III

AN EXPERIMENTAL STUDY OF SOME BISMUTH COMPOUNDS OF ARSINIC ACIDS FROM THE POINT OF VIEW OF THEIR THERAPEUTIC ACTION IN EXPERIMENTAL SYPHILIS AND SPONTANEOUS SPIROCHÆTOSIS OF THE RABBIT

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IN a communication¹ made to the Academie des Sciences in 1925, it was shown that by the admixture, under certain conditions, of concentrated aqueous solutions of the sodium salt of *p*-hydroxy-*m*-acetylaminophenyl-arsinic acid (sodium Stovarsol, As = 27 per cent.), and of sodium potassium bismuth tartrate (Bi = 30 per cent.), a copious white precipitate was obtained. This precipitate after being washed and dried at 56° C. gave a yellowish amorphous powder, insoluble in water, but soluble in alkalies. The product on analysis gave figures which showed it to have the composition represented by the formula

It was thus a basic bismuth salt of *p*-hydroxy-*m*-acetylaminophenyl-arsinic acid. It contained 41 per cent. Bi and 15 per cent. As. (Theory requires Bi = 40.2 per cent.; As = 14.5 per cent.)

This was the first example of this type of bismuth salt of an arsinic acid. It afforded at the same time the first opportunity of examining the therapeutic effect in human

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and experimental syphilis of a product containing both arsenic and bismuth in the molecule. In collaboration with MM. Fournier and Schwartz ² we have published in another communication the results obtained in human syphilis by means of this compound. These results were also embodied in a lecture delivered before the Section of Dermatology of the Royal Society of Medicine early in 1926.³

Further investigations have led to the recognition of certain new facts which it is proposed to present and discuss in the present paper.* These investigations have been concerned with the following products :—

(1) The basic bismuth salt of bismuth *p*-hydroxy-*m*-acetyl-amino-phenyl-arsinic acid in solution (soluble bistovol).

(2) The basic bismuth salt of *p*-amino-phenyl-arsinic acid (bismuth arsanilate).

(3) The basic bismuth salt of N-phenyl-glycinamide-4-arsinic acid (bismuth tryparsamide).

I. SOLUBLE BISTOVOL

This product has been employed in the form of a 2 per cent. or 10 per cent. solution. These solutions have been examined (particularly in 10 per cent. solution) for toxicity and for their curative action in experimental syphilis (*virus Truffi*), and in the spontaneous spirochætosis of the rabbit (*Sp. cuniculi*). The solution has been administered either by injection or *per os*.

TOXICITY

(a) Intramuscular Injection

Dose injected.	Rabbit.	Variation in weight.	Result.
0.1 gm. per kilo	516 D	Loss of weight, 1,900 to 1,350 gm.	Died
0.07 "	533 D	No loss of weight	Survived
0.05 "	522 D	" "	"
0.01 "	514 D	" "	"

Tolerated Dose = 0.07 gm. per kilo (or 0.0287 gm. Bi and 0.01 gm. As).

* Certain of our experiments have been made in collaboration with M. Nicolau, the histological work has been carried out in collaboration with Mlle. Schoen.

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TOXICITY—continued.
(b) Intravenous Injection

Dose injected.	Rabbit.	Variation in weight.	Result.
0.05 gm. per kilo	530 D	Loss of weight	Dead 3rd day
0.025 "	529 D	"	"
0.01 "	532 D	Loss of weight, 2,150 to 1,500 gm.	Dead 7th day.
0.005 "	751 D	No loss of weight	Survived.
0.002 "	753 D	"	"
0.001 "	712 D	"	"

Tolerated Dose=0.005 gm. per kilo (=0.002 gm. Bi and 0.00075 gm. As).

(c) Per Os

Numerous experiments, the details of which will be found later in the paper, have shown that considerable quantities (up to 0.217 gm. per kilo) of the product are well tolerated by rabbits when administered by mouth.

