

Original Articles.

SYMPOSIUM ON SALVARSAN FROM THE CLINICAL STANDPOINT.

INTRODUCTION.*

BY HARVEY P. TOWLE, M.D., BOSTON.

As you know, salvarsan (Ehrlich's "606") has been widely discussed. The medical literature has been overrunning with reports of the drug, its action and its indications. Nevertheless, we are still in doubt as to very many of the facts concerning it. It is still under fire. It became very evident during the recent discussion of this subject at the Massachusetts General Hospital that the average man was doing his reading for himself. The questions which followed that meeting were all variations of "What do you know about this drug?"

At this meeting the speakers have been asked to give their own personal experiences. It was by no means planned that we were to settle the question of salvarsan, or its place in therapeutics, but to give you ideas, practical points in handling, indications for its use, something about doses, the accidents and mishaps attending its use and ways of avoiding them; all as illustrated by personal experience.

In order to make the subject, or the symposium, complete, as you will notice by the program, we have begun with the chemistry of the drug, which takes in, of course, Ehrlich's idea of chemotherapy, then follows the parasitology of syphilis.

Unfortunately the paper upon the Wassermann reaction cannot be given, owing to Dr. Moers' death a few days ago.

We have also planned to give you a practical demonstration of the making of the solution, and finally Dr. Cabot, Dr. Pollitzer and Dr. Post have been good enough to come here and give their experiences, each in the light of his previous large experience with mercury.

THE PARASITOLOGY OF SYPHILIS.†

BY HAROLD C. ERNST, M.D., JAMAICA PLAIN.

THE etiology of syphilis has of course been the subject of much attention and of extensive research for many years. With the advent of the methods of bacteriology many investigators took up its study from this new point of view, and hasty and ill-considered assertions were made as to bacteria found in the lesions of the disease. For some time special attention was paid to the statements of Lustgarten (1884), who claimed an etiological relationship to the disease for an acid-fast bacillus three to four microns in length, which occurred in small bundles in the cells or free in the intercellular spaces. Other observers were unable to confirm his results so far as finding this bacillus in the tissues, and the conclusion seems to be justifiable that Lustgarten's bacillus was in fact the smegma bacillus — at that time

not recognized, but soon demonstrated to be of common occurrence in the smegma and in parts contaminated by it.

In 1905 Schaudinn and Hoffman¹ described *spirocheta pallida* and *spirocheta refringens* as occurring in all the lesions of syphilis. They were at first inclined to think that both these organisms were concerned in the production of the disease, but later study served to convince them that *S. refringens* is merely a common accompaniment of the lesions and is not concerned in their causation. All observations since that time have served to confirm the belief that *S. pallida* is the chief, if not the only, cause of this infection, and this in spite of the fact that thus far pure cultures have not been obtained, and inoculation experiments have been successfully carried out only with material from syphilitic lesions containing the organism. In default of pure cultures, collateral evidence, such as bactericidal or agglutination tests, are lacking.

The organism has been demonstrated, however, in practically all stages of syphilitic lesions, — even the tertiary, — as well as in the tissues of monkeys and other animals inoculated with syphilitic material. In some of these inoculated animals, too, the serum has presented the Wassermann reaction.

The terminology applied to the organism has varied — this as the result of a widespread discussion as to the place to be assigned to *spirochetæ*. *S. pallida*, according to Schaudinn, differs from others, often accompanying it in syphilis (*S. refringens*, *S. plicatilis*), and from the *spirochetes* of Vincent's angina, of ulcerated cancers and others, in that it has no trace of an undulating membrane, is circular — not flattened — on transverse section, and has a long flagellum at each end. Inasmuch as true *spirochetes* have at least traces of an undulating membrane, are always somewhat flattened and have no flagella, the so-called *S. pallida* should be taken out of this genus. Schaudinn proposed the name *spironema pallida* (*σπειρα*, a coil, and *νήμα*, a thread), but this name was abandoned almost at once for it was found to be already claimed, and the name *treponema pallidum* (*τρέπεν*, turn; *νήμα*, thread) is the one properly applied to the organism at present, it thus forming the leading member of a new genus. It varies from four to fourteen microns in length and is but one fourth of a micron in thickness. In fresh preparations in salt solution it is very actively motile, rotating, moving to and fro, and making flexing movements which are easily seen. These characteristics separate it from *spirillum* (diminutive of Latin *spira*, a coil) which are spiral cells, rigid, but with flagella which propel them to and fro. They also separate it from the *spirochetes* (*σπειρα*, a coil, and *χαίτη*, a bristle), which are long slender threads usually with narrow spiral windings, with active to-and-fro movements, and ability to bend in varying directions.

Treponema pallidum has usually six to eight

¹ Deut. Med. Wochenschr., May 4, 1905, p. 711.

* Read at the annual meeting of The Massachusetts Medical Society, June 13, 1911.

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curves, and is not very difficult to demonstrate in the fresh condition if a good dark ground illuminating apparatus be employed. Its movements under such conditions make it fairly easy to differentiate. Stained preparations can be secured by making cover glass smear preparations as thin as possible from tissue scrapings. Harden in absolute alcohol for ten minutes, or in osmic acid vapor for a few seconds and stain with Giemsa or Borrel blue. Sections of the organs in syphilis — from adults or cases of congenital disease — often show the organism in enormous numbers.

Treponema pallidum being placed in a new genus and removed from among the spirochetes, the relationship between it and the trypanosomes has become less probable than before. It is, however, interesting to note the discussion that has gone on in this direction, for later evidence may be brought forward connecting the two. If this should happen, certain histological resemblances between dourine (*mal du coit*) and syphilis would be of increased interest by such grouping of the etiological factors. Dourine is, of course, a disease produced by a true trypanosome (*Tr. equiperdum*), but certain of the histological changes — especially of the nerves — are allied to those seen in syphilis, and it would be interesting if these two diseases should come to be grouped together, as has been done in so many other cases in recent years, by better knowledge of the causal agent.

THE CHEMISTRY OF SALVARSAN.*

BY WILLIAM F. BOOS, M.D., PH.D., JAMAICA PLAIN.

DURING the past year a number of medical journals have published papers on the chemistry of salvarsan that were intended to make the matter clear to the medical practitioner. The treatises on the subject which I have seen show one fault in common — they do not emphasize the close relationship which exists between the immediate forerunners of salvarsan and the mother substance, arsenic acid. This relationship can only be shown by the use of structural formulas.

In the teaching of inorganic chemistry, the very important structural formulas are sadly neglected, and many facts which may be learned at a glance from such formulas are never completely mastered by the student because the empirical formulas so commonly used do not explain "the reason why." I have known trained chemists taught in the old-fashioned way to be ignorant, for example, of the fact that an oxygen acid contains all the hydrogen atoms which are replaceable by a metal (or other basic radical) to form a salt, in the state of OH, a group known as the hydroxyl, or, for short, as the "oxy" group. It seems to me that a knowledge of this fact is essential to an intelligent understanding of the simplest chemical changes.

Let us consider, for example, four of the common acids, namely, nitric acid, sulphuric acid, phosphoric acid and arsenic acid. The empirical formulas HNO_3 , H_2SO_4 , H_3PO_4 , H_3AsO_4 tell us

nothing about the arrangement of the atoms, nor do they explain why nitric acid contains only one replaceable hydrogen atom (NaNO_3), while phosphoric acid has three such atoms (Na_3PO_4). If, however, we apply the law given above, namely, that every replaceable H-atom is in the form of OH, and by means of the law construct pictures of these four acids, the reasons for the various formulas are at once apparent. Nitric acid contains only one H-atom replaceable by bases to form a salt; therefore it contains one, and only one, OH group. In sulphuric acid there are two replaceable H-atoms (Na_2SO_4); this acid must, therefore, contain two OH groups; phosphoric acid, H_3PO_4 , and arsenic acid, H_3AsO_4 , both have three replaceable H-atoms (Na_3PO_4 , Na_3AsO_4); each of these acids must, therefore, contain three OH groups, as shown by the first chart.

The structural formula of an acid salt such as NaH_2PO_4 contains one ONa group and two OH groups; that of the salt Na_2HPO_4 contains two ONa groups and one OH group; that of the neutral salt Na_3PO_4 contains three ONa groups and no OH groups. The presence of the OH groups in the acid phosphates explains their partial acid character, which is sufficiently pronounced to render their solutions acid to litmus (acid reaction of the urine).

Since oxygen always shows a valence of 2 and the OH or oxy group a valence of 1, it is easy from the structural formula to determine in each case the valence of the non-metal characteristic of the acid. Thus we find that the nitrogen in HNO_3 has a valence of 5, that the sulphur in H_2SO_4 has a valence of 6, that the phosphorus and arsenic in H_3PO_4 and H_3AsO_4 respectively have a valence of 5.

I shall attempt in this paper to show by easy stages how salvarsan may be developed from arsenic acid, using for this purpose the simple structural formulas of some of the landmarks, so to speak, established in the process of investigation.

Taking the formula of arsenic acid as shown in Chart 1, it is possible to replace not only the H-atom, but the entire OH group by a basic radical such as CH_3 , the methyl group, for instance (Chart 2). When the entire OH group is replaced in this manner, the fact is indicated by a change in the name of the acid to arsinic acid. The replacement of one oxy group by CH_3 gives us mono-methyl arsinic acid, commonly called methyl arsinic acid. When two OH groups are replaced by methyl groups, we have di-methyl arsinic acid, and so on.

