HISTORY, ACTION AND THERAPEUTIC USES OF SALVARSAN, (EHRLICH-HATA "606").

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by

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INTRODUCTION.

The introduction of any drug which holds out some prospect of success in the treatment of spirillar and trypanosome diseases must, of necessity, attract great attention but no remedy has, up to the present, caused such a furore as Salvarsan. Although quinine, salicylates and tuberculin have all had great ovations they have not created such a universal enthusiasm as "606". Medical men have described its effects in glowing terms and the lay press has contained some extraordinary statements about its curative properties.
All these statements err on one point - the mention of the word cure. It cannot be too strongly insisted that we cannot promise that yet and the circulation of false powers will bring disappointment to some people and throw some discredit on the drug. On the other hand accounts of amaurosis after it are erroneous and they will tend to limit its use unfairly. Wechselmann, Ernest Lane, Pernet, Hutchinson and others have all tried to moderate the excessive enthusiasm which has arisen about it.

In a third way false statements have been published. Some say it will supplant mercury and iodides but that is impossible. Cases are on record where these old and trusted remedies have acted and Salvarsan failed. There/

There is no doubt however that it will limit their use.

It marks the commencement of a new era in the treatment of parasitic diseases and, in time, it may become the parent of new substances which may have a still better action. At present it is doing excellent work and if we improve its technique and dosage or combine it with other substances we may, in time, wipe out the scourge of syphilis which has done so much evil since the middle ages.

THE HISTORY OF SALVARSAN.

The discovery of Salvarsan is not the result of an accident, but is the outcome of extensive biological and chemical investigations, conducted by Professor Ehrlich, to discover a substance which would destroy parasites without injuring the host. By the word parasites is meant spirilla and trypanosomes.

Before Ehrlich commenced his profound experiments, parasitic diseases were empirically treated by drugs which ameliorated symptoms or had a definite effect upon the causal organisms. In some cases the patient was cured but in others he only obtained a temporary relief and the disease recurred again. This was due to the fact that the tissues, assisted by the drugs employed, could not overcome the parasites. Ehrlich noticed/

noticed this and determined to discover how remedies acted and also how they could be applied most appropriately for therapeutic purposes. His recognition of the fundamental idea of the failure of drugs to cure these diseases is responsible for the great success which has followed his researches. As an example we may state that Donovan and others employed arsenic in syphilis but the results were not permanent. Ehrlich, on the other hand, used forms of arsenic which he had studied experimentally in connection with his fundamental conception and his results bid fair to become permanent.

All his work is embodied in chemotherapy, a form of experimental science founded by him for the study of the action and employment of remedies and the history of Salvarsan, its latest production, is an account of the steps in the development of the science itself.

In order to trace the history of Salvarsan we must go back to the year when Ehrlich was a medical student in his third semester. At that time he became acquainted with the work of Heubel on lead poisoning. His own accounts of the manner in which he did so vary in his different works. In his book, written along with Dr. Hata[1] he says he was reading Heubel's/

Heubel's work, but in his volume, written in conjunction with Dr. McDonagh,(2) he says he attended a lecture by Heubel. Whatever one is correct does not matter very much, but the important thing is the idea which he conceived that the manner in which a drug is distributed over the body is a determining factor, of great value, in its therapeutic action. He was so interested in this thoughtthat he altered his course of medical study, to some extent, in order to pursue it further. In his early experiments he encountered many failures, partly from lack of sufficient money, and partly because he was working on unknown ground which was so extensive that it included biology, chemistry and pharmacology. On many occasions he almost abandoned the whole work but scientific friends, especially his cousin Carl Weigert, who saw that something valuable would come from the experiments, spurred him on. As a result of his perseverance he has founded many important laws regarding the action of drugs and he has introduced the most potent anti-parasitic substance known with the exception of quinine.

After he had conceived his idea about the distribution of drugs in the body, he proceeded to prove it by experiment and he came to the conclusion that the cell is the place where all the actions of drugs take/

take place and the cell can be either tissue or parasitic. No drug can act unless it is fixed to the cells. Different cells have varing degrees of affinity for different remedies so Ehrlich divided drugs into two classes - Organotropic or those acting on the tissue cells of the host and parasitotropic or those acting on the parasites. All parasitotropic substances are more or less organotropic so we must only employ those with both affinities in proper proportion in disease in man. That relation is most ideal in Salvarsan where organotropism is practically nil. The therapeutically useful chemicals must also possess what Ehrlich calls the "therapia sterilans magna" or power of destroying all the parasites at one blow. In short we may say that chemotherapeutic researches have been directed towards obtaining a substance with proper tropism and therapia sterilans magna.

The first experiments were carried out with the trypanosomes which have biological characteristics which make them suitable for therapeutic and pharmacological studies. Later on the close relationships which exist between them and the spirilla were described so Ehrlich transferred his studies to the latter organisms and worked in succession with the spirilla/

spirilla of relapsing fever, fowl spirillosis, and syphilis. In the later experiments he was assisted by Dr. Hata and Salvarsan, which is also called Ehrlich.-Hata "606", will always be a monument to their work. It is rather peculiar that the name of Dr. Bertheim is not as often mentioned as it should be for he did all the chemical synthesis while Hata did the biological experiments.

The substances tested by Ehrlich were very numerous and may be classified as organic dyes and arsenical salts. The dyes were investigated first and certain results were obtained which assisted him later in settling the true formula of atoxyl. They possessed a strong organotropic action. No attempts were made therefore to discover a dye which could be administered to man so the arsenical salts were then investigated. In historical sequence these were arsenious - acid, atoxyl and the derivatives of phenylarsinic acid - Aracetin, Arsenophenylglycin, and Salvarsan. No mention is made in any of Ehrlich's books on the effects of arsenious acid but atoxyl is the first substance fully described.

In 1903 Ehrlich and Shiga tested the action of atoxyl upon trypanosomes in vitro and they found that it did not check the movements of the organisms so they abandoned it.

In 1905 Thomas/

In 1905 Thomas and Breinl of Liverpool described good results with atoxyl in trypanosomiasis so Ehrlich took it up again and determined to find out how the beneficial effect was produced. He also decided to prepare derivatives of atoxyl which would be quite as active and not so toxic as the parent substance. In this quest the value of his well founded logical conclusions from previous experiments became manifest. All his former researches had shewn him that the therapeutically active substances contain an amido group in their chemical constitution which is not connected to other radicles and can therefore enter into chemical reactions. At that time atoxyl was supposed to be a meta-arsinic-acid-anilide. Now such a substance has the amido group connected to the arsenic and it is not free to enter into chemical reactions. Ehrlich felt sure that the formula of atoxyl was wrong and his idea was confirmed by the observation that diazotised atoxyl behaves like some of the organic dyes which he had already studied. They had not an encumbered amido group like anilide. Accordingly he set to work, with Dr. Bertheim, to discover the true nature of atoxyl and together they proved that it was the soda salt of p-amino-phenyl-arsinic acid. This discovery was of extreme importance and Ehrlich said it was the axis of the entire progress/

progress towards Salvarsan.[3] It shewed him that atoxyl is a stable salt of p-oxy-phenyl-arsinic acid and by suitable treatment many important salts might be prepared from it.

Then he proceeded to synthesise derivatives of atoxyl and the experiments were carried out on definite lines laid down by him. The centre of attack in almost all cases was the amido group. By treating it in appropriate ways he could obtain any substance he chose in order to get any desired effect and the results all led towards one goal - Salvarsan. Many of these synthetic compounds could not be administered to man on account of their great toxicity.

The first important derivative of atoxyl was its acetylic salt called arsacetin. Ehrlich thought that the introduction of the acetyl radicle into atoxyl would diminish or abolish its toxic effects. He was specially led to this by the fact that the toxic bodies anilin and phenetidine give rise to the comparatively harmless acetanilide and phenacetine upon acetylation. Neisser tested it as well as many other arsenical substances upon apes in Java and got excellent results.[4] In man, however, toxic symptoms arose so it was abandoned. At the Frankfort Congress of the German Dermatological Society in 1908 Ehrlich/

Ehrlich reported his reasons why he determined to discover better substances and even predicted some later ones than arsacetin. He concluded by saying that he would not throw up the cards or abandon hope of anything better.

Arsenophenylglycin was the first most valuable salt after arsacetin. It bears the diary number 418 for it was the four hundred and eighteenth drug tested. It is a trivalent substance whereas the others were pentavalent and it was less toxic than them. It did not fully come up to Ehrlich's idea of the therapia sterilans magna so it too was laid aside.(5)

Between arsenophenylglycin and Salvarsan nearly two hundred complex salts of phenylarsinic acid were investigated. Two of them deserve mention - Arsenophenol and Dichlorphenolarsenic acid. Two injections of the former and one of the latter freed animals from spirilla but they possessed a dosage which would be poisonous if compared with the human standard. They were not investigated further.

Last of all came dioxydiamidoarsenobenzol which is number "592" and its hydrochlorate salt which is number "606". The last one is the famous Salvarsan. It is identical in its action to number "592" and is the form in which we administer it. The first experiments, which were carried out with it in relapsing fever/

fever, settled the toxicity for different animals - mouse, rat, hen and rabbit.

In the following table taken from Hata's work[6] the results of many experiments are set down :-

Species of Animal	Application	Dosis tolerata
Mouse	Subcutaneously	1:300 per 20 grms
"	Intravenously	1:350 " 20 "
Rat	Subcutaneously	0.2 " 1 Kilo.
Hen	Intravenously	0.25 " 1 "
"	Intravenously	0.08 " 1 "
Rabbit	Intravenously	0.1 " 1 "
Rabbit	Subcutaneously	0.15 " 1 "

In the mouse a dose of 1:700 of 592 would free it from parasites in twenty-four hours. A dose of 1 in 1000 only had an uncertain effect so Hata tried repeated injections of reduced doses and he had good results.

The next series of experiments determined the maximum dose necessary to bring about a permanent cure with one injection or repeated inoculation. After that was done Hata determined the limits within which a cure could be effected. He summarised the results in the following table :-

Permanent/

Permanent Cure obtained after			
Dose	One Application	Two Applications	Three Applications
1:600	100 per cent		
1:700	100 " "		
1:800	100 " "		
1:1000	75 " "	100 per cent	100 per cent
1:1500	18 " "	75 " "	100 " "
1:2000	16 " "	66 " "	100 " "
1:3000	0 " "	0 " "	3 " "

The maximal doses for permanent sterilisation are in each case :-

With one injection - 1:800

With two injections - 1:1000

With three injections- 1:1500.

Then he estimated the dose necessary to keep the animal alive when infected so severely that death must inevitably occur unless it was treated. Doses of 1:500 to 1:3000 prevented death in nearly all cases. This concluded the therapeutic researches so Hata next tried it as a prophylactic.

A dose of 1:400 could not be relied on to stop an infection twenty-four hours later in mice. Two animals only remained immune. If inoculation was performed three days after the dose was given the animals all had/

had the fever though in a mild form. Prophylactic measures were unsatisfactory in the mouse. Rats gave better results. In them inoculation ten days after injection only resulted in slight fever and relapses.

In fowl spirillosis and syphilis of rabbits similar methods were carried out with good effect.

Hata then tried combination products of "592" to see if the parent substance could be improved upon but he could not do so and found that these compounds were too toxic to use in man.

All his researches shewed him that number "592" or number "606" was the best drug which he had ever tested and he could recommend it for clinical use without any serious doubts.

In September 1909 Ehrlich sent some of the drug to Professor Conrad Alt, a nerve specialist, at Uchtspringe to test its toxicity in man. The latter's great interest in it is warmly commended by Ehrlich.(7) He carried out a few preliminary experiments upon dogs to settle the toxicity and in them he was assisted by Drs. Hoppe and Fischer. Then two physicians - Hoppe and Wittneben - permitted themselves to be injected with a small dose and all they complained of was pain and swelling at the site of injection. These

investigations/

investigations shewed Alt that he might administer it to patients so he gave it to twenty-three paralytics and they all improved. The results formed the groundwork of a paper in which he introduced it to the medical profession on March 15th 1910.(8) He proved that 0.3 gramm is a safe dose.

It may be mentioned that in June 1909 a patent of the Dye Works of Meister, Lucius and Bruning described the effects of dioxydiamidoarsenobenzol on the spirilla of relapsing fever.

Alt handed the remedy to Professor Schreiber at the Alstädter Hospital in Magdeburg for use in cases of recent syphilis in man. Twenty-seven cases of florid lues were treated with striking success. He reported (9) rapid changes in syphilitic lesions, improvement in general condition and a loss of the Wassermann Reaction in 14 of the 27 cases.

Iversen(10) then reported improvement and cure in cases of relapsing fever at the Society of Russian Physicians at St. Petersburg.

Wechselmann, Neisser, Hoppe and others all reported valuable results and they all helped to bring salvarsan to the forefront.

It was patented in England on June 30th 1910 and the number it bears is 13485.

After it was once before the profession reports about/

about it began to appear in the medical journals of the different countries. Most of these dealt with clinical cases and some added facts about its action. A great number of modifications in the technique which have followed one another rapidly, constitutes much of the history of the drug after its introduction.

At first Salvarsan met with a good deal of opposition in certain quarters but the reserve has gradually been broken down and now it is looked upon favourably by most medical men. On the other hand some have lost part of their blind enthusiasm which they had at the beginning.

Anyone reading the book by Ehrlich and Hata on their researches after the now notorious "606" will admire the painstaking work of the pioneers of chemotherapy and cannot consider that the discovery of Salvarsan is the result of an accident. It represents Ehrlich's life work and marks the termination of thirty years of brilliant research.

REFERENCES :-

(1) Ehrlich and Hata - "Chemotherapy of the Spirilloses". page 117.
(2) Ehrlich and McDonagh - "606" in Theory and Practice. page 1.
(3) Ehrlich and Hata - "Chemotherapy of the Spirilloses." page 121.
(4) Neisser - Deut med Woch 1908, No. 35.
(5) Ehrlich and McDonagh - "606" in Theory and Practice. page 4.
(6) Ehrlich and Hata - "Chemotherapy of the Spirilloses". page 23.
(7) " " " " " page 138.
(8) Alt - Münch med Woch 1910, No. 11.
(9) Schreiber - Münch med Woch 1910, No. 15.
(10) Iversen - Münch med Woch, April 12, 1910.

THE ACTION OF SALVARSAN.

The action of Salvarsan which is exhibited to the eye by very striking clinical phenomena is best described, in the words of Ehrlich, as many-sided. In considering it we approach some of the problems of immunity and serum therapy to which chemotherapy is the sister science. Many of the effects are specific to Salvarsan but others are not peculiar to it alone. It destroys parasites or inhibits their multiplication and it neutralises their irritant products. After doing so it aids the tissues to repair the damage done to them by the organisms by acting as a cicatrising agent.

The parasiticidal action depends on conditions present in the organisms themselves and on peculiarities in the structure of its own molecule. The anti-toxic properties also are due to the latter.

CONDITIONS PRESENT IN THE PARASITES.