THERAPEUTIC ACTION

I. INTRAMUSCULAR INJECTION

(a) *Sp. Cuniculi*

Doses of from 0.05 gm. to 0.001 gm. have been administered to rabbits with prepuccial lesions showing numerous spirochætes. The following table summarises the results obtained:—

Dose gm. per kilo.	Rabbit.	Weight. Gm.	Lesions.	Spirochætes.	Cicatrisation of lesions.	Disappearance of spirochætes.	Relapse.
0.05	314 D	2,100	+++	++++	2nd day	2nd day	Nil
0.025	130 D	2,200	++	++++	"	4th "	"
0.01	175 D	2,300	+++	++++	"	2nd "	"
0.005	325 D	2,450	++++	++++	6th day	6th "	"
0.002	336 D	2,650	++	++++	"	2nd "	"
0.001	333 D	3,000	++++	+++	No action	No action	—

This table shows that soluble bistovol when injected intramuscularly exerts an obvious and very rapid curative action, even in doses of 0.002 gm. per kilo (0.00082 gm. Bi, 0.0003 gm. As). None of these animals showed any subsequent relapse.

It follows, therefore, that in this soluble form bistovol

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possesses remarkable spirochæticidal properties and is superior to many known other arsenical or bismuth compounds.

(b) *Treponema Pallidum* (virus Truffi)

The following experiments have been carried out:—

Exp. 1.—*Rabbit 916 D.* Two scrotal lesions showing numerous spirochætes. Weight, 2,300 gm. Received by intramuscular injection 0.025 gm. soluble bistovol per kilo.

Motile spirochætes had disappeared after the second day. Non-motile forms were observed up to the fourteenth day. The lesions gradually diminished in size (the residual nodule was finally excised for examination on the seventeenth day). Meinicke's reaction had become negative. For the virulence of the popliteal ganglia, see p. 35.

Exp. 2.—*Rabbit 917 D.* Lesions as in previous experiment. Weight, 2,300 gm. Received 0.01 gm. per kilo soluble bistovol intramuscularly. Motile spirochætes had disappeared by the second day. Total absence of spirochætes after the fourth day. The lesions rapidly healed, and the Meinicke reaction became negative (Chart 1).

Exp. 3.—*Rabbit 740 D.* Lesions as in previous experiments. Weight, 2,700 gm. Received 0.005 gm. per kilo soluble bistovol by intramuscular injection. Spirochætes non-motile on the second day and disappeared

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from the fourth day onwards. The lesions obviously diminished and cure was effected in fourteen days. Meinicke's reaction negative (see Chart II.).

In a further series of experiments four rabbits with very pronounced scrotal lesions of various duration received intramuscularly 0.01 gm. per kilo of soluble bistovol. The following table summarises the results obtained (see also Chart III.):—

Rabbit.	Duration of chancre.	Spirochætes.	Cicatrisation of lesions.	Disappearance of spirochætes.	Meinicke reaction.
776 N	105 days	++++	6th day	2nd day	—
624 N	128 "	++++	25th "	2nd "	Negative
494 N	68 "	+++	8th "	2nd "	—
149 N	68 "	++++	8th "	2nd "	—

The experiments demonstrate that soluble bistovol exerts a curative action in experimental syphilis of the rabbit (*virus Truffi*) in doses of 0.005 gm. per kilo, equivalent to 0.00205 gm. Bi and 0.00075 As. It is possible, although this has not been tried, that the curative dose might even be as low as that found to be effective in natural spirochætosis (*Sp. cuniculi*), viz., 0.002 gm. per kilo.

It follows, therefore, that the ratio

$$\frac{\text{Curative dose}}{\text{Tolerated dose}} = 1/35.$$

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This ratio demonstrates

(1) That the curative effect of soluble bistovol is of the first order.

(2) That this efficacy is actually superior to that of bistovol (insoluble) when employed in oily suspension for injection where the ratio $\frac{C}{T} = 1/10$ (6). This is naturally what might be expected since the absorption of soluble

bistovol would be more rapid and more complete than that obtained by the administration of the same product in an insoluble form.*

This question of absorption has been determined by the quantitative estimation of bismuth in the muscle (at the site of injection) and in the organs of the *rabbit 740 D*, and in the kidneys of *rabbits 776 D and 149 Z*. These analyses have been carried out by Mlle. Manin. The results obtained were as follows :—

Rabbit 740 D. Killed thirty days after administration of 0.005 gm. per kilo (soluble bistovol).