The sodium salt of methyl arsinic acid is well known in medicine under the name of arrhenal. The di-methyl acid is even better known; it is cacodylic acid, the sodium salt of which has recently been highly recommended in this country and France as a specific in syphilis, just as if Ehrlich had not tried it out thoroughly and found it quite inadequate, many years ago. Cacodylic acid and its sodium salt owe their action in part, as was shown by Schultz,¹ to the decomposition

* Read at the annual meeting of The Massachusetts Medical Society, June 13, 1911.

¹ Schultz: Arch. für Exp. Path. u. Pharmacol., 11, 131, 1879.

products formed in the system. They are not only unreliable in their action, but are apt to cause sudden and serious intoxication from the liberation of arsenic acid. Heffter² found that

arsenic acid. One of the first of these which he tried was atoxyl.

Atoxyl was described by Béchamp in 1863; he called the free acid an anilid of arsenic acid.

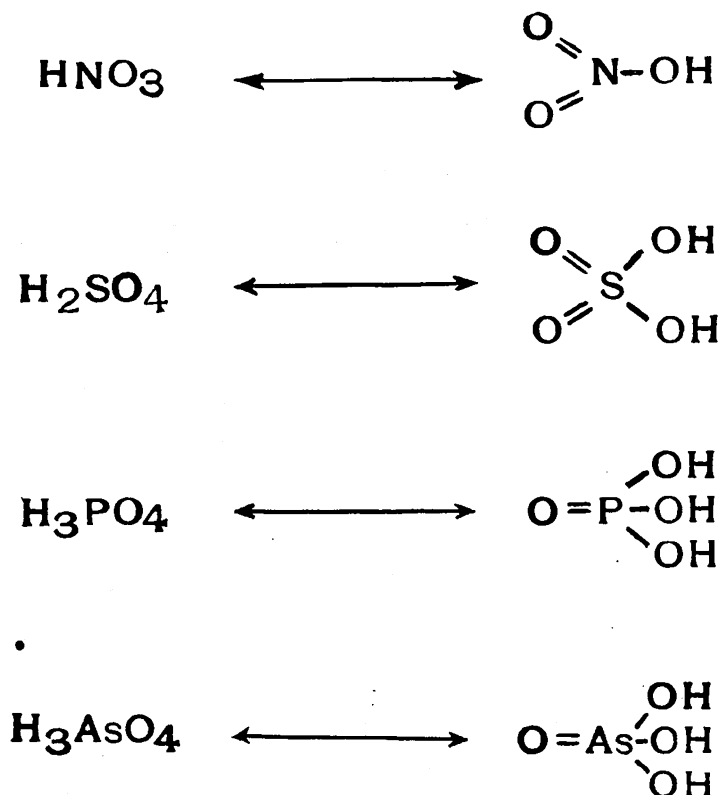


CHART 1.

a part of the acid or of its salt is excreted unchanged in the urine.

Ehrlich was in search of a stable organic derivative of arsenic acid which itself would act as a

Experimenting with the compound, Ehrlich found that it was easily diazotized and converted into an azo dye. From this property he reasoned that the substance must contain a free NH_2 or amido

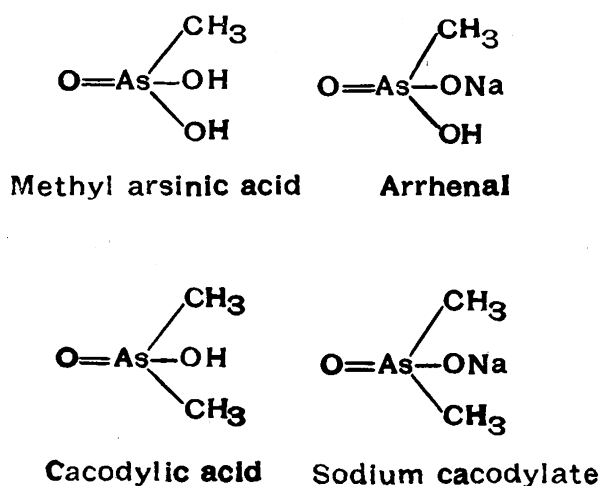


CHART 2.

parasiticide and not through highly toxic decomposition products formed in the system. He hoped for better results from the benzol derivatives of

group, and that it was in truth p-amidophenyl arsinic acid. The compound is derived from arsenic acid by the replacement of one OH group by $\text{C}_6\text{H}_4\text{NH}_2$, the amidobenzol or aniline group.

² Heffter: *Ibid.*, 46, 230, 1901.

For the purpose of simplification and better to show the structure of the compound, the benzol ring, so-called, is shown in the charts as the conventional hexagon to which the various groups

is synonymous with benzol) obtained by replacing one H-atom by Na.

Atoxyl was found by Ehrlich to be an efficient parasiticide, particularly as regards the spirillum

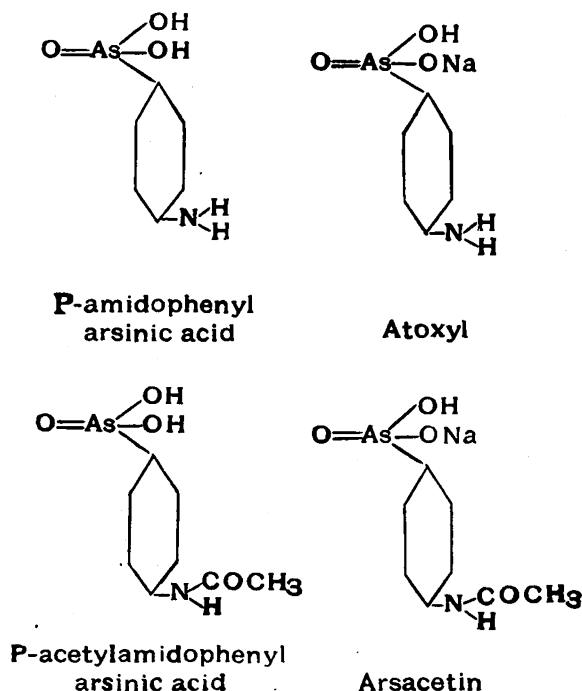


CHART 3.

NH₂, OH, etc., are attached at definite fixed points. The point of the hexagon directly opposite the arsenic atom is known as the para (p) position, while the angle of the hexagon nearer by

of relapsing fever. Its action on the parasite of syphilis was not efficient; atoxyl, moreover, contrary to its name, was found to be very toxic and too dangerous for human therapy.

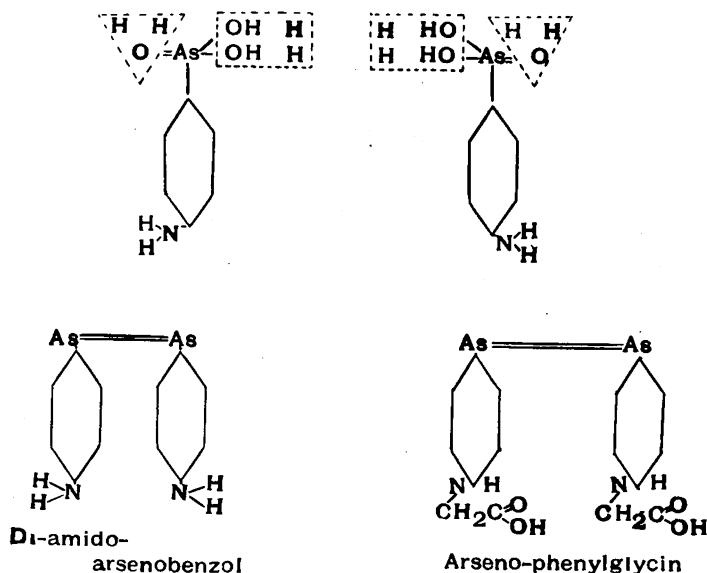


CHART 4.

one on either side to the arsenic atom is known as the meta (m) position. It will be seen from Chart 3 that atoxyl is simply a sodium salt of p-amidophenyl arsinic acid (the term "phenyl"

By the use of acetyl chloride it is possible to replace one hydrogen atom of each NH₂ group in p-amidophenyl arsinic acid by the acetyl group. The sodium salt of the resulting compound is

known as arsacetin. Arsacetin is less toxic than atoxyl, but this substance also is inefficient in its action on the parasites of the syphilis group.

In the course of his extensive experimentation Ehrlich conceived the idea of combining two molecules of p-amidophenyl arsenic acid into one compound by causing the two atoms of arsenic to unite with each other. Chart 4 shows how, by means of reduction (H) and dehydration, six molecules of water are split from two molecules of p-amidophenyl arsenic acid, leaving nothing for the two atoms of arsenic to combine with but each other, their valence being reduced to 3. The resulting compound is di-amido-arsenobenzol. By treating this compound with monochloroacetic acid one H-atom of each amido (NH₂) group may be replaced by the acetic acid radical. From its close relationship to methyl acetic acid or glycocoll the resulting compound is called arseno-phenyl-

Ehrlich used this compound extensively on rabbits with relapsing fever; later, on rabbits inoculated with syphilis from humans and from one another. His remarkable results with "606" prompted him to recommend this substance for use in human syphilis.

