2. Tincture of Digitalis shows little variation in p_H whether stored in flint, blue or amber glass. The preparation tends to become more acidic upon standing.

3. Fluidextract of Cascara shows little variation in p_H whether stored in flint, blue or amber glass. The preparation tends to become slightly more acidic upon standing.

4. Elixir Glycerophosphates Comp., N. F. shows little variation in p_H whether stored in flint, blue or amber glass. It becomes discolored in flint or blue glass. The preparation tends to become slightly more acidic upon standing.

5. Elixir Iron, Quinine and Strychnine, N. F. becomes decidedly less acidic when stored in flint or blue glass which is accompanied by a marked deterioration of the elixir.

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THE THERAPEUTIC ACTIVITY OF NEOARSPHENAMINE.*

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Neoarsphenamine was first introduced by Ehrlich, the discoverer of its forerunner, arsphenamine. While arsphenamine was immediately recognized as an effective antisyphilitic there were certain objections to this preparation in practical use which were based on the necessity for dissolving it in a large volume of water and alkalinizing this solution before injecting it. This objection was overcome in neoarsphenamine by treating arsphenamine with sodium formaldehydesulphoxylate to obtain a product which was rapidly water soluble and which could be administered in much more concentrated solution without adjustment. This product, further, had the advantage of being less toxic than arsphenamine.

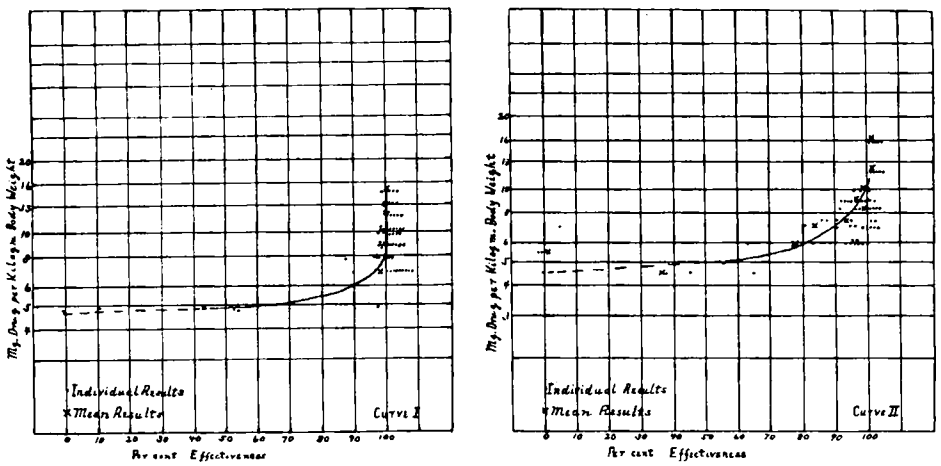
However, certain objections were also made to neoarsphenamine by some clinical workers treating syphilis; these being that neoarsphenamine was less efficacious therapeutically and more variable in its results than arsphenamine (1). This criticism was justified at least in part but it is proposed to present here the re-

* Scientific Section, A. PH. A., Rapid City meeting, 1929.

sults of an extensive research which has resulted in the manufacture on a large scale of a neoarsphenamine having therapeutic activity closely approaching that of arsphenamine when compared on an arsenic weight basis. (Neoarsphenamine has usually only two-thirds of the arsenic content of arsphenamine.) Also it is proposed to present some considerations concerning the relation between certain chemical, biological and physical characteristics of neoarsphenamine.

It has often been shown (2) that the activity of neoarsphenamine toward trypanosomes in animals is an excellent measure of its activity toward spirochetes in man. Consequently three different market brands of neoarsphenamine have been tested for trypanocidal activity toward *trypanosoma equiperdum* according to the method of Voegtlin and Miller (3) in Albino rats. The materials used represent a blend of three lots from one manufacturer, a blend of three lots from a second manufacturer, and three lots from a third manufacturer. These lots are designated by the letters A, B and C to indicate the different manufacturers and by numbers to indicate the different lots of each manufacturer. The materials were samples

Neoarsphenamine.—Curves I and II.



acquired on the open market or selected at random from stocks of routine plant production.

In order to clarify the data presented in the tables and curves it will be necessary to define certain terms used as follows.

Minimal Lethal Dose.—(M. L. D.) The lowest dose in milligrams per kilo required to kill 50% of the rats.

Minimal Effective Dose.—(M. E. D.) The lowest dose in milligrams per kilo required to reduce the trypanosome count in the blood to 4% of the original count.

