SALVARSAN OR 606 (ITS ADMINISTRATION & THERAPY.)

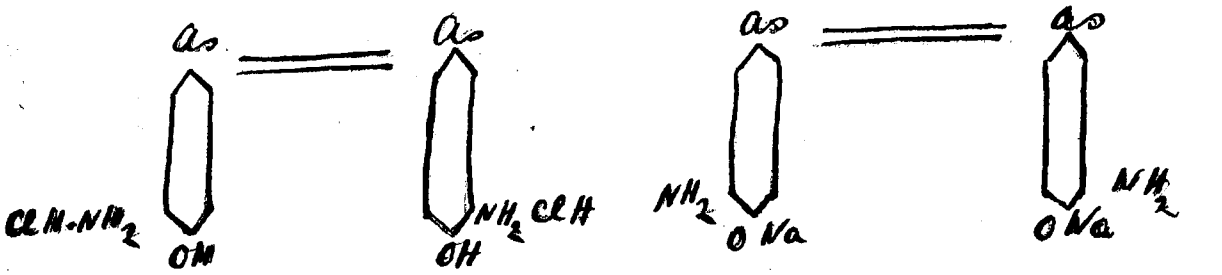
During the past few years great advances have been made in the treatment of Syphilis. The road of progress has been marked by three discoveries :-

In 1905 Schaudinn and Hoffmann demonstrated the micro-organism - the Spirochaeta Pallida - in Syphilitic lesions. This discovery threw further light on the treatment of the disease and emphasised the importance of early and abortive treatment.

The Wassermann discovery in 1906 of the serum reaction has furnished a test for the disease which is proving of the greatest value in the recognition of cases which would otherwise have gone undetected. It is also a guide to the efficacy of treatment and to the progress of the case.

Lastly, Ehrlich introduced Salvarsan as a specific drug and it is of this drug that it is proposed to treat.

CHEMICAL COMPOSITION OF SALVARSAN & HISTORY OF THE DRUG.



Dioxydiamidoarsenobenzol di-Hydrochloride (Salvarsan)

Dioxydiamido arsenobenzol disodium Salt (alkaline Solution)

In the Chemotherapy of Trypanosomiasis hundreds of substances have been used but as Ehrlich[5] points out such drugs as possess

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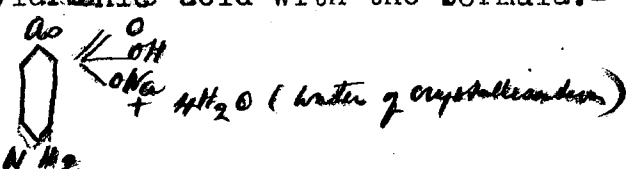
curative properties fall under three classes :-

1. Arsenical Compounds.
2. Certain Azo-dyes such as trypan red and trypan blue.
3. Certain Basic dyes such as parafuchsin and Methyl violet.

As far back as 1903 it was recognised by Laveran that arsenious acids had a destructive effect on trypanosomes and Spirilla. In England, Thomas and Breinl proved that Atoxyl had a destructive effect on trypanosomes. Atoxyl had been used by R. Koch in the treatment of sleeping sickness in West Africa and in Europe had been extensively employed in the treatment of syphilis, malaria and Relapsing Fever.

Soon, however, reports came to hand of cases of optic atrophy arising from its use. Koch, for instance, reported 23 cases among 1630 treated with Atoxyl. Other complications such as Nephritis have also been reported. This predilection for the optic nerve caused the drug to fall into disuse.

Recognising the chemical composition of Atoxyl as a sodium salt of p-amino-phenylarsenic acid with the formula:-



Ehrlich attempted to obtain other arsenical compounds of greater parasitic action and of less toxicity to the tissues. In collaboration with Bertheim, Ehrlich succeeded in obtaining a great variety of chemical compounds each having a radical of

of organically fixed arsenic acid.

By transforming the amido group it was found that the toxicity of these products could be increased or diminished and their action could thereby be studied on host and parasite.

A search was therefore instituted for a compound which would approach the therapeutic ideal of combining the maximum parasiticidal action with the minimum toxicity for the tissues . In Salvarsan it is claimed that the therapeutic ideal has been approached.

Diamidoarsenobenzol is a yellowish powder insoluble in water and readily oxidisable: consequently it must be kept in vacuo, as it is reduced to toxic compounds. Salvarsan is the dihydrochloride of Diamido arsenobenzol. It is soluble in water, forming a strongly acid solution. If the solution is neutralised by the addition of caustic soda, the base diamidoarsenobenzol is precipitated but on the further addition of the alkali goes into solution as the disodium salt.

