

THE RATIONALE OF CHEMOTHERAPY IN SYPHILIS,

WITH A DESCRIPTION OF SOME NEW DRUGS
PREPARED WITH THE KNOWLEDGE
GAINED THEREFROM.

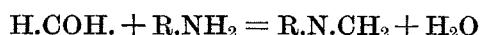
BY J. E. R. McDONAGH, F.R.C.S. ENG.,
SURGEON, LONDON LOCK HOSPITAL.

As the discovery of some new antisyphilitic remedies is only one of the links in my research chain on syphilis, it will be necessary first of all to state the steps by which this link was forged.

When I had shown that the spirochæta pallida was not the sole cause of syphilis, but only the adult male phase of a protozoon, which I named the "leucocytozoon syphilidis," it was necessary to confirm it, and this I did by working out the chemistry of the organism—a piece of research in which I was ably assisted by R. L. Mackenzie Wallis. As this chemical investigation opened up some new paths which were ultimately to lead to the solution of the *modus operandi* of the Wassermann reaction, it will be necessary to mention the salient points.

I found that the phases of the leucocytozoon syphilidis consisted mainly of a lipid-globulin, which was more resistant to reagents than the lipid-globulin of the host's cells—viz., the protoplasm of the plasma cells and of the nucleoli. Further, that its reducing action was also greater, especially in the case of the spirochætal phase, owing to its containing in its molecule a fatty acid not completely saturated. Later I found that the lipid-globulin of syphilitic sera possessed certain chemical and physical properties similar to those of the organism, and that it was derived in the former from the lymphocytes and from their offspring, the plasma cells, the protoplasm of which was also of a like nature.

The next step resulted in the discovery that the "reagin"—that is, the reacting substance in the syphilitic serum, which is responsible for the positive Wassermann reaction—was the lipid-globulin of the serum. The complement proved to be the phosphate and bicarbonate systems, which regulate the hydrogen-ion concentration of the fluid part of the serum, and that part of the oxidase-reducase system attached to the lipid-globulin particles, which regulates the hydrogen-ion concentration of the solid particles of the serum, enabling them to be kept in "solution." Complement proved to be a catalyst or, in other words, the exciter or accelerator of the linking between the reagin and the antigen particles—a linkage which proved to be a purely physical one of adsorption. The active part of the antigen appeared to be its nitrogen content, which was usually present in an amino (NH_2) form. If the amino groups were replaced by methylene imino groups with formalin, according to this formula—



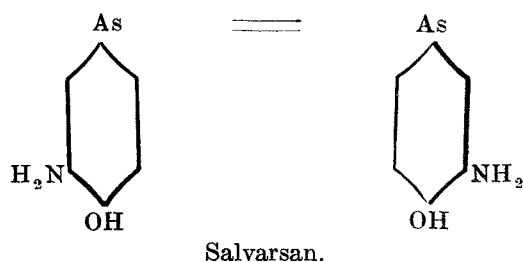
the antigenic action was increased. This was due to the fact that the methylene imino particles were larger than the amino particles. Abundant proof was obtained to show that the colloidal lipid-globulin particles of syphilitic sera had not only greater adsorptive capacities than their homologues normal sera, but that they had much bigger

molecules. From this it became clear that the Wassermann reaction was a physical reaction, depending upon certain physical properties that syphilitic sera naturally possessed, but which ordinary sera could easily be made to possess; and that it was not in any way a specific reaction.

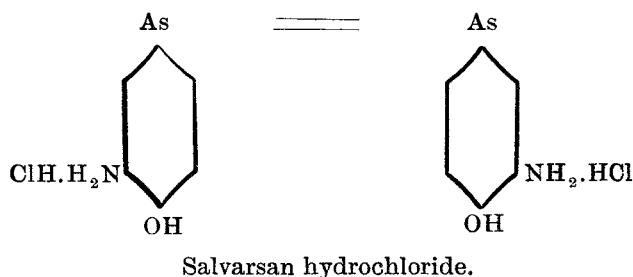
The chief points which stand out will now be seen to be (a) the importance of the amino (NH_2) groups, since it is upon the presence of these groups that adsorption is largely dependant; (b) the importance of the size of the lipid-protein colloidal particles; and (c) the importance of the physical phenomenon of adsorption.