In the parasite cell there are certain groupings of the atoms of the protoplasm which have an avidity for chemicals. To these Ehrlich has given the name of chemoreceptors or, shortly, chemoceptors. They are similar to the side chains which he had already described in his theory of immunity. We shall see later how the Salvarsan molecule attaches itself to them /

them in the same way as a toxin becomes fixed to the side chains in the case of diphtheria. Where these receptors occur in the cell is unknown. They may be either in the cell substance or in the complex lipoidal cell wall. Dr. Mott described this in an address to the Royal Society of Medicine.(1)

Much is yet to be done in biochemistry before we can be sure of such matters. Many trypanosomes and spirilla have identical chemoceptors so Salvarsan, which attacks the common ones in an ideal manner, has a wide therapeutic possibility before it. Not only are they present in the parasites but they also occur in the tissue cells of the host. The former are more powerfully attacked by Salvarsan than the latter and this may explain how that drug is parasitotropic and not organotropic. They are of a most varied character and it is probable that the cell has receptors for every known chemical. In connection with Salvarsan, however, we need only consider two - the arsenoceptor and the oxyamidoceptor.

THE ARSENOCEPTOR.

The arsenoceptor has a special attraction for organic arsenical preparations as they occur in the trivalent form. Pentavalent arsenic is not so readily fixed to the receptor as the trivalent form and cannot therefore be such a powerful therapeutic agent.

Certain/

Certain forms of spirilla, it is true, can attract pentavalent arsenic but nearly all have an affinity for the triad form. Atoxyl, for instance, attacks the spirilla of syphilis and fowl spirillosis but it does not affect the spirillum of relapsing fever so much whereas Salvarsan attacks all three. It may be argued that atoxyl is broken up in the body into trivalent and bivalent groups and the former should act similarly to the trivalent Salvarsan but laboratory experiments have not borne that out. The receptor ofthe host may have an attraction for bivalent arsenic and the bivalent element which is split off from atoxyl in the body becomes attached to it and in time blindness may result. Ehrlich has attributed the toxic effects of atoxyl to this.(2)

THE OXYAMIDOCEPTOR.

This receptor links the Salvarsan molecule to the cells and, after this union has been established, the arseno group exerts its destructive action. It has an affinity for an amido group and a hydroxyl group arranged in a special order in organic arsenical compounds. What that order is will be seen later but, for the present, it is sufficient to say that Salvarsan satisfies it in an ideal manner.

ARSENIC-FAST STRAINS OF PARASITES.

When the drug has become fixed to the receptors of/

of the parasites the latter's affinities for the preparation become much diminished and larger doses are necessary to affect them further. The organisms become acclimatised to the remedy and are called arsenic fast strains. This occurrence, however, is seen more among trypanosomes than spirilla and only when the doses administered are too small to destroy them. Different trypanosomes have different degrees of resistance to chemical agents and this makes it very hard to obtain a drug which will destroy all species of the parasite.(3) Although a variety of organism resists all members of one class of chemicals it falls a victim to members of another. Ehrlich(4) found that certain strains of trypanosomes are immune to basic dyes such as parafuchsin and pyronin whereas they were not fixed against azo dyes such as trypan red and trypan blue. Margulies(5) observed that strains resistant to Salvarsan were also resistant to atoxyl, arsacetin, and arsenophenylglycin. These strains were produced experimentally by Margulies. She found that by gradually increasing the dose of Salvarsan from a tenth of the curative dose to very large amounts the organisms could be made to tolerate much more than the curative dose.

In spirillar diseases, on the other hand, it is hard or even impossible to produce arsenic-fast strains and/

and this is very important especially in connection with syphilis.

Oppenheim[6] thought they could occur from his researches. Margulies[5] could not produce an arsenic resistant strain, in the true sense of the word, in any of the three spirillar conditions - relapsing fever, fowl spirillosis, and syphilis.

Wechselmann[7] states that they have not been definitely observed clinically in connection with the Salvarsan treatment of syphilis. He says that it is unlikely that different varieties of the spirochata pallida can exist at the same time in the body. On this account a second dose of the remedy will complete what the first has not finished. The cases in which the first dose did not completely sterilise the patients are ones in which many so-called spirochaetal foci are present.

Certain organisms are shut up in connective tissue nodules which do not become vascular for some time and no remedy can possibly reach the contained parasites till that has been done. The first dose becomes lost to a certain extent because it has not attacked all the spirilla but the second one passes through the newly developed vessels of these nodules and completes the cure. Salvarsan may soften the nodules and the second dose passes in more easily.

If/

If, by any possibility, spirilla immune to Salvarsan could exist it would be necessary, according to Ehrlich's observations, to make the second dose much larger than the first in order to affect them. Clinically we do not do this for, when a second dose is necessary, it is the same as the first.

The therapia sterilans magna was devised by Ehrlich to guard against the occurrence of these strains. Its intention is to give, at the outset, sufficient of the remedy to destroy every single organism. It is possible to get it with Salvarsan alone but it is more likely to occur if we antedate Salvarsan, in other than cases of primary syphilis, with mercury. Wechselmann (7) states that mercury aide the absorption of the fibrous tissue of the foci and allows the powerful Salvarsan to attack all the spirilla at once. All my cases had been treated for a long time with mercury before they obtained Salvarsan and the good effects of the latter drug in them may have been due to the fact that the mercury had brought about the absorption of most of the foci.

PECULIARITIES IN THE STRUCTURE OF THE SALVARSAN MOLECULE.

The peculiar structure of the Salvarsan molecule gives it a great trypanocidal and spirillocidal action. It makes the drug suitable for fixation to the receptors/

receptors in the parasite cell. Three groupings of its atoms come up for consideration - arseno, amido, and hydroxyl. Their arrangement constitutes what Ehrlich calls a eutherapeutic maximum.(8) Each one becomes fixed to a receptor.

THE ARSENO GROUP.

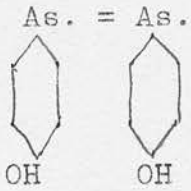
This consists of arsenic in the trivalent form and, as such, it appropriately satisfies the arsenoceptor. Pentavalent arsenical compounds will destroy the parasites if given in large enough doses but toxic effects such as tremors, blindness, and dancing movements are apt to follow. Ehrlich(9) found that the pentad substance paraoxyphenylarsinic acid will only free mice of the spirillum of relapsing fever if it is given in doses on the verge of toxaemia. Hata(10) found that atoxyl, in dilution of 1 in 300, was not certain to free them from the same organism and that dose sometimes killed the animals and dilution of 1 in 450 in some cases made them blind. If such results were applied to man the effects might be very serious. No such bad symptoms have followed the use of Salvarsan and we must, to a certain extent, attribute this to the fact that its trivalent arsenic makes it parasitotropic and not organotropic. Ehrlich(9) says that the final destructive action of the drug is due

to/

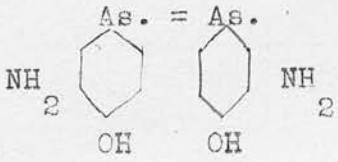
to the same cause.

THE HYDROXYL GROUP.

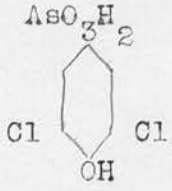
The hydroxyl group is situated in the para position in the benzene nucleus of salvarsan and, as such, it exerts a strong action on spirilla. Other drugs with a similarly placed hydroxyl were found by Ehrlich to be powerful spirillocidal substances. Arsenophenol, Dichlorphenolarsenic acid, and Salvarsan all destroy spirilla but of these the last one only can be administered to man. The others are too toxic.



Arsenophenol.



Salvarsan.



Dichlorphenolarsenic Acid.

THE AMIDO GROUP.

Ehrlich ascribes great value to the amido group for much of the action of Salvarsan is due to it. It links the preparation to the parasites and, after it has done so, the arseno group exerts its destructive action. He[11] also thinks it gives Salvarsan its anti-toxic properties. Much of its value depends on its being in the ortho position to the hydroxyl group. The Salvarsan molecule may be compared to the molecule of diphtheria toxin, and as such it will have toxo-

phorous/

phorous and haptophorous elements. The amido group takes the place of the haptophorous element and the arseno and hydroxyl groups replace the toxophorous one.

Now the receptors of the host have not the great avidity for the chemical which the parasitic ones have so the salvarsan molecule combines with the latter. The amido group links them together.

THE INHIBITORY ACTION ON THE REPRODUCTION OF THE PARASITES.

When salvarsan has exerted its full lethal action on the parasites a few may still remain alive but their reproductive powers are inhibited. A dose which is too small, on the other hand, to cure may prevent the organisms from multiplying.

Hata(12 found that dilutions of 1 in 10,000 up to 1 in 4000 did not kill the spirilla of relapsing fever but the mixture of drug and organisms was not followed by disease when injected into a mouse. If any fever resulted, as it did in exceptional cases, it was due to a few very resistant spirilla.

THE ANTI-TOXIC ACTION OF SALVARSAN.

This property of Salvarsan brings greatest relief to the patient. It consists of the neutralisation or destruction of the irritant products of the organisms. These/

These substances give rise to the pain present in some syphilitic lesions and the rapid disappearance of that symptom after an injection of "606" can only be explained by the anti-toxic theory although Wechselmann[13] considers that it is due to the destruction of the spirilla themselves. One thing is certain and that is the fact that the relief of pain is not due to changes in the syphilitic tissues. No syphilitic tissue can be repaired within 48 hours. Ehrlich[14] considers that the feeling of overpowering weakness and depression in some cases is due to the syphilitic toxin.

E. W. Frank of Berlin[15] reported a case of tonsillar gumma attended by great pain and the patient could eat a sausage sandwich five hours after injection.

The following two cases of mine also exhibited the anti-toxic action of the remedy :-

Case I. W. U. was suffering from hoarse voice, dry throat and severe pain on swallowing and smoking. His voice was so weak that it could not be heard outside the door of his bedroom. For a year and a half he had been taking mercury and iodide of potassium from which he derived some benefit but the throat pain did not disappear. A sloughing phagedena of his penis was cured with autogenous vaccines by Drs. Roderick/

Roderick and Roberts of Llanelly, Wales. At 9-30 p.m. on October 15th 1911 he received an intra-muscular injection of 0.6 gramme of Salvarsan and next day the pain in the throat had vanished. He could then eat crusts of bread and smoking became a pleasure to him. When asked how he felt he replied "champion". The changes in his lesions will be described later.

Case 2. Mrs. G. was infected, during the month of March 1911, in marital intercourse. Secondary symptoms appeared in June 1911 and took the form of ulcers on the tonsils and fauces and psoriasis affecting the arms and legs. The plantar and palmar manifestations were very severe and the skin was cracked and bleeding. The pain in the throat was very bad and the patient's voice became weak and husky. She had great pain in the palms and soles and when the bedclothes pressed on them at night she would cry out. She could not walk without some support. Loss of sleep made her very weak. Before Salvarsan was mentioned to her she underwent a course of mercury and iodides with the result that the bleeding stopped from the palms and soles and the pain diminished till it became bearable. She was only too willing to have Salvarsan and she chose the intramuscular method after the advantages and disadvantages of all forms of injection/

injection were carefully explained. At 9-30 p.m. on November 28th, 1911 she received an intramuscular injection of 0.6 gramme. For a few days afterwards she had some pain and swelling at the sites of injection but, after the first night, she had no more pain in the palms and soles. She too is loud in her praises of the drug and one of her expressions was :- "Doctors must be clever to make such things which cure people of pain." The changes in her lesions will be described later.

Periostic pains and the severe headache of gummatous meningitis promptly disappear after an injection. Ehrlich and McDonagh (16) report a case where pain in meningitis was gone completely in four days.

All these phenomena are due to the destruction of the toxins which become united to the Salvarsan by the ortho-amido group of the latter. This will be considered further after the mode of action after injection has been described.

THE MODE OF ACTION AFTER INJECTION.

When a dose of Salvarsan is injected into an animal or a patient, a complex series of changes, occurs. The molecule of the drug becomes fixed by the amido group to the corresponding receptor of the parasite and then the arseno and hydroxyl groups join theirs/

theirs. The bodies of the organisms become so affected that they give up their contained endotoxins. The latter circulate in the blood stream of the host and arrive at the place responsible for the production of anti-bodies and stimulate it so that substances antagonistic to parasites are generated. The endotoxins really act as soluble antigens. The anti-bodies then act on any remaining organisms, whether they be spirilla or trypanosomes, and destroy them. It is perhaps a mistake to call these anti-bodies anti-toxins, as is often done, for their function is to antagonise parasites. If the modern conception of the zoological place of the spirilla in nature is correct we should call them anti-protozoal substances. These anti-bodies do not, according to Ehrlich's hypothesis, destroy the irritant products of the parasites for that is done by the Salvarsan itself. Schilling[17] has shewn, in the case of the arseno-phenylglycin treatment of trypanosomiasis, that the drug only kills some of the parasites and the others are destroyed by the anti-bodies.

There are many proofs that anti-bodies do exist after the administration of Salvarsan. Ehrlich found that the rabbit reacts better after Salvarsan than the mouse because its tissues are better suited for their production/

production. Schilling's observations, aforementioned, also prove this. Clinically we can observe them in man. The first surmise in this connection came from Neisser but the first description to arouse general attention came from Taege.[18] He observed the fact that a syphilitic suckling loses its specific manifestations if fed at the breast of a syphilitic woman who has been injected with Salvarsan. At first he thought that the cure was due to small amounts of arsenic which had been injected with the milk. By chemical tests, however, he could only detect a minute trace of inorganic arsenic in the milk and that could not possibly bring about the cure. He concluded therefore that anti-bodies were at work.

Duhot,[19] Dobrowitsch[20] and others report similar cases. Jesionek[21] said, on the other hand, that he found arsenic in 100 cc. of milk.

The second clinical proof lies in the fact that the serum of Salvarsan-treated patients exerts a remedial action on others. Ehrlich[22] has seen cases of hereditary infantile syphilis benefited by this method of treatment. He does not think it will be an absolute cure, however. Dr. Alston[23] treated cases of yaws by salvarsan serum with success. He applied cantharides blisters to Salvarsan-treated patients/

patients and injected others with the fluid obtained therefrom and excellent results followed. His article in the journal made Gibbs and Calthrop[24] treat cases of syphilis in a similar manner and their patients improved. Plant, Marinescu, Meirowsky, and Scholz all report cases treated with the serum.

Dr. Robertson[25] employed Salvarsan serum in cases of general paralysis of the insane in the wards of Morningside Asylum. He combined the serum with Salvarsan. He considers that the previous results with Salvarsan in that disease, were disappointing because the amount of anti-body was deficient. The reason is that the spirilla are few and may have retreated into the cerebro-spinal fluid where no remedy can get at them. The injection of serum of a case of syphilis in the secondary and tertiary stages will supply the deficit. The serum must be given in the earliest stages if it is to cure the parasyphilis for if that is not done the tissues are damaged by the disease.

The patient first receives 10 cc. of serum into the abdominal wall and 20 cc. within a fortnight after that. He also gets a dose of Salvarsan. Striking results have been observed in one case. 30 cc. of blood yield about 15 cc. of fluid. Dr. Alston's results/

results in yaws have had an important bearing on Dr. Robertson's work in general paralysis.

The use of Salvarsan serum may be called passive treatment as in serum therapy. It is not a method which will become general because its results will not be permanent although it has several advantages. A most ingenious objection to it was mentioned to me, namely, that it resembles arm to arm vaccination too much.

