RECENT INVESTIGATIONS ON ANTILUETIC DRUGS.*

BY H. B. CORBITT AND C. N. MYERS.

Constitution and physiologic action are the two important factors which determine the partition coefficient of a drug in its distribution in the tissues and in the body fluids. A third and very important factor deals with the physical structure of the drug in its solid phase, its solution phase, and finally in its combining action in the biological medium. In other words, drugs possess an organotropic and a parasitotropic action, and the ratio between these two factors determines an index which renders a decision as to whether or not the drug is safe for therapeutic use—a favorable proportion of organotropy and parasitotropy.

On this basis the Ehrlich chemoceptor and side chain theory still find application in the present use of drugs.

At this time it is only possible to discuss briefly the antiluetic drugs now available. To preface these remarks it should be stated that arsenic in some form should be synergized by means of mercury. At present, no single drug is at our disposal which will dispense with the other. Intramuscular injection of mercury finds preference in the hands of the largest dispensers of this drug. Physiologically it seems preferable to use the soluble form of mercury prepared in a suitable manner to eliminate pain to the greatest degree. The salicylate and the benzoate find application in the hands of those who prefer the insoluble salts of mercury.

The work of Cole is significant in pointing out the failure of absorption in some instances. The other mercurials have been adequately discussed in the *Journal of the American Medical Association* and contain the consensus of those skilled in their therapeutic application. There has been no outstanding therapeutic work in mercurials beyond that of the above author.

At the present time bismuth is receiving considerable attention among foreign syphilologists and many very satisfactory reports have appeared, darkened by the usual bismuth forms of acute intoxication such as convulsions, dyspnea, and bradycardia; the chronic type showing diarrhoea, lassitude, albuminuria, and ulcerative stomatitis.

Bismuth preparations may probably find a place in antiluetic therapy, replacing mercury in some instances where the patient has shown a Wassermann fastness or possibly an intolerance to mercury medication. Bismuth has the advantage of possessing both acid and basic properties thereby adapting it to cases where there is need of an amphoteric condition.

There are three distinct types of bismuth compounds available. Bismuth quinine iodide, bismuth oxybenzoate, and the alkali salts of tartrobismuthate comprise the group now being utilized. The literature on this subject has been very comprehensively reviewed by us in the *American Journal of Syphilis*, April 1923.

Bismuth is entirely too toxic for intravenous use, and finds application only in intramuscular therapy. Oily suspensions of the soluble and the insoluble tar-

* Read before the Scientific Section, American Pharmaceutical Association meeting at Asheville, N. C., Sept. 3 to 8, 1923.

trobismuthates have been used, but in most instances they have been accompanied by considerable pain.

Bismuth alone like mercury shows practically no trypanocidal activity in sublethal doses, as pointed out by Myers and Corbitt (1923).

In the field of arsenicals a much greater variety of research has been carried out. Ehrlich "606," Salvarsan, or, in official terms, arsphenamine, without doubt continues to be the most potent drug in the series with the exception of the silver salt. To this group has been added a variety of neoarsphenamines differing from the original in physical, chemical and therapeutic characteristics.

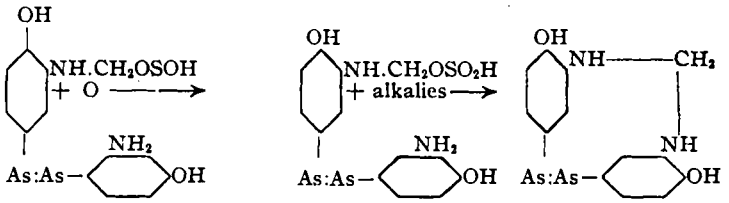
In 1913, Bertheim, in his excellent monograph on arsenic compounds, pointed out the essential features in preparing the large series of arsenicals which had been accurately described in the scientific and patent literature found mainly in the *Berichte der deutschen chemischen Gesellschaft.*

There remain two types of arsphenamine available ranging from a hot water soluble product to one readily soluble in cold water. It should be distinctly pointed out that the method of preparation of the solution is not interchangeable and under no circumstances is it advisable to alkalinize the solutions while they are warm on account of the tendency toward increased toxicity. Lake of the Hygienic Laboratory has shown conclusively that the toxicity of arsphenamine is decreased by allowing the solution to stand 15–20 minutes after the alkali has been added to the solution. This feature finds clinical application in reducing the table reactions on account of the formation of a more ideal solution.