In the data just given lies the solution of the *modus operandi* of chemotherapy in syphilis, but before explaining the rationale it will be necessary briefly to discuss the chemistry of salvarsan and neosalvarsan, and also to refer to Ehrlich's views as to the mode of action of these drugs.

Salvarsan is the commercial name given to di-oxy-di-amino-arseno-benzol. The constitutional formula of this body is the following:—



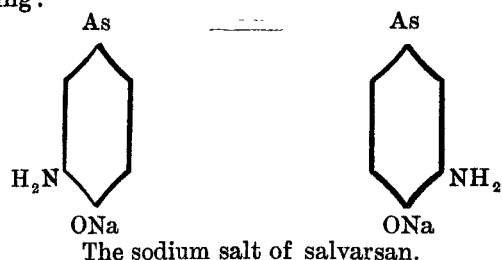
It will be seen that salvarsan contains two hydroxyl groups (OH) attached to separate benzene rings, two amino (NH_2) groups attached to separate benzene rings, and two arsenic atoms attached to separate benzene rings. The two benzene rings are linked together by the two arsenic atoms. This body has several interesting properties: 1. Arsenic is at once metallic and non-metallic in its properties; here it is tri-valent, but it may be penta-valent. 2. The amino (NH_2) group is basic in nature. 3. The hydrogen in the hydroxyl (OH) group is acidic in nature. Here, then, we have a body which is at once acidic and basic or amphoteric, and it also contains an element, which is both metallic and non-metallic and one which has a varying valency. The body is insoluble in water, and on this account the hydrochloride of the body was prepared.



The hydrochloride dissolves sparingly in water, but its solution is strongly acid; hence it is not very suitable for intravenous administration. It may be injected intravenously, and is on the whole more potent than the basic solution prepared from it, but it is at the same time more toxic.

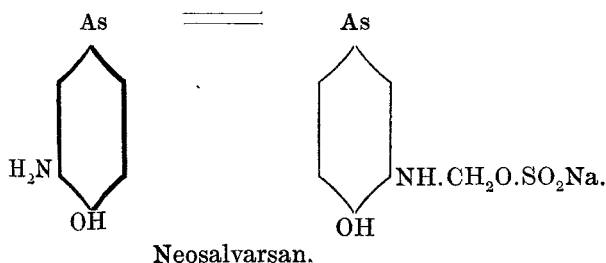
From the hydrochloride the sodium salt is prepared by adding sodium hydrate to the acid solution, and this renders it more soluble in water. Therefore the drug is generally administered in

this form. The formula of the sodium salt is the following:—



Comparing this formula with that of the fundamental substance, it will be seen that the two hydroxyl groups have been replaced by two ONa groups. The two hydroxyl groups were acidic; the two ONa groups are basic, as are also the amino groups, so that the compound injected is distinctly basic. From this it might appear that "reaction" between the phases of the leucocytozoon syphilidis, since some are more basophilic than others, and vice-versa, and the amphoteric salvarsan plays a rôle in the action the drug exerts upon the syphilitic organism. Investigation later showed that reaction did play a rôle, but it is one which cannot be fully discussed here. As a matter of fact, it is not necessary to have the hydroxyl groups in the salvarsan molecule; they are probably only there so as to prepare the way for making the compound soluble. To render the compound freely soluble it is necessary to sacrifice one or more amino groups, and any interference whatsoever with an amino group at once diminishes the therapeutic action of the drug, and that is why neosalvarsan is not so active as salvarsan.