There are certain stages in syphilis in which the body is more prone to produce anti-bodies than in others. In tertiary syphilis of the ulcerative and malignant classes the tissues are in a state of allergy. That is to say they react very readily to the products of the spirilla which, although present, are few in number. (Finger and Landsteiner[26]). For this reason gummata may reach a large size. If Salvarsan is injected in this stage the spirilla are destroyed and the scanty endotoxins stimulate the host to produce many anti-bodies.

The amount of endotoxin liberated from the dead organisms may be so great that poisoning is the result. In infants the spirilla are destroyed in a wholesale manner and the endotoxins are so numerous that they kill/

kill the child. It is dangerous to inject them directly so we must treat them through the mother, because the milk contains a supply of antibody which brings about a gradual cure and cannot kill the patient. This question will be considered further in connection with hereditary syphilis.

HYPERSENSITIVENESS TO ARSENICALS.

Many of the serious effects of the arylarsonates employed before Salvarsan was discovered were due to hypersensitiveness of the optic nerve. These substances were administered in small repeated doses. Much of the arsenical was retained in the body and, in time, it caused biological changes in the cells. Every dose encountered a more and more damaged cell until the summation of injuries led to poisoning. Ehrlich(26) said that atoxyl becomes split up in the body into trivalent and bivalent substances and the latter accumulates and brings about the disastrous consequences.

If the arsenical is given in one large dose the phenomena of hypersensitiveness do not occur. It is the summation of small amounts which is deadly. Hata(17) found a similar condition in his experiments with Salvarsan on relapsing fever in mice. More than three injections of salvarsan caused the animals to become/

become hypersensitive.

In the clinical application of Salvarsan it is not likely that such a condition will occur. In the first place the drug is rapidly excreted from the body. Secondly the method of administration is to give one large dose to effect the therapia sterilans magna. Thirdly if we give a second dose we wait till most of the arsenic of the first one is eliminated from the body.

In only one condition will hypersensitiveness result and that is if some other arsenical has previously damaged the cells. Arsacetin, for instance, may so injure the cells that Salvarsan may cause toxic phenomena if given after the arsenic. Finger (28) reported a case where Salvarsan caused blindness but his patient had previously been saturated with arsacetin and enesol.

We must always, therefore, enquire into previous treatment before giving Salvarsan.

SALVARSAN v. SERUM DISEASE.

Several phenomena following Salvarsan injections resemble the serum disease. This has been carefully studied by Wechselmann. It brings chemotherapy into a line with serum therapy. The symptoms begin from the eighth to the tenth day after injection. The temperature rises, sometimes to 105.5°F., and the pulse/

pulse remains of good quality though rapid. Diarrhoea, thirst, and vomiting set in. Most striking is the appearance of exanthemata. These are of a morbillous or scarlatini form character. Schreiber (29) has seen urticaria. At the site of injection there appears a red patch with a central scar marking the needle puncture. On this area blebs may form. Albumen is not present in the urine.

Michaelis has described similar phenomena to the above.

Repeated observations have shewn that these phenomena are closely allied to the serum disease after injection of diphtheria anti-toxin. Both appear in eight to ten days after injection and the rashes are similar in both cases. They are not due to the anti-toxin or the Salvarsan. In the case of the anti-toxin or of Salvarsan injected intravenously, the symptoms set in long after they have left the patient's body. In the case of Salvarsan injected intramuscularly the phenomena occur when the drug is encapsulated by inflammatory connective tissue which only allows small amounts to enter the circulation at once. In both cases antigens bring about the development of anti-bodies which persist after all the antigens have left the blood. It is these bodies which bring about the phenomena of hypersensitiveness.

Many/

Many attempts have been made to test a patient's idiosyncracy to arsenic. McDonagh[30] carries out a test like Von Pirquet's cuti reaction with tuberculin. He uses arsacetin in the strength of 4½ grains in 3 cc. of water. If he obtains a positive result he does not administer the Salvarsan. This method is not certain because the tests do not bear the same ratio to drugs, like arsenic, as they do to bacterial products, such as tuberculin.[31]

JARISCH-HERXHEIMER REACTION.

For some time it had been observed that syphilitic skin eruptions became more intense for a short time under mercurial treatment. The same condition has followed the use of Salvarsan and constitutes the Herxheimer Reaction. The development of a new rash which is urticarial or erythematous is also included. Some call the aggravation of any syphilitic phenomenon a reaction.

Truffi[32] and others saw it after the injection of small doses of Salvarsan (0.025 - 0.25 grm.)

Herxheimer saw it after both small and large doses.

There are several theories as to the causation of the Reaction. Ehrlich[38] said it is due to the dose of Salvarsan being too small or insufficiently absorbed. The spirilla are irritated and produce an extra/

extra supply of irritant substances. His view is supported by observations of others. Browning[34] found that fractional doses of methyl violet stimulate trypanosomes to increased activity. Iversen[35] observed that minute doses of Salvarsan stimulate the spirilla of relapsing fever instead of killing them.

Wechselmann[36] and Gennerich[37] do not think that it is due to a ~~small~~ dose which is too small, for cases of theirs rapidly lost their syphilitic manifestations after it appeared. They consider it to be due to endotoxins liberated from the dead spirilla.

Of these sets of views Ehrlich's one is probably correct. The Reaction appears shortly after the injection. Loeb[38] saw it appear in two hours, reach its maximum in twelve and vanish in four days.

Many of the transient nerve phenomena seen after the injection are similar to the Jarisch-Herxheimer Reaction. Arsenical neuritis does not explain them because they are unaccompanied by vital depression and they are often unilateral. Spirochaetes are present in the nerves affected. Hoffmann[39], Ehrmann,[39] Strassmann,[40] Verhoeft,[41] and Benario[42] have all seen them in different nerves, either in the nerve sheaths or in the nerve fibrils. The dose of Salvarsan stimulates the spirochaetes situated in the nerves/

nerves affected. The phenomena are very similar to syphilitic neuro-recurrences. Many of the cranial nerves have been affected. The facial nerve was affected in two cases and the auditory in seven out of nine patients studied by Browning and McKenzie.

THE ACTION OF SALVARSAN ON SPIRILLA AND BACTERIA.

Hata (43) found that Salvarsan has no destructive action on the spirillum of relapsing fever in vitro. He observed that any effect was probably due to the alkali in the solution. The following are his results in tabular form :-

TABLE XII - Destructive Experiment with Dioxydiamidoarsenobenzol.

Solution with 0.85 per cent. NaCl Solution further diluted.

Final Concentration	Experiment with "592".		Control (with corresponding alkaline content).	
	In Test Tube	Mixture injected into mouse	In Test Tube	Mixture injected into mouse.
1:2000	Immobile		Immobile	
1:4000	"	Negative	"	Negative
1:10000	Mobile	"	Mobile	+ after 2 days
1:20000	"	only after 7 days	"	
1:40000	"	+ after 6 days	"	
1:100000	"	+ " 2 "	"	

In the body, however, the action on spirilla is strong. The results of most observers are very similar on this point. The factors on which this depends/

depends are the size of the dose administered, the manner in which it is injected, and the rate of absorption from intramuscular deposits.

We can most easily study the changes in the organisms by using the dark-ground illuminating microscope and the chinese ink method of staining. Sieskind(44) at the request of Wechselmann, made a systematic examination of the spirilla in sixteen cases of syphilis. He saw changes in form and motility and his words are as follows :-

"The usual screw-like and oscillating motion of the spirocheta-pallida is considerably decreased and frequently only slight movements are seen which gradually cease entirely. In addition, not only their motility, but also their form is changed. The very spirochates, which because of their frailty and slight refracting power have been surnamed "pallida", become bulky and swollen. Nevertheless they retain their spiral form even in the condition of immotility. On the whole it would seem undeniable that Ehrlich's new arsenic preparation exerts a distinct, specific effect on the spirochactes."

Reinke(45) saw them agglutinated. Sometimes they break up into granules. Theymay disappear without a trace.

Not only do the spirochaetes undergo changes in form/

form and motility but they disappear from the blood and lesions. The disappearance goes parallel with the involution of syphilitic symptoms. If the dose is an intravenous one they vanish quicker than if it is intramuscular.

The following is a table of the observations by several physicians on the time of disappearance of the organisms :-

Observer	Disease.	Time of Disappearance.	
		Shortest	Longest.
Glück (46)	Syphilis	24 hours	48 hours.
		16 hours in a sclerotic	
Favento (47)	"	2 days	14 days
Neisser (48)	"	24 hours	48 hours
Géronne (49)	"	6 hours	
Tomasczewski (50)	"	12 hours	36 hours*
Reinke (45)	"	Only a few degenerate ones in the lung 2 days after injection.	
Spiethoff (51)	"	24 hours	48 hours
Scholz (52)	"	24 hours	4 days
Hoffmann (53)	"	12 hours	1 week.
Grouven (54)	"		2 months
Neisser and Kutznitsky (55)	"		10 days
Truffi (56)	"	12 hours	8 days
Pasini (57)	"	24 hours	36 hours
Sieskind (44)	"	2 days	7 days
Inversen (58)	Relapsing Fever.	4 hours	5 hours
Georgiewsky (59)	"	4 hours	5 hours
Dreyer (60)	"	24 hours	
McIntosh (61)	"	24 hours*	

*These results were obtained in animal experiments.

From this table it may be seen that, in syphilis, the average time the spirilla take to disappear is

24 - /

24 - 48 hours. The shortest is six hours and the longest is two months. In relapsing fever they disappear very quickly except in Dreyer's cases which were seen in Egypt. Salvarsan is known to take longer in Egypt to sterilise the patients than elsewhere.

Gerber observed a change in the spirochaetes of the teeth but Pasini[62] found none in them or in the spirochaeta refringens.

Ehrlich and Hata[63] found that dioxydiamidoarsenobenzol cures fowl spirillosis and acts as a prophylactic for thirty-five days.

Ornstein[64] obtained good results with it in spirillosis of hens.

Dschunkowsky[65] got good results with it in spirillosis of geese.

The spirochaeta pertenuis, which causes yaws, is readily destroyed by it. Alston and Strong have published cases.

Gonococci and tubercle bacilli which may be in the body along with spirochaetes are unaffected by the remedy. It has some destructive action on the bacillus of leprosy. Pus from abscesses at the site of injection is sterile. It is not known, however, if the condition is due to any action on staphylococci, etc./

etc. Martindale and Westcott[66] intended to study the "Carbolic Coefficient" on B Typhosus and B Coli but their results have not been published. Ducrey's Bacillus is unaffected.

It may be seen, therefore, that Salvarsan has a strong action on the causal organisms of syphilis, relapsing fever, fowl spirilosis and yaws and, as time goes on, it may be useful as a destroyer of many more.

THE EFFECT OF SALVARSAN ON WASSERMANN'S REACTION.

The reports of the effect of Salvarsan on the Wassermann Reaction vary very much and there are many reasons for the discrepancies. All the cases are not examined long enough nor in the same manner. The initial strength of the Reaction before treatment is not always estimated and a standard cannot therefore be set up with which all results may be compared. Treatment is not always carried out promptly enough. Lastly the variations in the methods of performing the tests vary. Neisser and Kutznitsky[56], for example, found that 44% of their cases gave a negative reaction when they carried out Wassermann's original test whereas only 19.2% give negative results when Stern's modification was used.

Karl Lange[67] carried out all his experiments on /

on the same plan. He used aqueous extracts of the livers of syphilitic foetuses as antigens. He inactivated the sera by shaking with barium sulphate instead of heating them to 56°C. The minimum amount of extract which gave a positive reaction with the weakest sera was the quantity he constantly employed in the test, and the amount of extract which just is enough to fix a distinct amount of complement expresses the degree of positive reaction. Strong sera fix all the added complement but weaker sera leave some over for haemolysis. He distinguished different degrees of severity as : (++++), (+++), (++), (+), and (±). Complete haemolysis represents a negative reaction. The results of 268 cases will be found in the table subjoined.

Much depends on the initial strength of the reaction for if it is weak at first it becomes negative more quickly than if it were strong.( ) A serum of the strength (++++) becomes negative in 4 - 5 weeks, but one of the strength (+) is negative in eight days.

After salvarsan injections the reaction may shew the following changes :-

(1) + may become - and remain so or change to + again.

(2) - may become +.

(3) - may become + and then change to - again.

(4) + may be unaltered.

POSITIVE REACTION BECOMING NEGATIVE.

This is the usual change which occurs but the reason why Salvarsan helps to bring it about will not be known exactly till we understand the Reaction itself properly. It is probably due to the fact that the amount of complement fixed by the serum of the treated patient is gradually diminished until no more becomes attached. That usually occurs in four to six weeks, when the reaction becomes negative. The process is a gradual one and is uninterrupted by fluctuations.(67) Serum of the strength (++++) passes through successive stages of (+++), (++), (+), (±) and (−).

This change is regarded by Ehrlich as a sign of the specific action of Salvarsan on the spirochaetes. When the Reaction is negative, however, it does not necessarily mean that all the spirilla are destroyed for they may be in too small numbers to excite it. In many cases it really means thorough sterilisation of the system as clinical and serological histories shew.

The ease with which a positive Reaction becomes negative varies very much. The earlier and more prompt the treatment the easier it is to bring about the change. It is hard to convert it in congenital and parasyphilitic cases. In the former the Wassermann Reaction /

Reaction tends to remain negative in spite of the most excellent treatment and in the latter we must attribute it to the fact that we are dealing with late manifestations of the disease. It is always easier to alter the Reaction in earlier than in later cases.

The form of injection modifies the rate of conversion. Intramuscular injections do not act so promptly or so permanently as intravenous ones and two of the latter give the best results. The times of disappearance and the percentages of permanent results as observed by authorities will be seen in the annexed table.

Zaroubine(68) observed the interesting fact that the Reaction becomes negative before infiltrated lesions disappear and negative after non-infiltrated lesions vanish.

If the Reaction remains negative for a year we may presume that it will always be so in that particular case and that the disease has been absolutely cured. Any return of a positive Reaction indicates a recurrence of the trouble and it usually antedates the recrudescence of symptoms. We can therefore renew treatment with vigour and prevent the appearance of signs of the disease. Any patient who has been treated with Salvarsan should be examined serologically for/

for a year afterwards so that we can anticipate any relapses beforehand and prevent them.

NEGATIVE REACTION BECOMING POSITIVE.

Some syphilitic patients may have a negative or veiled Reaction and a dose of Salvarsan may convert it into a positive one. Wechselmann[69] attributes the negative Reaction to the fact that complementoids block the action of the amboceptor. Ehrlich[70] has explained the conversion of the negative to the positive as due to the fact that the spirochaetes which are too few to excite a Reaction are killed off en bloc and the total amount of material obtained by their disintegration is mobilised and produces a positive Reaction. This is most likely to occur in tertiary syphilis when the spirochaetes are few and Lange[67] has confirmed this.

After the negative Reaction has been converted into a positive one it may gradually return again to its previous condition. Lange[67] has observed a case where (-) increased to (++++) and then reverted to (-).