In the action of Arsenical compounds, it is found that trivalent arsenic is more efficacious in the destruction of parasites than the pentavalent preparations: thus Salvarsan is more parasiticidal than pentavalent atoxyl. Again the introduction of the amido group in Salvarsan makes for much lessened toxicity, while the stability of the compound is maintained.

Attention is drawn by Ehrlich[5] to the para position of the hydroxyl group (O.H.) in Salvarsan, whereby as in arsenophenyl a maximum spirillicidal. activity is gained.

CHEMOTHERAPY. ACTION OF SPECIFIC DRUGS. TROPISM.

The action of specific drugs on the parasites is explained by Enrlich on the basis of the side-chain theory. He states that if in chemistry the law applies"Corpora non agunt nisi liquida " then in Chemotherapy "Corpora non agunt nisi fixata" is appropriate.

Briefly, the theory is that the parasites or organisms are only destroyed by the substances which have a special chemical affinity for them, by which they are fixed or anchored to the organisms.

Such drugs as are destructive to parasites are likewise toxic to the tissues of the host: thus Ehrlich distinguishes parasitotrophy and Organotrophy: and in studying the action of the synthetically prepared compounds of arsenic ,Ehrlich found that Salvarsan possessed a maximum parasitotrophic action with a minimum organotrophic action.

EHRLICH & HATA'S EARLY EFFORTS IN REGARD TO SPECIFIC THERAPY.

The measure of success attained in the experimental therapy of trypanosomatous disease suggested to Ehrlich the further extension of study to Spirilla diseases. Attention was first directed to relapsing fever and Spirillosis of fowls. These diseases are particularly suitable for Chemotherapeutical investigation. Infection can be produced with uniformity and the intensity of the infection be readily varied, as desired, by the virulence of the strains, and the amount of infective material employed.

In the course of investigation, Trypanosomicidal substances, several hundred in number, belonging to the following groups were examined :-

1. Arsenical Compounds, Atoxyl, Arsacetin, Arsenophenol glycin, Salvarsan etc.
2. Azo dyes of the Benzidine Group.
3. Basic dyes of the Triphenyl-methane class.

The action of these drugs was observed on spirilla by test tube experiment and by injections into inoculated animals.

These experiments proved the preeminent activity of Salvarsan as a curative agent in that the parasiticidal doses were small as compared with the maximum tolerated doses and further , there was an absence of toxicity for the organs of the host.

RELAPSING FEVER.

Observation was first made with reference to Relapsing Fever in mice and rats. The convenience with which the disease can be produced in these animals and the readiness with which infection can be noted by microscopic examination of the blood, render them suitable for experiment. The course of the disease was first studied by inoculating these animals with blood containing spirilla from an infected animal. A series of animals was then infected with highly attenuated blood, appropriately diluted with ordinary blood serum in order to produce a uniformity of infection.

The course of the disease was followed by daily microscopic examinations of the blood.

Doses of drugs to be tested were now injected into the infected animals. According to circumstances one or more injections were employed. Previously, however, the doses used were experimentally proved to be tolerated by healthy animals.

If after injection of the drug the blood invariably showed absence of spirilla, the dose was assumed to be effective. The examination of the blood was daily carried out for two months and, if after that time there was no relapse, the animal was considered cured. In some cases the spirilla disappeared from the blood in a few days, to re-appear again perhaps, demonstrating that either the dose or the drug was ineffective.

ACTION OF ANILIN DYES..

These proved unsatisfactory. Only a few appeared to possess spirillicidal properties. Test tube experiment showed that with some, the spirilla became immobile. The treatment of inoculated animals by the injection of the drugs proved unsatisfactory.

ARSENICAL COMPOUNDS.

The action of Atoxyl, Arsacetin, and Arsenophenyl glycin in Trypanosomiasis, suggested their use in spirillar affections. Hata,[5] however found that ,injected subcutaneously into mice, Atoxyl failed to produce any definite curative results.

With Arsacetin the treatment was more satisfactory but even large doses failed to cause permanent results.

In the case of Arsenophenyl glycin ,curative results were only obtained when the maximum dose was injected simultaneously with the infective material. The drug was inefficient when injected a day or two after inoculation with Arsenophenol: curative results could only be obtained when the maximum dose was injected twice: the maximum dose tolerated, failed when injected once.

Tetrachlorarsenophenol and Tetrabromarsenophenol were not satisfactory. Dichlorphenolarsenic Acid was active, but fourteen days after injection, nervous disturbance in the mice, treated, was observed, as shown by nervous tremors etc. The drug was therefore considered unsatisfactory.

SALVARSAN.