In the next group are found the heterogeneous neoarsphenamines. Bertheim (1913) first pointed out these possibilities from a chemical point of view, indicating that a normal mono-methylene sulphoxylate and a normal di-methylene sulphoxylate compound could be formed as a result of the condensation of salvarsan and sodium formaldehyde sulphoxylate. No extensive clinical and therapeutic comparisons were made, thereby leaving the devious way open for a series of mixed compounds although the original patent calls for the production of the mono-substituted product.

As to the arsenic content of the neoarsphenamines, theoretically the mono-substituted product should contain 32.1 per cent. arsenic, whereas the di-substituted product contains 26.4 per cent. arsenic. During the condensation of the dihydrochloride of dioxy-diaminoarsenobenzene with sodium formaldehyde sulphoxylate considerable quantities of physiologically inert, inorganic salts are formed. When this solution is precipitated by means of alcohol, ether, or acetone, some of the physiologically inert, inorganic impurities are precipitated simultaneously with the neoarsphenamine. The presence of these products tends to lower the arsenic content without disturbing the pharmacodynamic arsenic which is present. It is quite absurd to indulge in some of the commercial subtleties employed to suggest a purification of the product or produce one of high arsenic content.

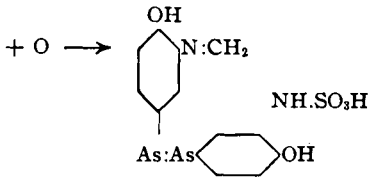
Attention was first called to the mono- and di-substitution products of neoarsphenamine by Macallum (1920) who pointed out that the original Ehrlich "914" was a mono-substitution product. The observation of this author in its relation to sulpharsphenamine is so pertinent that the formulas are here reproduced.



Dihydroxy-diamino-arseno-benzene-N-monomethylene sulphoxylic acid

-methylene sulphurous acid

-methylene compound



Corresponding sulphamic acid

Dale (1922) considering the problem toxicologically and clinically took up this matter for the British Medical Research Committee and stated that the composition of Neo-compounds of English origin differed so widely from various manufacturers that there was need of control and he describes the situation as follows:

TWO DISTINCT CLASSES OF NEOSALVARSAN TYPE.

"A short experience with the application of this test sufficed to indicate that the preparations of the neosalvarsan type submitted for test fell into two well-marked classes. On the one hand were those which resembled the German product more or less closely in appearance, in solubility, and in the rapidity with which their solutions underwent decomposition if left standing exposed to the air. On the other hand, there were others which had an advantage over the German product in their extremely free and rapid solubility, and which gave evidence of much greater stability in solution. Preparations of the former class had a border-line toxicity from the point of view of the test; many samples just passed it, and many others failed. A slight raising of the standard would have excluded nearly all. Those of the latter class—the freely and immediately soluble type—passed the routine test with an almost unbroken regularity; when, experimentally, sample batches of this type were tested on higher doses, it was found that many were tolerated in a dose of 0.5 mg., some even in a dose of 0.6 mg. per Gm.; *i. e.*, the toxicity was often only one-half of that at which they would still have passed the official control.

"No question of a control of therapeutic efficacy arose at this time. It would have been impossible, in any case, to carry it out with the staff available under war conditions. From the clinical side there was no hint of dissatisfaction; here again, in the hurry to get men through their treatment and return them to duty, no adequate control of results was possible. The practitioner appreciated the additional convenience afforded by rapid and perfect solubility, and the freedom from constitutional reactions, even when highly concentrated solutions were injected. The demand for the more soluble and less toxic type of product grew very rapidly, until manufacturers whose endeavor had been rather to copy the German product found themselves forced to modify their process, so as to produce a more soluble type. Therewith the toxicity of their products fell likewise to the lower level. When, under peace-time conditions, it became possible to follow more thoroughly the effects of treatment, it was reported from several sources to the Salvarsan Committee (appointed meanwhile by the Medical Research Council) that the curative action of the 914 products in use, which by that time had almost entirely conformed to the more soluble and stable type, was under serious suspicion of being inadequate. An investigation was therefore undertaken by those charged by the Medical Research Council with the duty of testing these

