flame. Place it in the sunshine with a white screen close behind it and the zone casts a shadow upon the paper. Hold a line of print or a black horizontal line behind it and the line is effectually removed. Place the tube in an upright slit in a pasteboard box or before the pinhole in the dark room, and reflect a ray of sunshine against it by a mirror parallel with the surfaces of liquid contacts. The zone of division casts a dark band shadow.

This band with glycerin and acetone is of perceptible thickness and seemingly must be a stabilized medium of different refractive power from either of the adjacent solutions, intercepting some of the rays of light, torturing others. There seem at the zone of disturbance to be several solutions (mixtures) in unequal tensions, balanced in the aggregate, through which the struggling ray of light cannot pass directly. Such are the appearances of glycerin with acetone (Fig. 38) or acetic ether (Fig. 39) or sulphuric ether (Fig. 40). It is impossible for a ray of light to penetrate these gray refractive mediums and locate an anterior object either in exact outline or in substance correctly.

Fig. 38. Acetone on glycerin.

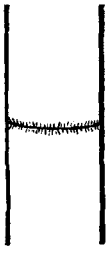


Fig. 39. Glycerin and acetic ether.

Fig. 40. Glycerin and sulphuric ether.

Reverting now to other liquids as well as those we have already considered, and examining them with the foregoing phenomenon in mind, now that the fact is mentally located, we often find a like disturbance (more or less prominently) exhibiting itself above or below the plane, even though the surface contacts may appear brilliant.

It will be observed in these instances that near the point of liquid contact there seems to be a swell as if the glass of the tube were here of uneven thickness. Whatever may be the cause of the phenomenon, its effect is to prevent the true line of liquid separation, as well as the precise curve of the meniscus between such liquids, from being accurately located.

Invisible Zones.

And, that perfectly invisible zones may be located about the contact surface of liquids of different densities at equilibrium or rest, may be exemplified as follows: Make a mixture of glycerin and acetone.

ARSENIC THERAPY.*

BY HOMER W. SMITH.

Mingo Park has said that Africa was fatal but fascinating. The same may be said of arsenic, for it has fascinated mankind since ancient days, and as to its being fatal—history is replete with evidence.

Hippocrates, the father of medicine, used regular (As_2S_2) and orpiment (As_2S_3) as an outside remedy for ulcers and similar ailments, according to Sharp,[1] who has written some interesting notes on the history of arsenic. It was known to the Romans and the Egyptians and played a large part in the endeavors of the latter

* Presented before the Indianapolis Branch, American Pharmaceutical Association, March 21, 1922.

to effect the transmutation of elements. The Jews are said to have carried the knowledge of arsenic into Europe when they fled there after the Arabs drove them out of Egypt. Schabir, an Arabian chemist who lived in the eighth century, was the first to roast realgar and obtain white arsenic (As_2O_3), which he so named to distinguish it from the yellow sulphide. His knowledge became widely diffused and a new era opened in the history of this metal and its salts. Schabir has much to answer for, because the introduction of a soluble, tasteless and odorless poison put a new instrument in the hands of the poisoner—an instrument much needed in the dark days of the middle ages. Previous to the introduction of white arsenic all poisons hitherto known and employed possessed something of taste, smell or color. Here was something altogether negative—just what was desired—and in addition, incapable of being detected by any known methods.

Poisoning by arsenic was not carried out extensively, however, until the fifteenth century. It was first effectively used, it seems, by the Borgias, Caesar and his sister Lucretia, about 1500, who poisoned or caused to be poisoned so many of their opponents that they attained an evil reputation even in their day. Men came to believe anything of it—that it could be used to kill its victim in an hour, day, month or year—an alleged advantage in which there is no little truth. Various arsenic powders and liquors received enduring names, and its use spread ultimately from Italy to France where it became a very influential political weapon. During the reign of Louis XIV (1638–1715) the practice of poisoning became so widespread that he set aside a *Chambre des Poisons* in which to try, and a *Chambre Ardente* in which to burn, convicted poisoners. The practice became a fine art, and persisted in France for a hundred years.

There are many accidental deaths on record due to food or beer contaminated with arsenic, and not a few of the pioneer chemists working in recent years on the separation or preparation of arsenic derivatives have come to harm through ignorance of its poisonous qualities.

