THE THERAPEUTIC ACTION OF BISMUTH IN SYPHILIS*

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IN a recent contribution to the *Presse Medicale*¹, I discussed the question of the use of bismuth, particularly of basic tartro-bismuthate of potassium and sodium (trépol), in the treatment of syphilis. Since the publication of that article, numerous reports have been added to the collection of evidence which may be quoted in favour of the use of this new preparation in all forms of syphilis. I propose to analyze these later reports, quoting the earlier works when necessary.

Historical

Bismuth has been employed as a cicatrizing agent in cutaneous lesions since the seventeenth century. In 1786, Odin² recommended its use in gastric affections. Masucci³ employed bismuth proto-iodide for dressing mucous papules, seeking to obtain a local reaction only. Not till 1899 did Balzer⁴ make the first experimental tests of toxicity, with a view to the treatment of syphilis by bismuth. These attempts, however, were not successful; the sequelæ observed in dogs by Balzer caused him to abandon the use of the drug. In 1916, Santon and Robert⁵ used bismuth with success in the treatment of spirillosis of fowls. Their experiments were confirmed by Sazerac and myself⁶ at the beginning of 1920, and by many repeated trials we proved, in animals and man, the rapid cicatrizing action of sodium and potassium tartro-bismuthate on various syphilitic lesions. These results were verified clinically by Fournier and Guenot,⁷ using bismuth in the form of sodium and potassium tartro-bismuthate. It is of interest to follow the results obtained by various workers in different manifestations of syphilis at the several periods of the disease.

Primary Syphilis

Bernard reported, in several cases of syphilis, three of them primary, the disappearance of lesions in a few days, following two or three injections of several centigrammes of trépol; the treponema frequently disappeared after a single injection. Duhot⁹ stated that the action of trépol is rapid and manifest in syphilitic chancre. Truffi¹⁰ noted the regression of a syphiloma, and its rapid cicatrization, a few days after the first dose. He attributed a powerful spirillicidal action to sodium and potassium tartro-bismuthate. Nicolas, Massia, and Gaté¹¹ observed rapid disappearance of chancre and cicatrization in from 8 to 12 days. In nine cases of syphilis treated with bismuth, Pasini¹² observed the rapid disappearance of treponema after the first injection (24 to 48 hours). The drug provoked a very rapid cicatrization of syphiloma, of which infiltration was more slowly re-absorbed. Induration might persist for several weeks. There is, according to Pasini, a certain opposition between the cicatrizing action and the slower resolvent action. Disease of the glands appeared to be less beneficially influenced; however, the enlarged glands in the neighbourhood of the chancre quickly diminished in size. De Bella¹³ treated seven cases of recent syphilis with trépol; according to him, results were steady and lasting, but not rapid. Bismuth approaches more to calomel than to the arsenobenzols. He speaks of the use of bismuth in syphilis as "a great and real acquisition, a new weapon for use against specific infection, a weapon of choice, particularly in those cases showing resistance against or intolerance of other drugs." Define¹⁴ treated

seven cases of syphilis (one primary) with sodium and potassium tartro-bismuthate in oily suspension, in doses of 0.2 to 0.3 g., and reported rapid disappearance of the treponema, with early cicatrization of lesions. Ducrey¹⁵ reported that in patients suffering from primary syphilis bismuth brought about a rapid healing of lesions, even when the latter were much ulcerated; glands disappeared and a huge ulcerated chancre was cured in a fortnight. The treponema disappeared from the surface of the ulcer after the first injection. Berthet¹⁶ agreed with these findings. He found that in primary syphilis, with W. R. still negative (preserological stage), the results obtained up to the date of his communication, were encouraging and seemed to indicate that bismuth, like the arsenobenzols, would prove a very useful sterilizing agent. Grecho and Muschietti¹⁷ observed that chancre was modified to a degree dependent upon the extent of infiltration and that primary lesions lost their induration; epithelization and cicatrization followed. Posadas¹⁸ observed cure of chancres in from four to ten days.