Six hundred and six, or salvarsan as it is now called, is very stable and acts as such rather than through decomposition products. That is why relatively much greater quantities of arsenic may be given in form of salvarsan than as cacodylate of sodium or atoxyl. A considerable part of the dose injected is probably bound immediately by the liver, which, then, permits a small quantity at a time only to pass into the circulation on its way to excretion. In this way long-continued action is insured.

It was originally supposed that when salvarsan is given intravenously the entire dose injected is

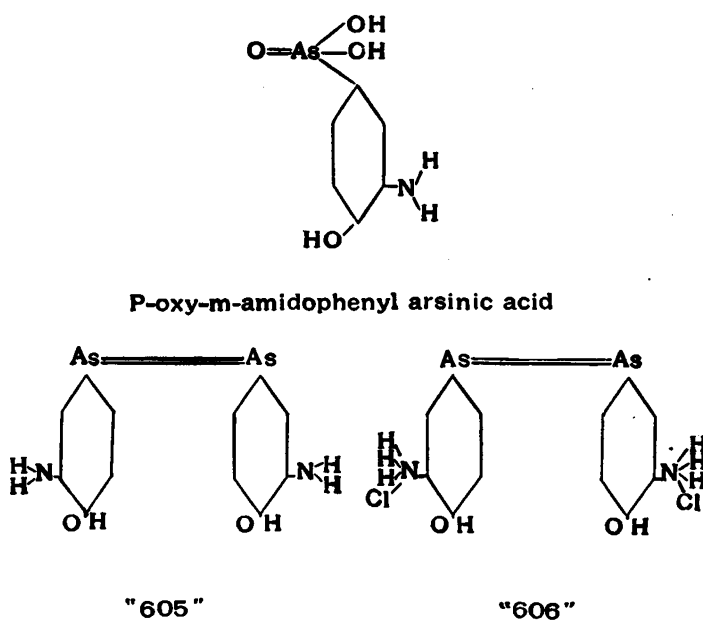


CHART 5.

glycin. This substance Ehrlich found to be very effective against trypanosomes, but its action on the parasite of syphilis was unsatisfactory.

After many experiments with different derivatives of diamido-arsenobenzol, Ehrlich used other compounds in his arsenobenzol condensation. One of these was p-oxy-m-amidophenyl arsenic acid, which differs from the original compound used for the condensation in having one OH group in the para position and one NH₂ group in the meta position (Chart 5). The product of condensation, di-oxy-di-amido-arsenobenzol, number 605 in the series, was found to be very effective against the spirocheta pallida of syphilis.³ The compound is, however, very difficultly soluble, and to obviate this fault Ehrlich converted it into its hydrochlorid which is shown in Chart 5 as "606."

excreted in a few days. While it is undoubtedly true that more of the drug is excreted within twenty-four hours after intravenous injection than when it is given intramuscularly, it has been shown on the other hand that the subsequent excretion after intravenous application may continue for weeks. I examined the twenty-four-hour urine of one of my patients ten days after giving him an intravenous infusion of .6 gm. of salvarsan and I was able to recover a little over 1 mgm. of arsenic. Jesionek⁴ found arsenic in the urine of a patient during the fourth week after the intravenous application of .4 gm. salvarsan.

I found the excretion of arsenic in the urine after the intramuscular injection of salvarsan to average .7 mgm. a day for the first five or six days, then it gradually fell until at the end of two weeks it was about .3 mgm. in twenty-four hours. I think the intramuscular method does not permit enough

³ Hoffmann: "Ueber die Benennung des Syphiliserregers, etc." München. med. Wochenschr., vol. lviii, p. 1796 (1911).

⁴ Jesionek: München. med. Wochenschr., 1911, vol. lviii, p. 1169

salvarsan to enter the circulation at any one time to be sufficiently effective against the parasites, it having been shown repeatedly that two intravenous applications will do more than six injections given into the muscle. The intravenous method is, therefore, I think, the only method to be used. If it is properly carried out by physicians with extensive experience, it is not only as safe as the intramuscular method, but even safer, because the great number of unavoidable sloughs which follow the application into the muscle are a very serious menace to the health of the individual. Of course, only strictly suitable cases should receive salvarsan, but this is true of either method of application.

THE PREPARATION OF SALVARSAN FOR INJECTION.*

BY MR. JOSEPH GODSOE,

Pharmacist Massachusetts General Hospital, Boston.

A FEW suggestions relative to the mixing of salvarsan, or "606," may be of some benefit to the physician who wishes to mix the preparation for patients in his private practice.

The following articles are all that are required for mixing the substance for intramuscular or intravenous administration:

Mortar and pestle (wedgewood, glass or porcelain). One-ounce wide-mouth bottle. Graduated burette with stand. Cylindrical graduate, 10 cm. Mixing bottle (ordinary graduated nursing bottle). Glass beads (or glass rod cut in small pieces). Glass funnel and filter-paper. Flask of salt solution, 0.6%. Bottle of normal sodic hydrate solution.

All apparatus should be sterilized, and the solution should be prepared under aseptic conditions.

It requires from 0.7 to 0.75 ccm. normal NaOH solution to dissolve 0.1 gm. of salvarsan. If the normal NaOH solution cannot be obtained, use a 4% solution. If the 4% solution is used, it may require more or less to dissolve salvarsan than is stated above, because the strength of the NaOH varies considerably.

To make the solution for intramuscular use, place 0.6 gm. of the powder in the mortar, add 4 ccm. of salt solution, triturate thoroughly until a clear solution is obtained. To this solution add 4.5 ccm. of normal NaOH solution, using about 1 ccm. at a time. Upon the addition of the first cubic centimeter of NaOH solution a gelatinous mass will form, which will redissolve when more of the NaOH solution is added. Triturate thoroughly after each addition and add the last 0.5 ccm. drop by drop until the solution is perfectly clear. Transfer to the one-ounce wide-mouth bottle, wash the mortar out with a small quantity of the salt solution, and finally add salt solution up to 16 ccm.

For intravenous use:

Place the glass beads and 0.6 gm. of the powder in the mixing bottle, add 15 ccm. of salt solution and shake thoroughly until the solution is per-

fectly clear and free from transparent gelatinous clots. Then add the normal NaOH solution, using the same quantity and method as directed in the former preparation. Then make up with salt solution to 200 ccm. It is essential that this solution should be filtered, because it is liable to contain particles of glass that may have been chipped off from the glass beads during the shaking process.

CLINICAL OBSERVATIONS ON THE USE OF SALVARSAN, WITH SPECIAL REFERENCE TO ITS ADMINISTRATION.*

BY HUGH CABOT, M.D., BOSTON.

ANY judgment which we may now form as to the indications for and the value of this drug must be purely tentative as it is yet entirely in the experimental stage. Our peace of mind has not been enhanced, to say the least, by the extremely variable and rapidly changing theory of its effects emanating from its discoverer and his associates. We were at first asked to regard this as the *therapia sterilisans magna*, and we were told that the function of this drug was to destroy the spirochete at one fell swoop. It was pointed out that any dose smaller than the maximum was extremely likely to result in an acquired immunity on the part of the organism, and that the drug became less and less active. This theory must have commended itself to thoughtful students, and we seemed upon the brink of having achieved a miracle, when, lo and behold, comes the information that the best effect of the drug is produced by multiple small doses. This entire change of heart has come through the failure of the drug to live up to the expectations raised by early work. We have had to admit that it is not a miracle, that one dose does not destroy all the organisms, and that in truth it behaves very much as do other drugs and not wholly unlike our friend and ally, mercury.

Our judgment has been further confused by the conflicting evidence in regard to the best preparation. At the outset the acid solution was used, but this was promptly abandoned as being too toxic. Then we were urged to use the neutral solution, which was in fact not a solution at all, but a suspension. The drug is not soluble in an exactly neutral medium, and when this is obtained a precipitate forms which may be either yellowish or grayish. It is a good suspension, to be sure, but one cannot but question the evenness of its absorption, whether or not it may become encysted and some of it be absorbed only after long periods, if at all. From this dilemma we emerged to the use of the alkaline solution, an irritating preparation, to be sure, but nevertheless a real solution, upon the absorption of which one could rely. It is this preparation which the great majority of observers are now using, the effort being to obtain a solution in as mildly alkaline a medium as possible.

The decision as to the efficiency of the drug

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has also been confused, because many observers will insist upon regarding as a cure any retarding of the disease. Now it must at once be obvious that the question of cure will not be decided in one year or even in three years, and that a very considerable time must elapse before we can intelligently compare this last comer in the field with mercury and the iodides, with whose effects we have long been familiar. It must constantly be kept in mind that all we can expect for the present is a prompt and lasting effect upon present lesions, the question of cure being left wholly for the future to decide.

I will now review for you briefly our experience with the drug at the Massachusetts General Hospital, where it has been used chiefly under the auspices of the Skin Department.

METHOD OF ADMINISTRATION.

With one exception we have used entirely the alkaline solution which has been prepared for us by Mr. Godsoe by the method described by him to-day.

INTRAMUSCULAR INJECTIONS.

