an intravascular injection, as the fluid is rather thin. After the needle is put in, an aspiration must always be made before the injection, to ascertain that the needle is not placed inside a vein or an artery. But even if blood does not appear, the needle should be retracted slightly during the injection, because experience proves that even with a negative result of the aspiration test it may happen occasionally that the fluid is forced into the lumen of a vein or, still worse, of an artery. In the last case a serious infarct of the muscle and of the skin covering it may be the result (Freudenthal, Gammel). I have seen a few such arterial infarcts—fortunately not very serious—also during the use of the preparation mentioned here, but after the outlined scheme of injection was adopted it was not seen any more. If the opening of the needle should pass another vascular lumen during the retraction, insignificant quantities only can be pressed into it, because the needle is withdrawn slightly but continuously.

A factor of great importance in syphilis treatment, especially in the intermittent scheme, is the retention of bismuth in the organism. This is composed of two quite different parts: (1) the diffuse storage of bismuth in the different organs and tissues of the organism; and (2) the injected deposits. The latter have already been discussed above. The bismuth contained in them may amount to a large quantity, especially with preparations of slow absorption. Sometimes a continual, even stream of bismuth may be absorbed from these deposits over a long period, maintaining thereby a most useful antisymphilitic effect. Sometimes the stream flows most irregularly, and sometimes a compact encapsulation will stop all absorption. Large deposits represent a certain risk of intoxication, as a sudden strong absorption may occasionally, and quite unexpectedly, take place—for example, after unusual exercise. This risk must, however, not be overestimated, as these cases are by no means frequent.

The diffuse storage has been estimated quite differently by different authors. Gruhitz (loc. cit., p. 101) found in experiments with dogs that "bismuth was retained and stored in the different tissues to the extent of about 50 per cent. over a period of six months." I have never been able to confirm these findings; on the contrary, I found in experiments with guinea-pigs that after ten days only 5 to 12 per cent. of the injected quantity was stored in this way. Details were given in a recent publication (*Arch. Derm. and Syph.*, June, 1929).

The therapeutical results of this watery suspension of bismuth, which was prepared after my instructions by a Danish firm under the name of "Ido-Bi," were in all respects satisfactory. It was always combined with treatment by neosalvarsan (Höchst). This makes it difficult to state the role played respectively by the bismuth and by the salvarsan. It may be of some interest to study the clinical result of this treatment by neosalvarsan combined with watery suspension of bismuth, first of hydroxide, later, and chiefly, of oxychloride.

In the period July 1st, 1924, to January 1st, 1928, 161 cases of syphilis, not treated before, were put under treatment. Of these, 9 discontinued treatment before a serological control of the effect was made. Of the remaining 152, 96 were men—29 in the primary sero-negative stage, 36 in the primary sero-positive stage, and 31 in the so-called secondary stage. No men were seen with old, unrecognized neglected syphilis. This is now very rarely met with in men in Copenhagen, owing to the ample access to free treatment provided by the municipality. Practically all men with venereal diseases go now to a specialist as soon as the first sign is observed. It is slightly different with the women. Out of the 56 women with unrecognized syphilis 5 were in the primary stage, 4 were suffering from latent syphilis, which was not recognized until the birth

of a child with congenital syphilis, 3 had tertiary signs, the remaining 44 were suffering from recent secondary syphilis.