The following is a table of the results of observations of different authorities on the alterations in the Reaction as produced by an injection of Salvarsan :-

Observer	No. of Cases.	No. of Conversions	Percentage.	Time.
Alt (71)	18	2 complete 2 partial 2 slight		
Neisser (48)				
(Series 1)			10%	
(Series 2)			50%	
Schreiber (72)			84.6%	within 50 days.
Géronne and (49)	10	6		4-6 weeks.
Huggenburg	25	6		less than 4-6 weeks.
(58)				
Iversen	2	2		8 - 10 days
				Most 20 - 40 days.
Pick (73)				Most take 4 weeks.
				Limits 1 - 7 weeks.
Herxheimer (33)	2(primary.)	2		7-20 days.
	4 (Secondary)	4		1 - 1½ weeks
(51)				
Spiethoff (74)		Most cases		8 weeks
Michaelis				2 - 10 weeks
Braendle and Clingstein. (75)	27	1		
Glück (46)	20	5		35-40 days.
Willige (76)	21	6		
Géronne (49)	77	37		
Behring (77)	76	26		4 - 5 weeks
Kromayer and (78)				
and Stern			50%	
Bayley (79)	37	21	57%	Over 4 weeks
"	50	9	18%	under 4 "
Favento (80)	40	21	52%	Over 4 weeks
"	70	19	27%	under 4 "
Harrison (81)	159	121	76%	Over 4 weeks
"	91	21	23%	under 4 "
Lange (67)	268	153	63%	4 - 5 weeks
Jones (82)			50%	

It may be seen that the number of percentages of alterations vary from ten to nearly ninety and the average time of disappearance is four to six weeks though/

though shorter and longer periods are recorded.

Many of the facts about the mode of action of Salvarsan are, in our present state of knowledge, purely speculative and they will remain so until biochemistry has made further progress. There is a complex process occurring in which the drug, parasites and tissues participate.

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THE LOCAL AND GENERAL EFFECTS OF SALVARSAN INJECTIONS, BYE-EFFECTS AND COMPLICATIONS.

I. LOCAL EFFECTS.

Pain.

The occurrence of pain at the site of injection has caused intravenous methods of administration to replace intramuscular and subcutaneous ones. If any suffering results from the first form it is due to faulty technique allowing some of the preparation to escape into the tissues surrounding the vein. Intravenous injections should have no more pain than that produced by the needle puncture.

After intramuscular and subcutaneous injections there is always some pain and the amount depends on several factors. The form in which the drug is given and the size of the dose both must be taken into account coupled with the individuality of the patient. Even though the most painless form of injection is employed there is some trouble which may be aggravated by/

by the patient rising too soon.

The form in which the preparation is administered has most to do with the production of pain. Clear solutions are said to be most painful and neutral suspensions and emulsions least so. Very often we find, however, that this order is reversed. I have had a patient suffering from intense agony after an injection of 5 cc. of neutral emulsion into each buttock. These solutions and emulsions really always come in contact with nerve fibres, however small, and much of the pain is due to their action on them.

The size of the dose administered always plays a part also. The greater the bulk of the solution employed the severer is the pain. 10 cc. injected into one buttock cause more suffering than 5 cc. injected into each one. There are always some muscle fibres lacerated by the stretching caused by the solution and the size of the dose must therefore cause a variable amount of injury and a varying degree of pain.

If the patient rises too soon after he has been treated he may bring on very great pain. A conductor of the orchestra in a theatre was injected by me one Saturday night. He rose on the Monday morning and the/

the pain which he was already suffering was greatly intensified as a result. At the theatre performance that evening he could hardly wait through the whole play and after it was over he had to go to bed. I always inject my patients on the Saturday evenings and keep them in bed till Tuesday night. Too early rising causes the particles of encapsulated Salvarsan to be dislodged and, by the action of gravity and muscular movements, they may come in contact with large nerves and give rise to severe pain. One patient of mine suffered intense agony by rising on the second day and taking up his duties on board a trawler. An abscess, which formed in his right buttock, was also due to moving too soon.

The individual susceptibility of the patient exercises some influence on the expression of suffering. Robust and phlegmatic people may hardly complain of pain but neurotic individuals may be much affected. Lunatics may magnify their sufferings very much. Women may complain more than men but I have usually found it otherwise.

The intensity of the pain varies very much from a mere sense of tightness, due to the stretching of the tissues by the drug, to the most intense agony which prevents sleep and necessitates the administration/

administration of morphia.

The character of the pain also varies. It begins within an hour after the injection. It may be a sensation of tightness or a smarting and pricking feeling which extends round to the back and down the legs. As time goes on it increases in severity and becomes cramping and shooting. In some cases it is limited to the coccygeal or ischiadic region. Much of the pain can be eliminated if the injection is made slowly.

Hot fomentations applied to the part mitigate the sufferings to a great extent. In many cases opium in some form is necessary.

Necrosis.

Also cannot occur after intravenous injections but it sometimes appears after subcutaneous and intramuscular ones. Clear alkaline solutions are more likely to be followed by necrosis than neutral ones. The necrotic area of muscle may be isolated by a wall of inflammatory connective tissue or it may be continuous with an area of inflamed and discoloured skin. The muscular fibres are degenerated and the cell nuclei have diminished staining power. Fatty tissue is also in a pathological state. It is necrotic although we may see here and there a droplet of fat which has normal/

normal staining reaction. Vessels in the necrotic area are thrombosed. The skin over it may slough.

In many cases the amount of necrotic tissue is small and quickly absorbed but in some it persists for a long time and may not be absorbed at all.

Abscess may also follow the injection of Salvarsan. Its contents are greenish-yellow pus and masses of necrotic tissue usually muscle. Arsenic is detectable often in considerable amount in the pus. As a rule there are no organisms present but in one or two cases the streptococcus longus has been cultivated from the contents. Abscess occurred in one of my cases.

Thrombosis of Vessels can follow any of the three forms of injection and serious results have been recorded of thrombosis after intravenous application. Parts of the thrombi have been observed to cause pulmonary embolism.

Nerves may be involved in the area occupied by the Salvarsan.

Neuritis which lasts long is the result. Ehrlich and others have described cases of peroneal paresis due to involvement of the corresponding nerves.

Muscular spasm affecting the muscles of respiration is sometimes seen after subcutaneous injection in/

in the scapular region. It causes transient difficulty of respiration. Patients usually are plethoric.

Oedema of the sites of injection is sometimes seen after intramuscular applications. It can also occur if an intravenous injection is faultily given. Ernest Lane(1) described a case of great oedema of the arm due to some Salvarsan solution getting into the tissues around the vein.

Interscapular Cysts have occurred after subcutaneous injections. Pautrier and Eyrand-Dechaux(2) had to remove a large one by surgical operation.

Arsenic may be retained within the gluteal muscles for a long time after the injection and the drug may hardly be absorbed at all from these deposits. This lack of absorption has been responsible for some of the failures attributed to the drug. Many cases which have been brought to the autopsy for other causes have had considerable amounts of arsenic in their gluteal muscles. Wechselmann(3) has seen it thirty-six days after the injection.

The occurrence of arsenic retention is the main difficulty in estimating the amount of Salvarsan which is acting upon the spirochactes. All the dose administered cannot be effective for some of it probably undergoes chemical changes in the depot.

We /

We cannot say whether the arsenic retained is in the form of Salvarsan or its decomposition products for it is a very unstable substance. These products may give rise to toxic symptoms. Some have said that we can no longer give the intramuscular injection, on the ground that there is formed a deposit from which Salvarsan is continuously absorbed and exerts a prolonged action, because of the unstability of the preparation.

Most of these local accessories will rapidly disappear because the intravenous route is replacing the intramuscular one.

GENERAL EFFECTS OF SALVARSAN INJECTIONS.

The intravenous form of injection gives rise to general symptoms whereas the intramuscular one is responsible for local phenomena. Much depends again on the individual for some people hardly are disturbed while others are profoundly affected. If the drug is pure, the technique faultless and the case a suitable one these symptoms should be reduced to a minimum. Organotropism on the part of the Salvarsan is nil practically so we have nothing to fear in that direction. Many have questioned this point in regard to certain ocular, auditory and urinary complications, but it has been proved that conditions/

conditions in the organs of special sense are really syphilitic neuro-recurrences and those in the urinary system are due to decomposed Salvarsan or some impurity such as old methyl alcohol in the solution employed. The last condition was settled in the discussion which followed some serious symptoms in cases injected by Bohac and Sobotka.

GENERAL PHENOMENA.

During the process of injection the patient may complain of fullness in the head, a metallic taste in the mouth and peculiar prinkling or numb sensations in the fingers and toes. He may have some tightness in the chest. There may be some burning feeling at the site of the injection if the technique is faulty and some of the solution escapes into the tissues around the vein.

In a few hours the general symptoms make their appearance. The chief are sickness, vomiting, rise in temperature and blood pressure and possibly skin eruptions.

Sickness is a constant occurrence but vomiting is not necessarily so for it can be rendered practically impossible if the patient is properly prepared, as for a surgical operation, beforehand. The nausea and gastric irritation may be due to mild arsenical intoxication/

intoxication. Lockemann[4] found $\frac{120}{1000}$ mg. of arsenic in 280 cc. of vomited fluid.

Rise of temperature up to 101°F. or 103°F. occurs and in cases of cerebro-spinal syphilis it may rise even to 106°F. The blood pressure also rises and this must be carefully taken into account in practice. An aneurism might rupture if the pressure rises high enough after the injection. Temperature rises and increased blood pressure may also occur after intramuscular injections and the more we massage the glutei the greater they are.

Constipation occurs after intramuscular injections but not so readily after intravenous ones.

Polyuria lasting for three days has been observed by Spatz[5].

Herpes Zoster and acne are sometimes seen among other skin affections. Toxic dermatitis occurs in those who have an idiosyncracy to arsenic. Desquamation of the facial skin was observed by Treupel[6]

THE EFFECT OF SALVARSAN ON THE BLOOD.

Michaelis[9] has studied the solubility of Salvarsan in the blood and concludes that it is never more than 1/1000 per cent. The low toxicity of "606" compared with that of other arsenical bodies is due to the slight concentration in the blood.

After/

After an injection there occurs a leucocytosis of varying amount. Zieler[7] saw an increase to 13,700. McDonagh[8] has seen a count of 30,000 but he states that the average is 17,000. Hirschfield, Herxheimer, Braendle, Clingstein, Fraenkel and Grouven have all observed leucocytosis. The increase is most marked in the neutrophile cells but eosinophilia sometimes occurs.

The red corpuscles and haemoglobin both shew an increase although Levy-Bing and Doureux[10] observed a fall in the corpuscles to 1,400,000. Syphilitic anaemia rapidly disappears after an injection. The leucocytosis is only temporary.

Methaemoglobin is never present after the administration of Salvarsan.

Schwarz and Flemming[11] studied the effects of Salvarsan on haemolysis and concluded that it has no haemolytic action at all. In high concentration it arrests haemolysis.

The effects of "606" on the blood are therefore of a beneficial nature and some of them may explain its effect on the Wassermann Reaction.

THE EFFECT OF SALVARSAN ON METABOLISM.

The metabolic processes in the body receive a very/

very powerful stimulation from Salvarsan. Mercury cannot be compared with "606" in this connection and it will be hard to mention any drug which is so powerful in producing such a beneficial effect.

Very shortly after an injection the patient experiences a delightful sensation of well-being and comfort. He feels as if years had fallen away from him and he begins to take a renewed interest in life. Much of this change is due to the destruction of the irritant products of the spirochaetes but some is due to metabolic changes following the injection.

The weight of the patients shews an increase which varies from $6\frac{1}{2}$ to $15\frac{1}{2}$ lbs. One case of mine put on 10 lbs. in six weeks, another shewed an increase of 7 lbs. in a month and a third put on 4 lbs. in fifteen days. The increase is more rapid at first and it becomes slower later.

Lecithin metabolism is said to improve very much. The excretion of arsenic is performed by the kidneys and intestines. The rate is modified by the condition of the patient, the form of injection employed and whether mercury has been given along with the Salvarsan. In any case the drug is not eliminated so quickly as atoxyl, arsacetin, and arsenophenylglycin.

In paralytics the rate of elimination is slower than /

than in epileptics.

If Salvarsan is given alone the arsenic is excreted more rapidly than when mercury is combined with it. Lockemann[4] found that a subcutaneous injection of .4 gm. of "606" is eliminated in the urine during an average period of fourteen days. If mercury were given also this period was increased to twenty days on an average.

Hoppe and Fischer[12] have made a most exhaustive series of experiments about the rate of elimination and came to the following conclusions :-

I. Method Subcutaneous :-

After 0.1 gm. the urine shewed traces of arsenic on the 8th day but none on the 10th.

After 0.3 gm. the urine had traces on the 11th day but none on the 12th.

The total amount eliminated in the urine after an injection of 0.3 gm. was 0.02 to 0.07 gm. in all cases.

In epileptics after a dose of 0.3 gm. the arsenic was gone on the 5th day.

II. Method Intravenous :-

The dose given was 0.3 gm. In all cases the urine was free from arsenic on the 2nd, 3rd, or 4th day.

III. Method Rectal :-

After/

After the second day no more arsenic was found in the urine. Only traces were ever found after this form of administration.

The excretion via the intestines goes on for a long time and most of the arsenic is got rid of in this way. After an intramuscular injection of 0.3 gm. arsenic could be detected on the tenth day and after an intravenous one it was definitely present on the sixth day.

In the faeces the arsenic is combined with the lecithins and not with the albumens and soaps.

Arsenic could not be demonstrated in the blood after the fourteenth day.

We can see that, even when the dose given is the same in every case, the rate of elimination varies very much, and we cannot be absolutely certain when a second injection can safely be given, without causing poisonous symptoms. We can also easily see how the therapeutic effects of "606" differ according to the manner in which it is administered.

COMPLICATIONS AND BYE EFFECTS.

Several complications have been ascribed to Salvarsan but it is uncertain how many of them are really due to the drug. Many have been proved to be the/

the result of some error in technique or some impurity in the solutions used or to some contra-indicating condition in the patient. Some deaths are due to the latter. Organisms in the solution injected may be responsible for some.

The following is a tabular statement of some recorded complications and bye-effects :-

Lesion	Observer	Remarks
Diarrhoea	Iversen (13)	Only transient
	Géronne and Huggenburg (14)	
	Finger (15)	
Urticara	Finger (15)	Temporary.
	Schreiber (16)	
Herpes Zoster	Finger (15)	
Melanosis	Finger (15)	Temporary.
Cyanosis of Face	"	
Oedema of Face	"	
Clouding of Mind	"	
Cramps of diaphragm	"	
Syncope	"	
Retention of Urine	Bohac and Sobotka (17)	Due to impurity in methyl alcohol used for the solutions.
"	Eitner (18)	Ampoule had been opened previously.
"	Malinowski (19)	Solution had been prepared some time before.
"	Browning and McKenzie (20)	Due to reflexes from site of injection.
"	Herxheimer (21)	Patient was a neurasthenic.
"	Wechselmann (22)	Was part of a severe angina.
"	Deneke (23)	Patient had similar attacks before
Salivation	Finger (15)	

Lesion	Observer	Remarks
Albuminuria		Transient.
Renal Haemorrhage	Wechselmann[22]	
Nephritis	Sellei[24]	Was latent before injection. Observed in two cases.
Nephritis (Acute)	Weiler [25]	No sign before. Cases very rare.
Jaundice	Klausner[26]	Three were due to absorption of toxic substances from the injection.
"	Waelsch[27]	Due to toxic Substances.
"	Browning and McKenzie[20]	".
"	Rille[28]	
"	Pinkus [29]	

SYPHILITIC NEURO-RECURRENCES AFTER SALVARSAN.