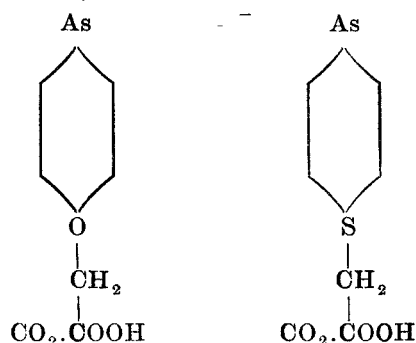
Neosalvarsan is the commercial name for sodium-di-oxy-di-amino-arseno-benzene-mono-methane-sulphonate, and its formula is the following:—



Ehrlich's work is based upon the principle that there are, in the protoplasm of the parasite, certain chemical groups which are capable of combining with certain chemical groups of the drug injected. The name given to this affinity is "chemoceptor." So far as the arsenical compounds were concerned, Ehrlich was primarily of the opinion that the sole receptors between the chemical groups in the protoplasm of the parasites and the drugs used were the arsenic receptors. That other receptors existed as well was shown only when it was noted that the action of arseno-phenyl-glycine was not affected by previously working on the parasites with an arsenic derivative of the phenyl-oxy-acetic acid and the corresponding thio-compound. The chemical formula of the arsenic compound used is shown in the next column.

Hence it was assumed that acetic acid receptors existed as well. As fatty acid receptors were said to exist in the protoplasm of the parasites, it was only logical to suppose that amino receptors would be found there also. Working upon this hypothesis, Ehrlich discovered salvarsan. According to Ehrlich, salvarsan works by means of its arsenic receptors and its ortho-amino-phenol receptors. When it was discovered that a certain drug had a fatal action on one kind of parasite and not upon

another kind, although in both instances a combination occurred, between the drug and the bodies of the parasites, some further elaboration of the



The arseno-thio derivative of phenyl-oxy-acetic acid.

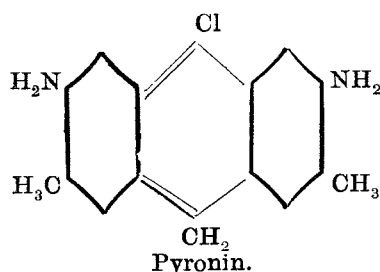
action of salvarsan was required. Consequently salvarsan was stated to act in the following way. The arsenic was considered to be the toxophore group, the benzene ring the carrier, and the amino atoms the haptophore group.

Summing up Ehrlich's views as to the mode of action of salvarsan, all that can be really said is that a union takes place between the drug and the parasite, with a destructive action upon the latter. What the nature of the union is, and why the death of the parasite should follow, are not explained. As a result of Ehrlich's statements, everyone believed that the only active principle in salvarsan was the arsenic. A little investigation soon showed me that the action of arsenic was catalytic—i.e., that it accelerated an action going on spontaneously, but more slowly without its assistance. Since mercury probably acts in the same way, it was necessary to find out why the arsenic in salvarsan should be more powerful than mercury, since, in ordinary circumstances, the latter is a more powerful anti-syphilitic remedy.

A ratio exists between the intensity of action of a catalyser and the degree of the colloid state in which the catalyser is. In salvarsan the arsenic is in a colloidal state, hence its action would necessarily be greater than that of any mercurial compound which we are in the habit of using. The proof of what has been said can be found if we compare the action that different manganese compounds have on plant oxidases. Manganese formate, for instance, has nothing like such a powerful accelerating action upon plant oxidases as colloidal manganese hydroxide. The latter is colloidal and the former is not.

It will now be seen that the action of arsenic is somewhat analogous to that of complement in the Wassermann reaction, while the double benzene ring with its amino groups is analogous to the reagin or the antigen. The reaction between reagin and antigen is one of adsorption, a reaction accelerated by the catalyst complement. The reaction between the syphilitic parasites, the lipid-globulin molecules of the serum, and the amino groups of salvarsan is also one of adsorption, a reaction accelerated by the complement present, allowing the arsenic to fulfil its action in increasing the amount of active oxygen. Not only does adsorption take place between salvarsan and the phases of the leucocytozoon syphilidis, but also between the drug and the colloidal lipid-globulin molecules of both the serum and the plasma cells. Therefore Ehrlich's statement that the drug is parasito-tropic only, and not organo-tropic, cannot hold good. For a drug to be parasito-tropic it must be organo-tropic. Indeed, its organo-tropic properties are more important, since most of the organisms are killed indirectly.