Experiments with this drug ,demonstrated its great spirillicidal activity in inoculated animals, the smallness of the curative dose as compared with the maximum tolerated dose, and the entire absence of toxic symptoms. Dioxydiamidoarsenobenzol and the Hydrochlorate salt of "606" were found to be equal in action and toxicity. 606 has an acid reaction, dissolves slowly in water, with the addition of excess of caustic soda the disodium salt is formed which is freely soluble. Dioxydiamidoarsenobenzol does not destroy spirilla in test tube experiments and with concentrated solutions, it was proved by experiment that the alkali present was sufficient to cause the immobility of the spirilla. The accompanying table from Ehrlich Hatà's book illustrates this fact.

Final Concentration	Exp. with "592"		Control (with corresponding Alkaline content)	
	In tube.	Mixt. Injected into Mouse.	In Tube	Mixt. Injected into Mouse.
1 : 2000	Immobile		Immobile	
1 : 5000	"	Negative	"	Negative
1 : 10000	Mobile	"	Mobile	+ after 2 days.
1 : 20,000	"	+ after 7 days	"	
1 : 40000	"	+ " 6 "	"	
1 : 100,000	"	+ " 2 "	"	

It was found that mice will tolerate 1 C.c. of 1/300 dilution of Salvarsan for every 20 grams of body weight. Mice inoculated with Spirilla could be sterilised by employing 1 C.c, of 1/800 dilution for every 20 gram. of body weight.

	Tolerated dose.	Curative dose	C/T.
Thus in mice	1/300 per 20 grams	1/800 per 20 grms.	1/2.7
" " rats	.2 per Kilo.	.06	1/3.3

The toxicity of the drug for various animals was now determined and the maximum tolerated dose noted.

The table taken from Ehrlich's book shows the toxicity for various animals.

Animal	Application	Dosis tolerata
Mouse	Subcutaneously.	1 : 300 per 20 grms
"	Intravenously	1 : 350 " 20 "
Rat	Subcutaneously	.2 " 1 Kilo
Hen	Intramuscularly.	.25 " 1 "
"	Intravenously.	.08 " 1 "
Rabbit	"	.1 " 1 "
"	Subcutaneously	.15 " 1 "

Having proved that the drug was markedly destructive to the spirilla in the relapsing fever of mice, experiments were carried out to determine the minimum doses with which curative effects could be produced.

The table shows the results of the experiments.
1 - 600 means that 1 c.c. of 1 - 600 dilution was employed.

"606" in Mice

Dose	Permanently Cured after		
	1 App.	2. App.	3. Applications
1 : 600	100 %	—	—
1 : 700	100 "	—	—
1 : 800	100 "	—	—
1 : 1000	75 "	100 %	100 %
1 : 1500	18 "	75 "	100 "
1 : 2000	16 "	66 "	100 "
1 : 3000	— "	— "	33 "

Hata's experiments on relapsing fever of mice and rats proved that Salvarsan had a superior spirillicidal action to all other arsenical compounds investigated. In the experiments, nervous disturbances such as tremors, dancing etc. were not observed such as occurred in the use of atoxyl, arsacetin, and of dichlorphenylarsenic acid.

Given in frequent doses the animals developed a hyper-sensitive to the drug but it was found that the effect of more than three injections was not greater than if one, two , or three doses had been given. Observation demonstrated the prophylactic action of Salvarsan in both mice and rats but especially in the latter . In mice, for instance, a dose of 1-400 injected subcutaneously twenty-four hours before inoculation with spirilla prevented infection in two out of three mice. This prophylactic action was however, of very brief duration, for if delayed three days after inoculation, infection occurred, but of a mild type.[3]

SPIRILLOSIS OF FOWLS.

Having proved the curative and prophylactic action of SALVARSAN in relapsing fever of mice and rats and its superiority over other compounds, Hata carried out further chemotherapeutic experiments in the spirillosis of fowls. The results obtained with Salvarsan were even more striking than those with spirillar infections of mice and rats.

In the spirillosis of birds, it was found that fowls develop immunity very rapidly. In the production of the disease, the employment of undiluted blood - blood containing a large number of spirilla, - the illness sets in rapidly but at the same time immunity is developed quickly. In order to test the parasitic action of a drug, it is important to obviate this as much as possible, otherwise correct deductions as to the curative value of the drug cannot be made: therefore in the experiments very dilute solutions of blood were employed i.e. containing few spirilla. The table shows in the case of fowls, the dose of the drug tolerated, and the curative dose. If C. be the curative dose, and T. the maximum dose tolerated then C/T shows the ratio of the curative to the maximum tolerated dose.