Therapeutic Ratio.—Minimal Lethal Dose divided by the Minimal Effective Dose. Thus a high Therapeutic Index indicates high effectiveness in relation to dosage.

Minimal Sterilizing Dose.—(M. S. D.) The lowest dose in milligrams per kilo required to completely eliminate the trypanosomes from the blood.

Curative Ratio.—The Minimal Lethal Dose divided by the Minimal Sterilizing Dose.

In Table I the results of these studies are summarized, the data being taken from the tables from which the curves shown were plotted. The results are expressed both in terms of the milligrams of drug per kilogram used and milligrams of arsenic per kilo. The results obtained with neoarsphenamine are compared to those obtained with arsphenamine.

Neoarsphenamine.—Curves III, IV, V and VI.

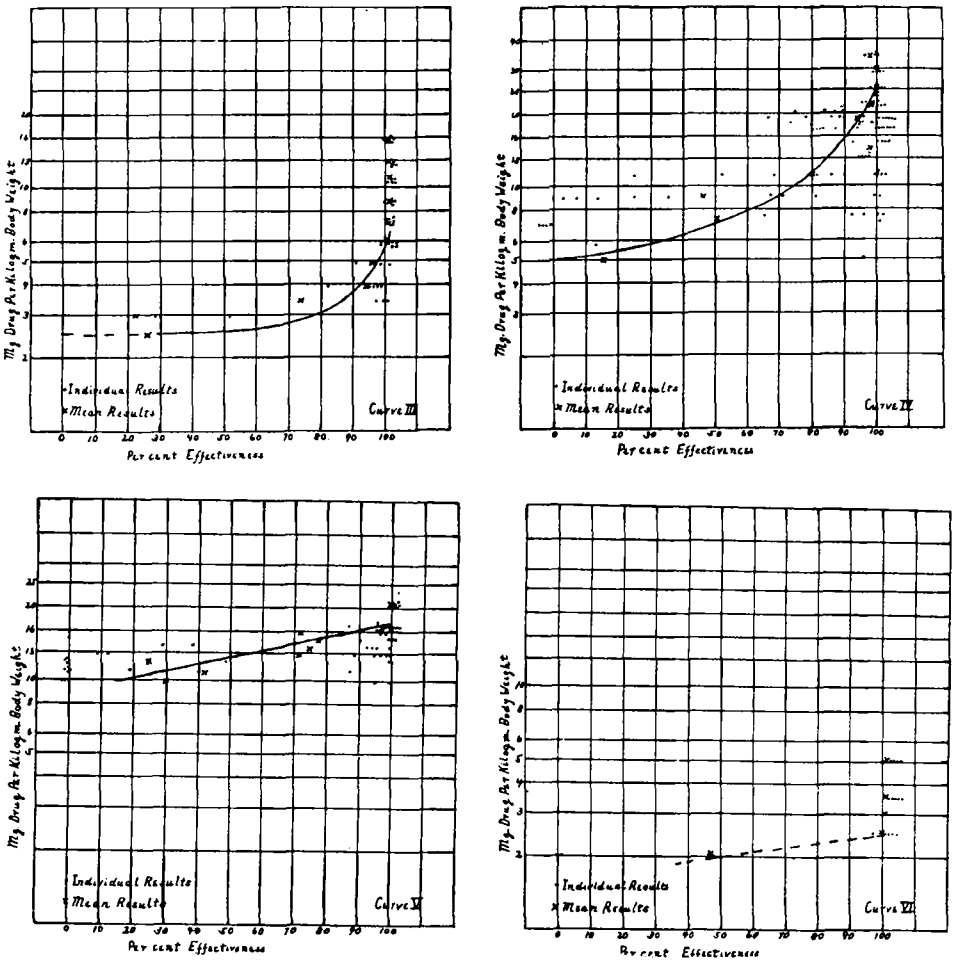


TABLE I.—SUMMARY OF RESULTS OF TRYPANOCIDAL ACTIVITY STUDIES ON NEOARSPHENAMINE.