The solution varies in quantity from 16 to 19 ccm., the difference in amount depending entirely upon the variable solubility of the drug.

CHOICE OF SITE FOR INJECTION.

In all our cases we have employed the buttock, though the infrascapular region and lumbar muscles have been frequently used by other observers. We have selected the buttock because we believe that absorption is here reasonably prompt, that it produces rather less pain than in other regions, and should abscess formation occur less damage will be done. We prefer the upper outer quadrant of the buttock, care being taken to avoid the region of the sciatic nerve. The infrascapular region has seemed likely to be unnecessarily painful and one where considerable damage might be done by abscess formation. The lumbar muscles have been extensively used by many sound observers, and the work of Meltzer makes it appear that the absorption through this muscle is more prompt than elsewhere. In spite of this advantage we have thought it best to continue to use the buttock, as it seemed to us a very satisfactory location.

The skin is prepared by the ordinary method of scrubbing with soap and water, followed by the application of alcohol. The injection is made with a syringe holding 10 ccm., with a needle not less than three inches long. We have found 10 ccm. all glass syringe of Luer well suited to this work. As the amount of solution is in the neighborhood of 20 ccm., 8 or 9 ccm. are injected in each buttock.

IMMEDIATE RESULTS.

When using the alkaline solution the injection is always followed by pain. This is somewhat variable in amount, often requiring morphia for its control during the first twenty-four hours, but not infrequently being satisfactorily mitigated

by aspirin. It is most severe during the first twenty-four hours, but persists as a dull ache, not infrequently referred along the sciatic nerve, for a week, sometimes ten days. The local results of the injection are interesting, sometimes acutely so. There is considerable infiltration and some edema. In a few cases, with us about 10%, there has been a blush of the erysipeloid type covering the buttock and extending upward into the lumbar region.

Some of the cases had every appearance of going on to abscess formation, but this occurred in only one, an ill-nourished child of nine months. Other observers, however, have had abscess formation in from 5 to 10% of their cases. These sterile abscesses are excessively chronic, heal slowly and occasionally require excision of the slough. Constitutional symptoms, fever, increased pulse rate, general malaise are observable, to some extent, in practically all of the cases. In only one or two of the cases did the temperature exceed 101, and in most it was below that point. Change of pulse rate was unimportant, and all constitutional disturbances subsided in two or three days.

EFFECT UPON THE KIDNEY.

It is known that arsenic in general and this salt in particular at times has an unfavorable effect upon the kidney. No untoward results have been noted in our cases beyond a moderate amount of diminution in the amount of urine, but we have not used the drug in any case known to have chronic nephritis.

As a result of the disturbances above noted it has been necessary to keep these patients in bed for a week or ten days, and some patients have been too uncomfortable to be about for two weeks.

INTRAVENOUS METHOD.

For intravenous injections we have used the alkaline solution diluted up to 200 ccm. In this dilution it has a very mildly alkaline reaction. A great variety of different kinds of apparatus have been used for administration, and it may be given either by direct injection with a large syringe, or by the use of a reservoir which can be elevated to the desired height. The apparatus which we have used consists of a reservoir connected by rubber tubing with a two-way cock which is again connected with a suitable needle. At the two-way cock is connected a 10 ccm. syringe filled with salt solution, which we have found useful in ascertaining that the needle has entered the vein and the blood is flowing freely, also in preventing clotting of blood in the needle and in washing the salvarsan away from the point of injection in the vein in order to diminish the probability of thrombosis.

The vein selected for injection has been one of the large veins in the neighborhood of the bend of the elbow. The skin is prepared as usual, and a tourniquet lightly applied to the upper arm so as to produce venous stasis. If the veins stand out prominently the needle may be plunged directly into the vein with very satisfactory results. In

our experience, however, it has generally been easier to infiltrate the skin with cocaine and expose the vein for about half an inch. It can then be punctured by one not particularly skilled in intravenous medication with ease and certainty. It is particularly important to make sure that the needle is in the vein and the blood flowing freely. In a few cases when the needle was believed to be in the vein, the flow of blood was unsatisfactory and injection of salt solution showed infiltration of the surrounding tissue. Should this infiltration be made with salvarsan, marked irritation will occur, and the injection be nearly, if not quite, as irritating as the intramuscular. We believe it, therefore, to be important to test the satisfactory nature of the flow with salt solution before allowing the salvarsan to enter. When this precaution is observed, the wounds heal quickly by first intention.

THE IMMEDIATE EFFECTS.

The intravenous injection when executed with good technic is painless. On the other hand it always causes some nausea, frequently a little vomiting, and always some diarrhea. All these symptoms occur during the first twenty-four hours. In one case we have had a transient headache, but in none of the cases has the patient been confined to bed more than twenty-four hours. If the technic is faulty, considerable irritation about the wound may result in an amount of discomfort varying almost directly with the amount of salvarsan infiltration of the tissue. One of our cases showed thrombosis of the vein throughout its entire accessible course, and should this occur, it must cause some uneasiness in regard to the possibility of embolus. We think it probable that improved technic will avoid the occurrence of thrombosis and its attendant possibilities.

OBSERVATION UPON THE EFFECT OF SALVARSAN ON THE SYMPTOMS.

Our observations are based upon a study of 50 cases, most of which have been selected because they were doing badly under the recognized methods of treatment, or were the subjects of some emergency condition. These emergencies may either be due to the presence of lesions endangering important organs, or may be of a social character. We have made exceptions to this rule in a few early cases and a few cases of tabes of syphilitic origin.

EARLY CASES.

This group includes 7 early cases with primary lesions, some having also early secondary symptoms. They were treated with one intramuscular injection, and 4 have remained well, while 3 have had recurrences. Of the cases showing recurrences, 2 have been injected again, one is free from symptoms, and one has again relapsed. Of those free from recurrences, 2 have been taking mercury, one has been lost sight of, and one is apparently well three months after injection.

SECONDARY CASES.

There have been 28 cases showing secondary lesions. In these the immediate effects were in general excellent, most of them showing a prompt disappearance of the symptoms. In 4 cases a single intramuscular injection relieved, but did not cause disappearance of the symptoms. In the balance the lesions healed, but recurred in 12 cases. The effect upon some of the late secondary lesions was very striking.

TERTIARY CASES.

We have had 6 cases having so-called tertiary lesions. In these the benefit has been less striking. Three are apparently well, and 3 are known to have recurred.

CONGENITAL CASES.

Of the 2 cases belonging to this group, one, a child, was lost sight of at the end of a month, when it was apparently well. The other, a boy of twenty-two, is much improved at the end of three months.

CASES OF TABES.

We have injected 5 cases of tabes, one by the intramuscular and 4 by the intravenous method. In none has there been any apparent benefit.

Before venturing to express any opinion based upon our use of the drug, I would again remind you that our experience with the drug has been limited and extends over a short period of time. It must be purely tentative, and, therefore, subject to change.

CHOICE OF METHOD.

The intramuscular method is safe, painful, causing considerable confinement to bed and consequent loss of time, and results in abscess formation in some cases, possibly as much as 5%. The drug is absorbed much more slowly than when given in the vein. It exerts its influence over a considerably longer period, and I am at present of the opinion that it produces a more profound effect upon the disease.

The intravenous method is technically more difficult, it is painless, causes but little confinement to bed with loss of time, but is not in the light of our present knowledge an entirely safe proceeding. Its effects are prompt, but I doubt if they are as lasting as that produced by the intramuscular method.

CLASSES OF CASES IN WHICH INJECTION MAY BE DANGEROUS.

Patients having disease of the optic nerve, organic lesions of the heart with failure of compensation or marked disease of the kidney are likely to react badly to this drug, and for the present at least it should be used cautiously and given only with a full knowledge of the possibilities.

I might sum up my view by saying that the intramuscular method is best suited for the use of the general practitioner, and that some knowledge of surgery, or at least of intravenous medica-

tion, will be required by those using the intravenous method.

Prediction is notably dangerous, but my present small experience leads me to suggest that some modification of the intramuscular method which will remove or mitigate the pain is likely to become the method of election. I still cling to the view that the production of a profound effect upon the disease is desirable and that the use of repeated small intravenous injections is less likely to produce this effect. In the light of our present knowledge I think we may safely affirm that the drug is a valuable addition to our means of treating syphilis, but it has yet to be shown that it will revolutionize our practice.

PERSONAL IMPRESSIONS OF THE VALUE OF SALVARSAN.*

BY S. POLLITZER, M.D., NEW YORK CITY.

So much has already been written on the subject of salvarsan that it would seem to me desirable now to wait with any further expressions of opinion till sufficient time has elapsed to enable us to form a final judgment on the subject. We know to-day probably as much of the action of salvarsan as we are likely to know for some years to come, and, indeed, it must be left to the next generation to assign a true value to the action of the drug. We know to-day after a year of trial of the drug little more than its immediate effects on the symptoms of the disease. It lies in the very nature of syphilis in all that four hundred years of clinical observation has taught us that the value of any cure for this disease can be determined only after the lapse of at least a score of years. We cannot say with certainty of any case of syphilis that it is cured till the patient has died of old age without having manifested any symptoms of his disease for a long period. This is of course an extreme view, and theoretical rather than practical. We know that many syphilitics recover entirely from the effects of their original infection; that they marry, produce healthy children and live to old age without showing any further symptoms of their disease. But we cannot with certainty say of any patient that his disease has been eradicated. It is no uncommon occurrence to find gummatous lesions developing in a patient who has shown no signs of his disease for a period of twenty or thirty years or more. Even the Wassermann complement deviation test is of little help in answering the question as to whether a given case is cured or not; the patient's blood serum might give a negative reaction for many years and still later become positive. It complicates the matter that the late gummatous lesions occur in a fairly large proportion of cases that yield a negative reaction. It is evident, therefore, that we have no absolute criterion of the cure of syphilis. Practically, however, we may regard that man as cured who after several years of treatment shows no signs of his disease, who remains free from any such signs for a number of years, and whose blood serum constantly yields a

negative Wassermann test throughout a number of years.