In Ehrlich's own work there appear to me to be two points which require very careful consideration. One is, that parasites which have been rendered arsenic-fast are also pyronin-fast; and the other is, that although salvarsan may be linked on to a parasite it need not necessarily prove fatal to that parasite. If there is a relationship between arsenical immunity and pyronin immunity it cannot be the arsenic to which the parasites become immune. If the formula of pyronin is studied:



it will be noticed that there are two amino groups. Now, there are two amino groups in salvarsan, and, from what has been already said, it would appear to be due to these two amino groups that the drug becomes attached to the syphilitic parasites, the plasma cells, and the lipid-globulin molecules of a syphilitic serum. Note that the amino groups in both salvarsan and pyronin are in the ortho position.

The fact that salvarsan can become attached to parasites, and yet not be fatal to them, is an observation in which there is a great deal wrapped up. During the time when I was working at the rationale of the Wassermann reaction I thought that for adsorption to take place between two molecules, both of which possessed amino groups, it was necessary that they should have homologous stereo-chemical molecular configurations. This idea soon proved to be wrong when fixation occurred of a non-specific antigen and of an antigen whose amino groups had been converted into methylene imino groups by formalin, respectively, with the serum lipid-globulin from a case of syphilis. As a result of further experiments I proved that the complement-fixation test, as applied to syphilis, in contradistinction to the true bacterial complement-fixation tests, depended not upon the molecules having homologous stereo-chemical molecular configurations, but solely upon their number and size. Application of this to the action of salvarsan confirms the points just mentioned. The attachment of salvarsan to the syphilitic parasites, to the plasma cells, and to the lipid-globulin molecules in the serum in a case of syphilis cannot possibly be due to an homologous stereo-chemical molecular configuration between the adsorbed molecules, since for one thing alone salvarsan is an optically inactive body. The adsorptive capacity as a whole appears to be greater in the case of a syphilitic serum than in the case of a serum from any bacterial disease, and it appears to be greater according to the stage of the disease.

As the lipid-globulin molecules from a late case of syphilis are richer in carboxyl groups than those from an early case of syphilis, it follows that any substance they happen to adsorb will tend to break down the molecules. The first action of breaking down the lipid-globulin molecules is to increase the area over which they can work; hence the reason why late syphilitic lesions disappear more quickly under treatment than do early ones. In my opinion, in the case of syphilis and in all protozoal diseases, the lipid-

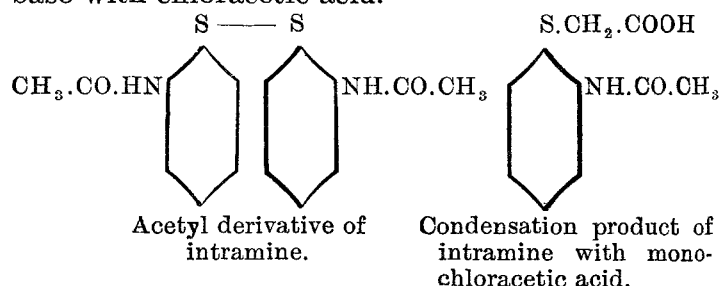
globulin molecules appear to be bigger and to have a greater adsorptive capacity than the lipid-globulin molecules in the serum of bacterial diseases.