TREATMENT FOR CHICKEN SPIRILLOSIS

Infection Intermuscular — Treatment 2 days after Infection also Intermuscular

Remedy.	Dosis Tol. Per Kilo	Dosis Curativa Per Kilo	$\frac{C}{T}$
Atoxyl	·06 gm	·03	1/2
Arsacetin	·1 "	·03	1/3
Arsenophenylglycin	·4 "	·12	1/3·3
Arsenilate of Mercury	·1 "	·04	1/2·5
Salvarsan	·2 "	·0035	1/58
Amidophenolarsenoxyd	·03	·0015	1/20

From the table it is seen the results with atoxyl. Arsacetin, Arsenophenylglycin and Arsanilate of Mercury are less satisfactory than with Salvarsan and Amidophenolarsenoxyd, the ratio of C/T , 1/58 with Salvarsan is most striking.

The results of Prophylactic experiments with Salvarsan in spirillosis are very remarkable. They are more marked then those obtained in relapsing fever of mice and rats. Further they illustrate the now well known " depot " action of the drug when injected intramuscularly.. When the drug is intravenously injected in fowls the protective effect does not last more than six days, the drug having by this time been completely eliminated from the body. On the other hand .07 grams per Kilo injected intramuscularly as shown by Ehrlich, gave immunity to infection which lasted thirty five days. After this period the infection appeared on inoculation although of a mild type. After fifty days a prophylactic action could no longer be determined.

On cutting down at the site of injection, a deposit of Salvarsan in the muscles surrounded by a necrosed & coagulated area of muscle was found. The slow absorption of Salvarsan had produced the long period of immunity.

SYPHILIS OF RABBITS.

It has been previously noted that atoxyl and similar arsenical compounds have been used, with a certain amount of success in the treatment of syphilis.

The experiments of Metschnikoff[16] and Salmon on apes and of Uhlenhuth, Hoffmann and Levaditi[17] on syphilitic keratitis of rabbits proved without doubt, a certain specific value. The reports of optic atrophy arising from their use and the further proof by Schirmer and Wendelstadt of their predilection for the optic nerve caused atoxyl, arsacetin etc. to pass into disuse, at any rate in the treatment of syphilis.

As Hata's experiments in relapsing fever and spirillosis of fowls had conclusively proved the superiority of salvarsan over other arsenical preparations, it was only natural that investigation should be directed to the treatment of syphilis.

Experimental syphilis however, unlike relapsing fever and spirillosis presents difficulties for chemotherapeutical study. In syphilis it is difficult to produce uniformity of infection, due in great measure to the differences in individual animals of natural resistance. Some animals do not respond at all or only slightly to infection. In other cases while infection does occur, the disease very soon retrogresses: in other instances a slight lesion was apparently followed by a spontaneous cure. Therefore in carrying out experiments with Salvarsan etc. it is necessary to inoculate a large series of animals and to select for treatment only these animals in which the disease is well developed and persistent.

In syphilis too, the spirochaetes are for the most part in

the connective tissues and not in the blood: therefore, the course of the disease cannot be followed as in relapsing fever and fowl spirillosis, by microscopic investigations of the blood. The only criterion then, as to the progress of the disease is the presence or absence of spirochaetes at the seat of infection.

Hata's experiments were carried out on rabbits. Experimental syphilis can be produced in rabbits in three ways.

1. As syphilitic Keratitis.
2. As syphilitic orchitis.
3. As chancre of the scrotum.

In syphilitic Keratitis the lesion is not very suitable for chemotherapeutic observation. The course of the disease is often erratic, the lesion may heal spontaneously or it may heal up temporarily to reappear again. Farther, the cornea cannot very satisfactorily be examined for spirochaetes, at any rate repeated examinations, such as are necessary, cannot be made.

Syphilitic orchitis as first described by Uhlenhuth,[37] while suitable for obtaining a pure culture of spirochaetes, is not so suitable for chemotherapeutic investigation. The size of the testicles alternately increases and decreases of its own accord. It is therefore inconvenient for repeated examinations for spirochaetes.

In the case of chancre of the scrotum however, frequent examinations can be made for spirochaetes.

The scrotum is inoculated by making a small incision in the soft skin in the lower part of the scrotum of a full grown rabbit. A small pouch is formed and a small piece of infective material placed in the pouch. The wound heals up immediately and if the inoculation is successful infiltration and thickening occur at the seat of infection in about fourteen days. A small nodule is then formed which in six or eight weeks forms an ulcer, which greatly ressembles the human hard chancre. The edges of the ulcer are thickened and cartilagineous and the surface is covered with a moist crust which on removal presents a bleeding sloughing base. This ulcer lasts for several months and on examination spirochaetes are usually found in abundance.

This examination is easily performed by pricking the edge of the chancre with a needle and examining the sero-sanguineous fluid exuded , under the microscope with the dark field illumination.