It is not known who first reasoned that there might be something of good in this powerful poison and who daringly experimented with it as a therapeutic agent. About the middle of the eighteenth century there appeared on the market an alleged specific remedy called "Tasteless Ague and Fever Drops." In 1786 a London physician, by the name of Thomas Fowler, was led to investigate these "Ague Drops" and to formulate a solution which he considered to be a satisfactory imitation. This is called Fowler's solution to this day. This solution was recognized by the London Pharmacopoeia in 1809, and was extensively used in fevers, St. Vitus' Dance, chronic affections and pernicious anemia.

Moderate amounts of arsenic in any form appear to have a remarkably stimulating effect, leading to increased appetite, an increase in red-blood corpuscles, a gain in weight and a feeling of well-being. You have no doubt heard of the inhabitants of Upper Styria who through the continued ingestion of arsenic acquire a great tolerance for it. It is said that these Styrians possess remarkable physique and vitality as the result of its use, but the good effects are offset by ultimate injury and premature loss of these superlative benefits.

All organic compounds of arsenic are synthetic, with the exception of diethylarsine which is formed by certain moulds growing in the presence of arsenic. The first synthesis of organic arsenic is accredited by Morgan[2] to the French chemist,

Cadet, who, in 1760, separated arsenic from the mineral smaltite, or cobalt arsenide. Cadet's interest lay chiefly in the preparation of cobalt for the purposes of making "sympathetic" ink, but as a secondary matter he was led to experiment on the arsenious oxide which was a by-product from his invisible-ink manufacture. He heated together in a distillation flask arsenious oxide and potassium acetate and obtained in the distillate two liquids: a lighter fraction consisting, as Bunsen was later to show, of an acetone solution of the highly inflammable dimethylarsine (or cacodyl) and arsenious acid, and of a heavier liquid of dimethyl arsenious oxide. The latter possessed a remarkable stench resembling garlic, so unpleasant that Berzelius was led to name the parent substance, dimethylarsine, *cacodyl*, from the Greek for "foul odor."

Cadet's memoirs on this subject led to a detailed investigation by Bunsen in 1843, and they form the beginnings of what is to-day a very extensive field of the organic reactions of arsenic and the closely related element antimony.

The aliphatic group of compounds derived from dimethylarsine have not proved to be very important from a medicinal point of view, however, and I will therefore give them only slight attention here.

The synthesis of aromatic arsenicals was carried on for many years in the preparation of the dye magenta without knowledge of the discrete chemical processes involved. Magenta and other allied dyes are prepared by heating arsenious oxide and anilin together. In 1860 this process was made the subject of an investigation by Béchamp who noted that a mixture of anilin and arsenic acid does not give rise to colored products until a fairly high temperature (190–200°) is reached. At intermediate temperatures colorless products are formed, and it was in these colorless products that Béchamp was particularly interested. His investigations led him to conclude that the colorless product, which was afterward named atoxyl, was an acidic anilide ($C_6H_5NHAsO(OH)_2$) and so it was regarded until 1907 when Ehrlich and Bertheim demonstrated its true constitution. The latter investigators showed that at moderate temperatures the anilin arsenite undergoes a molecular rearrangement, the arsenic entering the ring in the para-position, giving rise to para-aminophenylarsenious acid.

I have already said that the use of inorganic arsenic dates back many centuries. The less poisonous organic combination, atoxyl, was first used in general therapy by Schild, Blumenthal and others in 1902. Shortly afterward Thomas and Breinl introduced atoxyl in the treatment of trypanosomiasis, or sleeping sickness. It also found use in the treatment of other tropical fevers, nervous disorders and anemia.

The specific causative agent of syphilis, the *Spirocheta pallida*, was discovered by Schaudin and Hoffman in 1905. On the strength of Schaudin's statement regarding the close biologic relationship between the spirochetes of syphilis and trypanosomes, Uhlenhuth was led to employ atoxyl in the treatment of experimental spirilosis in fowls, and, subsequently, in the treatment of human syphilis. Up to this time, syphilis had been treated by mercury and iodine. Though possessing a beneficial influence, atoxyl soon came into disfavor for human administration because of the digestive disturbances, nephritis and especially the impairment of vision which could be traced directly to its use.

It was then (1907) that Ehrlich and Bertheim made the discovery of the true chemical constitution of atoxyl, a discovery which indirectly led Ehrlich into the search for arsenic compounds possessing more powerful parasitocidal properties but lacking in the disadvantages of atoxyl.