From all this it follows that any discussion of the action of salvarsan in syphilis can have only a relative value. We can discuss only the immediate effects of the drug, and must be clear in our minds that we cannot possibly have more than a shadow of knowledge of its probable ultimate effect on the disease as a whole, as distinguished from its effect on the lesions of the disease.

I have been asked to present in this discussion my own experiences with salvarsan and my personal impressions of its value. In the first place, a few words as to the technic. You know that salvarsan is employed in dilute alkaline solution for intravenous injection, in concentrated alkaline solution for intramuscular injection, in suspensions in paraffine or oil, and in suspension of the neutral drug, its sodium salt, in water. The last method, the neutral suspension and the Wechsellmann technic of interscapular injections, was extensively employed in the early months of this year of salvarsan, and, to judge from a number of cases that have come under my observation, is still the favorite method with the general practitioner. It is, however, the least effective of all the modes of application of the drug. Its subcutaneous injection is invariably followed by a tumor which persists for many months, which often becomes very painful after several weeks, which occasionally breaks down into a large and obstinate ulcer, and which frequently retains in local collection most of the salvarsan injected, with the result that the remedy fails of any general effect. Much of the disappointment that has followed the use of salvarsan is attributable to this technic. It has generally been abandoned by those who have had any considerable experience with the drug.

The intramuscular injection of the alkaline solution, the method of Alt, is probably the most effective of the methods of employing the drug percutaneously. It has the disadvantage of being extremely painful, the patients often requiring an opiate the first day or two after the injection, and the dose, as with the neutral suspension, must be freshly prepared for each case.

The suspension of the unchanged drug in paraffine oil as first proposed by Kromayer, or in iodopin as I have been using it, has at least this advantage over all other methods, that the suspension is easily prepared, and that it may be made up in large quantities, so that it may be kept on hand in the office or in the clinic ready for use as occasion requires. The use of an iodopin-lanoline ointment containing 40% of salvarsan was proposed by Schindler, an assistant of Neisser, but the exact formula has never been published and such an ointment is difficult to handle and hard to inject. I prepare the iodopin suspension by simply triturating thoroughly in a warm sterile mortar the contents of ten or twenty ampules of salvarsan in sufficient warm iodopin to give a 40% suspension of the drug, and putting it up in a dark glass bottle. It keeps indefinitely; I have used it without harm and with good effect as long as three months after its preparation.

* Read at the annual meeting of The Massachusetts Medical Society, June 13, 1911.

I make the injections with a glass syringe into the erector spinæ muscle as recommended by Meltzer, at about the level of the second or third lumbar vertebra. The injections are but slightly painful at the time, but considerable pain follows after two or three days if the patient puts any strain on the muscles of the back.

As to the value of this mode of exhibiting salvarsan, it is my opinion that it is more effective than the Wechsellmann technic, and but little if at all inferior to the Alt method. Such estimates of relative effectiveness, however, are difficult to make; I can give only my impressions. I have seen a patient with secondary lesions in the throat, that for weeks had made the swallowing of even liquids a torture, eat solid food three hours after an injection of the iodopin-salvarsan suspension; I have seen bullous lesions in an infant with hereditary syphilis dry up in twenty-four hours, and the rash disappear within a week after such an injection. One need, therefore, have no fear that in this convenient method of using salvarsan the drug may possibly not be absorbed.

With regard to all these methods of employing salvarsan, the subcutaneous, and the various intramuscular injections, it must be noted that the presence of the drug, neutral, alkaline or acid, produces necrosis of the tissues with which it is in immediate contact. The wall of necrotic tissue must certainly to some extent prevent or at least delay the absorption of the drug, and it seems to me likely that the striking immediate effects which follow these injections result from the absorption of the moiety of the drug that is taken up before the wall of necrotic tissue is formed. If the necrotic abscess remains sterile, no great harm is done the patient, and the tissue detritus together probably with the remnant of salvarsan is gradually absorbed. This absorption may, I think, be favored by the exhibition of iodides. A patient with very extensive gummatous lesions of the skin and the bones and a ++++ Wassermann reaction received four injections of salvarsan between Dec. 3, 1910, and Feb. 25, 1911, three of them intramuscular and one intravenous. All his lesions were healed within a month of the first injection, but his Wassermann reaction as late as April 8, four months after the first injection, and six weeks after the last, remained ++++. He was then put on moderate doses of potassium iodide with the result that five weeks later, May 16, his Wassermann reaction was negative. I should ascribe this action of the iodide, which we know does not *per se* influence the Wassermann reaction, in part to its effect in releasing unabsorbed masses of salvarsan and in part to its causing at the same time the softening of syphilitic infiltrations and thereby exposing encapsuled spirochetæ to the action of the freshly released salvarsan. This of course only theoretical, but I have several times had this experience with iodides in cases of syphilis in which the lesions have healed under salvarsan, the Wassermann reaction remaining positive; a few weeks of iodides converted the positive into a negative reaction.

I need say but little about the intravenous

infusions of salvarsan. The intravenous method is by all means the most agreeable from the patient's point of view. The little operation gives no pain beyond the prick of the needle and a systemic reaction (chill, temperature and vomiting), occurs in only about half the cases, and is a passing phenomenon of very little consequence. I have never seen any effect on the kidneys beyond a slight albuminuria with a few hyalin and granular casts coming on about twelve hours after the injection and disappearing by the next day. The drug thus introduced directly into the circulation necessarily exercises the full effect of the entire dose. It is, however, rapidly excreted, and it can therefore destroy only those spirochetæ which are at the moment so located that the salvarsan comes in contact with them. If all the organisms of syphilis were in the blood as are the spirilla of relapsing fever in that disease, a single intravenous injection of salvarsan would probably cure syphilis as certainly as it cures relapsing fever, but in syphilis the organisms are in the tissues, and, furthermore, some of them are sure to be enclosed in dense fibrous tissues or in the midst of compact syphilomata, and these organisms probably escape the action of the drug in the short time that it remains in the circulation. It is a good plan, therefore, to follow the intravenous infusion in four or five days by an intramuscular injection to spread the action of the drug over a longer period; and this is the plan I have followed whenever circumstances have permitted.

As to the immediate effects of an injection of salvarsan on the active lesions of syphilis, it can scarcely be necessary to speak at this late day. Its effect may be summarized as far superior in promptness and efficiency to that of mercury and iodides. The healing of gummatous ulcers may be said to begin almost immediately after an injection of salvarsan, and the time required for complete epidermization of an ulcer depends only on its size. I have dealt for many years with a fairly large number of cases of syphilis, which I have generally treated with very large doses of mercury by intramuscular injection. My normal dose of salicylate of mercury is $2\frac{1}{2}$ gr. (0.15) and bad cases get as much as 5 gr. (0.3) at a dose. I speak, therefore, from a considerable experience with syphilis and with intensive treatment with mercury, and I do not hesitate to say that the curative action of salvarsan on the active lesions of the disease, as a rule, far exceeds that of mercury. At the present time I have not a single case of syphilis that has been under my care for more than three weeks that exhibits any lesions of the disease. At no time in the past twenty years, before the introduction of salvarsan, could I have made such a statement.

As to the permanent value of these symptomatic cures, after a single injection of salvarsan, the matter is quite different. In the first months of our experience with salvarsan, under the influence of the brilliant idea of a *sterilisatio magna*, we were trusting to a single injection of the drug. There were some complete failures, especially with the Wechsellmann technic, and many re-

currences after only a few weeks. But since I have employed intravenous and intramuscular injections, and especially since I repeat the injections at intervals of four, six or eight weeks, till the Wassermann reaction becomes negative, I have not seen any lesions of syphilis develop even after six months, and this applies to all kinds of cases in every stage of the disease. With repeated doses of salvarsan I have thus far kept my patients free from any visible lesions of their disease.