In Hata's experiments with Salvarsan, only those animals were selected in which a severe chancre had developed, which showed evidence of continued growth, and where numerous spirochaetes were found on repeated examination.

On experiment it was found that the tolerated dose of Salvarsan given intravenously was .1 gram. per Kilo of body weight. Given a single dose of Salvarsan of .04 - .02 grams per kilo the spirochaetes disappeared from the cnancre in 24 hours and the lesion healed completely in 2-3 weeks.

The rapidity of complete destruction of spirochaetes depends upon 1. The size of the dose administered. 2. The size and especially the thickness of the chancre. 3. The number

of spirochaetes present.

In small doses of Salvarsan or if the chancre is very thick, the spirochaetes may take several days to disappear. In event of suppuration being present (mixed infection) the healing of the chancre may be delayed. Therefore the presence or absence of spirochaetes is the best means of judging the progress of the disease.

The following table gives the result of the treatment of syphilitic rabbits with Salvarsan.

One Injection of "606" on Rabbits.

Dose per Kilo.	Relation to Dose Tolerata	Spirochetes Disappeared within.	Complete Cure -
·04 =	1/2·5	24 hours	2 - 3 weeks
·03 =	1/3	"	— do —
·02 =	1/5	"	— do —
·015=	1/7	"	— do —
·01 =	1/10	2 days.	— do —
·0075=	1/14	2 to 3 days	— do —
·005 =	1/20	"	— do —
·004	1/25	} still present after 30 days	} not cured
·003	1/30		

It is seen that the dose necessary for immediate sterilisation is between .015 & .01 grams per kilo. The maximum tolerated dose is .1 grams per kilo. Therefore the C/T or the relation of the curative to the tolerated dose is C/T 1/7 - 1/10.

Having proved the curative action of Salvarsan in syphilis produced in rabbits, Ehrlich decided to try Salvarsan on man.

EFFECT OF SALVARSAN IN SYPHILIS OF MAN IN REGARD TO PROGRESS OF THE DISEASE AND THE WASSERMANN REACTION.

On the conclusion of the experiments upon rabbits Ehrlich entrusted the clinical administration to Prof. Alt in order that the toxicity of the drug might be determined. Alt first gave injections to dogs. Two of his assistants then permitted themselves to be injected: these injections which were given intermuscularly gave rise to no ill effects beyond pain and swelling at the site of injection.

Intermuscular injections were then given to a number of paralytics: these patients , it is reported, gained weight and generally improved. In several cases the wassermann reaction decreased and in two cases even entirely disappeared. Alt had previously obtained similar results with arsenophenyl glycin. As a result of his experiments Alt concluded that Salvarsan was specific in action and that .3 grams could be administered with safety.

Furtner experiments were then carried out by Dr. Schreiber[12] of Magdeburg. Recent cases of syphilis were treated, the dose administered being .3 grams. In twenty seven cases treated, the rapidity with which the symptoms disappeared was remarkable. Primary sores cicatrised in a few days, macular rashes disappeared condylomata healed up rapidly and severe sore throats quickly cleared up. In four cases the Wassermann reaction disappeared.

Hoppe and Shrieber[13] then reported the treatment of over 100 cases to the German Congress of Internal Medicine (Munich Med. Wochenschrift 1910 No. 27.) In 84.6 % of cases the Wassermann reaction changed from positive to negative within fifty days.

While these experiments were in progress Ehrlich further

entrusted Wechselmann of Berlin with the drug in order that trials on a more extensive scale might be undertaken. Having a very extensive clinical field at command Wechselmann was able to try this new remedy in a great variety of cases. In the Monograph published in 1911 the report of observations in fourteen hundred cases is given. Wechselmann tried the drug first in severe cases of hereditary syphilis associated with pemphigus, cases which with or without mercurial treatment are almost certainly foredoomed to early death. Intramuscular injections of .05 grams were given. Some of the cases improved but three died. No symptoms of arsenical poisoning were revealed by post mortem examination.

Wechselmann suggested that the cause of death in these cases was due to the rapid liberation of endotoxins by the spirillicidal action of the salvarsan. No deaths occurred when smaller doses of from .015 -.02 grams were administered, the dose being repeated in eight days. Wechselmann then administered the drug to cases of syphilis which had proved resistant to mercurial treatment administered over a period of years. His observations proved that Salvarsan had a most remarkable effect in these refractory cases; very remarkable results were obtained too, in ulcerating malignant forms of syphilis where extensive ulceration of the skin and mucous membranes were present. Having satisfied himself of the good effect of Salvarsan in these cases Wechselmann employed the drug in a wide variety of cases.

PRIMARY CASES.