I. On the Eye.

Schanz[30] and others have shewn that "606" has no neurotropic action on the eye. Finger recorded a case which is the only one of amaurosis observed after "606" but the blindness was due to hypersensitiveness of the optic nerve to arsenic produced by previous injections of arsacetin and enesol. Inflammatory conditions can arise however. Browning and McKenzie[20] have seen iritis, choroiditis, and optic neuritis. Schanz has observed optic neuritis in two cases. These conditions generally pass off.

Sometimes we see alarming symptoms connected with the eye some weeks after a Salvarsan injection but it has /

has been proved that they are recrudescences of the syphilis and not due to the drug at all.

Benario's[31] work has settled this point conclusively. The phenomena have also been seen after mercury and occasionally independently of any drug treatment. In all three cases the phenomena are very similar. The ophthalmoscope shews that optic neuritis after "606" is identical with syphilitic neuritis and different from atoxyl neuritis. They are often unilateral and a second dose of Salvarsan clears them up. This fact alone militates against the drug being the cause of the trouble. If the primary sore is extragenital in the head region there is greater likelihood that an optic neuro-recurrence will occur than if it is of the genital variety. Benario,[31] Werther,[32] Rille[28] and others have recorded optic neuro-recurrences in cases of cephalic chancre. All ocular neuro-recurrences are ushered in by severe headache and all are in patients who have received one intramuscular injection. Anatomically they are favoured by the fact that the optic nerve is sheathed in dura mater for a considerable part of its course and this prevents it swelling when the spirochaetes become active in the nerve.

II. In the Ear /

II. In the Ear -

The conditions here are identical to those in the eye in most points. They follow cases treated in the same way, i.e. by one intramuscular injection and the disease is usually of recent standing, i.e. up to seven months. Anatomically the nerve runs through the narrow internal auditory meatus and this favours its compression when it swells after the spirochaetes have become active again. Benario,(31) Mauriac,(33) Finger(15) and Urbantschitch(34) have described cases.

Other cranial nerves have shewn recurrences of a similar nature.

The following table by Benario shews that 158 recurrences in different nerves occurred in 126 cases out of a total of 14000. Of these 126 cases, eight were in tertiary and metasyphilitic stages, and were not included in the analysis. Of the other 118, five were treated in the primary stage, 22 in primary and secondary and 91 in the secondary stage. Of 115 cases, 30 occurred one month after injection, 46 in second month, 27 in third month, and eight in the fourth month.

	On right side	On left side	On both sides	Not record-ed	Total	Per cent
II. Optic	11	11	15	4	41	26
III. Oculomotor	2	6	0	4	12	7.6
IV. Trochlear	2	1	0	1	4	2.5
V. Trigiminal	1	2	0	1	4	2.5
VI. Abducens	1	3	0	0	4	2.5
VII. Facial	11	9	5	0	25	15.9
VIII Auditory	15	16	30	7	68	43
Total	43	48	50	17	158	

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CONTRA-INDICATIONS

These are now fewer than Ehrlich first mentioned. They now are :-

1. Severe derangement of the circulation.
2. Advances degeneration of the central nervous system.
3. Foetid Bronchitis.
4. Cachexia not due to syphilis.
5. Patients with an idiosyncracy to arsenic.
6. Severe non-syphilitic renal disease.
7. Non-syphilitic eye diseases.
8. Fevers.
9. Diabetes.?

THE THERAPEUTIC USES OF SALVARSAN.

Salvarsan has been used in a great number of diseaseswith variable results. The following is a tabular statement of the conditions in which it has been employed. We may classify them into parasitic and non-parasitic groups.

I. Parasitic Diseases.

1. Syphilis
2. Relapsing Fever
3. Yaws
4. Malaria
5. Trypanosomiasis
6. Filariasis
7. Kala Azar.
8. Bilharziosis.
9. Marsh Fever.
10. Tick Fever.
11. Leprosy.
12. Fowl Spirilloses.
13. Vincent's Angina.
14. Variola.

II. Non-Parasitic Diseases.

1. Psoriasis.
2. Lichen.
3. Pemphigus.
4. Leukaemia.
5. Pernicious Anaemia.
6. Lymphadenoma.
7. Lymphosarcoma.
8. Scurvy.
9. Verruca.

It is probable that its sphere of activity will be increased in the future especially when some more of the diseases of tropical countries are traced down to their proper cause.

SALVARSAN IN SYPHILIS.

Before considering the use of Salvarsan in human syphilis it is advisable to study the phenomena in the rabbit which was employed by Hata for experimental purposes.

Uhlenhuth,[1] Levaditi,[2] Yamanouchi[3] and others have shewn that syphilitic keratitis can be experimentally induced in rabbits and that atoxyl can be used here both therapeutically and as a prophylactic. It was said to free the animal of spirilla in five or six days. Uhlenhuth[4] and Mulzer[4] also demonstrated that syphilis of the testicles in rabbits can be cured by atoxylic acid mercury.

Truffi(5) and Mezincescu[6] described syphilis

of /

of the scrotum of rabbits and shewed that it closely resembles the chancre in man. We can see, therefore, that three forms of syphilitic disease can be produced in rabbits -

1. Syphilitic keratitis.
2. Chancre of the scrotum.
3. Syphilitic orchitis.

SYPHILITIC KERATITIS.

This form is produced by the introduction of a small piece of diseased cornea into the anterior chamber of the eye. The cornea becomes opaque and newly formed vessels pass in towards the opacity from the periphery. The disease may make a steady progress or it may spontaneously heal up. The opacity gradually clears up and the vessels disappear. When Salvarsan is injected into the animal, even in such a small dose as .006 gram per kilo., of body weight a cure results. (Hata[7]) It takes about two weeks to clear up the diseased cornea. The effects of Salvarsan can only be estimated from clinical phenomena because one cannot make repeated examinations for spirilla without destroying the cornea.

SYPHILIS OF THE SCROTUM.

If we want to infect the scrotum of a rabbit we must not simply vaccinate the animal with syphilitic virus/

virus but the infective material is to be placed in a pocket made in the skin. The rabbit must be an adult because the scrotum of young animals is not yet thin and soft. (Hata[7]) The skin wound heals rapidly. At the end of ten to fourteen days there appears a red infiltration which enlarges from the size of a hemp-seed to that of a pea or bean. In four to six weeks the skin necroses and an ulcer with a projecting indurated edge results. The base is dirty and covered with a moist crust. It bleeds easily if the crust is removed. Induration persists even up to five months (Hata[7]). Spontaneous cure may take place here as in the case of keratitis. Spirilla can be obtained repeatedly by expressing a drop of juice from the chancre and this allows us to study the effects of Salvarsan on them properly. The inguinal glands become enlarged as in human syphilis.

After an injection of Salvarsan the spirilla rapidly disappear if the dose is adequate. The ulcer cleans and the induration diminishes. Gradually epithelium spreads in an cicatrisation occurs. Hata[7] found that .015 to .01 grm. per kilo thoroughly cured the disease in rabbits. The minimum effective dose is 0.005 grm. per kilo.

SYPHILITIC ORCHITIS.

This form of experimental syphilis is only good for /

for maintaining a strain of spirilla. The testicle swells and decreases of its own accord so it does not afford a good medium for chemotherapeutic research.

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SALVARSAN IN HUMAN SYPHILIS.

Salvarsan is of value in all stages of syphilis but it yields better results in some of them than it does in others. Some patients derive a permanent effect from it alone but others benefit from a combination of Salvarsan with mercury and iodides. Its administration must always be controlled by the Wassermann Serum Test. Every case must be carefully selected and Ehrlich's list of contra-indications must be observed to the letter with very few exceptions.

SALVARSAN IN PRIMARY SYPHILIS.

All are agreed that we must be prompt in our administration of the drug in this stage and we must employ it in a heroic manner. If we do so we may prevent the onset of secondary symptoms. Observations upon the Wassermann Test have shewn this for primary cases need never give a positive Reaction if treated sufficiently drastically with Salvarsan. Mercury did not have such a good result. McDonagh and others have described such cases. I recently injected the following case :-

J. N. was infected with syphilis while he away on a tour connected with his business as a traveller. He was a married man and he was consequently desirous of being cured as speedily as possible. 0.4 gramme of Salvarsan was injected intravenously. Since he got it (5 months ago) no secondary symptoms have appeared and the chancre on his glans penis has been his only manifestation of syphilis.

Some have advocated the destruction of the chancre because they say that spirilla may persist in the superficial parts and be uninfluenced by the remedy. These may be responsible for a relapse at the site of the previous chancre. Géronne and Huggenburg,(1)

Gibbard /

Gibbard and Harrison,[2] and Manuel[3] have reported such cases. Destruction can be carried out by hot air, injections of Salvarsan round the chancre (Hallopeau[4]) or carbon dioxide snow.[5] Most cases have not needed this so it may be discarded.

The chancre usually disappears quickly but a few cases have persistent induration for a long time. The rapidity of disappearance depends on the amount of induration present and the size of the dose administered. Usually spirilla cannot be seen next day in the initial lesions. In this stage we have a good example of the specific action of Salvarsan. (Neisser[6]).

The following table gives a summary of the times of disappearance of the primary sore as observed by authorities :-

Observer	Time of Disappearance of Chancre.
Alt[7]	3 - 14 days according to amount of induration.
Herxheimer[8]	8 - 14 days.
Fleckseder[9]	15 days in one case.
Spatz[10]	Within six days.
Pick[11]	5 - 14 days.
Halberstadter[12]	5 - 14 "
Duhot[13]	5 - 14 "
Browning and McKenzie[14]	7 - 17 days.
Gibbard and Harrison[15]	10½ days on an average.
Home[16]	48 hours in one case.
McDonagh[17]	7 days in one case.
Wechselmann[18]	8 days in a case of chancre of the lip.

We can see from these results that the average time taken to heal the primary chancre is three to fourteen days. The earliest period is forty-eight hours, in Home's case, and the latest is seventeen days in Browning and Mackenzie's data. Neisser[19] Schreiber,[20] Hoffmann,[21] Snitowsky,[22] and others all say that the primary chancre heals in a few days.

Extra-genital chancres yield, as readily as genital ones, to Salvarsan although Beneke and Schild say otherwise. Wechselmann,[23] Snitowsky[22] and McDonagh[24] all describe good results.

Induration of primary lesions takes a variable time to soften and disappear according to its extent. Wechselmann[23] says it is markedly softened in twenty-four hours. Schreiber[25] describes rapid disappearance. According to Glück it persists for a long time after injection in the cervix uteri. The persistence of induration anywhere is due to the fact that the drug gets with difficulty to all the contained organisms.

Specific Phimosis disappears without operative interference. (Wechselmann[23]) Spiethoff made studies about the value of large doses of Salvarsan over small ones in such cases. He found that the larger the dose the quicker the phimosis disappears. It/

It yielded in three weeks to 0.3 gramme subcutaneously and in one week to 0.6 gramme given in the same way.

Lymphadenitis and lymphangitis also yield to Salvarsan but not so rapidly as the chancre. Before the glands diminish they may first swell up, a phenomenon observed by McDonagh[24] and attributed by him to stimulation of the spirilla in them. They rapidly diminish, according to Géronne and Huggenburg,[1] in the first week or two and then they subside more slowly. Some cases are recorded of rapid diminution. Wechselmann[23] saw a maxillary bubo the size of a goose's egg disappear in eight days. Ivanyi[26] saw a lymphoma in the neck reduced to half its size in six days. Blumenfeld observed a bubo recede to one fifth of its original size in eight days. Others, on the other hand, have seen cases unchanged.

Lymphatic Oedema of the Labia Majora disappears quickly. (McDonagh[27]).

Phagedenic ulceration of the primary sore has been checked. (McDonagh[28]).

Balanitis erosiva, which is analogous to Vincent's angina, has been benefited by Salvarsan.

The dose to be administered in primary syphilis must always be large. Spatz[10] puts the minimum amount /

amount at .5 - .6 gramme. Much depends on the constitution of the patient for some can tolerate 1 gramme intramuscularly without evil consequences. Probably the best method is to give an intravenous injection of 0.5 - 0.6 gramme repeated in five or six days.

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20. Schreiber - Münch. med. Woch., No. 15, 1910.
21. Hoffmann - Med. Klinik., No. 33 - 1910.
22. Snitowsky - Russki Wratsch., No. 34 - 1910.
23. Wechselmann - Berl. klin. Woch., No. 27 - 1910.
24. McDonagh - "606" In Theory and Practice.
25. Schreiber - Münch. med. Woch., 1910 - No. 15.
26. Ivanyi - Wien. med. Woch., 1910 - No. 36.
27. McDonagh - "606" In Theory and Practice. page

SALVARSAN IN SECONDARY SYPHILIS.

Here we find, as in the case of primary syphilis, that the rate of involution depends on the dose and the method of administration and the amount of induration present in the lesions. Intravenous injections act more rapidly than intramuscular ones and the more indurated lesions take longer to heal than the less infiltrated ones. The variations in the results recorded depend upon these conditions. Most secondary phenomena yield to Salvarsan though some are refractory to it and are only curable by mercury.

THE EFFECT OF SALVARSAN ON THE CUTANEOUS MANIFESTATIONS OF SECONDARY SYPHILIS.

I. The Macular and Roseola Exanthemata.

Salvarsan exerts a very rapid action in these conditions. The rash pales quickly and disappears in a few days. After an intravenous injection they are distinctly faded in twelve hours. The following table of statistics indicates the times of disappearance observed :-

Observer	Time of Disappearance	
Gibbard and Harrison (1)	7 days.	
Loeb (2) (3)	1 day	
Glück (series 1)	3 - 5 days.	
Spiethoff (4)	10 - 20 days	Dose of .3-.6 gm.
Wechselmann (5)	Faded in 4 hours	
Géronne and Huggenburg (6)	2 - 4 days	
Michaelis	2 days.	
Glück (3) (series 2)	5 - 8 days	
Pick (8)	3 - 4 "	
My own case	2 "	

From these observations we can see that macules and roseola vanish in two to eight days. Spiethoff's cases took longer for the doses he used were small ones.

In contrast to the rapid disappearance of these eruptions, Miekleys found that in some cases the rash alters in character and remains in a pigmented state for some days. This is accompanied by slight hyperplasia of the tissues.

II. Maculo-papular eruptions also heal and leave only some pigmentation.

III. The Papular Syphilide is the slowest eruption to disappear. Large ones may take weeks. Gluck[3] however, reported a case of hypertrophic papules of the tongue which was cured in sixteen hours after an intramuscular injection. A period of six days to four weeks covers most observations as the following table shews :-

Observer	Time of disappearance of Rash.
Gibbard & Harrison[1]	6.3 days
Wechselmann[5]	1 to 3 weeks.
Schreiber[9]	1 " 4 "
Géronne & Huggenburg[6]	3 "
Duhot[10]	2 "
Iversen[11]	10 - 14 days.

IV. Psoriasiform Syphilide is another lesion which disappears /

disappears slowly. The scales first increase in amount and then gradually decrease till they are gone entirely. A pigmented area is left which pales to a greater or less extent but always leaves a trace.