As to the ultimate effect of this course of treatment, time only can tell. The effect on the Wassermann reaction, however, affords us perhaps some index of its value. In the literature, the reports on the Wassermann reaction after salvarsan are at present of very little service. They deal promiscuously with cases of early and of late syphilis, and they include cases treated by various methods and with various doses. To bring about a negative reaction in the early stages of the disease is not a difficult matter. Three months of mercury will generally do it, a couple of injections of salvarsan will quite certainly do it. It is not so with the later manifestations of the disease, with the cutaneous and especially the bone lesions of the tertiary period. Taking all the cases together, a negative Wassermann reaction seems to result from a single injection of salvarsan in about 20% of the cases, in from four to eight weeks after the injection. This corresponds with my own experience. The early cases considered by themselves will give a much higher percentage of negative reactions, the late cases a lower rate. But with repeated injections of salvarsan the results in my experience are quite different. I have to-day very few cases of syphilis treated with salvarsan that still show a positive Wassermann reaction; between 80% and 90% of the cases treated more than eight weeks ago are negative. In a few obstinate cases this result was brought about by the exhibition of potassium iodide after salvarsan as I have mentioned above. In another class of case, refractory tertiary lesions treated for a long time with large doses of mercury and still giving a positive Wassermann reaction, a single dose of salvarsan promptly healed the lesions and converted the positive into a negative reaction. I may say here that I regard a positive Wassermann persisting after a long course of mercury as a clear indication for salvarsan.

A word as to the dangers from the use of salvarsan. In my own experience I may say at once it has been my good fortune to have escaped with only a single serious accident from the use of the drug. This is, no doubt, purely a matter of chance, for serious accidents have happened to some of the most careful observers. I have, however, been very conservative in the use of the new drug; I have given it only when I considered it clearly indicated and, of course, in cases that showed no grave cardiac or renal disease. I am still treating the majority of my patients with mercury. The single serious accident to which I refer is a case of deafness in one ear that developed after a second injection of salvarsan. The patient

was a man in the secondary stage of his disease who had received an injection of salvarsan from Professor Wechselsmann in Berlin last August. On the recurrence of lesions in December, I gave him an injection of salvarsan in iodipin. Within a week his lesions had disappeared, but he noticed a total deafness in one ear, which was diagnosed as due to a lesion of the vestibular branch of the auditory nerve. The patient has since moved to the West, and I heard last month from his physician that function in the affected ear was almost restored. A number of such cases have been recorded, and Ehrlich explains them as due to the hyperemic swelling of a syphilitic focus in the nerve, a kind of Herxheimer reaction in the narrow bony channel in which the nerve runs. The prognosis in these cases is generally good; the deafness is not permanent.

As to injury to the optic nerve analogous to the optic atrophy that has occurred after other arsenical drugs like atoxyl and arsacetine, there seems to be little, if any, danger. Optic neuritis occurs in a not insignificant proportion of cases of syphilis even in an early stage of the disease, and should not, of course, be ascribed to the salvarsan. Since the introduction of this drug our cases of syphilis have been studied and watched as never before. Wechselsmann's statistics of cases examined before treatment with salvarsan show that more or less grave lesions of the optic nerve without loss of vision occur in about 3% of cases of syphilis in an early stage. Becker's statistics, made two years before the introduction of salvarsan, give about the same proportion of optic nerve disease in early syphilis. If salvarsan affected the optic nerve it is reasonable to suppose that it would produce a lesion like that of other arsenical poisons, — a descending peripheral atrophy of the nerve. The cases of diffuse optic neuritis that have been recorded as developing after salvarsan may safely be ascribed, I think, to the syphilis and not to the salvarsan. I have recently seen my first case of this kind.

A young woman with a recent infection, a generalized macular rash, a sore throat and a 4+ Wassermann reaction received 0.4 salvarsan in iodipin April 29. I did not see her again till June 10. Her throat and cutaneous symptoms had disappeared within ten days, she had gained in weight and was feeling well. She complained, however, that there had been a blurring of vision in the right eye for the past three days, and an examination disclosed a beginning optic neuritis of that eye, with a slight congestion on the other side. I gave her at once an injection of the salicylate of mercury, and the next day a second injection of salvarsan in iodipin.¹ This treatment illustrates at least my personal conviction that the optic nerve lesion is a part of the syphilis and not an effect of the salvarsan. I should, however, decline to give the drug in any case of syphilis which had previously been treated with an arsenical preparation.

A number of deaths have occurred after sal-

¹ The optic neuritis disappeared within three weeks; the patient received only a single dose of mercury.

varsan, many more, I have reason to believe, than are recorded in the literature. These deaths, when they are not directly due to a grave error in technic, have occurred for the most part in feeble, debilitated, marantic individuals who would probably soon have succumbed to their syphilis, and in patients with diseased kidneys or heart muscles. I have elsewhere referred to chronic alcoholism as a contra-indication to the use of salvarsan, and I desire here to emphasize this point. These patients often have bad hearts and almost invariably grave lesions of the kidneys. In general, I should say that there is no serious danger from the use of salvarsan in any ordinary case of syphilis with such fairly normal organs as we are likely to find in these cases, who for the most part are young people in the prime of life.

I should sum up my impressions of salvarsan in the treatment of syphilis by saying:

That it is the most effective drug we possess for the symptomatic cure of the active lesions of the disease.

That its best effect is produced by an intravenous followed by an intramuscular injection.

That while one or two injections are not likely to cure the disease they will materially advance its cure.

That its use, together with treatment by mercury or sometimes by iodides, will bring about a negative Wassermann reaction far more certainly and more quickly than is possible with mercury alone.

That properly used it is practically harmless even in repeated doses.

PERSONAL EXPERIENCE WITH SALVARSAN.*

BY ABNER POST, M.D., BOSTON.

In the excitement which has followed the introduction of Ehrlich's great remedy, we are in danger of undervaluing the drugs that we possessed before salvarsan existed.

In 1895, Dr. R. W. Taylor wrote in his most valuable textbook, "The experience of more than three hundred years has shown in no uncertain manner that mercury has the most marked and salutary effect in the treatment and cure of syphilis, and that if properly handled it may almost be termed an antidote or specific for that dread and potent disease."

Another author wrote about the same time something to the effect that "in nothing does man approach so nearly the power of the Creator as in the use of the iodide of potash."

Before salvarsan it was a relief to find certain lesions were syphilitic and not cancerous, for that made us sure that we could cure them. Persistent headache and osteoscopic pains vanished almost like magic before our old-time syphilitic medication.

Experiments on apes showed that it was possible to inoculate and then destroy the poison *in situ* by calomel ointment — and one daring medical student repeated the experiment in his own person with success.

There is no doubt whatever that in mercury and iodide of potash we have remedies that produce, at times, effects which deserve to be called miraculous; but the name of specific has come to be applied with less assurance. As our knowledge of the sequelæ of syphilis has increased, mercury has grown less satisfactory. In the sentence just quoted from Dr. Taylor, it was said that when properly handled mercury was almost a specific, but there was no uniformity of opinion as to form of drug or method of administration. Under the older treatment, a series of years was required for a cure, but the great fault in medication has been that after no matter how many years, there was no positive assurance that our patients were cured. No matter how faithfully, nor how long, nor by what method our patients were treated, some small percentage of them were sure to show late lesions of a more or less serious character. It has become painfully evident that mercury is a most valuable remedy, but that with our present methods it cannot be called an infallible cure.

Personally, I have been inclined to believe that in mercury we had the necessary agent, but that we did not know how to use it; that better knowledge and better methods of controlling dosage and gauging effects would eventually make it nearer the specific that it was once supposed to be.

Perhaps the final explanation of the difficulties in treatment will be that there are different varieties of spirochetæ, some of which are followed by late lesions, while others are not.

Syphilis seems to be a malady in which the natural history of disease has been neglected — or rather the supposed remedy has been studied in preference to the disease. Starting with the assumption that mercury must cure when properly handled, it follows, when the disease persists, that the remedy has not been properly handled — perhaps the doctor did not know; perhaps the patient was unfaithful. Whatever the explanation, it certainly is the fact that recurrences are too frequent. Serious late lesions occur probably in a small percentage of the total number of syphilitics, but they are much too common to allow us to rest content.

There have been for many years attempts to find more effective methods of treatment. The different combinations of mercury and iodine introduced within the last few years are very numerous, and salvarsan, while its composition is based upon scientific data which differentiate it from its predecessors, is only the last of a series of arsenical preparations. In attempting to appreciate the value of a new remedy, it is necessary to recall that syphilis is a chronic disease. There is a pessimistic view held by some that it is incurable, though the more hopeful among us believe that it is incurable only in a minority of cases. It is characterized by remissions, during which it is utterly unrecognizable, and it is a disease which varies so much in symptoms as to present cases so widely different that it is hard to believe that they have a common origin. We must also remember that we have already remedies which, with all their faults, hold the very highest rank

* Read at the annual meeting of The Massachusetts Medical Society, June 13, 1911.

among remedial agents. There are to be considered, then, certain difficulties in estimating the value of new remedies.

In the first place, in speaking of salvarsan, a single year is not a long enough time in which to fully test its value, but it is long enough to gain a very great deal of information.

It is already demonstrated that salvarsan does not always cure the disease at a single dose. Recurrences are much too frequent to allow us to believe that they are accidental or exceptional. It is, however, recognized that the signs of the disease disappear in a wonderful way after its administration.

The fact has been demonstrated that doses may be repeated without harm. The theoretical danger that a race of spirochetæ would be raised, by the survival of those that outlived the first dose, that would be practically unconquerable, has fortunately not been realized. Second and third doses are perfectly practicable.

Syphilis presents so large a variety in its manifestations that we may properly consider the effects of drugs upon these separate varieties.

Having assured oneself that salvarsan is not going to be an absolute antidote, the first question may well be, "What will it accomplish in those cases which prove refractory to earlier methods of treatment?"