Quantity of bismuth found in micrograms per gram of dried substance :—

Muscle	0 micrograms.	Kidney	4 micrograms.
Lung	0 „	Liver	2 „
Appendix	2 „	Spleen	0 „

* The same cannot be said for its prophylactic action. As the duration of the prophylaxis is in direct relation to the accumulation of bismuth in the tissues (*Tissue metallic potential*), it follows that bismuth in an insoluble form is more active prophylactically than bismuth in the soluble form (4).

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Rabbit 776 D. Killed eighteen days after administration of 0.01 gm. per kilo (soluble bistovol).

Kidney, 16 micrograms.

Rabbit 149 Z. Killed eighteen days after administration of 0.01 gm. per kilo (soluble bistovol).

Kidney, 6 micrograms.

These figures show that, in the case of the first animal, there was no trace of bismuth remaining in the injected muscle, and that the amount in the kidneys varied in the three cases from 4 to 16 micrograms per gram of dry substance, figures which indicate a rapid absorption and elimination of the metal from eighteen to thirty days after treatment.

The absorption of bismuth, administered in the form of soluble bistovol, produces an intensive action, which constitutes a definite advantage from the point of promptness of therapeutic action. This efficacy is confirmed also by the fact that in every case where we have examined the serum of the animal by the Meinicke reaction, the result has always been negative. Now it is known from the observations of Mutermilch and Nicolau, (5) which have been confirmed by Navarro Y. Martin, that this reaction is always positive in animals affected with scrotal chancres due to *virus Truffi* and otherwise untreated.

Conclusion.—Soluble bistovol is an arsinic bismuth preparation, the therapeutic efficacy of which in experimental syphilis and spontaneous spirochætosis (*Sp. cuniculi*) of the rabbit is of the highest order.

II. SOLUBLE BISTOVOL PER OS

The results obtained in syphilis by oral administration of stovarsol [curative and prophylactic action, Levaditi and Navarro Y. Martin (6)] have led to the carrying out of similar experiments with soluble bistovol. Our first results were so far encouraging that we were led to persevere in this direction, which finally yielded results of practical importance in the treatment of human syphilis. These we propose to publish later in collaboration with M. Fournier.

(a) Natural spirochætosis of the rabbit (*Sp. cuniculi*). A series of rabbits having prepuccial lesions with numerous spirochætetes (*Sp. cuniculi*) were given by the mouth doses of soluble bistovol, varying from 0.05 gm. per kilo to 0.217 gm. per kilo. The following results were obtained.

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after four consecutive such doses given at the commencement and after seven, nine and twelve days. Relapse occurred on the thirty-ninth day.

(b) Experimental rabbit syphilis (*virus Truffi*).

Exp. 5.—Rabbit 926 D. Two scrotal nodules containing numerous spirochætes. Received 0.2 gm. per kilo soluble bistovol *per os*. Disappearance of the spirochætes on the second day. Progressive diminution of the lesions and almost complete cure by the eighth day. The animal was then killed in order to determine the virulence

of the scrotal nodules and the popliteal ganglia (see Chart VII.)

Exp. 6.—Rabbit 94 A. Extensive ulcerated scrotal lesions containing numerous motile spirochætes. Received 0.2 gm. per kilo *per os*. Disappearance of the spirochætes on the second day, progressive diminution of the lesions. The animal was killed on the fifth day and the virulence of the lesion and the popliteal ganglia determined.

The *general conclusion* to be drawn from these experiments, which could be supported by many others, is that soluble bistovol (soluble bismuth *p*-hydroxy-*m*-acetyl-amino-phenyl-arsinate) administered by the mouth is capable of producing a definite therapeutic effect, both in the spontaneous spirochætosis and experimental (*virus Truffi*) syphilis of the rabbit, but while in the first of these conditions this therapeutic action is followed by relapses

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at long intervals, in experimental syphilis (properly so-called), the cure is definite and complete.

This conclusion is drawn, not only from the observable results obtained by the application of this treatment to certain of our experimental syphilitic rabbits, but also, or rather above all, by the experimentally demonstrable, absolute sterility of the chancre nodules and the popliteal ganglia.

It is well known that the lymphatic glands of the popliteal junction, if removed from syphilitic rabbits, are almost constantly virulent. Inoculation of such into normal rabbits results in the production of nodules, rich in spirochætes after a period of incubation which may be somewhat lengthy (Truffi and Ossola (7), Truffi (8), Brown and Pearce (9), Kolle and his collaborators, etc.). Now the ganglia of the rabbits which were treated with soluble bistovol *per os* inoculated into the scrotum of normal rabbits have been found to be totally devoid of virulence. The same is to be said of those nodules which persist at the edge of the scrotum for some time after commencement of treatment (cf. the protocols given below).