A case of mine, already mentioned, namely Mrs. G. had an extensive eruption of this character on the extensor aspects of the legs and arms and the palms and soles. The palmar and plantar affections were severe and the skin was cracked and bleeding. The head and trunk were unaffected. Mercury had somewhat lessened the severity of the eruption and it caused the bleeding to stop. 0.6 gramme of Salvarsan in neutral emulsion was injected. During the first four days after the injection the scaling increased in amount and then it gradually diminished till it was gone in ten days leaving a pigmented area which became paler and paler. The colouring has not absolutely vanished. Isolated circular patches about the knees were slower in clearing up than the large areas.

Spatz[12] says that scaling lasts till the thirteenth day.

V. Pustules and Rupia vanish quickly and Lichenoid Syphilides, which are very resistent to mercury heal rapidly/

rapidly after Salvarsan injections.

VI. Mucous Tubercles and Condylomata react quickly to "606" because they have an excellent blood supply. The process of healing may be only a matter of hours in the case of mucous patches. These lesions vanish quickly and they are the first to recur if the injection has not cured the disease.

Condylomata lose their moist succulent character and become dry, shrivelled and flaccid and finally they are absorbed. They may be treated by an ointment of .5 gramme of Salvarsan in an equal amount of vaseline. The observed times of disappearance are :-

Observers	Time of Disappearance.
Géronne and Huggenburg (6)	2 - 3 weeks.
Glück (3)	7- 17 days.
Mondschein (13)	8 days.
Fraenkel and Grouven (14)	7 -10 days.

VII. Impetiginous syphilides and echthyma benefit very well.

VIII. Pemphigus was successfully treated with "606" by Wechselmann in cases of two infants. Fehr had good results also.

IX. Syphilitic Ulcers rapidly clean and granulate.

Syphilitic Eczema reacts very well to salvarsan.

The/

The following case of mine illustrates this.

The patient, J.H.K., was infected seven years ago. The primary chancre was on the inner surface of the prepuce close to the frenum. Secondary symptoms appeared in due course and have steadily got worse in spite of treatment. Mercury, iodides, sarsaparilla and iodalbin have all been tried without avail. When I saw him, in January 1912, the face was covered with an ulcerating ecxematoid syphilide and the ulcers are covered by crusts. The eruption extended over his forehead to the roots of his hair and there was a large patch on the back of his neck. The axillae and scrotum had similar patches. No ulcers or mucous plaques were present in his throat. He weighed eight stones, ten pounds and his height is five feet, eight inches. He feels very depressed and is much addicted to alcohol.

On January 18th 1912, he received an injection of 0.6 gramme of Salvarsan intramuscularly. On the 25th of the month the crusts had all dropped off, the ulcers were healed and only some pigmentation was left which gradually diminished. He had put on 1½ lbs. of weight and his mental state was much better.

SALVARSAN ON SYPHILITIC AFFECTIONS OF THE MUCOUS MEMBRANES.

Lesions /

Lesions of mucous membranes are healed with extraordinary rapidity after an injection. So quick is the process of resolution that one would almost attribute it to magic. Excessive smoking does not hinder it. (Wechselmann). Mucous patches disappear and ulcers of the tonsils are so quickly removed that Michaelis has likened the action of Salvarsan to that of the diphtheria anti-toxin. Before the healing begins there may be a preliminary swelling of the ulcers and patches.

A case of mine had redness and congestion of the uvula, fauces and palate. In the middle line of the roof of the mouth were two small ulcers and on the inner aspect of the lower lip, close to the frenum there was an ulcer the size of a sixpence. 0.6 gramme of Salvarsan was injected intramuscularly because the patient preferred that to the intravenous method. Next morning the congestion was almost gone. The ulcers were all clean and their margins were hyperaemic. Three days afterwards they had all healed except a small piece of the ulcer on the lower lip. Pain rapidly diminished and all trace of hoarseness of the voice was gone in eight days.

SALVARSAN IN AFFECTIONS OF THE HAIR AND NAILS.

A. The Hair

Alopecia /

Alopecia stops after Salvarsan. McDonagh[15] says the hairs do not fall out from the second day onwards. Gibbard[1] has had good results with "606" in alopecia.

B. The Nails.

The effect of the drug on onychia is slow although some have seen no change in this condition. In a case which I injected with .6 gramme intramuscularly the nails which were dry, shrivelled and fissured were slowly shed. Two months after the injection they were cast off and new ones were not complete till three and a half months after the administration. Intramuscular injections would be more efficacious here probably than intravenous ones for the action of the drug is more prolonged. The slowness of resolution is due most likely to the great amount of induration present.

SALVARSAN IN THE OCULAR LESIONS OF SECONDARY SYPHILIS

When Ehrlich supplied Salvarsan for clinical use he forbade its employment in cases where the ophthalmoscope revealed any abnormality. Physicians carefully observed this order at first because the disastrous effects of the arylarsonates made them cautious.

Soon the inevitable happened, however, and syphilitics /

syphilitics with ocular troubles were accidentally injected. Instead of blindness following this action the eye conditions improved or disappeared, and the question then arose whether syphilitic lesions of the eye were to be denied the use of the drug. Many favourable reports then appeared which modified Ehrlich's original hypothesis and now it is stated that no ocular lesion which can really be attributed to syphilis debars the administration of the remedy. Only non-syphilitic diseases are contra-indications to the employment of "606".

The literature contains many reports about its favourable action in all the manisfestations of ocular syphilis and the following table briefly indicates the varieties which have been benefited by it :-

Lesions.	Observers.
Corneal Opacities	Neisser[16] Wicherkiewiez[17] Wechselmann[18]
Vitreous Opacities	Wechselmann[18]
Episcleritis	Fehr[19] Seligsohn[19]
Iritis	McDonagh[20] Treupel[21] Glück[3] Zeissl[22]
Irido-cyclitis	McDonagh[20] Fehr[19] Seligsohn[19]
Choroiditis	Fehr[19] Seligsohn[19]
Parenchymatous Keratitis	Treupel[21] Glück[3] Fehr[19] Seligsohn[19]
Scotomata	Wechselmann[18]

Lesions.	Observers.
Choked Disc.	Wechselmann[18]
Haemorrhage in Papilla	Schanz[23]
Neuroretinitis	Schanz[23]
Syphilitic Optic Atrophy.	Wicherkiewiez[17] Wechselmann[18]
Ophthalmoplegia	McDonagh[20] Neisser[16]

It is also of value in the eye diseases of hereditary syphilis and tabes dorsalis but these will be described later.

Irregularities in the pupils become somewhat rectified and the field of vision improves.

It may be said that "606" benefits all syphilitic eye diseases and, from numerous statistics, we find that it does so in from one to ten days. It should prove of great value in ophthalmological practice.

SALVARSAN IN SECONDARY AFFECTIONS OF THE BONES AND JOINTS.

Cases of periostitis react well to Salvarsan. The severe pain disappears as if by magic (Wechselmann and others) and the inflammatory material is absorbed without leaving any trace. Glück,[3] Herxheimer[24] and Flechseder[25] all describe cases where it had disappeared by the sixth day. There may be some preliminary /

preliminary increase in the swelling.

Ostalgic pains suddenly cease. Wechselmann attributes this to destruction of the spirochaetes but Ehrlich says it is due to Salvarsan neutralising their products.

Old osseous and arthritic processes heal wonderfully. Mondscheim[13] cured a case of luetic synovitis rapidly.

SALVARSAN IN AFFECTIONS OF THE MUSCLES.

Intercostal and pectoral myalgia with excessively tender points occasionally appears in secondary syphilis. It reacts well to Salvarsan. The following case of mine is an example :-

The patient, A. C., a sea-captain, was infected eighteen months ago (i.e. July 1910). The primary sore was situated on the dorsum of his glans penis. Secondary eruptions appeared on the dorsa of his hands and his throat became ulcerated and tender. He took mercury and iodides continuously and all the symptoms disappeared except the intercostal and pectoral myalgia and a few of the spots on the hands.

On January 24th, 1912 I saw him, in company with Dr. Roberts of Llanelly. He is a well-built man although he says he has lost much weight. The insertions /

insertions of his great pectoral muscles are so tender that moderately firm pressure makes him gasp. In the lower interspaces close to the sternal margins there are similar spots. On the dorsal aspects of his hands there are a few roseola spots. His right submaxillary gland is enlarged and tender.

On January 25th, 1912, he received an intramuscular injection of 0.6 gramme. During the first night he had severe pain which necessitated opium but that was gone next morning and some tenderness only was left. He also felt like a new man next day. The pain over the pectoral muscles was gone completely in six days. The roseola spots were no longer to be seen on the second day after the injection.

By a curious coincidence another patient with the same condition came into the surgery the same day. He denied syphilis but he was given a course of mercury and iodide of potassium. The pain did not leave him for fifteen days. This shews the superiority of Salvarsan as an analgesic over mercury and iodide.

DOSAGE.

The following table indicates the dosage of Salvarsan employed in secondary and tertiary syphilis.

Intramuscular /

Intramuscular :-

1.	For robust men	0.6 to 1.0 gramme.
2.	For feeble men	0.5 to 0.7 gramme.
3.	For robust women	0.5 to 1.0 gramme.
4.	For feeble women	0.4 to 0.6 gramme.

Intravenous :-

1.	For men	0.5 to 0.6 gramme
2.	For women	0.4 to 0.5 gramme

The ideal method is to give two intravenous injections with an interval of five days between. If a third dose is necessary it should be administered between the fourth and sixth week , when Wassermann's Reaction is positive. (McDonagh)
More than three injections are useless as was shewn by Hata's experiments for no value is got after the third one.

SALVARSAN IN TERTIARY SYPHILIS.

It is in this stage of syphilis that we get very remarkable results. The drug seems to be a specific against gummata. It causes them to be speedily absorbed and excites the proliferation of endothelium. The malignant and ulcerous forms rapidly yield to it on account of the "Law of Allergy" already mentioned. These cases are practically saved from an early grave. The /

The dosage and method of application are the same as in the secondary stage.

EFFECT ON GUMMATA.

According to McDonagh[26] it is exceptional for gummata of the skin to be refractory to Salvarsan whereas many never disappeared under mercurial treatment. This statement also applies to gummata of other parts except the heart, liver and brain.

The rapidity of disappearance is modified by two conditions - the amount of connective tissue present and the existence of secondary septic infection. McDonagh[26] describes a case where the gumma did not clear up until iodide of potassium was given to absorb the tissue and one in which peroxide of hydrogen completed the curative process by destroying the accompanying organisms.

In very exceptional cases Salvarsan may make the gumma worse. McDonagh[27] has seen this on two occasions.

Medical literature contains accounts of gummata in all situations which have been treated with Salvarsan. The following table shews some of these :-

Situation of Gumma	Observers
1. Skin	McDonagh[26]; Kromayer[23]; Eitner[29]; Mondschein[13]; Browning & McKenzie[30]; Gibbard and Harrison[1].
2. Pharynx	McDonagh[27] Gibbard & Harrison[1]
3. Larynx	Glück[3]; Wechselmann[18]; McDonagh[27]
4. Nose	Spiethoff[4]; Mondschein[13]; Browning and McKenzie[30]
5. Palate	Meirowsky[31]; Zeissl[22]; Herxheimer[24]
6. Tonsils	Herxheimer[24]
7. Liver & Heart	Fehr[19]
8. Testicle	Géronne & Huggenburg[6]; McDonagh[27]; Herxheimer[24]
9. Pons Varolü	Pick[8]
10. Viscera in general	Duhot[10]

In order to get rid of a gumma rapidly and completely we must combine Salvarsan with iodide of potassium internally and local antiseptics externally. (McDonagh)

EFFECT ON TERTIARY ULCERS.

Ulcers, whether they be due to breaking down of gummata or not, heal well under "606". There is first a process of cleaning and then one of resolution. The resulting scar is smoother, paler and less adherent to subjacent parts than that which forms under mercurial treatment. This is of value when the scar overlies a bone which is close to the skin surface /

surface for new breaking down is less likely to occur. According to observations recorded, a period of five days to three weeks is necessary for complete resolution.

RESUME OF CASES OF TERTIARY SYPHILIS OF THE DIFFERENT ORGANS REPORTED IN THE LITERATURE OF SALVARSAN.

Lesion	Author.	Remarks.
Gumma of Tonsils	Herxheimer (24)	Disappeared in 6 days. Dose 0.3 gm.
The Palate.		
Multiple Gummata	Herxheimer (24)	Cured in 10 days.
Gummatous Ulcer	Duhot (10)	Heal in 4 to 5 days.
Ulceration	Meirowsky (31)	Rapid healing.
	Zeissl (22)	Rapid healing.
Necrosis of Hard Palate	Gibbard and Harrison (1)	Sequestrum separated in 14 days. Ulcer healed in 21 days.
The Tongue.		
Interstitial Glossitis	Geronne and Huggenburg. (6)	Had lasted 2 years. Tongue moveable in 8 days and pain so much abated that patient could swallow easily.
Interstitial Glossitis	Pick (8)	2 cases completely healed in a short time.
Indurated Glossitis	Fleckseder (25)	Symptoms practically gone in 7 days. Had previously received 20 courses of mercurial inunctions and injections.
Chronic Superficial Glossitis	McDonagh (27)	Quite well in one week.
Chronic Superficial Glossitis	" (27)	Conditions disappeared.
Fissures of Tongue	Gibbard and Harrison (1)	Well in 35 days.
Late Ulceration	" (1)	Well in 6 days.
Leukoplakia	Wicherkiewiez (17)	Symptoms disappeared.
Intestines.		
Duodenic Stricture	Wechselmann (32)	Completely cured.

Lesion	Author	Remarks.
The Liver		
Gummata	Fehr (19)	Unaffected.
Cirrhosis	Meidner (36)	Unaffected
Gummata	Kakels (37)	Good effect in 2 days. Dose 0.3 gm.
Icterus	Wechselmann (32)	Had existed long. Disappeared in 10 days.
"	Michaelis	Almost gone in 9 days. Dose 0.4 gm.
The Respiratory System.		
Larynx		
Gumma	Gluck (6)	3 cases practically saved from death
Gumma	Wechselmann (32)	Contemplated tracheotomy obviated.
Perichondritis	Korczynski (38)	Lesion first aggravated and then diminished.
Gummatous Ulcer	McDonagh (27)	Soamin, mercury and iodides failed to cure it. Condition cured in less than a month.
Gummatous Ulcer	Friedlander (39)	Great success in 15 cases.
Inflammation of Epiglottis.	Gibbard and Harrison (1)	Voice normal in 18 days.
Lung.		
Cough, Haemoptysis and some fever	Korczynski (38)	Dose.5 gm. Symptoms gone in 10 days. Only slight dulness left.
Atelectasis of left lung.	Lesser (40)	Dose .3 gm. Cough gone in 5 days and slight vesicular breathing audible. Coexistent albuminuria much less.
Circulatory System		
Gumma of Heart	Fehr (19)	Unaffected.
Arteriosclerosis and heart irregular but without disease.	Korczynski (38)	Dose .4 gm. In 4 weeks the heart was regular, sounds pure, pulse of good tension.
Kidney.		
Haemorrhagic Nephritis	Schreiber and Hoppe (35)	Abated after injection.