Secondary Syphilis

Grecho and Muschietti¹⁷ reported rapid disappearance of non-ulcerated mucous patches and of hypertrophic papules, together with slower but evident clearing up of roseola and papular syphilides of iritis. Malignant syphilis, was also successfully treated with bismuth, and roseola, papules, and condylomata rapidly cleared up (Bloch).¹⁹ Spillmann²⁰ observed, in one patient, rapid disappearance of various cutaneous and mucous manifestations following intramuscular injections given every four days over a period of 36 days. Veber²¹ reported a case where, after the fifth injection of trépol, a patient suffering from secondary syphilis with specific jaundice, and circinate rash and papular serotol syphilides, the jaundice cleared up completely. The W. R. became negative after six injections. Jeanselme observed a general improvement after the fifth injection in a patient with febrile secondary syphilis and poor general condition. Pasini¹² stated that the conditions most readily treated with bismuth are mucous patches of the mouth, genital organs, and peri-anal region. He observed cicatrization of these papules within a few days; hypertrophic papules of the scrotum disappeared in from three to four days. On the other hand, papular infiltrations (papulo-lenticular and papulo-squamous) appeared to be more resistant to bismuth. Define¹⁴ noted that the W. R., positive before treatment, became negative soon afterwards; he used bismuth with success (sodium and potassium tartro-bismuthate) in cases of persistent headache. Ducrey¹⁵ observed that in secondary syphilis the effect of trépol was a remarkably rapid cicatrization of mucous patches and condylomata (in 12 days, after the third injection). Spirochætes were destroyed in these lesions after the second injection. In a case of hypertrophic mucous patches of the tonsils and soft palate the latter were healed in a week. Fifteen days sufficed for disappearance of roseola. Truffi²² found that with this drug secondary manifestations were rapidly cleared up, that a few days after the beginning of treatment spirochætes were no longer found in lesions where they had been very numerous and that the humoral reactions tended to become negative. Berthet described rapid cicatrization of lesions. Wallon,²⁴ in a recent communication, stated that mucous papules disappeared

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most frequently after two injections, and sometimes after the first injection—i.e., in from four to five days of treatment with trépol (in from 5 to 20 days, according to Posadas). With colloidal bismuth, mucous papules became cicatrised, according to the degree of infiltration, in from 6 to 15 days. Using neo-trépol, I have personally observed cicatrization of buccal mucous papules within four or five days, and disappearance of treponema after the first or second injection. The same effects are obtained in the treatment of hypertrophic papules, roseola, and palmar syphilides. Headache, fatigue, and osteocopic pains frequently cease after the first injection.

Tertiary Syphilis

Fournier and Guenot²⁵ reported great benefit derived from the use of trépol in syphilitic periostitis and in cutaneous lesions with encrusted ulcers. They also observed excellent effects in two cases of aneurysm of the aorta. Grecho and Muschiatti and Berthet noted very rapid cicatrization of cutaneous lesions; Fournier and Guenot, and Bloch reported rapid disappearance of gummata. In two cases of tertiary syphilis (crusted ulcers) of the buttock of 12 years' duration and not previously treated, cicatrization was obtained after seven injections of tartro-bismuthate and one month of treatment. Another case was a chancre-like lesion of the fourchette which became cicatrised after two injections of tartro-bismuthate (Wallon). Bismuth treatment is of great benefit in the specific headaches and general malaise of tertiary syphilis; Ducrey reported cure of an ulcerated gumma of the soft palate in 20 days. Pasini reported excellent results in two cases of tuberculous syphiloderma, in two cases of multiple dermo-hypodermic gummata, in a case of gummatous osteo-periostitis of the tibia, and in a case of necrotic osteo-myelitis of the cranial bones. Re-absorption of infiltration and cicatrization of open lesions was obtained in a month, after from eight to ten injections. Posadas has reported concerning the action of trépol in syphilitic endarteritis. I have seen rapid regression of tertiary lesions as a result of bismuth treatment (trépol and neo-trépol).

Syphilis of the Nervous System

Various statements testify to the benefit derived from bismuth in treatment of syphilis of the nervous system. Frequently, in these cases, resistance against arsenic has developed, and bismuth has been the more valuable on this account (Hudelo,²⁶ Milan²⁷). Dessert has reported considerable amelioration in acute meningitis and chronic syphilitic meningitis. In two cases of general paralysis mental trouble was clearly relieved, and in one case locomotor troubles were greatly diminished. A. Marie and Fourcade²⁸ also obtained favourable results. Tixier²⁹ found a case of heredosyphilis of the nervous system to be distinctly benefited by tartro-bismuthate. Localized lesions benefit most from the treatment. Tabetics suffering from repeated gastric crises, again, are considerably benefited by trépol and neo-trépol.