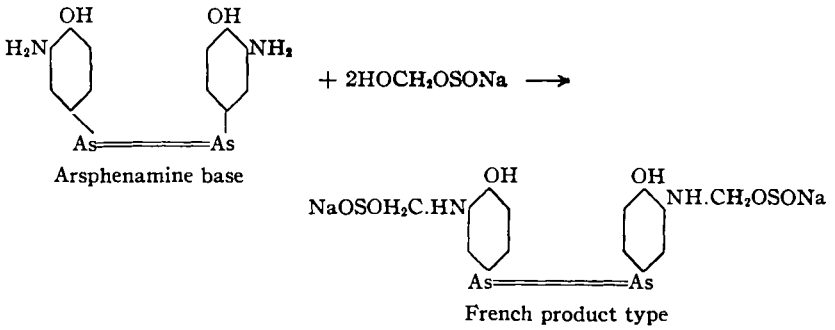
remedies. They were able to use, with slight modifications, the method, then recently recommended by American workers, of evaluating the therapeutic power on mice infected with a strain of trypanosomes. They found indications of a pronounced inferiority in therapeutic action of the 914 products of this country, as compared with the original German product, or with the former output of some British manufacturers. The facts were fully presented to the manufacturers concerned; the latter, with their experience, were then able to produce preparations which, while retaining some of the advantages of rapid solubility, showed as good therapeutic qualities as the German preparation, according to the experimental indication, and still satisfied the official control as regards toxicity. There are the British products of the 914 type which are now being supplied.

THE NEED FOR OFFICIAL CONTROL OF PRODUCTS OF THE 914 TYPE.

"The result of this investigation made obvious the desirability of imposing, if possible, an official control of products of the 914 type for therapeutic potency, in addition to the existing one for absence of abnormal toxicity. The existence of the latter alone in the case of a substance of ill-defined composition, such as 914, tempted the manufacturer to secure a smooth passage for his product, by slight changes in the process, which gave it regularly a lower toxicity than that which the test allowed. It was clearly desirable to make certain that, in so doing, he was not weakening its therapeutic action. Before steps in this direction could be considered, however, it was necessary to ascertain whether the difference in efficacy of different samples in removing trypanosomes from the peripheral circulation in mice corresponded with a clearly recognizable difference in their efficacy in removing the spironemes from syphilitic lesions in the human patient. The following sections of this paper describe the details of the investigation, in which the same representative samples of the different types of product were compared both experimentally and clinically. It will be seen that, so far as the clinical observations permit conclusions as to relative therapeutic efficacy in syphilis, the results of the clinical trial are in full accord with the experimental estimates."

These laboratory tests were put in routine use in the Medical Research Council's Department of Biological Standards at Hampstead.

Following this report a second article appeared by Macallum (1922) comparing the American neoarsphenamines with those of French origin which consists entirely of doubly substituted arsphenamines illustrated by the following formulas.



These same observations of chemical constitution have been made by Elvove (1922), and Raiziss (1921).

According to Government regulation the arsenic content must be between 30 and 32 per cent. for arsphenamine, and 18 to 20 per cent. for neoarsphenamine. It has been suggested from official sources that the minimum arsenic content of all products is to be increased. Likewise the application of a therapeutic test should be advocated by those who are desirous of giving the patient a truly active product.

This is substantiated by the work of Dale, Macallum, the U. S. Public Health Service and by the therapeutic tests of our own laboratories. As pointed out above

Drug.	Dose mg. per Kg.	No. of organisms per cu. mm. before treatment.	No. of organisms per cu. mm. 24 hrs. after treatment
	12	76,000	2000
	12	104,000	1500
	18	88,000	0
	18	82,000	0
Neoarsphenamine	27	68,000	0
	27	116,000	0
	40.5	74,000	0
	40.5	76,000	0
	60	72,000	0
	60	104,000	0
	12	82,000	8000
	18	102,000	250
	18	92,000	1500
	27	74,000	4000
Sulpharsphenamine	27	64,000	0
	40.5	60,000	0
	40.5	146,000	0
	60	106,000	0
	60	80,000	0
	12	108,000	256000
	18	96,000	6000
	18	106,000	10000
	27	118,000	4000
Sulpharsphenamine 154	27	60,000	0
	40.5	134,000	0
	40.5	92,000	0
	60	98,000	0
	60	106,000	0
	12	78,000	208,000
	18	98,000	14,000
	18	104,000	4000
	27	102,000	6000
Sulpharsphenamine N. U.	27	126,000	3000
	40.5	114,000	0
	40.5	88,000	0
	60	108,000	0
	60	94,000	0
	12	82,000	25,000
	18	80,000	14,000
	18	108,000	4000
	27	116,000	2000
Sulpharsphenamine L-121	27	126,000	0
	40.5	104,000	0
	40.5	86,000	0
	60	70,000	0
	60	120,000	0

these products are usually the di-substituted N-methylene sulphoxylate compounds or those oxidized to the next higher stage as illustrated by sulpharsphenamine.

Therapeutically sulpharsphenamine is less active than neoarsphenamine. Commercial products from the open market gave the accompanying trypanocidal tests when examined according to the methods of the U. S. Public Health Service.