Lot number.	Curve number.	Arsenic content in per cent.	Minimal Lethal Dose. Mg. drug per kilo.	Minimal Lethal Dose. Mg. arsenic per kilo.	Minimal Effective Dose. Mg drug per kilo.	Minimal Effective Dose. Mg. arsenic per kilo.	Therapeutic ratio M. L. D./M. E. D.
A-1	1	19.91	350	69.6	7.0	1.39	50
A-2	2	19.15	350	67.0	8.4	1.61	41.7
A-3	3	19.22	350	67.2	5.0	0.96	70.0
Average A type		19.42	350	68.0	6.8	1.32	51.5
B-1	4	20.68	425	87.9	21.0	4.34	20.2
C-1	5	20.68	300	62.1	16.5	3.41	18.15
606	6	30.19	220	66.4	2.5	0.75	88.0

These results show variations in therapeutic ratio from 18.15 to 70.0 for neoarsphenamines which are compared to a therapeutic ratio of 88 for arsphenamine. The products A-1, A-2 and A-3, made commercially according to a process developed in this laboratory, show an activity from 100% to 250% greater than any of the other lots studied, with an average therapeutic ratio two and one-half times that of the best of the other samples tested.

It is apparent that Lots A-1, A-2 and A-3 have an average therapeutic ratio much more closely approximating that of arsphenamine than the other samples. Also, if the Minimal Effective Dose of these preparations is compared to that of arsphenamine on the basis of milligrams of arsenic used per kilogram of body weight it is apparent that the Type A is the only one which approaches the low figure for arsphenamine, the arsenic dosage used being but 75% more than for arsphenamine, while Types B-1 and C-1 have Minimal Effective Doses on an arsenic basis greater than arsphenamine by 480% and 350%, respectively. Further, it is noteworthy that no preparation approached within 50 milligrams per kilo the toxicity standard of 240 milligrams per kilo set by the United States Public Health Service. The results further show that Type B while having a higher Minimal Lethal Dose than Type A by 75 milligrams per kilo has but 40% of the activity toward trypanosomes of Type A, whereas Type C has both a lower Minimal Lethal Dose than Type A by 50 milligrams per kilo and has less than 40% of its activity.

The results show that it has been possible to develop a commercial neoarsphenamine closely approaching arsphenamine in therapeutic efficacy and it is obvious from the foregoing results that a very distinct improvement has been obtained without high toxicity but rather with a low toxicity allowing an ample margin of safety for clinical use especially in view of the high therapeutic ratio of this product permitting the use of lower doses in the treatment of patients. Further, it is interesting to note that no relation exists between toxicity and therapeutic ratio since the least toxic and most toxic preparations, B-1 and C-1, have approximately the same therapeutic ratio whereas Type A, which is less toxic than Type C but more toxic than Type B, has a much higher therapeutic ratio than either of the other two types.

The curves given here show very clearly one further similarity between Type A neoarsphenamine and arsphenamine which is not shown by the others. Examination of Curves 1, 2 and 3 discloses that the results obtained on the various individual animals used in the tests at various doses lie in an area either on or very close to the curves, whereas in Curves 4 and 5 the results are widely scattered. This serves to emphasize the consistent results obtained with the three samples of Type A and the inconsistent results obtained with Types B and C. In fact the results obtained with Type A are more consistent than those obtained with the sample of arsphenamine used for comparison and serve once more to demonstrate the superiority in its biological reactions of Type A neoarsphenamine.

To further emphasize both the uniformity and effectiveness of the one type of neoarsphenamine as compared to the others and arsphenamine a further study is made of the results in the foregoing curves based not on the Minimal Effective Dose which calls for a 96% reduction in the trypanosome count in the blood but based on the Minimal Sterilizing Dose which calls for complete elimination of trypanosomes from the blood. The results are summarized in the following Table

II. All results are based on milligrams of arsenic per kilo of body weight to allow a more rigid comparison with arsphenamine.

TABLE II.—COMPARISON OF THERAPEUTIC RATIO AND CURATIVE RATIO.

Number.	Minimal effective dose from tables in mg. per kilo.	Estimated minimal sterilizing dose in mg. per kilo.	Therapeutic ratio M. L. D./M. E. D.	Curative ratio M. L. D./M. S. D.
A-1	1.39	3.19	50	21.9
A-2	1.61	3.07	41.7	21.9
A-3	0.96	3.08	70.0	21.9
Average Type A	1.32	3.11	51.5	21.9
B-1	4.34	6.0	20.2	14.61
C-1	3.41	More than 4.34	18.15	Less than 14.3
606	0.75	3.02	88.0	22.0

These results show that the arsenical in the form of neoarsphenamine of Type A required to free the blood of trypanosomes is uniform for the three lots within experimental error and but slightly different from that required in the form of arsphenamine. Furthermore, the amount of arsenical required to accomplish the same result in Types B and C is about double that for Type A or arsphenamine. The curative ratios of Types B and C are lower than for Type A, and Type A and arsphenamine have the same curative ratio within experimental error. The results emphasize once more the fact that neoarsphenamine can be made with a therapeutic efficacy closely approaching that of arsphenamine.