Lesion	Author	Remarks.
Albuminuria	Ivanyi (41)	Dose .5 gm. Only trace left in a few days.
Glycosuria	Ivanyi (41)	1% sugar gone in 6 days after .5 gm.
Waxy Disease	Mondschein (13)	Salvarsan did not injure the kidneys.
Albuminuria	Herxheimer (33)	Albumen gone 3 days after injection.
Albuminuria	Browning and McKenzie (30)	In one week the albumen diminished in Esbach's tube from 2 to 1.
Albuminuria	Lesser (40)	Much improved in 5 days.
Incipient Uraemia	Treupel (21)	Symptoms stopped after dose of .6 gm. was given.
Albuminuria	Gibbard and Harrison (1)	Dose .6 Albumen gone next day but traces in 3 or 4 days again.
Albuminuria	Gibbard and Harrison (1)	Albumen gone in 2 months.
Testicle.		
Gumma	Geronne and Huggenburg	In 16 days the testicle was nearly normal in size.
Gumma	Herxheimer (24)	Change apparent in 24 hours after dose of .5 gm.
Bladder.		
Retention of Urine	Duhot (10)	After 14 days the patient could empty 2/3 of the bladder.
Weakness of Sphincter vesicae.	Wechselmann (32)	Disappeared in a few days.
Nose		
Ozoena Syphilitica	Hoffmann (34)	Very favourable action.
Ulcers of Nose	McDonagh (27)	Healed in 14 days after .45 gm.
Gumma of Nostril	Spiethoff (4)	Ulcer had skimmed over in 3 days and only slight infiltration present.
Gummata of Sinuses	Browning and McKenzie (30)	Completely healed in 2 months.
Ear.		
Weak hearing	Wicherkiewiez (17)	Greatly improved.

Lesion	Author	Remarks.
Labyrinth Deafness	Fraenkel and Grouven (14)	Much improvement in 12 days after .6 gm.
Eye		
Visual field reduced and cornea dry and epithelium denuded	Wicherkiewiez (17)	.4 gm. given. Dryness of cornea abated and visual field improved.
Optic neuritis and opacity of lens and iris.	Wicherkiewiez (17)	.4 gm. given. Opacities diminished and vision improved.
Choked Disc	Michaelis (7)	.6 gm. given. Condition gone in a month.
Glands.		
Recurrent Enlargement	McDonagh (27)	Almost disappeared in a fortnight.
Joints.		
Arthritis with pain and fever.	McDonagh (27)	Cured in a few days.
Bones		
Periostitis of Skull	Herxheimer (33)	Disappeared in one week.

THE EFFECT OF SALVARSAN ON DISEASE OF THE NERVOUS SYSTEM IN SECONDARY AND TERTIARY SYPHILIS.

The deadly effects of syphilis of the nervous system make us very anxious to test the powers of Salvarsan in them. If it should prove of value Ehrlich has conferred an inestimable boon on mankind by discovering it.

When he introduced "606" Ehrlich mentioned extensive degenerations of the central nervous system as /

as contra-indications to its use. It can easily be understood that the drug is useless in these cases for it cannot replace the destroyed neurons and it may still further damage the remainder which have low vitality. It is quite another thing to use it in recent cases for it may arrest the progress of the disease and raise the resistence of the whole nervous system by its tonic action. Nevertheless it must be used very cautiously even in early cases.(Zeissl, Schreiber).

All the symptoms of secondary syphilis of the nervous system have been benefited by the remedy. Some physicians, however, have found it valueless. Meidner,(36) for example, could not improve the symptoms of spinal syphilis with it.

Pain of cerebral syphilis rapidly vanishes. Headaches which make the lives of the patients almost unbearable disappear promptly. There may be first an intensification of the pain. McDonagh, Gibbard and Harrison and many others have described cases.

Paralyses which occur during secondary and tertiary stages and in parasyphilis are improved or cured by the remedy. In the secondary stage the facial and ocular muscles are mostly involved. The drug may act on them by absorbing inflammatory deposits or gummata /

gummata which are pressing on the nerves. McDonagh, Neisser[16] and Treupel[21] have all reported successes in ophthalmoplegia.

Hemiplegia, paraplegia and epilepsy occurring in the tertiary stage are caused by sclerotic and thrombotic changes in the vessels, meningitis and gumma pressure. These etiological conditions are all favourably influenced by Salvarsan and the curative process may be brought about in this way.

Epilepsy has been treated by Alt[42] Bonhöffer[43] and Duhot.[10] Duhot's case had no more crises after the injection but Bonhöffer's case had a fresh attack as a sequela.

Amnesia was much improved in a case of Duhot's.[10] In it as in cases recorded by Schreiber,[44] Gibbard and Harrison[1] there was marked betterment in the mental condition.

Luetic Apoplexy has been treated on several occasions. Treupel's case was cured. In those patients in whom no benefit resulted, there were no serious by-effects of the injection.

Meningitis may occur in secondary or tertiary stages. McDonagh has treated cases in both with excellent results.

Neurasthenia accompanying syphilis was improved by /

by Korczynski.[38] He found a great diminution in the number and intensity of the tremors.

Hemiplegia must be treated very cautiously with "606". If the dose administered is too large tremors may occur in the paralysed limb. (Schreiber[44]). Zeissl[22] observed improvement in the speech and power of writing in one hemiplegic and Schreiber[44] saw an increase in the mental clearness and speech powers in another.

SALVARSAN IN TABES DORSALIS.

The discovery that Tabes and General Paralysis are due to syphilis in most cases and the recorded cases of the beneficial value of Salvarsan in that disease make us hopeful that we shall be able to cure these conditions. The possibility of cure is no longer doubtful so all cases where the symptoms are recent must be injected with the drug. We can only employ it with safety in the pre-ataxic and ataxic stages of tabes. The paralytic stage will not derive any lasting benefit and the administration of the drug here may be followed by very disastrous consequences.

All the symptoms of the pre-ataxic stage are affected by Salvarsan - pains, ocular manifestations, bladder /

bladder symptoms, trophic disturbances and loss of deep reflexes.

Pains :-

McDonagh[45] made observations on the effect of the drug on the pains in nineteen cases. In two cases they were made worse, in five they vanished and in twelve they were unaltered. Collier[46] saw them disappear in most of his patients. Intercostal neuralgia is quickly relieved. Any increase in the pain may be analogous to Herxheimer's Reaction.

Ocular Symptoms :-

Optic atrophy was treated by Wicherkiewiez,[17] Browning and McKenzie[30] and the perception of light improved. Gibbard and Harrison[1] found that optic atrophy was the only tabetic symptom uninfluenced by the remedy. McDonagh[45] says that optic neuritis approaching atrophy is not affected at all.

Ptosis may be completely cured as in cases reported by Meidner,[36] Gibbard and Harrison[1]. The Argylle-Robertson Pupil was observed by McDonagh[26] to give way to a normal condition. Myosis and Ophthalmoplegia both react well.

Bladder Symptoms improve. Retention of urine and weakness of the sphincter vesicae are overcome. In most of the cases reported the conditions returned later. Bladder symptoms may be the only ones of early /

early tabes to return.

Loss of Deep Reflexes is not much affected. In those cases in which they return we must exclude auto-suggestion on the part of the patient. Wechselmann[32] described a case in which such an influence was at work. The patient deceived him and Oppenheim for some time by making his limbs move when the reflex was elicited. Wicherkiewiez[17] saw transient return and McDonagh[45] also.

Trophic Disturbances are checked and in some cases healed. Meidner and others have described rapid cures in perforating ulcers but McDonagh[45] says the results are only temporary.

Sexual power returns and some patients have indulged in intercourse.

In the ataxic stage good results have been obtained also. Ataxia, Rhomberg's Sign and crises have all benefited.

Ataxia was improved in cases recorded by Meidner[36] and Collier.[46] Ivanyi[41] and others have seen no benefit whatever.

Rhomberg's Sign disappeared in one of Wechselmann's patients.

Tabetic Crises may cease. Cardialgia disappeared in a case mentioned by Zeissl.[22] Collier[46] records four patients with severe gastric crises which improved remarkably /

remarkably. In one of them he had previously tried all known remedies without avail.

In the third or paralytic stage the drug has been employed with due care by certain physicians but the results have only been temporary.

The general condition of the tabetics improves. They put on weight, have better appetite and feel more comfortable.

As regards the permanent cure of the disease it is too early to speak yet. The trouble itself may die down and lie quiescent for years and then break out again. If a case has been apparently cured with Salvarsan it will have to be kept under observation for many years in order that we may see if the drug has conferred a lasting benefit on the patient. As far as we can judge from cases recorded we may entertain some hope that we have, in Salvarsan, a remedy which will exterminate the fatal locomotor ataxia. We must not, on the other hand, be too ready to ascribe loss of symptoms to the drug.

SALVARSAN IN GENERAL PARALYSIS.

Most writers record only temporary improvement in this disease or no success at all, still early cases should have the chance of cure or improvement even if it /

it is slight.

The patients must be selected very carefully and we must always remember Ehrlich's warning that the drug must not be used in patients with advanced degeneration of the nervous system. In the early grandiose stage Salvarsan may be advantageous but in the stage of dementia it is absolutely valueless and may bring about the death of the patient. We cannot be guided so much here by the Wassermann Reaction as in the earlier stages for some patients have a negative one at the start and others never lose the positive result. Alt[42] found that only two patients out of eighteen permanently lost their positive Reaction. Accordingly clinical results must be relied on.

The most prominent symptoms disappear or diminish after the injection. Skin, mucous and bone lesions all improve well. Salvarsan may therefore make the patient more comfortable although it does not stop his paralysis from progressing to a fatal issue.

The following table gives the opinions of several clinicians based upon their observations in paralytics.

Physician	No. of Cases	Remarks.
McDonagh[45]	1	Apparent Recovery.
Marcus[47]	1	Apparent Recovery.
Robertson[48]	1	Striking improvement with human serum and Salvarsan.

Physician	No. of Cases	Remarks.
Treupel (21)	-	Frequently slight improvement.
Oppenheim (49)	9	Two improved very much.
Gluck (3)	2	No apparent benefit.
Behring (50)	6	No beneficial effect.
Meyer (51)	16	No obvious benefit.
Willige (52)	24	Symptoms ameliorated in seven of them.
Browning and McKenzie (30)	58	Noticeable improvement in 12.6 have been discharged from asylums.

Although many of these statistics would point to the fact that the drug is not of much value in general paralysis, others make us hopeful that we can do something to make the last years of the life of the paralytic more endurable to himself and his neighbours.

In connection with tabes dorsalis it will be interesting to note whether Salvarsan given in the early stages may cause the symptoms to continue by preventing optic atrophy.

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SALVARSAN IN CONGENITAL SYPHILIS.

Primary and congenital syphilis are the two conditions which we must be especially prompt in treating. In the former we prevent the appearance of secondary symptoms, and in the latter we try to prevent the disease getting such a hold on the patient that certain chronic nerve lesions follow.

Children of all ages from sucklings upwards have been treated directly or indirectly with Salvarsan with varying results. In all cases the symptoms rapidly clear up but a few conditions such as interstitial keratitis do not respond very readily.

The methods of employment of Salvarsan differ at different ages for several reasons. In the case of sucklings it is dangerous to inject the child directly because the drug causes such a great dissolution of spirochaetes that death from endotoxaemia results. Several cases of this are on record. The child must be fed at the breast of a syphilitic woman whether it/

it be the mother or a wet nurse, who has been injected. The child then ingests a constant supply of anti-body in the milk which destroys spirilla in small amounts and the patient's life is not endangered. Treupel,[1] Duhot[2] and Dobrowitsch[3] all observed the cure which the milk produces in these patients and concluded that it contains anti-bodies because only minute traces of inorganic arsenic are present in it. Jesionek,[4] on the other hand, said he found considerable amounts of arsenic in 100 cc. of milk. His evidence is not conclusive about the action of the drug. Ehrlich[5] says that both mother and child should be injected and the dose for the latter is .008 to .01 grms. per kilogramme of body weight.

In children from three to six years of age we give an intramuscular injection because it is hard and sometimes impossible to get a vein large enough for intravenous injections.

After the age of six or seven years we may employ the intravenous method but we may have to dissect down to the vein first.

In children we administer a dose of .004 to .005 gm. per pound weight.

It is a question of vital importance whether we can, by injecting the mother, prevent the foetus being /

being born a syphilitic. It is certain, of course, that we can do this if we treat the woman so drastically in her primary stage of syphilis that secondary symptoms do not appear.

The number of pregnant luetic women who have been injected in the different months of pregnancy is not inconsiderable. In only one case[6] was the injection followed by abortion. All the rest tolerated the drug well and the movements and heart sounds of the foetuses were unaffected.

The children were born apparently healthy in most cases. In one[7] the infant was also well six months after its birth. We cannot, however, attribute the effects to the Salvarsan in all the cases for syphilitic women may produce healthy-looking children. There are so many possibilities that we can only come to definite conclusions by observing a large number of cases for many years.

The following table shews the successes and failures in the treatment of pregnant women as recorded in literature :-

Physician	No. of Cases	Remarks.
Wechselmann[8]	5	Dose .45 gm. No harm to foetus.
Wechselmann[8]	10	No ill effects on child. Delivery normal in three cases.
Bar[9]	4	No harm to foetus.

Physician	No. of Cases	Remarks.
Tissier & Geraudt[9]	1	Child born healthy.
Browning & McKenzie[10]	1	Child healthy even six months after.
Fraenkel & Grouven[11]	3	No visible effect.

Pfeiffer[12] recommended it in cases of habitual abortion.

The infant loses many if not all of its symptoms. Mucous plaques and maculo-squamous eruptions quickly clear up. (Jeanselme,[13] Bokay[14] and others.) Pemphigus neonatorum, which is usually followed by death, may be cured. Wechselmann[8] reports two successes in five cases and Fehr[15] records three cures. Bone lesions such as osteochondritis and epiphysitis improve. Deep visceral lesions may react unfavourably and the child may die as a result. Jeanselme insists[13] therefore that the organs of the child must be very carefully examined. Gaucher[16] only uses Salvarsan when mercury is useless.

The following cases of hereditary syphilis treated by Salvarsan have been described in literature :-

Lesion	Observer	Remarks.
Dactylitis	McDonagh[17]	Fingers freely moveable in a few days.
Ascites	"[17]	Free fluid gone in 24 hours.
Iritis	Treupel[18] (7)	Some improvement.
Interstitial Keratitis.	McDonagh	Not much improved.

Lesion	Observer	Remarks.
Interstitial Keratitis	Treupel (18)	Some improvement.
Periostitis	Fraenkel and Grouven (11)	Rapidly disappears.
Parenchymatous Keratitis.	Ivanyi (19)	Ciliary injection gone in 3 days.
Otitis Media	Ivanyi (19)	Associated deafness gone in 14 days.
Ulcer of whole Pharynx	Michaelis (20)	All healed in one month.
Coryza		

Of all the lesions of congenital syphilis interstitial keratitis is the hardest to improve. McDonagh wonders why keratitis of rabbits is so tractable while the corresponding lesion of syphilis in man is not. He comes to the conclusion that the biological characters of the parasites have become so altered in the passing of time that they don't respond so readily to Salvarsan.

Cases are on record where Salvarsan serum has benefited congenital syphilis. Meirowsky (21), Plaut, (22) Scholz (23), Browning and McKenzie (7) have all obtained results more or less successful.

The recorded cases of congenital syphilis treated by Salvarsan are now very numerous. They are also good and they encourage us to investigate further the value of "606" in this unfortunate form of the disease.