Primary superficial chancres were usually healed within forty eight hours. Hard indurated chancres healed more slowly taking from eight to fourteen days. It was noticed in mixed infections i,e. when hard and soft chancres were combined, the induration of the hard chancre disappeared under treatment leaving the soft chancre unaffected. This important observation of Wechselmann was also confirmed by Sieskind.

Generally speaking Wechselmann found that the initial lesions disappeared more quickly with Salvarsan than with Mercury.

It was observed however, that the Inguinal glands which enlarge as a result of the infection remained harder than normal although they had returned to their normal size.

Those observations on primary lesions have been confirmed by many after observers by Neisser,[29] Schreiber,[32] Zeissel,[39] Iversan[16] McDonagh[20] and by Browning & McKenzie.[3]

SECONDARY CASES.

Wechselmann[35] noticed that the primary cases treated by him did not for the most part, develop secondary symptoms. He also noticed that the earlier the case was treated the less likelihood there was of secondary symptoms arising. This has been confirmed by other observers, by, McDonagh,[20] Scott,[34] Harrison and Gibbard[11] also by McKenzie and Browning.[3]

Secondary symptoms such as mucous patches of tongue, and gums, throat conditions etc. cleared up rapidly. Condylomata disappeared , Macular rashes disappeared but it was found that papular rashes were more resistant to treatment. Cases refractory to mercurial treatment presenting deep ulcers of

skin and mucous membrane, necrosis of tonsil and soft palate and turbinate bones were arrested and healed up rapidly. These results have been confirmed by numerous writers, D'Arcy Power,[4] McDonagh,[20.11.22] Browning and McKenzie,[3] Goldenberg,[10] Gennerich[38] etc.

Wechselmann found that the severe headaches often present in the secondary stage were relieved 24 hours after treatment. Severe Glandular enlargements were found to decrease in size but most observers agree that they remain hard and shotty, and palpably enlarged after all other symptoms have disappeared. Most observers agree also in confirming these results obtained by Wechselmann. They also found that Salvarsan cured the symptoms of secondary syphilis in a much shorter time than Mercury.

Tertiary Syphilis.

Here the results are also very remarkable. Wechselmann, McDonagh, Gibbard, and McKenzie to mention only a few writers, found that tertiary lesions were cured in many cases. Gummata indolent ulcers of skin, periosteal thickenings, and chronic superficial glossitis were completely cured. Wechselmann found that ulcers of the larynx and Gummata of the brain were greatly improved.

PARASYPHILITIC CONDITIONS.

General Paralysis and locomotor ataxia.

The results obtained in these conditions have been less satisfactory than with the earlier manifestations.[43] The lesions present in these conditions would naturally contra indicate arsenical treatment: for it is hardly possible to expect

~~that~~ that Salvarsan would regenerate Neurons . Many cases however, show a positive and persistent Wassermann reaction and would therefore presuppose spirochaetal activity.

Alt reports that a number of cases of general paralysis were improved, and that in two cases the serum reaction was rendered permanently negative. Browning and McKenzie report 58 cases of general paralysis and 7 cases of locomotor ataxia treated with Salvarsan. In twelve cases of general paralysis the symptoms were ameliorated and two cases were cured so far as to enable them to pursue their ordinary work. Three cases of tabes were greatly improved.

Two cases of tabes treated by Salvarsan have come under my own observation. One patient, a male, contracted syphilis 15 years ago for which he underwent mercurial treatment. Seven years ago he developed symptoms of locomotor ataxia, lightning pains, slight ataxia, loss of knee jerks, and a slight bladder trouble, with impairment of vision. The eye sight gradually got worse and he developed typical optic atrophy for which he consulted many oculists. For two years the patient has been practically blind but can distinguish between daylight and darkness. Last summer he heard about Salvarsan and insisted on undergoing treatment. He consulted two specialists and it was agreed to administer Salvarsan. He received .3 Grams twice within a month.

No ill effects occurred and he has gained a little in weight. The optic condition is as before but patient says he can see more light. He also says that before the Salvarsan treatment he often suffered form headaches which have now entirely

disappeared. His serum has been examined recently and still shows a positive reaction.

CONGENITAL CASES

Treatment of these cases by Salvarsan is not very satisfactory. J. 38-20 The lesions disappeared but slowly and are apt to recur.[20] The Wassermann reaction tends to remain positive.[20]

RESULTS OF WECHSELMANN AND OTHER OBSERVERS' WORK OF THE EFFECT OF SALVARSAN ON THE COURSE OF THE DISEASE.