The investigations of Ehrlich and his co-workers are too extensive to receive more than brief mention in this sketch. Attention was drawn to organic arsenic by the fact that it was much less poisonous than inorganic arsenic, it being possible to give forty to fifty times as much arsenic in the organic as in the inorganic form. It was from this low toxicity, in fact, that the compound atoxyl derived its name. Ehrlich, who had had exemplary training and experience in organic chemistry and who had long been interested in the behavior of living and dead cells toward various dyes, became interested in the use of dyes, and afterward of arsenic, in the treatment of experimental trypanosomiasis in mice.

He instigated in the Institute for Experimental Therapy, at Frankfort, a systematic procedure in the synthesis of organic arsenicals and the quantitative testing of these substances, first on experimental animals infected with trypanosomes or other protozoal parasites, and then on human cases. As you are well aware, a great many substances were tried out before the product of principal interest to us to-day—arsphenamine or salvarsan—was achieved. The first detailed report on the use of salvarsan was made less than three years after Ehrlich and Bertheim's discovery of the constitution of atoxyl.[3]

Arsphenamine and neoarsphenamine are not the only substances produced during these researches which had therapeutic possibilities, though they are undoubtedly the best. Among the milestones marking the endeavors of the Frankfort Laboratories must be mentioned arsacetin which received an extended clinical trial, and arseno-*p*-phenylglycine which also received clinical consideration and which was chemically a forerunner of arsphenamine. The chemical and pharmacological properties of these and other substances will be discussed later on.

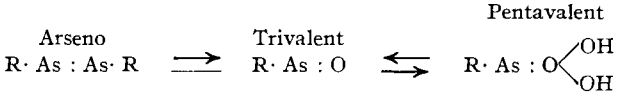
Antimony has not received as much attention from the professional poisoners as arsenic, but its legitimate use is certainly as old. Its introduction into therapy is supposed to have been made by Johann Thölde in the seventeenth century, who wrote under the pseudonym of a mythical fifteenth century monk, Basil Valentine. This pseudo-Valentine is supposed to have given to chemistry hydrochloric acid, sugar of lead, the means of preparing ammonia and sulphuric acid, and in a manuscript entitled the "Triumphant Chariot of Antimony" (1604) fastened the latter metal upon medical practice for centuries. He initiated the use of antimony in fevers, and recommended a mixture of antimony, lead and mercury for the treatment of syphilis. In the light of our present knowledge these prescriptions have considerable merit, for, as I shall point out later on, there is little difference in the essential therapeutic activity of antimony and arsenic in protozoal diseases. Tartar emetic was first described by Adrian Mynshicht in 1631, and its widespread use in typhoid and other febrile affections followed the curing of Louis XIV of a dangerous illness about thirty years later (1657).[4] I do not know how it was administered in those days, but certainly its merits must have contended with and overcome the disadvantages attendant on its administration by mouth, the only route by which it exerts its marked emetic action. Intravenous injection of drugs was introduced

about this time and perhaps this was an instance of necessity being the mother of invention.

The modern history of antimony is completely submerged by that of arsenic and it is on the latter that our attention is principally centered at the present time.

I have said that Ehrlich was a pioneer in the study of the behavior of protoplasm toward dyes and other chemical substances. The complexities of the phenomena which he observed led him, in an endeavor to explain and simplify these relations, to the postulation of his well-known "side-chain theory." He likened the protoplasmic molecule to a stable nucleus with many more or less unstable peripheral side-chains or chemoceptors, which enable it to combine chemically with food substances, toxins and antitoxins, dyes and other biologically reactive substances. Throughout his work on arsenic compounds, this chemoceptor theory played a very large part. As you will see from the experiments I am about to discuss, such an explanation of the toxic or therapeutic activity of various arsenic or antimony compounds is untenable. On the other hand I shall endeavor to illustrate how these differences in toxicity and therapeutic activity can be explained on a substantial chemical basis.