From the figures on the preceding page it is observed that sulpharsphenamine is *two* and a *half* times less efficient than an average grade of neoarsphenamine but may be equally efficient therapeutically to a low-grade neoarsphenamine of the di-substituted class. (Lake, 1923.)

Neutral neosalvarsan may be used equally as well for intramuscular injections. This type of therapy has been utilized for more than three years by several leading syphilologists in the treatment of congenital lues in babies without the appearance of a single necrotic area on the buttock.

Silver arsphenamine has already taken its place among the antiluetic drugs that have proved their value in therapy. It finds its most valued application in cases where primary and secondary lesions are to be cleared up rapidly and also in that type of neurosyphilitics where a drug free from reactions is desired together with a high active arsenic penetrability into neural tissues.

It is *not* the *quantity* of arsenic which penetrates into the central nervous system but it is the *quality* (parasitotropic) and the *availability* at the site of the neural lesion which is to be considered the important factor.

Toxicologically it is rather difficult to produce any of the arsenical series that will not pass the present standards when men skilled in the handling of arsenic are engaged in the manufacturing process. The authors of this paper have been unable to find any arsphenamine or neoarsphenamine which is still in good condition that has ever been made either during the war or since the war that will not pass the present toxicity standards when normal, healthy, standardized rats are used. Myers and Corbitt elsewhere have shown that regulation of the inorganic salt content, principally the calcium, and amino acids are the chief factors in getting rats of this type. The composition of this diet is described in the *American Journal of Syphilis*, April 1923. Rats fed on ground wheat and corn, calcium carbonate, sodium chloride, milk powder, and cod-liver oil show a normal growth curve and a uniform resistance to the toxic effects of the drugs.

In other words all our rats are standardized by growth curves and it has been ascertained by these methods that salvarsan will pass according to the Government methods at 200 mg. per Kg., neosalsarvan at 380–420 mg. per Kg., sulpharsphenamine at 600–800 mg. per Kg., and silversalvarsan at 180–200 mg. per Kg.

From a toxicological point of view products in hermetically sealed ampules need not be kept in ice boxes. Products which have been carefully prepared do not deteriorate at least during a period of three years. The data on these points are to be found in other publications by us and are too comprehensive to include in this article. Preservation of the ampuls on cool, dark shelves will suffice.

The physical condition of the blood stream of the animals is made more uniform by regulating its composition so that colloidclasia is avoided, as well as giving a uniform resistance to the tissues of the animal. Animals with pathologic con-

ditions of the lungs and the liver occasionally may escape notice even under these circumstances. If at any time the death of an animal takes place immediately in the case of arsphenamine administration or in a few hours after the injection of the neoarsphenamine group, the animals in this group should be submitted to careful examination for liver or lung lesions which are magnified by means of arsenic intoxication.

As a result of these experiments, studies on man have been carried out by one of us (M.) and it has been shown that about 60 per cent. of the arsenic leaves the blood stream within the first five minutes. Unusual retention leads to such symptoms as jaundice, *dermatitis exfoliativa*, and gastro-intestinal disturbances. Briefly speaking investigation of antiluetic drugs has largely been directed toward the patient and his tolerance. All of the arsenic drugs are safe enough but unfortunately unusual variations in the efficacy of these products have often made it difficult to hold patients to a proper course of procedure in therapeutic application. Experimental data in practically every instance have been substantiated and closely paralleled in the clinical uses of these products.

To this may be added the words of a well-known old pharmacologist, Friedrich Wilhelm Vogt, who says:

"Arsenic has the common lot of all powerful drugs, that it is now praised, now blamed, and as its dynamic efficacy on the organism cannot easily be reached by any drug, and still less surpassed, one cannot be surprised that it is descried, especially by those physicians who fight shy of all power in a drug, while it is always appropriately esteemed by those who understand how to make use of such an important power. That arsenic was the most terrible poison under all circumstances was the general opinion of the former, and they expressed this without considering that no absolute poison could exist, and that it is precisely these poisons which are our most powerful weapons. Therefore, if any one wishes to realize the curative power of arsenic, then he must adhere solely to what observation of the healthy and diseased organism has taught us, and must entirely forget all the statements made by important men from a preconceived idea."