The treatment given was: injections of neosalvarsan, generally in doses of 75 cg. to men and 60 cg. to women. Persons of smaller size were given: 60 cg. to men and 45 cg. to women. The series used to be of four to six injections with an interval of a week. The routine scheme was a treatment of two years with three series of six injections of neosalvarsan, and with six series of ten injections of bismuth oxychloride. This amount was only obtained with the minor part. The average amount given to the 152 patients here considered was ten injections of neosalvarsan and thirty-five injections of bismuth. Also it must be emphasized that the treatment was by no means given in a definite routine way. Light cases were discharged with less treatment, resistant ones (with resistant gland swellings, resistant serum reactions, etc.) considerably more. The clinical result can be given quite shortly: No clinical relapse was seen; nine pregnant women all bore healthy children. At the last serological examination 143 out of the 152 patients gave a perfectly negative Wassermann reaction; two women gave a feebly positive test (one suffering from a latent unrecognized syphilis, the other from a neglected severe secondary eruption). Four men and three women showed a $\pm$ reaction of the Wassermann test. It seems justifiable to characterize these results as satisfactory. It is impossible to decide how much of the result is due to the salvarsan and how much to the bismuth treatment. However, it can be said that the scheme used has proved to be effective.

SUMMARY.

1. Bismuth as a substitute is superior to mercury.
2. Internal and percutaneous administration is ineffective owing to restricted and irregular absorption of bismuth.
3. Intravenous treatment is dangerous in large doses; not sufficiently effective in well-tolerated doses; impracticable, as it requires frequent injections.
4. Intramuscular treatment remains the treatment to be preferred. Its aim is to secure a fairly quick, regular, effective saturation of the body, without risk of intoxication. As to the different forms of treatment the following outlines may be given: (a) Watery solutions are effective, but somewhat painful and troublesome because they require frequent injection. (b) Oily solutions are almost painless, but not especially rapidly absorbed. Their therapeutical power is reported by many to be good. (c) Oily suspensions are generally painless, but their absorption is somewhat slow and therefore often rather irregular. Preference should be given to the compounds that are not quite insoluble in water. Bismuth salicylate seems to be one of the best.
5. Watery suspensions are absorbed rather quickly and are therefore slightly painful. Preference should be given to compounds of restricted solubility. The oxychloride possesses the qualities of absolute purity and stability. With particles of a size of 3 to 5 μ it is almost painless and very powerful. I think this preparation especially good on account of its reliability and effectiveness.
6. The daily dose of bismuth metal may be fixed at about 0.5 mg. per kilo of body weight. Higher doses are required with remedies of a slow and incomplete absorption.
7. I recommend as a routine measure the administration of neosalvarsan in doses of 60 to 70 cg. given in series of five to six intravenous injections, and of bismuth oxychloride in watery suspension in doses of 15 to 20 cg. and in series of eight to ten intramuscular injections; to a total number of about 18 neosalvarsan injections and 60 bismuth oxychloride injections in a period of about two years. Even in an incomplete form this scheme proved definitely effective. Of 152 patients with fresh syphilis no clinical relapse was seen during and after the treatment. None of the women treated gave birth to a child with congenital syphilis. By the end of the treatment 2 patients only showed a positive Wassermann reaction, 7 a doubtful, 143 a definitely negative test.

8. No treatment of syphilis should be given as a mere routine, but each single case must be considered by itself and treated accordingly.

9. Retention of bismuth in the organism depends on two different factors. Diffuse storage in the different organs of the body is a matter of slight significance; it amounts to scarcely more than 100-150 mg. after an intensive course.⁹ The unabsorbed deposits, however, may contain unlimited quantities of bismuth, especially in the case of compounds that are absorbed slowly. This second factor is an important but rather capricious and slightly dangerous item in intermittent syphilis treatment.

10. To avoid an intravascular injection taking the place of an intramuscular it is recommended not only to make an aspiration but also to retract the needle slightly during the injection.

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ETHYLENE ANAESTHESIA.*

BY

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ETHYLENE gas is administered as an anaesthetic along with oxygen, the proportions of the two gases in the mixture being to some extent variable. Usually the most suitable mixture contains about 88 per cent. of ethylene, 12 per cent. of oxygen; but anything from 10 up to 25 per cent. of oxygen may be found necessary. This variability depends on a number of factors—for example, the age and build of the patient, the condition of the heart and lungs, the nature of the operation, etc. In all administrations the oxygen percentage must be maintained at such a level as will prevent respiratory failure. More than a slight degree of cyanosis is not allowable, and should be regarded as a warning of impending danger. With due regard to this the anaesthesia is a safe one, trouble arising primarily from failure of respiration and corresponding to "blue collapse"—not the "white collapse" which originates from sudden heart failure. The corrective for "blue collapse" with ethylene is the same as with other anaesthetics—namely, an increase in the proportion of oxygen up to 50, 75, or even 100 per cent. until cyanosis disappears.