As you well know, arsenic and antimony can exist in chemical compounds in three states of oxidation, arseno, trivalent and pentavalent. These three states, or chemical conditions, can be represented by the following formulas, where R may be any organic radical whatsoever:



The transformation from left to right is a process of oxidation; from right to left a process of reduction. Under certain conditions arsenic may be present in all three forms, or in any one. The keynote to the biochemical phenomena associated with various arsenic compounds lies in the fact that this metal exerts a direct toxic action on living protoplasm only when it is in the trivalent-oxide state. In the more highly reduced arseno state, and in the oxidized or pentavalent state, arsenic exerts little or no toxic action on any form of life. These facts are equally true for antimony. Therefore it is not necessary, for general purposes, to consider the nature of the organic radical R with which the metal is combined. We need only note the degree of oxidation of the metal, *i. e.*, whether it is in arseno, the trivalent or the pentavalent state. All tissues, such as the blood and living cells, etc., possess some power to perform oxidations and reductions. Consequently when arsenic compounds are injected into the animal body, or even mixed with body fluids, alterations in the state of oxidation take place. Arseno arsenic is oxidized, first to the trivalent state, and then to the pentavalent state. The transformation from left to right in the graph is the easier, and is the predominant type of reaction taking place in the animal body. On the other hand it is known that when pentavalent arsenic is injected, small amounts are reduced to the trivalent state.

The pharmacological significance of these facts is illustrated by the rapidity with which various forms of antimony and arsenic produce symptoms of poisoning

after intravenous injection. When a lethal dose of the trivalent form is given, symptoms of acute poisoning appear immediately, *i. e.*, within one to five minutes, and death follows very soon afterward. If the animal survives one or two hours, it is very unlikely that it will die at all. When lethal doses of arseno or pentavalent arsenic are given, symptoms of poisoning do not appear for an hour or two hours, or even a day. Since these forms are not toxic, it is necessary, before they can exert any toxic influence, for them to be oxidized or reduced, respectively, to the toxic, trivalent oxide. This transformation is slow, and some time elapses before a sufficient concentration of the trivalent form is produced to cause acute injury.

A second fact of prime importance is that the reaction between a toxic arsenic compound and the parasites progresses in a smooth, definite way, just as does the reaction between two chemical substances. These facts are illustrated by the

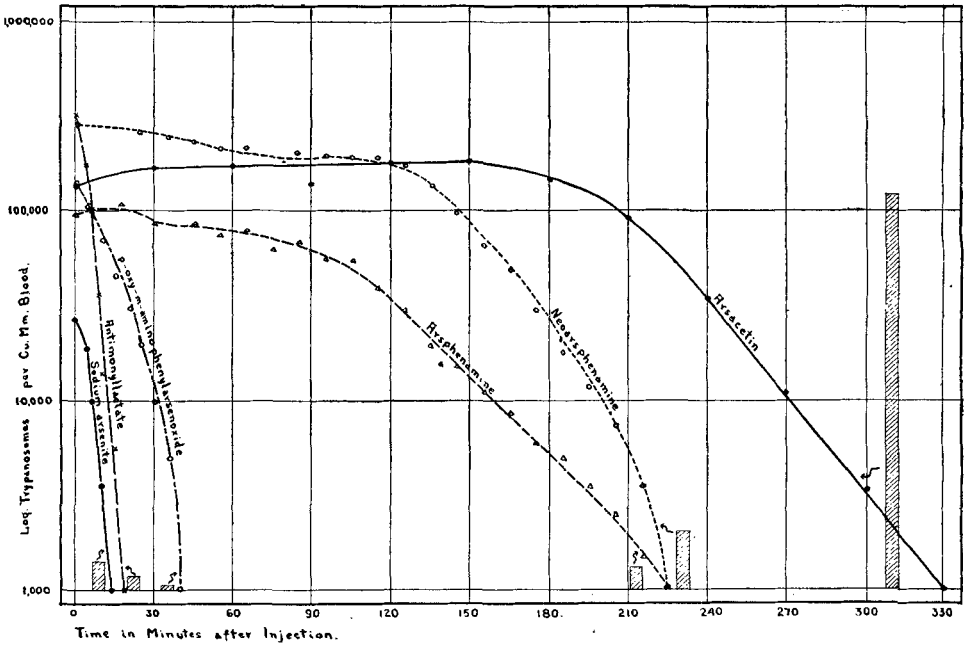


Fig. 1.—Rate of reaction between trypanosomes in the blood stream of white rats and various arsenic preparations when injected intravenously. Note the rapidity of action of compounds of the trivalent oxide type as compared with the compounds of the arseno and pentavalent type. The perpendicular rectangles indicate the actual amount of arsenic given in each case.