Having discussed the results of these studies on the toxicity and therapeutic efficacy of neoarsphenamine the relation between these results and certain chemical and physical characteristics of neoarsphenamine will be considered. For some time certain investigators have felt that there was a definite relation between the solubility, the chemical nature, the colloidal properties and the toxicity and therapeutic efficacy of neoarsphenamine. The results of previous studies on the chemistry of neoarsphenamine (4) when applied with these results show that there is no relation existing between the chemical composition and the solubility of neoarsphenamine since all the products described are of the so-called flash soluble type but differ widely in chemical composition. Further, there is obviously no relation between them in this latter respect but only the slightest detectable differences in solubility if any.

Preparations A-2 and A-3 show no significant chemical differences on analysis but they do show a marked difference in their therapeutic ratios, the therapeutic index of A-2 being 41.7 while that of A-3 is 70.0. This indicates that the chemical character of a preparation is not the sole controlling factor in determining its therapeutic activity but that its colloidal characteristics also are important. Freundlich, Stern and Zocker (5) have shown definitely that neoarsphenamine is partly colloidal in character although no evidence has yet been presented relating this fact to its therapeutic characteristics. Also, preparations B-1 and C-1 differ very widely in chemical composition but their trypanocidal activity is substantially the same, since B-1 has a therapeutic ratio of 20.2 while that of C-1 is 18.15. These results again show that the chemical nature of neoarsphenamine is not the principle factor determining its therapeutic activity.

To summarize the foregoing results, it is shown that a neoarsphenamine has been developed on a commercial scale which is less toxic than arsphenamine, only

slightly less active toward trypanosomes than arsphenamine, and as uniform in its activity toward trypanosomes as arsphenamine. It is further apparent that no relation between toxicity and therapeutic efficacy exists in neoarsphenamine; that its chemical composition is not closely related to the solubility of the product; that no relation between solubility and biological properties exists; and that although there appears to be a definite relation between chemical composition and trypanocidal activity this chemical factor is not the major controlling one in determining the trypanocidal activity of a preparation of neoarsphenamine. In conclusion the results show that a neoarsphenamine has been developed with a therapeutic index at least twice that of any other product so far tested.

The authors wish to express their thanks to Mr. H. A. Holaday and Mr. B. G. H. Thomas of the Biological Laboratories of E. R. Squibb & Sons for carrying out the trypanocidal activity tests which have been used as the basis for this paper.

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ABSTRACTS OF PAPERS READ BEFORE SCIENTIFIC SECTION, A. PH. A., RAPID CITY MEETING.

"The Rate of Oxygen Adsorption when Carstanjen's Compound Is Treated with Alkali Hydroxide," by A. A. Harwood and Edward Kremers.

When potassium sulphite and thymoquinone react di-hydroxycymene sulphonate of potassium, Carstanjen's compound is formed. KOH converts this to tri-hydroxy-cymene as may be expected. The rate at which this compound adsorbs oxygen is studied.

"The Inorganic Constituents of Echinancea," by S. H. Culter and Edward Kremers.

Large amount of potassium found in ash.

"The Heats of Formation of the Alcoholates of Chloral," by S. Chechik and Edward Kremers.

Heats of formation of series of hemiacetals made by reaction molecular amounts anhydrous chloral and alcohols of the methyl alcohol series determined.

"Cinnamal-hydroxy Sulphonates of the Alkali Metals," by S. S. Chao and Edward Kremers.

Heats of formation of Lithum, Sodium and Potassium cinnamal-hydroxy sulphonates determined. Also reaction with iodine.

"The antiseptic Action of U. S. P. and N. F. Ointments," by George F. Reddish.

A number of ointments were tested for bacteriostatic power by streaking on the surface of serum agar inoculated with Staph. aureus. Antiseptic action is indicated by a clear zone surrounding the streaked ointment, the remainder of the plate being turbid with the colonies of the test organism. Only about one-half of the U. S. P. and N. F. ointments are antiseptic, by this test.

"Methylene Blue, U. S. P. as Precipitant of Irish Moss," by George E. Éwe.

Experiments on nature of precipitation conducted.

"The Preparation of Cyclopropane," by W. A. Lott and W. G. Christiansen.

Modification of Gustavson's method developed which gives good yields of pure trimethylene free from isomeric propylene. Pure trimethylene gas has high anesthetic potency but its toxicity makes it dangerous for use.

"Transparent Life," by Arno Viehoever.

Heart beats and other body functions may readily be observed and counted in transparent forms of plant and animal life.