The bigger the size of the molecule, and the greater its adsorptive capacity, the more easily will a drug like salvarsan be adsorbed and the more readily the adsorbed compound will break down. When the lipid-globulin first breaks down the area of its action is widened; hence the catalytic action of the arsenic will have its fullest play. If salvarsan became attached to a small molecule the adsorbed compound would not break down; at all events, not until much later than it does in the case of syphilis. This would mean that the arsenic would get little chance of acting as a catalyst. Therefore salvarsan only acts in protozoal diseases because of the physical state of the lipid-globulin molecules of the serum, and it fails to act as a bactericidal agent because the lipid-globulin molecules in the serum of bacterial diseases do not possess the requisite physical properties. This shows how important the organotropic properties of the drug must be.

Salvarsan becomes attached to the lipid-globulin molecules of the syphilitic parasite, the plasma cells, and the serum by virtue of its ortho-amino groups and of the peculiar physical properties of protozoal lipid-globulin. It attacks those phases of the leucocytozoon syphilidis in which reaction is most marked, especially the spirochætal phase, in virtue of its free hydroxyl groups directly, while its main action on the other phases is indirect. The arsenic presumably becomes converted into an hydroxide, in which form it acts as a peroxidase. The action of a peroxidase is to convert a peroxide into active oxygen. If active oxygen is formed in this way it is only natural to suppose that an analogous process exists to produce active hydrogen. In other words, the existence of an oxidase system necessitates the presence of a reducase system. All we know of a reducase system is that in vitro an extract of liver in the presence of an aldehyde will convert methylene blue into its leuco-base owing to the free hydrogen that is formed.

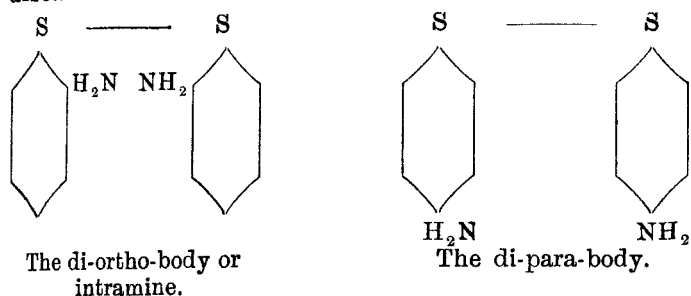
As a result of experiments, into which I cannot go farther here, I found that, in vivo, it was probably a di-sulphide protein which took the place of the liver extract, which in the presence of a perhydride formed mercaptan, peroxide, and active hydrogen. As a metallic element is necessary for the oxidase system, a non-metallic element appeared to be necessary for the reducase system—namely, sulphur. Therefore it struck me that the action of salvarsan, which I considered acted as a peroxidase, might be enormously enhanced if a markedly adsorbed sulphur compound could be prepared.

I prepared two basic and two acidic compounds. The first acid compound was the acetyl derivative of di-ortho-amino-thio-benzene, and the second acid compound was the condensation product of the base with chloracetic acid.



These two products may be quickly dismissed, as both were extremely painful when injected intra-

muscularly, and their therapeutic action was practically *nil*. The two basic compounds prepared were, di-para-amino-thio-benzene and di-ortho-amino-thio-benzene. As the therapeutic action of the former was not so good as that of the latter it was discarded.



Di-ortho-amino-thio-benzene is called, for short, intramine—a name registered by the British Drug Houses, Limited, who have kindly consented to supply the drug.

Although I thought I was the first to prepare this sulphur compound, I find that B. Hofmann had prepared it in 1879 and in 1887 by oxidising ortho-amino-phenyl-mercaptan with ferric chloride. K. Hofmann, the son of the former, in 1894 also prepared the same body by heating aniline with sulphur. Both father and son were working on the thio-anilines at the time, and neither prepared the substance for any therapeutic purpose. The same thing happened to Ehrlich, as the compound from which "606" was synthesised was isolated by Béchamp in 1863.