following experiments, quoted from some performed by Dr. Voegtlin and myself in Washington.[5] Various arsenic and antimony compounds were injected intravenously into white rats infected with the parasitic protozoön, *Trypanosoma equiperdum*. The number of parasites in the peripheral blood stream was determined at the beginning and throughout the experiment by drawing blood from the tip of the tail and counting the parasites in a given volume of blood, just as one counts erythrocytes or leucocytes. The trypanosomes are rapidly autolyzed in the blood stream after being killed by the drug, and hence the reaction of the drug

with the parasites can be followed very closely. A few "process curves," typical of various arsenic and antimony compounds, are given in Fig. 1. It can be seen from these curves that compounds of the trivalent type (antimony lactate, sodium arsenite and arsenoxide) react directly with the parasites, because the latter begin to disappear as soon as the drug is injected.

On the other hand compounds of the arseno type (arsphenamine and neoarsphenamine) and compounds of the pentavalent type (arsacetin and atoxyl) have no immediate effect upon the parasites whatever. Only after a long period of time do the parasites begin to disappear. During this early period when the drug is exerting no trypanocidal action, it is being partially oxidized in the case of the arseno compounds, or reduced in the case of the pentavalent compounds, to the corresponding trypanocidal, trivalent form. Only after the production of the trivalent form has proceeded far enough to yield a certain threshold value does it begin to exert a trypanocidal action.

The value of any substance for the practical sterilization of the animal body depends not only on its power to destroy the invading parasites, but also on its toxicity for the host. The ratio between the minimum dose effective to kill the parasites and the minimum lethal dose represents, as Ehrlich pointed out, the margin of safety to be expected in its use. Therefore it is interesting to compare this ratio for a few substances representing the three chemical types.

Sodium Salt of R · As : O	Minimum lethal dose.	Minimum effective dose.*	$\frac{\text{M. L. D.}}{\text{M. E. D.}}$
Arsenious acid	7.0	7.0	1
Phenylarsenoxide	3.75	0.75	5
Arsenoxide	10.0	0.75	13
R · As : As · R			
Neoarsphenamine	100.0	4.0	25
Arsphenamine	75.0	2.0	37.5
Arsenophenyl glycine	75.0	4.5	16.0
R · As : O(OH)(OH)			
Arsacetine	750.0	37.5	20
Atoxyl	150.0	37.5	4
Arsenic acid	50.0	37.5	± 1

* M. E. D. = that dose required to just destroy all the trypanosomes present in the blood stream. All doses are given in cc of an arsenic equivalent solution per kilo body weight.

Both the M. E. D. and M. L. D. are lowest with the trivalent oxides; this is because these substances act directly on the trypanosomes and on the host with a minimum amount of waste through excretion. They are not suited for therapeutic purposes, however, because the dose required to destroy the last parasite approaches too closely to the lethal dose; the arsenic is readily oxidized to the inert pentavalent state and in order to maintain a sufficiently prolonged action to destroy the last parasites, a very large fraction of the lethal dose must be given. The pentavalent compounds are both least toxic to the host and to the parasites because so little pentavalent arsenic is reduced in the body to the trivalent state. The arseno compounds, on the other hand, are readily oxidized to the corresponding trivalent form, and hence the differences in both toxicity and therapeutic activity between the arseno compounds and the corresponding oxides are very little.

The ratio M. L. D. over M. E. D. is greatest in the case of arsphenamine and neoarsphenamine, bearing out clinical experience with these preparations. A number of investigators have found that on the basis of arsenic content, arsphenamine and neoarsphenamine are equally effective against trypanosomes, spirochetes, spirilla, etc.[5d,6] The minimal lethal dose for white rats is also approximately equal.[7,5d] But it has been frequently said that in the treatment of human syphilis, neoarsphenamine is inferior to arsphenamine. This may be a result of the peculiar chemical properties of the latter. The dominance of the basicity of the amino group over the acidity of the hydroxyl group renders the compound insoluble in a neutral or slightly alkaline medium. It is precipitated from solution at the hydrogen-ion concentration of the blood. It is therefore probable that arsphenamine is precipitated as such in the tissues after injection into the blood stream, resulting in the formation of depots from which small amounts are constantly being taken up by the blood, and converted through partial oxidation to the reactive trivalent oxide. There is evidence that minute quantities of the drug will exert a cumulative toxic effect on parasites infecting the body if maintained for a long period of time.[8] Hence this tendency to precipitate and thus reduce the rapidity of oxidation must be a great practical advantage. We should expect arsphenamine to be better adapted to sterilize the deep-seated lesions of human syphilis than the readily soluble, and hence more rapidly oxidized, neoarsphenamine. It is interesting to note in this connection that, so far as experimental trypanosomiasis is concerned, arsphenamine and neoarsphenamine are equally efficacious whether given by intravenous or intramuscular administration.[5e] Arsphenamine has been found to be equally efficacious, and neoarsphenamine slightly more efficacious, against the spirochete of recurrent fever in mice when given subcutaneously as compared with intravenously.[9] In the case of intramuscular or subcutaneous injection of neoarsphenamine, absorption would be slow and a depot, similar to that obtained by the precipitation of arsphenamine, would be established to maintain a long-continued attack on the parasites.