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SALVARSAN IN MALIGNANT SYPHILIS.

Malignant syphilis is one of the principal indications for the use of "606". In it the drug acts with extreme rapidity and all symptoms and signs should be gone in ten to fourteen days. Mercury does not get a hold of the patients whereas Salvarsan acts promptly and, in some cases, it has snatched the patient from death. Some cases have not reacted, it is true, but they are very small in number. Meirowsky (1) got no result/

result. Gennerich[2] had relapses in his cases and Havas[3] also but his recurrences were due to inefficient absorption of the drug. Most cases are cured with one injection but Wechselmann[4] had a patient who required two. The following table indicates the opinions of physicians who have treated malignant syphilis.

Observer	Lesion	Remarks.
Wechselmann[4]	Ozoena: Ulcers of nose & throat. Pains in knees: Very decrepit.	Cured in 9 days after .4 gm.
Pick[5]		Rapid healing.
Isaac[6]	Ecthyma: Ulcers involving subdermal tissues.	Cured in 14 days.
Fraenkel and Grouven[7]	Pemphigus. Ulcerous processes of legs	Rapid epithelisation and cicatrisation.

Herxheimer[8], Jakowleff, and Grunfeld[9], Hoffmann[10], Mulzer[11] and Ledermann[12] all testify to the astonishing results obtainable with Salvarsan in malignant syphilis.

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SALVARSAN IN SYPHILIS COMPLICATED BY OTHER DISEASES.

Many diseases accompanying syphilis have been observed closely for some time after the injection and it has been found that they are not unfavourably influenced by the remedy although they have not been cured. They may be divided into venereal and non-venereal.

In the former class we include gonorrhoea and chancroid. They are not at all benefited by Salvarsan.

In the second class we chiefly mention pulmonary tuberculosis. The patients have not been harmed and some of them improved temporarily owing to the beneficial general effect of the drug. Three cases have been described in the literature of salvarsan :-

Observer	Variety of Tubercle	Remarks.
Treupel (1)	Phthisis	Unharmed.
Herxheimer (2)	Advanced Phthisis	General state improved.
Glück (3)	Chronic Phthisis	Cough diminished.

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SALVARSAN IN MALARIA.

Salvarsan by itself is not an absolute specific for malaria but it is a very potent weapon against the disease and it will be more so when used in combination with other drugs. Cases of malaria and syphilis will benefit very much from it because each of these diseases hinders treatment of the other. Ciamarelli Anthony[1] had a case of this combination which was practically cured by Salvarsan.

In malaria much depends on the species of the parasite and on the district from which the patient came. The injection is followed by disappearance of the parasites from the blood, abatement of the fever and diminution in size of the enlarged liver and spleen. Tertian forms are most easily affected. Quartan tropica varieties are more resistant.

Iversen[2] wished to make a special study of the action of Salvarsan in malaria so he made a journey to Batoum for this purpose as the disease is very rife there. He investigated sixty cases. Of these twenty-seven were tertian, four were quartan, twenty-seven were tropica and two tertiano-tropica. In the tertian patients 70% were cured by 0.5 grm. given intravenously. Attacks ceased and parasites disappeared from the blood in 12 to 24 hours. 30% had no more /

more parosysms but parasites could always be found. Of his four quartan cases, two had diminished paroxysms and less fever but the parasites still remained in the blood. Two were unaffected. Tropica and tertiano-tropica were hardly influenced at all. Iversen recommends a combination of salvarsan, quinine and methylene blue in the treatment of malaria.

Nocht and Werner,(3) in Hamburg, treated malarial cases from Brazil and the Madèira-Mamore River. The parasites in these districts are very resistant to quinine. Tertiana and tropica forms were studied. In the investigations large doses of quinine and methylene blue were tried but still the organisms persisted in the blood of the parients. They found that combined intravenous and subcutaneous injections of Salvarsan permanently cured their tertian cases but tropica cases were not much affected . They also advise a combination of salvarsan, quinine and methylene blue.

Flechseder(4) found improvement but not permanent cure in a case of malignant malaria.

From these experiments it may be seen that "606" is a valuable adjunct to our treatment of malaria. It should prove serviceable in cases where quinine fails or where there is an idiosyncracy to it.

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SALVARSAN IN LEPROSY.

Some cases of leprosy have been treated with Salvarsan but they are few in number and definite conclusions cannot be made from them.

Two cases in Russia lost their photophobia and the temperature fell one degree and remained so. An ulcer on the leg of one of them shewed signs of cicatrisation (1)

F. A. de Verteuil and F. L. de Verteuil (2) in Trinidad obtained some of the preparation from Dr. Rost. They prepared it according to Wechselmann's method of neutral suspension. Eight tubercular and one anaesthetic case were treated. All cases, except one who ran away from the asylum, experienced a sense of well-being and comfort. After a second injection was given some softening of the nodules could be perceived. There was not much subjective improvement however. Scrapings of the nodules shewed alterations in the bacilli. In the anaesthetic case they were reduced in number but in the tubercular cases they remained/

remained plentiful. In all the specimens examined bacteriolysis had occurred. The organisms were granular and coccothrix-like and many were clumped into granular masses. The changes were most pronounced in the anaesthetic case and they became most marked about fourteen days after the injection. They were greater than those observed by the authors after mastin treatment.

Ehlers[3] and Bjarulyédinsson obtained results in Iceland very similar to those of Verteuil.

Gioseffi[4] has seen no change in leprosy after Salvarsan injections.

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3. Ehlers - Münch med. Woch. 1910, No. 41.
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SALVARSAN IN YAWS.

Our knowledge of the value of Salvarsan in Yaws comes from the writings of Nicholls, Strong and Alston. All these three are agreed that "606" is a specific from framboesia and there are no special dangers connected with it.

Nicholls[1]/

Nicholls[1] studied the effect in experimentally produced yaws of the testicle of the rabbit and the eyebrow of apes. In the case of the rabbit no spirochaetes could be found twenty-four hours after an injection and the changes in the testicle were gone in two or three days. Lesions in the apes disappeared within twenty-one days.

Strong[2,3] treated twenty-five cases. One injection was given to each and it proved sufficient, for no relapses occurred up to four months after. Granulomata were gone in ten to twenty days. There were no constitutional disturbances. The doses were .25 - .3 grm. for a child and .4 - .5 grm for an adult.

Alston[4, 5] has made a very thorough investigation in Trinidad. He is to be specially mentioned for using Salvarsan serum with great benefit. Before using Salvarsan he tried mercury, arsacetin, soamin and orsudan in framboesia but they did not yield permanent effects.

With "606" his results were most gratifying. They were tabulated by him as follows :-

Of 500 cases :-

498 were permanently cured (99.6%).

409 were cured with one injection (82%).

75 " " " two "

14 " " " three "

2 were not cured.

Only five relapses have occurred whereas 12 - 14% recurred before Salvarsan was used.

Castellani found it of value in acute cases. It was not so good in chronic ones.

In nearly every case in which "606" has been used there has been temporary improvement or permanent cure and one injection suffices for most. As natives of the West Indies suffer much from yaws, Salvarsan should be a great boon to them.

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SALVARSAN IN RELAPSING FEVER.

Hata[1] and McIntosh[2] working separately proved that Salvarsan is a specific for relapsing fever in animals. When we come to study it in man we see the same fact.

Before it was employed in syphilis in man Salvarsan was patented in Germany as a cure for relapsing fever.

The /

The effects of the drug are more prompt here than in syphilis because the parasites are in the blood and not in the foci in the connective tissues as in lues. Consequently an intravenous injection of "606" will thoroughly and quickly sterilise the patient and it is the method which must be followed.

Iversen[3] treated fifty-eight cases of ralapsing fever with Salvarsan. He first used alkaline intramuscular injections of 0.3 gramme but he abandoned these later for intravenous ones. He reports that atoxyl and arsacetin gave good results in this disease but they were not permanent cures. Salvarsan, on the contrary, gave lasting results. The temperature came down in seven to fourteen hours. In 92% of cases recurrence was prevented by one injection. Spirilla disappeared from the blood in four to ten hours. The fall of temperature by crisis is accompanied by disappearance of symptoms. The dose recommended by him is 0.3 gramme given intravenously.

Georgiewsky of Charcow also observed that the spirilla disappear from the blood in four to ten hours.

Bitter and Dreyer[4] have used Salvarsan in relapsing fever at Cairo. They found that the spirochaetes disappeared in twelve to twenty-four hours. Their results are different from Iversen's but that is /

is because the parasites in Egypt are known to have greater resistance to Salvarsan than others.

In this disease we have another example of the destructive action of salvarsan upon spirilla. Its cure can be very systematically studied by changes in the pulse, temperature and blood.

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3. Iversen - Münch med. Woch 1910, No. 15.
4. Bitter & Dreyer - Chemotherapy of Spirilloses, p109.

SALVARSAN IN EXPERIMENTAL TIC FEVER.

W. L. Jakimow and Nina Kol-Jakimowa (Russki-Wratsch 1910, No. 27) studied the action of Salvarsan in this disease in the Pasteur Institute in Paris. They worked with rats and mice. Their conclusions are as follows :-

1. Salvarsan is a very effective drug here.
2. If the animal is injected with "606" and the parasites at the same time the disease does not occur.
3. It acts as a prophylactic if given 24 hours before injection.
4. The animal inoculated with the trypanosoma tugulense is saved from illness by an injection of Salvarsan within twenty-four hours.
5. Salvarsan communicates no permanent immunity against the disease.

SALVARSAN IN PERNICIOUS ANAEMIA.

The value of arsenic in this disease has led several to use Salvarsan in it for no substance contains such a high percentage of arsenic and is so therapeutically active at the same time. The results described are very variable and, as in the case of syphilis, it will be a long time before we can tell if the cure will be permanent with "606".

Lockemann[1] observed that .3 gramme caused a temporary improvement in strength but death was not averted. Meidner's[2] case tolerated the injection well although there was great cardiac weakness and low oxygen value of the tissues. Klemperer[3] did not get such good results with salvarsan as with arsacetin. Wechselmann[4] got no betterment in the condition of his patients but he observed no serious after effects. Spiethoff[5] observed some improvement whilst Byrom Bramwell[6] obtained gratifying results in two cases.

Even at this stage in the use of salvarsan some benefit has been obtained in pernicious anaemia but we cannot say whether that is due to the tonic action of the arsenic or to the destruction of some specific parasite. Time alone can settle that.

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Leukaemia, Hodgkin's Disease and Lymphosarcoma are unaffected by Salvarsan.

SALVARSAN IN FILARIASIS.

Pilcher[1] has cured a case unilateral chyluria caused by a Filaria sanguinis hominis. Reichmann[2] has also cured a case of filariasis.

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Kala Azar has also been included in the list of diseases treated by Salvarsan.

Haller (Nowojew Medizine 1910, No. 20) and Marks have used it with brilliant results in two cases of Variola.

Vincent's Angina, which is due to vibrio-like bacteria, improves under salvarsan. Gerber (Münch med. Woch, Feb. 28, 1911) found that the spirillae were /

were almost gone after forty-eight hours and those left were motionless. Cure resulted within a fortnight.

Scurvy was also cured by Gerber.

SALVARSAN IN TRYPANOSOMIASIS.

Animals infected with trypanosomes were treated with Salvarsan with encouraging results so Broden employed it in man and the trypanosomes disappeared from the blood. The drug has not been fully studied in this disease but its superiority over atoxyl in other parasitic conditions makes it likely to prove of value in this one also.

All these diseases, which have been treated with Salvarsan with more or less gratifying results, are due to parasites and they demonstrated the wide distribution of the same chemoreceptors among the causal organisms. When more and more diseases are traced to their proper cause the therapeutic field of "606" will be considerably extended.

In addition to parasitic diseases Salvarsan has been employed in non-parasitic affections such as psoriasis, lichen, leucoderma, scleroderma pemphigus and warts.

SALVARSAN IN PSORIASIS VULGARIS.

In cases of psoriasis which have been benefited by Salvarsan the eruption first increases in intensity. It becomes darker in colour and scaling increases in amount. Later on the scaling diminishes till it is gone. Some pigmentation remains. Glück,[1] Blaschko[2] and Ivanyi[3] all report complete cures. Fraenkel[4] and Grouven[5] treated three cases but only one was cured and the dose employed was 0.7 gramme. Schwabe[6] injected a case and the patches disappeared but they returned on the sixth day. Eitner,[7] Wechselmann[8] and others observed no change in their cases.

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SALVARSAN IN LICHEN.

Lichen undergoes the same changes as psoriasis after an injection of salvarsan. Schwabe[1] described the process but his case of lichen ruber planus recurred /

recurred on the tenth day. Lichen ruber mucosae was unaffected. Blaschko[2] has cured a case of lichen ruber simplex. Fraenkel and Grouven[3] got gratifying results in one case with a dose of 0.7 gm.

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2. Blaschko - Berl. klin. Woch. 1910. No. 35.
3. Fraenkel & Grouven - Münch med. Woch. 1910, No. 34.

Warts were cured by Blaschko. Scleroderma and Leucoderma are not much improved.

PERSONAL CONCLUSIONS.

Salvarsan which is a very potent drug has great value in many ways. These may be classified as mental, moral, economic, therapeutic, cosmetic and hygienic.

Mentally there is great improvement in the patient. The mere fact that he has not to continue taking dose after dose of mercury and iodide makes him forget that he has syphilis. Exaggerated reports together with the improvement in his own symptoms remove much of his mental depression. The knowledge that he was going to receive a dose of "606" made one of my patients brighten up immediately.

Morally /

Morally we should expect some good results from Salvarsan but we might get the very opposite. This question is closely connected to the public health or hygienic value of the drug. If we can get suitable state registration of prostitutes and treat them gratis we can do much to check the spread of syphilis. This might, however, lead to an increase in prostitution for men would not be so afraid of contracting syphilis. Syphilitic husbands or wives can be treated so as to prevent their bringing tainted infants into world.

The Expense of Treatment of syphilis by Salvarsan is nothing compared with that of mercury. One man told me that he had spent more than forty pounds on drugs during a period of seven years.

The Cosmetic Value of "606" will appeal especially to the better classes. In one of my patients the condition of her hands and arms was such that her people would not allow her to bake bread for them. Another one was an eyesore to the neighbourhood. Both these patients have now lost the appearances which made them distasteful to others.

Therapeutically, Salvarsan is a most potent drug. Few substances can excel it in the rapidity with which it acts on such a chronic disease as syphilis.

Even /

Even if its effects are not permanent one injection takes the place of weeks of mercurial treatment. It is almost a rule that heroic treatment of primary syphilis with it stops the disease at this stage but it is very rare for mercury to do so. Secondary and tertiary symptoms mostly clear up under its use and malignant syphilis responds almost immediately to it. Hereditary and parasyphilis may be improved but the results are not so gratifying as in other varieties. It must not be forgotten, however, that many years must elapse before we speak absolutely about it.

Ivan Bloch in his book entitled "The Sexual Life of Our Times" writes the following sentence; "When some day humanity has been freed from the sexual plague, from the hydra of venereal diseases, and when a monument is erected to the liberators, four names will there be commemorated: Ricord, Neisser, Metchnikoff and Schaudinn ". — To these four names it is now necessary to add three more - Bertheim, Hata and Paul Ehrlich.