Wechselmann's observations go to prove that Salvarsan has a very marked effect in curing the symptoms of syphilis. Most observers are agreed that the effect of Salvarsan is much quicker than with mercury. In early cases the effect appears to be almost magical. In very early cases i.e. before the appearance of the Wassermann reaction it appears possible according to observations of McDonagh,[20] Scott[34] and Gibbard,[11] to abort the disease by the administration of Salvarsan combined with local treatment.

The effect of Salvarsan in secondary symptoms is also very striking and in cases which have proved refractory to mercurial treatment for years, the results are often remarkable.

Wechselmann[38] at first employed the subcutaneous and intramuscular method of injection but was soon convinced that the intravenous method was the best.

Fewer recurrences happened after the intravenous method, and the injection could be repeated without risk as the whole of the arsenic was excreted within a few days.[38]

RECURRENCES AFTER THE USE OF SALVARSAN.[54]

During the first three months experience with Salvarsan, Wechselmann had no recurrences after its use. After six months he had three recurrences out of five hundred cases.

Geromne[11] and Huggenburg[16] had five cases of recurrence after three months. In these cases the serum was positive but became negative after a further injection of salvarsan when the symptoms disappeared. Neisser[29] also observed several recurrences among

his cases which he attributed to the smallness of the dose.

It would appear that recurrences were more frequent among the early cases where single amd small doses were administered.

It has been noticed that recrudescences of the disease were synchronous with the re-appearances of a positive Wassermann reaction[10], and that the injection of Salvarsan in the early stages where no reaction was present was followed by a positive reaction which gradually became negative in about two months time. As an injection of Salvarsan will not give rise to a positive reaction in a non-syphilitic,[2,10] such a reaction must be regardeu as indicative of the presence of disease.

ACTION OF SALVARSAN ON WASSERMANN REACTION.

Observers are agreed that Salvarsan cures the symptoms of Syphilis in a remarkably short space of time. How far such cases are permanently cured by a course of Salvarsan treatment it is difficult to determine.

The period during which the drug has been in use is too short for binding conclusions to be drawn. Besides, absolute scientific proof of cure cannot be adduced in a disease in which after decades of latency, may perhaps give rise to infectious secondary symptoms, as recorded by Fournier[8] in his book on secondary syphilis.

So far as our knowledge of the disease goes at present the two criteria for determining the progress of the disease and on which an opinion as to cure may be founded are :-

1. Permanent absence of symptoms.
2. " negative Wassermann reaction.

The importance of the Wassermann reaction is now universally recognised.[2] It is the most delicate test for syphilis and is of great value in ascertaining the progress of the disease under treatment. While a negative reaction does not exclude syphilis a persistent positive reaction may be taken as almost conclusive proof.[2]

In primary cases it is not usually present until five to eight weeks after infection. With mercurial or Salvarsan treatment it disappears and in latent cases it is frequently absent. In 95% -99% of secondary cases it is present. Tertiary cases give a reaction in 75% . In 50% of latent cases it is present and according to Reuben 99% of infants with

hereditary syphilis gives a positive reaction.

The early reports of the action of Salvärsan on the Wasserman reaction were conflicting. Hoppe & Screiber[32, 13] record a negative reaction in 84.6% of their cases. Neisser[29] records in his first series of cases a negative reaction in 10%. In the second series of cases a negative result was obtained in 50% Neisser pointed out that a negative result was more readily obtained when the cases are treated early.

Wechselmann's[38] observations went to show that if cases were observed long enough a negative result was obtained in nearly every case. One reason for the conflicting reports was, that the dose of Salvarsan given in many cases, appears to have been inadequate, and the intramuscular and subcutaneous methods of injection did not make for uniform results. Besides , there was no knowledge as to the time that should elapse between stopping the treatment and carrying out the tests.

Later it was observed that many primary cases gave a negative result just before treatment to become positive within a week after injection.

When a number of such cases developed,"recurrences" with the reappearance of a positive reaction, it was recognised that such negative reaction denoted a latent phase of the disease.

Gennerich and Milian were the first to recommend that the blood reaction should be tested at frequent intervals and that the injections should be continued until a permanent negative reaction is maintained.

McDonagh[20.21.22] who has made many hundreds of blood tests in

regard to the progress of the disease finds that in:-

PRIMARY CASES.

The reaction is often negative before treatment becoming positive shortly after. In most cases he found that the blood becomes positive in twenty-four hours to five days after . He tests the blood forty-eight hours after injection and again on the fifth day. If it is positive on either occasion he repeats the injection on the eighth day. He then tests the blood weekly and repeats the injections until the blood remains negative on the seventh day after the last injection: the blood is then further tested weekly for a month: should it become positive the injections are continued. At the end of six months a provocative injection is again given.

SECONDARY STAGE.

As a rule the reaction is strongly positive. If the reaction is strongly positive either before or immediately after injection McDonagh recommends four injections being given at intervals of a week, as in his opinion, four injections are the minimum likely to be required to produce a permanent negative result.