A very important practical point and one which has been much emphasized by Ehrlich is the ease with which protozoa can acquire resistance to arsenic and other therapeutic agents. Ehrlich showed that if the amount of drug administered to an infected animal was insufficient to produce sterilization it was very apt to produce resistance or even to stimulate the growth of the parasites and thus make the cure much more difficult than before. He therefore advised giving the largest dose practicable at the beginning of treatment. Almost every form of life can acquire tolerance to arsenic if exposed for long periods of time to non-lethal concentrations. Trypanosomes have been observed to acquire arsenic resistance simply through their propagation in the bodies of rats which had previously received arsenic.[5b] Spirochetes have been shown to acquire arsenic resistance by exposure to arsphenamine and neoarsphenamine *in vitro*.[10] That one-half a dose is not always one-half as good as a whole dose is evident from the fact that the minimum dose required to destroy all the parasites (*i. e.*, the minimum effective dose) is very sharply defined. Half this dose has almost no effect upon the number of parasites and successive half doses administered at intervals of 30 to 40 minutes have only a very slight additive effect. This is because the drug is rapidly being removed from the blood stream, either by excretion or by oxi-

dation to the inactive pentavalent form and consequently it must be supplied in a sufficient amount to furnish an excess during the time required to kill all the parasites. These facts show the practical importance of Ehrlich's idea of one sterilizing dose.

That antimony and arsenic act in very much the same manner on the parasites is indicated by the fact that one-half a dose of antimony and one-half a dose of arsenic will effect the destruction of the parasites while either half by itself has practically no influence upon them.

Ehrlich believed that arsphenamine was very easily destroyed by oxidation, a supposition which is borne out by subsequent investigation.[5c] The rate of oxidation bears a direct relation to the alkalinity of the solution, as the dihydrochloride, the form in which it is usually marketed, is not susceptible to oxidation by atmospheric oxygen. (This may or may not be true in the presence of contaminating substances which can act as oxidation catalysts.) As increasing amounts of alkali are added the rate of oxidation increases, being fairly rapid when the arsphenamine has been converted to the disodium salt. It is possible to demonstrate the formation of arsenoxide biologically as well as chemically because arsphenamine solutions containing it will exert an immediate destructive action on the trypanosomes when injected into infected rats. The rapidity of action of the injected solution increases with increasing time of incubation until the concentration of arsenoxide reaches a maximum after which the solution loses its therapeutic activity entirely as the arsenoxide is oxidized to the pentavalent form.[5h]

Roth[11] found that shaking alkalinized aqueous arsphenamine solutions with air for one minute increased the toxicity sixty percent, and shaking aqueous neoarsphenamine solutions increased the toxicity over four-fold. Therefore, care should be exercised that no more alkali be added in making arsphenamine solutions than is required to form the disodium salt, and that the solution should be exposed to the air as little as possible since an excess of alkali and aeration increase the rapidity of oxidation. Hunt[16] recently considered this question in connection with the untoward reactions frequently associated with the administration of arsphenamine. He did not find any toxic commercial preparations, the toxicity of which could be attributed to the presence of arsenoxide. He did find, however, that some preparations of arsphenamine are very toxic when the solutions are prepared at ordinary room temperature; the toxicity is greatly reduced by gently warming and in some cases by allowing the solutions to stand for a time at room temperature. Cold may preserve the toxicity for long periods. Hunt believes that the undue toxicity of such preparations is probably due to the physical state of the solution, and that this undergoes a rapid change when the solution is warmed.