My cases are all from private practice, and are already so scattered that no attempt has been made to tabulate them. With my colleague Dr. Morton Smith, over one hundred and fifty cases have been submitted to the action of the drug.

The first cases were carefully chosen from those which were not acting well under treatment by mercury and potassic iodide. They comprise a variety of lesions,—destruction of the nasal bones, perforation of the skull, obstinate ulceration of the throat, recurrent iritis, keratitis, disease of the ribs, and of the testis,—all of these cases improved with salvarsan.

My first case will illustrate this series.

His disease had lasted eleven years. It had disappeared quite readily at first and the patient had thought himself cured, but at the end of two years it had returned and attacked the bones of the nose, and for nine years in spite of faithful and intelligent treatment it had persisted. At the time I first saw him the nose was swollen and tender. There was slight discharge and odor, with headache. The bony structure was fast being eaten away, and I was warned by Dr. R. A. Coffin, who saw him for me, that if his nose was to be saved there was no time to be lost. For nine years he had treated it in different parts of the country, always putting himself under the best medical care available, once spending several weeks at the Arkansas Hot Springs, where he had daily inunctions. After nine years of continuous medication, he could see only constant progress in his disease. The attitude of the profession towards the disease and mercurial medication was illustrated by a little incident in this case. Shortly before I saw the patient he called upon a throat

and nose specialist in one of our large cities, who exclaimed on seeing him, "Why! how on earth did you *allow yourself* to get into such a condition?" a most discouraging remark to a young man who had for nine years spent his best endeavors in attempting to better his condition.

This young man gladly submitted himself to salvarsan. I explained to him that I had never administered it, that it was my first case, and he answered that he would put himself into my hands, that I should do whatever I liked, for unless I could help him, he was hopeless. The drug was injected beneath his shoulder blade in neutral solution. He laughed at me when I explained to him that he would probably have pain. He had little rise of temperature. He was unwilling to stay in bed because it was unnecessary. The week in the hospital that I had predicted for him he begged me to shorten. There was absolutely no necessity for so long a detention. At the end of a few days the fetid odor left his nose, the ulceration healed, leaving an absolutely healthy nostril behind it, in which no sign of disease could be discovered. Headache disappeared; appetite and sense of well-being returned, and the man was apparently well. He made long journeys to see me at intervals of a fortnight, and for three months he was apparently perfectly well. At the end of that time there was a little puffiness beneath one eye, and Dr. Coffin recognized a return of the disease.

His first subcutaneous injection was made in October. In February an intravenous injection was made. His symptoms again disappeared, and when I saw him a fortnight ago there had been no return, but the lump beneath his scapula, where the first injection had been made, still remained and was still tender.

Surely here was a case which was most encouraging. What evidence could make one more enthusiastic over the new drug?

A series of cases followed very much of the same character, involving disease of bone, ulceration of the throat, disease of the testis, ulcerations, etc., all of which healed in the same wonderful manner. Various cases of obstinate desquamation and deep ulcerations of the hands healed. Of these, several cases have required a second injection, but all are manifestly better up to the present time from the use of salvarsan. Of these cases one has had an abscess underneath the scapula. I doubt very much if that was the fault of salvarsan *per se*. I do not believe that the injection was in his case properly prepared. Anyway, injected in October, that young man has still an open sore beneath the scapula, which discharges but slightly. The slough, which was a chemical slough and contained no sign of bacteria, has largely come away, but the wound is not yet entirely healed. This young man, in addition, had a recurrence of the deep ulcerations of the palm and has received a second application of the drug, this time an intravenous injection; all symptoms have again disappeared, and he is apparently well, save for the as yet unhealed ulcer beneath his scapula.

With such experience in these mercury-resistant cases, one must of necessity go on to other cases. These cases were injected subcutaneously in the first three, eight intramuscularly, and since then I have used only the intravenous injection, and that directly into the vein by the Schreiber needle, without finding so far the necessity of cutting down on the vein. There are some 150 such cases, of which I cannot give an actual tabulation. They are all cases of private practice. Some of them have disappeared. They are difficult to follow, but they have left upon my mind very vivid impressions.

The cases of the application of salvarsan to primary syphilis have not been numerous, some six or eight perhaps only, but the primary sore has healed without exception very rapidly, much more rapidly than is usual with mercurial applications. The danger to the community from these cases has been greatly lessened. A young girl, a domestic, inoculated with a sore on the lip, is an extremely good example. She was obliged to earn her own living. She lost her place as a domestic, very naturally. The sore, on the application of salvarsan, healed within a very few days and left her absolutely without any sign of the disease whatever, and no further signs have followed, though the time is long past when secondary symptoms ought to have occurred. She has found employment in a family who know the conditions. There has been accomplished in her case in a few weeks a result which would have required many months with the old method.

But while the primary sore itself heals with great rapidity, the glands in the immediate vicinity do not disappear so rapidly, and it has seemed wise in most of these cases to keep the patient upon mercury in addition to the original dose of salvarsan, and to hold oneself in readiness to repeat the salvarsan.

In secondary syphilis salvarsan is certainly of very great power, but the marked papular eruptions do not disappear as readily as one would hope; they fade somewhat, but absorb much more slowly than one would expect from the rapid action on the primary sore. The moist lesions — lesions of the lips, which make cases particularly dangerous to their associates — heal, almost without exception, with wonderful rapidity.

Of cases that may be called tertiary, I have practically already spoken in speaking of cases of mercury-resistant disease. Many of these cases have required the administration of the drug for a second time, and I cannot help feeling hopeful that they are on the road to permanent recovery. By no means, however, can one feel as yet absolutely sure.

Nervous cases are the ones in which one would like to see the drug act with good effect, but one cannot expect salvarsan or any other miraculous drug to restore nerves that are destroyed, but perhaps the drug acts in limiting further destruction. For instance, I have two cases of tabes in which the pain has been extremely great. One individual has certainly come very near dying at various occasions from the severity of the pain

through the abdomen and down the legs. He has become a confirmed morphine taker, and is laid up every once in a while by severe crises. Salvarsan worked wonders in his case. The pains have practically disappeared. The amount of morphine that he takes has been diminished by at least two thirds. I am perfectly well aware that such crises are absent for a long time, and that it requires a very long time before one can feel certain that it has actually done such patients any permanent good; but, so far, that man and his family both affirm that the pains have been absent for a longer time than before, and he certainly has a great temporary comfort.

The same is practically true of the second case. The patient is not restored to health, but the uncertainty in his gait and his pains have diminished very decidedly.

There is one very interesting case which has come to my notice in which the value of the drug is as yet undetermined because the test has not yet been fully carried out. This was the advent of a man and his wife, in my office, who told a story something like this: They have a perfectly healthy child six years of age. At about the time this child was born the man acquired syphilis. In the intervening six years the mother has given birth to two children, both of whom died with syphilis a very few days after birth. The mother has shown absolutely no sign of syphilis, though she has borne and nursed these two syphilitic children. Now this father and mother desire healthy children. The Wassermann reaction in both father and mother was positive, and the positive Wassermann reaction in women of that class is extremely interesting. We know that women who have borne syphilitic children are practically syphilitic, although without signs of the disease. The Wassermann reaction has been found to be positive not only in this case, but in a long series of cases in the hands of other observers. This husband and wife have each of them received salvarsan, and the result in their family can only be determined at some future date.

The dangers of salvarsan most certainly cannot be passed over. Deaths, deafness and blindness have all been reported as results of its administration, none of which have so far happened in my experience; but even a very limited experience with the drug affords evidence that it is a drug of dangerous possibilities. When it is given intramuscularly, it is attended by very great pain, and the patients almost without exception require morphine during the first twenty-four hours. When it is given intravenously, there is no pain unless some portion of the drug is injected into the tissues outside the vein, which fortunately can usually be avoided; but some form of intestinal disturbance is present in a very large proportion of cases. Some patients are nauseated, some vomit and vomit seriously, some have serious diarrhea sometimes lasting for two or three days, though usually only an hour or two, and it has been my fortune to meet with one case of scarlatiniform eruption. This occurred in an individual with cerebral disease. After his second injection he

had a very high temperature, and in the morning was covered with a scarlatiniform eruption which was very bright, which, however, disappeared within forty-eight hours.

Two of my earlier cases of intramuscular injection had an experience which caused temporary alarm. In one the elbow, in the other the ankle, within forty-eight hours of the injection, became swollen, hot and painful. There were no unusual symptoms at the site of injection. The afflicted ankle-joint became normal within a few days. The man with the elbow did not return to report as he should have done, but was known to be using his arm a few weeks later in his ordinary occupation in a perfectly normal manner.

While the experiences with the drug at my hands have never been dangerous, they have been so marked as to make me feel that we are dealing with a dangerous drug; that every dose is an experiment; that sooner or later we shall meet with some individual who is especially sensitive to arsenic, with perhaps fatal results, and that fatal results cannot be absolutely avoided except by sticking to a dose which experience has shown to be practically safe.