Intramine is a pale yellow crystalline body, insoluble in water, but soluble in ether, alcohol, and acetone. It is best put up as an emulsion in olive oil, in which it is suitable for intramuscular administration. A lecithin adsorption compound of intramine can be prepared for intravenous administration. Ehrlich found that the *dosis tolerata* of salvarsan for rabbits was 0.1 gm. per kilo. Therefore, when I say that several times that amount of intramine can be injected into a rabbit weighing only 85 gm. it will be clear that intramine is an absolutely non-toxic substance. The biggest single dose I have given to a human being is 12 gm. without any untoward symptoms arising; 3 gm. can be injected every third day with impunity. When compared with salvarsan, I found that in the primary and generalisation stages salvarsan was superior to intramine, but that in the recurrent stages the opposite was the case.

If my theories on oxidation and reduction are correct the above is only what one would expect, as in some of my previous work I showed that oxidation was more to the fore than reduction in early syphilis, and that the reverse was the case in late syphilis. Moreover, if correct, then it would be expected that, if an oxidising agent was used in early syphilis first, the action of a subsequently administered reducing agent would be enhanced. This is exactly what happens. If in early syphilis a metallic compound is first injected and then intramine, the symptoms vanish very much more rapidly than if subsequent injections of only the former had been prescribed. To cite a case.

A man came to see me on a Monday with a chancre on the corona, which was slightly ulcerated and very indurated. An intravenous injection of galyl (40 cgrm.) was given and an intramuscular injection of intramine (2 gm.) made three days later, by which time no change had taken place in the sore. On the following Monday the sore and induration had completely vanished.

Severe papular syphilides which are often so resistant to the arsenical compounds can be made to vanish in a week if a dose or two of galyl is followed by one of intramine. In the recurrent stages, especially in gummata, the action of intramine is so rapid that, as a rule, the gummata have healed before an injection of a metallic compound would have been given.

I gave an out-patient one Saturday, who was suffering from gummata, which surrounded the corona, affected the whole of the under surface of the penis, and extended on to the scrotum, an intramuscular injection of intramine (3 gm.). By the following Saturday every lesion had healed.

When I came to realise that metals acted as oxidising agents and non-metals as reducing agents, I tried other metallic compounds to see if they would take the place of the arsenical products. As a result of several experiments I found that certain colloidal compounds of iron and aluminium—namely, their hydroxides, which I had converted into emulsoids with glycine, gelatin, or albumin—when injected intravenously acted tolerably well in early syphilis, and they also had the effect of increasing the action of intramine. Colloidal iron and aluminium compounds have a very great advantage over the arsenical drugs, as they are non-toxic, but to obtain an action equal to, or superior to that of, salvarsan it will be necessary to prepare more strongly adsorbed compounds than the hydroxides. Such compounds, I am glad to say, I have been able to prepare, but the dosage and the best method of administering them has yet to be determined.

I have treated over 80 cases with intramine, and the results, provided the rules suggested are adhered to—namely, salvarsan first and then intramine in early syphilis, and vice versa in late syphilis—are very much better than even the best of those obtained with salvarsan when it first came out. Several cases have healed at once with one injection, when they remained practically uninfluenced by an arsenic preparation and subsequent treatment with mercury and iodides. The pain caused by the intramuscular injections varies in different individuals, and is sometimes considerable, but it quickly passes off, and the swelling caused soon becomes absorbed. On the second and third days after the injection a rise of temperature to, in bad cases, as much as 103° F., is sometimes witnessed, but beyond this I have never noticed a toxic symptom.

Space forbids my going further into the subject of chemotherapy here, and, furthermore, it is to be the main theme of my Hunterian lectures in March. Nevertheless, I have said sufficient to show that my previous statement, to the effect that arsenic was not necessary, is correct, and when I state that intramine is more active in destroying the very phases of the leucocytozoon syphilidis which salvarsan does not, and vice versa, I think I am justified in saying that the last link of my syphilitic chain confirms the correctness of those forged before.

I wish to thank Mr. J. Ernest Lane, who has been so kind in giving me facilities for in-patient work at the London Lock Hospital, Mr. J. Patterson, for the great assistance he has rendered me in the chemical part, Dr. H. Spence in the clinical part, and the British Drug Houses, Limited, for the help given and interest taken in the work.

Wimpole-street, W.