Interest in pentavalent arsenic has recently been re-awakened by experiments with N-phenylglycineamide-*p*-arsonic acid on human trypanosomiasis.[12,13] Clinical experience indicates that when given in comparatively large doses it exerts a distinctly curative effect. Similarly there is promise of further investigations into the therapeutic possibilities of antimony derivatives.[14,15]

From what has been said it can be readily understood that arsphenamine owes its value in the treatment of human syphilis to a unique and fortuitous combination of physical-chemical properties. Its disadvantages are numerous, but we should not be too optimistic about avoiding them; it is not easy to alter the chemi-

cal nature of the compound without sacrificing something of this ensemble of physical-chemical properties which determine its efficacy.

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BIBLIOGRAPHY.

1. Gordon Sharp, "Notes on the History and Romance of Arsenic," *Pharm. Jour.*, 81, 186, 232, 1908.

2. Gilbert T. Morgan, "Organic Compounds of Arsenic and Antimony," Longmans, Green and Co., London, 1918.

3. Ehrlich and Hata, "Die experimentelle chemotherapie der Spirillosen," Springer, Berlin, 1910.

4. Fielding H. Garrison, "History of Medicine," W. B. Saunders Company, Philadelphia, 1917.

5. Carl Voegtlin and Homer W. Smith, "Quantitative Studies in Chemotherapy," *Jour. Pharm. Exp. Therap.*, (2) 15, 453; (*b*) *Ibid.*, 475; (*c*) 16, 199; (*d*) *Ibid.*, 449; (*e*) 17, 357.

6. Jay F. Schamberg, John A. Kolmer and George W. Raiziss, "A Comparative Study of the Trypanocidal Activity of Arsphenamine and Neoarsphenamine," *Amer. Jour. Med. Sci.*, 160, 25, 1920.

7. Jay F. Schamberg, John A. Kolmer and George W. Raiziss, "Comparative Studies of the Toxicity of Arsphenamine and Neoarsphenamine," *Ibid.*, 160, 188, 1920.

8. W. Kolle, O. Hartoch, M. Rothermundt and W. Schürman, "Ueber neue Prinzipien and neue Präparate für die Therapie der Trypanosomeninfektionen," *Deutsch. med. Wochenschr.*, 39, 825, 1913.

9. G. Castelli, "Ueber Neosalvarsan, Bestimmung der Toxizitat und der Heilenden Wirkung bei experimentellen Spirochätenkrankheiten," *Zeit. f. Chemotherapie, orig.*, 321, 1912–13.

10. Seinai Akatsu and Hideylo Noguchi, "The Drug Fastness of Spirochetes to Arsenic, Mercurial and Iodide Compounds *in vitro*," *Jour. Exp. Med.*, 25, 349, 1917.

11. George B. Roth, "The Effect of Shaking Alkalinized Aqueous Solutions of Arsphenamine and Aqueous Solutions of Neoarsphenamine in the Presence of Air," *U. S. Public Health Reports*, 35, 2205 (No. 38), 1920.

12. Wade H. Brown and Louise Pearce, "Chemotherapy of Trypanosome and Spirochete Infections," *Jour. Exp. Med.*, 20, 417, 437, 455 and 483, 1919; *Ibid.*, 31, 475, 709, 729, 749, 1920.

13. Louise Pearce, "Studies on the Treatment of Human Trypanosomiasis with Tryparsamide," *Ibid.*, 34, Sup. 1, 1921.

14. C. N. Myers, "On the Preparation of Metal Salts of Thioglycollic Acid," *Jour. Lab. Clin. Med.*, 6, 359, 1921.

15. Robert George Fargher and William Herbert Gray, "The Chemotherapy of Antimony," *Jour. Pharm. Exp. Therap.*, 18, 341, 1921.

16. Reid Hunt, "Some Factors Relating to the Toxic Action of Arsphenamin," *Jour. A. M. A.*, 76, 854, 1921.

PREPARATION OF NEOARSPHENAMINE[1]

BY FREDERICK W. HEYL AND GEORGE E. MILLER.

With the progress of clinical experience with the arseno compounds the attention of the medical profession is becoming centered upon neoarsphenamine for the reason that with it fewer untoward reactions are experienced, and because it is less toxic and may be readily administered in practice.

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[1] Received for publication April 24, 1922.