Exp. 1.—The chancre nodule and the popliteal ganglia of *rabbit 916 D*, details of which have already been given (see p. 28), have been removed on the eighth day after treatment and inoculated into rabbits as follows:—

(a) Chancre nodule (free from spirochætes under ultra-microscopic examination). Inoculated into *rabbit 336 N*. No lesion appeared during the course of 121 days' observation.

(b) Popliteal ganglia. Inoculated into two rabbits.

338 N } No lesion after 121 days' observation.

344 N }

Exp. 2.—*Rabbit 94 A* killed on the fifth day after commencement of treatment.

(a) Chancre nodule (free from spirochætes when examined under the ultra-microscope). Inoculated into *rabbit 300 N*. No lesion after forty-eight days.

(b) Popliteal ganglia. Inoculated into two rabbits.

306 N. No lesion after 88 days' observation.

308 N. No lesion after 100 days' observation.

These experiments demonstrate that soluble bistovol, administered orally, acts not only on the external lesion of experimental syphilis, but also on the virus present in the popliteal lymphatic ganglia. Its sterilising action is

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not only superficial, but is far-reaching, and on this account the product may be considered to be of considerable therapeutic value.

Is the activity of bistovol administered *per os* dependent upon its being in solution ?

The following is typical of our experiments undertaken to determine this point :

Rabbit 100 D, with prepuccial lesions containing numerous spirochætes (*Sp. cuniculi*), received 0.22 gm. per kilo

of (insoluble) bistovol, suspended in a little isotonic saline administered orally.

The fæces became black, showing that the compound is dissociated in the intestine and that part of the bismuth so liberated is converted into the sulphide. The spirochætes disappeared on the fourth day, the lesions commenced to become pale on the second day, and complete and definite cure followed a short time afterwards (Chart VIII.).

This experiment proves that in the rabbit * it is not necessary that bistovol should be administered *per os* in the form of a solution in order to produce its therapeutic effect. The same result is obtained if it is administered in the insoluble form. The appearance of the fæces shows that on the surface of the intestinal mucosa, by the action

* The same is also true for the human subject (Fournier and Levaditi).

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of the digestive juices and of the intestinal flora, the product is dissociated into its two components, stovarsol and bismuth, the latter being converted into the dark-coloured sulphide before elimination in the fæces.

Is this elimination partial or complete? In other words, is some small proportion of the bismuth absorbed by the digestive tract, or is it entirely eliminated with the fæcal contents? That the arsinical portion of the product is absorbed, no one will doubt, knowing how readily stovarsol is absorbed when administered orally. Can the same be said of bismuth? Experiments undertaken with human patients in collaboration with M. L. Fournier and Mlle. Manin, give the answer in the affirmative.

Without going into the details of these experiments, which will be published elsewhere, in the urine of patients who had received repeated doses of bistovol *per os* either in soluble form or in tablet form, quantities of bismuth varying from 40 to 800 micrograms per litre per twenty-four hours have been detected.

One analysis has so far been carried out in the case of the rabbit. This was 925 *D*, which presented two large scrotal chancres with very numerous spirochætes, which was killed on the third day after the oral administration of 0.1 gm. per kilo of soluble bistovol. Spirochætes had then disappeared.

The following figures were obtained :—

Lung . . .	0 micrograms.
Kidney . . .	6 „
Liver . . .	2 „
Spleen . . .	0 „

In each case the figures refer to bismuth per gram of dried substance.

There can, therefore, be no room for doubt ; administered orally, either in the form of solution or as an insoluble powder, it matters not which, bismuth is absorbed from the product by the intestinal mucous membrane and can be detected either in the organs (kidney and liver) of the rabbit or in the urine in the case of the human subject.

To what extent and by what mechanism does this absorption take place? It is impossible for us to suggest an answer at the moment.

Whatever it may be, it can only be by reason of this

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assimilation of bismuth that the efficacy of the product when given by the mouth can be explained. In our opinion, the bismuth is associated with the arsinic of stovarsol in increasing the curative action. Stovarsol facilitates the absorption of bismuth through the digestive tract, and, on the other hand, the bismuth reinforces the stovarsol, rendering it more spirochæticidal in its action.