Serological Action

Fournier and Guenot were the first to study the action of bismuth on the W. R. They found that whatever the phase of the disease, the reaction was favourably affected; sometimes the latter became negative before the end of the first series of injections. The following are my own results, already reported,¹ in this connection.

	Negative. Per cent	Partial. Per cent	Positive Per cent
Primary syphilis			
Before treatment	8	25	67
After treatment	63	37	0
Secondary syphilis			
Before treatment	0	28	72
After treatment	90.5	4.5	5

Bloch¹⁹ found that the W. R. was not affected to the same degree as the clinical symptoms. The W. R. is generally rapidly weakened, but almost always re-

quires several weeks, even two months or more, before becoming negative. For this reason Bloch employs bismuth in combination with arsenical preparations. Similarly Sedlak³⁰ found that combined treatment (trépol and neosalvarsan) results in the W. R. becoming more rapidly negative. Posadas¹⁸ found that with bismuth the W. R. became negative more rapidly than with mercury, less rapidly than with arsenic. Pasini¹² investigated the action of bismuth in the W. R. and Sachs-Georgi reaction, and found it slow and often incomplete. Thus, patients who had left hospital after having had 10 or 12 injections and a total dose of 2.5 or 3 g. trépol, showed only a lessened reaction, not a reaction completely negative. Wallon³¹ showed that the sero-reaction, even when it remained partially positive, was always distinctly bettered. Wallon found the W. R. negative in two cases of primary syphilis treated with tartro-bismuthate. In the secondary period, the reaction was negative 8 times in 16—i.e., in 50 per cent. of cases. With colloidal bismuth the W. R. became negative twice in eight cases.

Sirum,³² attempting to compare the weights of drugs (bismuth and novarsenobenzol) employed to render negative the W. R. in recently-acquired and active syphilis, found that this process required a mean weight of 2 g. tartro-bismuthate and of 0.5 g. precipitated bismuth or colloidal bismuth (neo-trépol). To obtain the same result, 5.6 g. novarsenobenzol were required. Define obtained a satisfactory result in two cases. Ducrey, on the contrary, affirmed that in all his cases trépol had no effect on the W. R.; this statement, however, does not disprove the anti-syphilitic value of bismuth. It is known, of course, that even with arsenic the reaction does not become negative, in certain cases, until some months after treatment; but no one contests the value of arsenical preparations. From all these results it is clearly too early to state that the W. R. will remain definitely negative after a single treatment with trépol. But it can be stated that from the point of view of its effect upon sero-reaction bismuth is comparable to the most valuable anti-syphilitic remedies.

Bismuth in Cases Resistant to Arsenic and Mercury

Several writers have commented upon the value of trépol in cases of syphilis recurring after arsenical or mercurial treatment. Fournier and Guenot,⁷ for instance, report the clearing up of lesions after three or four injections of tartro-bismuthate. Dessert reported good results in cases resistant against arsenic, and Wallon²⁴ also, the latter including cases resisting mercury as well as arsenic. Milian²⁷ obtained, with a fifth injection of bismuth, a cure in a case of long-standing generalized papular syphilides, which had resisted arsenic and mercury. Tixier²⁹ reported a case of heredo-syphilis of the nervous system which had resisted arsenic, but was rapidly ameliorated with trépol; Guibert³³ observed a chancre which continued to grow after 6.25 g. neosalvarsan and injections of calomel, but which was cured after eight injections of trépol. Razende³⁴ speaks highly of trépol in cases of syphilis resisting arsenic and mercury. Resistance against arsenic and mercury have been frequently observed, and such resistance must also exist against bismuth; Lortat Jacob and Roberti³⁵ have described a single case—secondary syphilis intensively treated with a bismuth salt. Mucous papules appeared during the treatment; after seven injections of 2 c.cm. (1.4 g.) of the salt on 20 days, the patient was covered with mucous papules in which treponema fornicated.* This is the only known case of resistance against bismuth. The latter drug, then, appears superior to other specific remedies, in the light of absence of recurrence, and of its usefulness in cases where arsenic and mercury have failed.

*It may be wondered whether in this case the use of trépol, or better still, of neo-trépol, would not have overcome the resistance of the treponema.