I cannot help feeling that there is a certain analogy between mercury and salvarsan. Both of them are toxic; with both we get apparent cures; with both we get recurrences. Salvarsan certainly acts more quickly. It certainly gives us apparent cures in cases in which mercury has failed; but we find occasionally cases in which the real value of salvarsan is doubtful. Most of these cases, I am glad to say, occurred during the earlier demonstrations of the drug, so that we may hope that they were due to faulty technic or dosage. We do not yet know that our patients are cured, but we certainly have in this drug a wonderful addition to our therapeutic resources, not necessarily an antidote, but certainly a wonderful help. I cannot help feeling that it makes possible the public care of the disease as was never before possible. Boards of health have hesitated to take charge of cases which they must keep for months before they could be considered safe to the public. The possibility of removing the contagious symptoms within a few hours or days puts a different aspect upon the matter and renders the care of such patients practicable.

It is not to be expected that this remedy will remain as it is. Ehrlich or some one will doubtless modify it in such a way as to make it more stable and easier of application. Perhaps it will be entirely superseded by another remedy even more reliable. Without doubt it is the first step towards a future of which one can only dream.

Certainly, I cannot but believe that the control of syphilis is much nearer at hand than it has ever been before.

There is one further effect of salvarsan that is worthy of mention. Syphilis has been a tabooed disease, which one spoke of only with reticence and with careful choice of the audience. Salvarsan has introduced it to the community. It is now possible to mention it in newspaper items or magazine articles. I am sure that such publicity

will go a long way towards helping us to recognize it, to study it, to treat it and eventually to cure it.

DISCUSSION.

DR. BOOS: I would like to say that I think that the method which Dr. Pollitzer uses to dissolve the "606" in the very same receptacle in which it is mixed has an element of danger. In a recent medical paper a man has published a method for the intravenous application of "606" in which he uses a very complicated apparatus. It will do away with the possibility of any sediment of any substance which might possibly do harm in the vein if carried into the vein. Very frequently little splinters of glass, which are not observed when you open the salvarsan, get in. I think it only fair to the patient, and wise in every case, to do something to prevent such sediment from being carried in. Sometimes it is a thread, sometimes one of those little fine particles of the gelatinous particles of salvarsan which has not gone into solution. Even by Dr. Pollitzer's method that might happen; so I think it wise always to filter the solution through a sterilized filter before putting it into the veins of the patient.

DR. E. MYERS: I would like to ask the amount of salvarsan used; that is, has there been a change in the amount decided on at the meeting on salvarsan at the Massachusetts General Hospital, when, I believe, it was four tenths of a gram for one hundred pounds of adult weight?

DR. BOOS: I can give Ehrlich's statement published last month. He said that six tenths of a gram intravenously for an adult was too large a dose, and recommended four tenths of a gram for an adult, irrespective of weight, to be repeated twice intravenously.

DR. TOWLE: I think the gentleman refers to a statement I made. I said in the course of our investigations we had not been able to decide upon any definite dose. We accepted these statements of Ehrlich, that it should be so much and so much, but so far as any rule was concerned we had been absolutely unable to discover any. It occurred to me that it might be of value, therefore, to determine so nearly as possible the proportion of the weight of the body to the size of the dose, and to try in that way to determine definitely the relationship, then to follow the cases through and to compare the results with the different proportionate doses, hoping that we might get some line upon a definite rule for dosing. That was nothing definite — simply a suggestion made at the Massachusetts General Hospital meeting.

DR. BOOS: In response to a question whether in giving salvarsan to the mother of a nursing child, that mother should be allowed to nurse her child, and if the arsenic will affect the baby or whether it will not, there is an article which was published only last week that goes into detail on that question. The two original men who spoke of the mother nursing her child found, after the intramuscular injection of salvarsan, the child was benefited. The syphilitic symptoms disappeared. After the intravenous injection this was not the case. In the cases described in detail the children, instead of improving, became very much worse. A peculiar thing happened about thirty-six hours after the nursing; the children, in both cases, had a very typical syphilid — a true syphilitic picture. These children became steadily worse. He found, as Dr. Pollitzer said, that the only thing that bettered them was to take them from the breast and administer potassium iodide and ordinary cow's milk.

DR. POLLITZER: I want to say just a word in regard to the use of the salvarsan unfiltered. Dr. Boos spoke

of the danger of the splinters of glass. That has been referred to. Well, of course, I use no glass beads. There is no necessity for it. The salvarsan is put directly in a large quantity of water. The water is taken first and the salvarsan dropped carefully on the surface of the water and then agitated. There is, of course, nothing added which should give a precipitate.

If one uses clean water and nothing but salvarsan and a clean vessel, one has a clean solution. There are no gummy particles of salvarsan if the water used is hot and one agitates sufficiently long. In other words, I get a perfectly clear solution.

As to the danger of splinters of glass, that of course exists, but in the first place, inasmuch as the dose of salvarsan contained in the ampules is at least six decigrams and one is not going to use at most more than five, perhaps not more than four, I have made it a practice after opening the tube of salvarsan, which I hold at a slightly oblique angle, to gently tap it so a little of the salvarsan spills out. That will take out any particle of glass which may have fallen down into the tube.

They have spoken of 200 ccm. of water. I think that it is a mistake to make it so concentrated. It is evident that this solution is an irritant to the tissues. If it were not for the time consumed and for other reasons we would do better, I think, to make our solution in 600 ccm. of water, not 200 or 300. I have now a solution of 300 ccm., and I am not going to use it all. I therefore hold my burette vertically for a few minutes or let the nurse hold it while I look after the preparation of the arm of the patient. In that time any little particles would have settled, particularly glass; before making the connection with the rubber tube or the needle, I open my stopcock and allow anything that is settled there to flow off, allowing perhaps 50 ccm. of the entire fluid to run out. That will take out any possible particles in the solution.

Dr. Boos: I have just one more little objection to Dr. Pollitzer's method. In his apparatus he had no method to clear the needle. There are certain cases of syphilis in which the blood coagulates very rapidly, and where after introducing the needle, when you connect to make the injection, the infusion simply won't go through the needle. To have some apparatus connected with the infusion apparatus is a very good idea, and I think it is a wise precaution to have one. Perhaps Dr. Pollitzer never had a case with such great tendencies to coagulation.

THE FREQUENCY OF VENEREAL DISEASES. A REPLY TO DR. CABOT.

BY PRINCE A. MORROW, M.D.,

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THE paper of Dr. Richard Cabot entitled, "Observations Regarding the Relative Frequency of the Different Diseases Prevalent in Boston and Its Vicinity,"¹ has only recently been called to my attention.

About one half of the paper is devoted to a study of the frequency of venereal diseases based upon an investigation of the Boston City Hospital, the Massachusetts General Hospital and the Long Island Hospital. As a basis of comparison with statistics drawn from the above-named hospitals, Dr. Cabot takes the statistics

given in my book on "Social Diseases and Marriage" of the prevalence of gonorrhea and syphilis in the adult male population and, at the same time, attempts to discredit them in advance by classing them in the category of the "many wild guesses published for campaign purposes."

In his opening paragraph upon statistics, he says:

"Many wild guesses about the proportion of adult males afflicted with venereal diseases have from time to time been published for campaign purposes, but so far as I know there is up to date no solid basis for estimate upon this matter. Thus Dr. Prince A. Morrow in his book on 'Social Diseases and Marriage' (page 25) states that 'we do know that gonorrhea is the most widespread and the most universal of all diseases in the adult male population, embracing 75% or more. The prevalence of syphilis, though not nearly so universal, is variously estimated at from 5 to 18%.' No authority or source for these figures is given in the text, and how they were arrived at I am unable to conjecture."

I cannot too emphatically repudiate the charge that the statistics given in my book were published for campaign purposes. The estimate in question was given on the authority of Neisser, the discoverer of the gonococcus, and other German authorities. It was based upon long and carefully conducted investigations of venereal morbidity in Breslau, and collated statistics from other German cities. Its substantial accuracy has been concurred in by leading specialists in this country as well as in Europe. It has been so long uncontroverted and so often quoted that I did not deem it necessary to refer specifically to the authorities.

In a later utterance, "Health and Disease in Relation to Marriage and the Married State," edited by Senator and Kaminer, Dr. Neisser says (Vol. II, page 483), "The assertion that of the adult male population inhabiting large towns permanently or temporarily, only an insignificant proportion escapes gonorrheal infection is probably, extreme as it may sound, not at all exaggerated."

It will be admitted that the exact proportion of venereal morbidity in any community does not admit of mathematical expression; the same is true of tuberculosis, leprosy and many other diseases. As stated in my book in the paragraph immediately preceding that quoted by Dr. Cabot, "Its prevalence escapes recognition and must always remain an unknown and unknowable quantity." But the facts of our knowledge are not based upon statistics alone. The accumulated experience of specialists, who have had large opportunities for observation and are qualified to judge, becomes, at last, scientific fact.

Briefly analyzed, Dr. Cabot's statistics may be divided into three categories:

(a) At the three hospitals above mentioned, there were treated in the eight years 1903 to 1910 inclusive, 35,852 cases of the different pyogenic infections,² 18,143 cases of tuberculosis, 5,546

¹ The Shattuck Lecture delivered at the annual meeting of The Massachusetts Medical Society, June, 1911. BOSTON MED. AND SURG. JOUR., Aug. 3, 1911.

² Among which he includes all septic diseases, all cases designated as local abscesses or boils, all cases of acne and impetigo contagiosa.