Conclusions.—From the experiments recorded above, it may be concluded that the bismuth salt of *p*-hydroxy-*m*-acetyl-amino-phenyl-arsinic acid (bistovol) administered in solution by intramuscular injection or in the form of solution or as a solid *per os* shows such strikingly therapeutic properties that its employment in the treatment of human syphilis is thoroughly justified.

III. BISMUTH ARSANILATE

Basic bismuth salt of *p*-amino-phenyl-arsinic acid.

Bi = 45.5 per cent.

As = 16.3 per cent.

Following the publication of our researches on bistovol, J. O. Shircore (10) effected the preparation of bismuth arsanilate and investigated the effects of this product in the treatment of syphilis and of yaws, the results of which were published in the *Lancet* of last year.

We have ourselves prepared and examined this compound with a view to studying its spirochæticidal properties in experimental syphilis. The results of some of our experiments are detailed below.

Bismuth arsanilate is a white amorphous powder, insoluble in water. For intramuscular injection, a 10 per cent. suspension of the powder in oil has been employed.

Exp. 1.—*Rabbit 597 D.* Prepuccial lesions. Numerous spirochætes (*Sp. cuniculi*). Received intramuscularly 0.1 gm. bismuth arsanilate in oil suspension. Disappearance of the spirochætes on the second day. Lesions cured by the same time. No relapse (Chart IX.).

Exp. 2.—*Rabbit 599 D.* Prepuccial lesions with numer-

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ous spirochætes (*Sp. cuniculi*). Received similarly 0.05 gm. bismuth arsanilate. Disappearance of spirochætes

Chart IX
Rabbit N° 597D Weight 2.900 gr.
Bismuth Arsanilate (oil suspension) 0,1 gr. per Kg. intramuscularly 5-X-26

and cure of the lesions by the fourth day. No relapse (Chart X.).

These experiments show that, in conformity with the

Chart X
Rabbit N° 599D Weight = 3.000 gr.
Bismuth Arsanilate (oil suspension) 0,05 gr. per Kg. intramuscularly 5-X-26

observations of Shircore on man, bismuth arsanilate given intramuscularly exhibits in the rabbit spirochæticidal properties at least equal to those of bistovol (Levaditi, loc. cit.).

We next experimented with a specially prepared 2 per

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cent. solution of bismuth arsanilate. The results obtained are detailed below :

Exp. 1.—Rabbit 131 Z. Prepucial lesions (*Sp. cuniculi*). Numerous spirochætes. Received by intramuscular injection 0.01 gm. per kilo bismuth arsanilate in solution. Disappearance of spirochætes after two days and healing of lesions after four days.

Exp. 2.—Rabbit 130 Z. As above. Received intramuscularly 0.05 gm. per kilo bismuth arsanilate in solution. No therapeutic effect.

Exp. 3.—Rabbit 192 Z. Slightly ulcerated scrotal nodule (*virus Truffi*). Spirochætes present. Received intramuscularly 0.01 gm. per kilo soluble bismuth

Chart XI
Rabbit N^o 192 Z Weight 2.500gr.
Soluble Bismuth Arsanilate 0.01gr. per Kg. intramuscularly 9-V-27

arsanilate. On the second day the scab became detached and the spirochætes disappeared. Lesion cured on the seventh day. Some loss of weight (Chart XI.).

It follows from these experiments, that soluble bismuth arsanilate when administered intramuscularly exerts a curative action in experimental syphilis and spontaneous spirochætosis of the rabbit. At the same time, its therapeutic action appears to be somewhat less than that of soluble bistovol.

To sum up, bismuth arsanilate is similar to bistovol so far as its anti-spirochætic action is concerned. Experiments carried out in cases of human syphilis in collaboration with MM. Fournier and Guénot, the results of which will shortly be published, confirm these experimental

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findings. Furthermore, they show that in addition to its curative effect, bismuth arsanilate possesses the advantage, when given in oily suspension, of being quite painless, and is consequently better tolerated than a similar preparation of bistovol.

IV. BISMUTH TRYPARSAMIDE

Basic bismuth salt of N-phenyl-glycinamide-arsinic acid.