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I always employ rebreathing. The administration, therefore, closely resembles that of nitrous oxide and oxygen, and the same apparatus serves very well for both gases. The principal difference lies in the slightly higher percentage of oxygen when ethylene is the anaesthetic, and the resulting absence of, or lesser degree of, cyanosis.

The question very naturally arises, Do we gain anything by using ethylene which nitrous oxide cannot give us? I think that in Great Britain, judging from the scanty references to ethylene, this has been answered for the most part in the negative, and there are undoubtedly grounds for this attitude. At the same time I feel that my answer to the question would be affirmative and that ethylene is finding a definite place among the anaesthetics which I regularly employ. In many respects the results obtained closely resemble those obtained by nitrous oxide and oxygen—for example, safety, rapid action, rapid excretion, and relative immunity from unpleasant after-effects.

There are two decided points of difference between the two gases, one favourable, the other unfavourable, to ethylene. The first difference is the more profound type of anaesthesia which ethylene develops. I have repeatedly had this clearly demonstrated. An anaesthesia which just failed to achieve the desired depth with nitrous oxide-oxygen would become quite satisfactory with ethylene-oxygen. True, in such cases the alternative is offered of supplementing nitrous oxide with ether, but the immunity from unpleasant sequels is then to a greater extent limited. In all cases where I expect a considerable demand as regards depth of anaesthesia I prefer to commence with ethylene. Even then if ether has to be added a smaller quantity suffices than if nitrous oxide had been used. Herein, then, lies the chief superiority of ethylene over nitrous oxide—the more profound narcosis which it produces. It is thereby rendered sufficient for a wider range of operations. It is quite adequate alone for some laparotomies, and for more with the minimum admixture of ether. The second difference, and the one in which ethylene compares unfavourably, rests on one of its physical properties. Ethylene gas, as ordinarily obtainable, possesses a very unpleasant odour. Fortunately, this property is practically without effect on the patient, but for the other inhabitants of the operating theatre it presents a serious objection. I can only suggest in mitigation the flavouring of the gas with oil of eucalyptus, which renders it more bearable.

In order to review the scope and usefulness of ethylene in a general way, I propose to regard it from three viewpoints: (1) the patient's; (2) the surgeon's; (3) the anaesthetist's.

The Patient's Point of View.

The patient's chief interest in his anaesthetic is centred in his experiences "going under" and "coming out." I ought to remark here that I rarely employ ethylene without a preliminary dose of morphine and hyoscine. The reaction to the taking of the anaesthetic is therefore modified by this preliminary narcotic. I regard the addition of hyoscine as valuable not only in allaying nervousness and inducing a drowsy condition favourable to the induction of anaesthesia, but also for its action on the memory. Many patients, especially the elderly, after a dose of hyoscine, have only hazy recollections, or none at all, of being moved from bed to the theatre. Very often there is a more or less complete blank lasting some little time after their return to bed. But even in the absence of preliminary medication the taking of ethylene does not give rise to the disagreeable sensations which one would expect. I have repeatedly questioned patients about their sensations, and not one has made any reference to the peculiar smell. By taking the gas in full, or nearly full, strength the smell appears to be unnoticed. Consciousness is rapidly abolished, and usually without evidence of resentment or excitement. As regards the "coming out" stage, again the sensations appear to be not unpleasant. Vomiting occurs fairly frequently (in about 75 per cent.), but as a rule within a minute or two of the end of the administration and before consciousness has returned. Thereafter there is seldom any more, though