"As a result of this importance of arsenic, the necessity and endeavor arose, long years ago, to find arsenical derivatives which should be free from the toxic secondary effects and yet be able to obtain their entire pharmaco-dynamic action. The first important stage in this direction is indicated by the introduction of cacodylic acid and its salts, a further one by the discovery and application of atoxyl, the curative action of which in sleeping sickness has been tested first, by means of experiments on animals, and then in different directions has been confirmed on human beings, especially by Robert Koch. Unfortunately, it has also been shown that secondary effects of an undesirable kind (amauroses) are attached to this very effective preparation. Even if, in such a serious disease as sleeping sickness, the value of atoxyl preponderates, and therefore its employment appears to be indicated, this does not apply in the usual forms of syphilis (Uhlenhuth, Salmon), in which this drug should only be used with the greatest hesitation."

BIBLIOGRAPHY.

A. Bertheim.—1913. "Handbuch der Organischen Arsenverbindungen." Verlag von Ferdinand Enke. Stuttgart.

H. N. Cole.—1920. "A Study of Mercury Injections by Roentgen Ray," *J. A. M. A.*, Vol. 74, p. 1559.

H. H. Dale.—1922. "Experimental and Clinical Comparison of the Therapeutic Properties of Neosalvarsan," *The Lancet*, April 1922.

Elias Elvove.—1922. "Estimation of Sulphur in Neoarsphenamine," *J. Ind. and Eng. Chem.*, Vol. 14, No. 7, p. 624.

G. C. Lake.—1921. "Certain Factors Connected with the Toxicological Testing of Arsphenamine," *Am. J. Syphilis*, Vol. 5, p. 86.

G. C. Lake.—1923. "Parasiticidal Values of Arsphenamine and Neoarsphenamine in 'Arsenic Fast' Strains of Trypanosome," U. S. P. H. S., No. 24, Vol. 38, June 15, 1923, p. 1347.

A. Douglas Macallum.—1920. "Examination of Neoarsphenamine," *J. Am. Chem. Soc.*, Vol. 43, No. 3, p. 643.

1922. "Examination of Neoarsphenamine. II. The Constitution of the French Drugs," *J. Am. Chem. Soc.*, Vol. 44, No. 11, p. 2578.

C. N. Myers, and H. B. Corbitt.—1923. "Toxicity and Trypanocidal Activity of Tartro-Bismuthate and Its Relation to the Treatment of Syphilis," *Am. J. Syphilis*, Vol. 7, No. 2, p. 352.

G. W. Raiziss and M. Falkov.—1921. "The Chemistry of Neoarsphenamine and Its Relation to Toxicity," *J. Biol. Chem.*, Vol. 46, p. 209.

RESEARCH DIVISION,
H. A. METZ LABORATORIES, INC.
NEW YORK, N. Y.

STUDIES IN THE GENUS MENTHA.*,†

XII. *Mentha piperita*, L. (Peppermint) as a Subject for Biochemical Research.

BY F. J. BACON, G. C. JENISON, AND R. E. KREMERS.‡

Students familiar with the range and variety of phenomena coming under the observation of pharmacists have often remarked upon the ignorance or indifference of other scientists to the possibilities for research upon these phenomena. To sketch the development of problems connected with a pharmacopœial substance into researches of very general interest is the object of this paper. The U. S. P. oil of peppermint, which was the original object of study, is not a natural oil, but one rectified to conform to certain standards. Since the peppermint industry is one of the largest in this country producing an essential oil, the problems connected with the growing plant as well as with the distillation of the oil are of obvious importance.

In order to become more familiar with this industry, the Wisconsin Pharmaceutical Experiment Station has been growing peppermint on a semi-commercial scale. The chemical studies at first concerned the recovery and identification of the compounds remaining in the aqueous distillate.[1,2] In 1921 acetone and methyl-I cyclohexanone-3 were found in these materials.[3] These substances result from the hydrolysis of pulegone, which in its turn was sought and found.[4] It was also observed that another mint, imported as a Japanese peppermint and growing in an adjacent field, was producing pulegone instead of menthol. These results at once suggested the existence of a common fundamental metabolism for oil production and offered a possibility for experimental investigation of the idea.

The further study of this proposition soon revealed that botanists consider

---

* Scientific Section, Asheville meeting, 1923.

† Contribution from the Wisconsin Pharmaceutical Experiment Station, Madison.

‡ Holders, respectively, of the A. M. Todd Co. Fellowship, the Fritzsche Bros. Co. Fellowship, and a National Research Council Fellowship in Chemistry, at the University of Wisconsin.

[1] E. R. Miller, *Bull. U. W., Circ.* 9, Feb. 1920.

[2] R. E. Kremers, *Ibid., Circ.* II, Oct. 1920.

[3] R. E. Kremers, JOUR. A. PH. A., 10, 834, 1921.

[4] R. E. Kremers, *Jour. Biol. Chem.*, 52, 443, 1922.