Bi = 40.5 per cent. As = 14.5 per cent.

Bismuth tryparsamide is a white amorphous powder. It has been employed in the form of a 10 per cent. suspension in oil. Its curative action has been shown in the natural spirochætosis of the rabbit (*Sp. cuniculi*).

Rabbit 676 N. Prepucial lesions with numerous spirochætes (*Sp. cuniculi*). Received intramuscularly 0.1 gm. per kilo bismuth tryparsamide. The spirochætes disappeared on the second day, and the lesions were cured on the twelfth day.

The delay in the cicatrization of the spirochætal lesions seems to indicate that this product is less active than the two already mentioned, but further experiments are required to properly evaluate the therapeutic efficiency of the compound, which may possibly be of greater interest from the point of view of treatment of tertiary syphilis of the central nervous system, tabes and general paralysis.

Conclusion.—Since the preparation of the basic bismuth salt of *p*-hydroxy-*m*-acetylamino-phenyl-arsinic acid (Levaditi), other derivatives of the same series have been prepared, *e.g.*, bismuth arsanilate and bismuth tryparsamide. It has also been possible to prepare these products in a soluble form, and the activity of these products against experimental (*virus Truffi*) and natural spirochætosis of the rabbit (*Sp. cuniculi*) when administered either intramuscularly or *per os* has been determined. Of these, we would lay special stress on bismuth hydroxy-acetylamino-phenyl-arsinic acid (bismuth sto-

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varsol, bistovol) and bismuth arsanilate, which have been more completely examined.

(1) Basic bismuth hydroxy-acetylamino-phenyl-arsinic-acid (bistovol).

(a) Employed in 2 per cent. or 10 per cent. solution injected intramuscularly, this compound shows remarkable therapeutic action, the chemotherapeutic index being $\frac{C}{T} = 1/35$. The minimum effective dose contains only 0.00205 gm. bismuth and 0.00075 gm. arsinic. Its absorption is rapid and complete, its therapeutic activity equally so.

Administered orally, this compound, either in solution or in powder or tablet form, exerts its curative action in experimental syphilis (*virus Truffi*) or natural spirochætosis (*Sp. cuniculi*) of the rabbit.

Its sterilising action in the former case is very marked if we consider the negativisation of Meinicke's turbidity reaction and the sterility of the popliteal ganglia. These effects appear to be due to the simultaneous action of stovarsol and of bismuth, the latter being absorbed by the intestinal mucosa, if not completely, at least in appreciable quantity.

From these considerations, the employment of these derivatives in the treatment of human syphilis, either by intramuscular injection or by mouth, appears to be definitely indicated.

Bismuth Arsanilate.—Employed in suspension in oil by intramuscular injection, bismuth arsanilate shows a therapeutic efficiency equal to the compound mentioned above. It affords the advantage of being painless when injected into the human patient, which is not always the case with different preparations of bistovol.

These experimental findings have led us to try the products in human syphilis; the results obtained will shortly be published in collaboration with M. Fournier.

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REFERENCES.

- (1) LEVADITI. *C.R. de l'Acad. des Sciences*, 1925, **180**, p. 1971.
- (2) FOURNIER et SCHWARTZ. *C. R. de l'Acad. des Sciences*, 1925, **180**, p. 1973.

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- (3) LEVADITI. *Lancet*, 1926, i, p. 215.
- (4) LEVADITI and MANIN. *C. R. de la Soc. de Biol.*, 1927, **97**, p. 655.
- (5) MUTERMILCH et NICOLAU. *C. R. de la Société de Biologie*, 1925, **93**, p. 1497.
- (6) LEVADITI and NAVARRO Y. MARTIN. *C. R. de l'Acad. des Sciences*, 1922, **174**, pp. 893 and 1380; *Annales Pasteur*, 1922, **36**, p. 729.
- (7) OSSOLA. *Soc. Med. Pavese*, 1909, May 7th.
- (8) TRUFFI. *Pathologica*, 1913, No. **110**.
- (9) BROWN and PEARCE. *J. Exp. Med.*, 1922, **35**, p. 39; *Amer. Journ. Syphilis*, 1921, **5**, p. i.
- (10) SHIRCORE. *Lancet*, 1926, **ii**, p. 43.
- (11) LEVADITI. *Loc. cit.*