Toxicity, Posology, and Method of Application

In collaboration with Sazerac I carried out investigations into the toxicity of bismuth in the rabbit. It required 200 mg. sodium and potassium tartro-bismuthate per kg., given subcutaneously, to kill a rabbit; intravenously, only 5 mg. were required. In oily suspension this preparation is no longer toxic; this form—i.e., trépol—is used in treatment. The symptoms which most frequently follow the injection of bismuth are a bismuth line on the gums, grey-blue or slate-coloured, and stomatitis—phenomena reported by Dalche and Viljean³⁶ as early as 1889. According to the researches of Azoulay³⁷ and Milian and Perin³⁸ a deposit of bismuth sulphide occurs in the cells of the dermal connective tissue, principally in the vascular endothelium. From the point of view of prognosis, bismuthic stomatitis is much more favourable than the mercurial form. It is usually found in subjects who take no care of their mouths. Wolfer, making a radiological examination of the gradual absorption of bismuth, found the process to be very irregular.

Bismuth is eliminated (1) by the kidney, (2) by the salivary glands, and (3) by the digestive system. Demelin³⁹ and others report that bismuth is found in the urine 18 hours after injection of soluble salts, and 24 hours after the injection of insoluble salts. Steinfeld and Meyer⁴⁰ found no more bismuth in the urine after 18 hours. Fournier and Guenot²⁵ found the elimination to be prolonged over 30 hours. According to Pasini¹² bismuth is already in process of elimination in the urine half an hour after injection. The elimination is quantitatively irregular. Ducrey observed bismuth in the urine 26 hours after injection, and remarked that it persisted a long time after the cessation of treatment. Azoulay found bismuth in the saliva 24 hours after the injection of trépol. By the large intestine bismuth is eliminated in the form of bismuth sulphide. Demelin observed bismuth in the bile, blood, and cerebro-spinal fluid.

The insoluble preparations trépol and neo-trépol should be used for intramuscular injection. Injection should be carried out with a 5 c.cm. syringe and a sufficiently large needle, as the liquid is sometimes thick. The most favorable region for injection is the whole of the superior gluteal area. Injections should be made alternately into either side, not too close to the site of previous injections. The intravenous route is too dangerous. The dose of trépol should be 2 c.cm. (0.2 g. of the active preparation) repeated every three or four days, until a total dose of 2.8 or 3 g. has been reached. The series of injections should be repeated after an interval of a month, until the W. R. becomes negative.

Various Bismuth Derivatives

As I have stated, most workers have used the intramuscular route of injection; the intravenous route has been more rarely used. After numerous experiments with other bismuth salts, I prefer trépol (sodium and potassium tartro-bismuthate) which has given me the best results. Grecho and Muschietti used basic salicylate of bismuth for intramuscular injection, which seemed to them to be better tolerated (3 g in 20 days) and more active in manifestations of secondary and tertiary syphilis; by the intravenous route they injected bismuth iodide. Bloch, having used bismuth citrate at first, now uses the painless trépol. Soluble tartro-bismuthate was used in glucose solution by Jeanselme and his collaborators. Fourcade experimented with bismuth oxide. Fouard and Wallon tried colloidal bismuth by the intravenous route (bismuth ionoid.).

Finally, working with Sazerac⁴¹ I have perfected the preparation neo-trépol, manufactured by Messrs. Chanal and Douilhet, Paris. It consists of metallic bismuth in suspension in a sterile isotonic solution. This prepara-

tion contains 95 per cent. of metallic bismuth; it is well tolerated and possesses remarkable therapeutic power in all three stages of syphilis. When neo-trépol is used, buccal symptoms are very rare and pain practically non-existent. At present I prefer neo-trépol to all other preparations; it may be used for intramuscular injections, in doses of 1.5 to 2 c.cm. repeated every three or four days. It is now in routine use at Dr. Fournier's clinic, at the Hôpital Cochin, Paris. Our researches have been confirmed by Barrio de Medina.⁴²

Conclusions

In the light of the above description of the influence of bismuth in syphilis, I feel I can maintain the conclusions published by me in July, 1922.¹ Sodium and potassium tartro-bismuthate and metallic bismuth achieve rapid cicatrization of syphilitic lesions at all stages of the disease. Although bismuth has only been recently employed, I have every reason to believe that, when used early and in sufficient quantity, it will cure syphilis. The absence of recurrences of the disease, and the effect on the W. R., only serve to confirm this opinion. Equal, from a therapeutic point of view, to arsenical preparations, better than mercurial preparations, bismuth (trépol and neo-trépol) is a valuable anti-syphilitic remedy, particularly in those manifestations of the disease which resist the action of arsenic and mercury.

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