TERTIARY CASES.

In many of these cases McDonagh finds that the conversion of a positive into a negative reaction is often a matter of difficulty. Even after four injections of Salvarsan, the serum in a few cases tends again to become positive.

From results, in these cases, McDonagh infers that in the early and secondary cases , Salvarsan should be employed with a view to curing the disease , while in tertiary disease to merely ameliorating the symptoms.

The observations of Gennerich, Milian and McDonagh in regard to the Wassermann reaction have been confirmed by other observers.

It must be apparent therefore, that the diagnosis of syphilis ought to be made at the earliest possible moment and should be followed by rigorous and thorough treatment and that such treatment cannot be considered adequate until it is followed by a permanent negative Wassermann reaction.

The reappearance of a positive Wassermann reaction must be regarded as a sign of spirochaetal activity and possibly the percursor of further mischief.

It has been conclusively shown that relapses after mercurial treatment and recurrences after Salvarsan have been heralded by the appearance of a positive reaction.

UNTOWARD EFFECTS OF SALVARSAN.

In a very small proportion of cases where untoward effects have occurred, there seems to have been an undue susceptibility or idiosyncrasy present[4,7,8]. In some of these cases a fatal issue has resulted. Browning & McKenzie[3] were able to collect only three cases however, where the toxic action of the drug appears to have played a part. Even in those cases however, unfavourable conditions were present or else details of the administration were lacking.

Mentberger[27] has recently collected reports of deaths in 273 cases after Salvarsan administration and of these he attributes death in 31% of cases to the toxic action of arsenic. But even this number cannot be weighed in the balance against the thousands of patients who owe their good health to the action of the drug. When we consider too, that the drug has been administered several million times, the death rate compares favourably with that from chloroform administration.

Idiosyncrasy is a factor to be considered in therapeutics but cannot be foreseen in a particular case. To avoid untoward effects therefore, attention must be directed to obvious contra-indications, to dosage and techinique.

An analysis of the literature shows that in the majority of instances the fatalities occurred in cases in a hopeless condition when the drug ought to have been contra-indicated. Ehrlich[5] in his book on Chemotherapy records four such cases in which the patients suffered from the severest cerebral degeneration and where death occurred from Salvarsan, an injection having been given as a last resort.

According to Ehrlich there are certain absolute contra-indications, among which may be mentioned:-

Diseases of the Heart and Bloodvessels.

The presence of Myocarditis, Angina pectoris, Aneurysm, Aortic stenosis, and insufficiency, and peripheral arterio sclerosis must be regarded as absolute contra-indications. Even in these cases a fatal issue might easily result from increased blood pressure, due to the injection or the pain. Zeissl of Vienna mentions a case of arterio-sclerosis in which he refrained from giving an injection, and which the patient died half an hour afterwards from cerebral haemorrhage. Had the Haemorrhage occurred after the injection in such a case, it would have been attributed to the Salvarsan.

Advanced Disease of the Brain and Cord are also to be regarded as contra indications. While early cases might be benefited, Salvarsan given in late cases might only make further mischief. Acute encephalitis has been the cause of death in several cases of early syphilis where no contra-indications could be found. 34, 27, 44, 48 Therefore where advanced degenerative changes are present, Salvarsan might only serve to light up fresh inflammation.

RETINAL & OPTIC NERVE LESIONS.

In Retinal cases where there is a tendency to haemorrhagic change Salvarsan is to be contra-indicated. The mere increase of pressure caused by the injection might of itself cause mischief.

OPTIC NEURITIS.

Wechselmann cites instances of syphilitic cases which have been benefited by Salvarsan treatment. In view of the reports of other cases however, which have not been benefited, such

cases must be regarded as contra-indications. Acute and Chronic Nephritis are absolute contra-indications. As Arsenic is to a great extent eliminated by the kidney, any interference of Renal function must be held to exclude Salvarsan administration. Certain of the fatal Salvarsan cases have been clinically characterised by Albuminuria followed by suppression of urine: post mortem examinations in these cases demonstrated an intense acute nephritis.

DIABETES MELLITUS.

One fatal case has been reported where coma and Acetonuria succeeded the administration of Salvarsan.[3]

GASTRIC ULCER.

The presence of an ulcer contra indicates Salvarsan : apart from the sickness, and vomiting which very occasionally follow Salvarsan injections, the mere increase of blood pressure from the injection might readily cause an access of bleeding. There are other relative contraindications to the use of the drug: such for example, as compensated cardiac disease. Irregularity of the pulse must be considered as an absolute contraindication.

Under certain cirsumstances pregnancy in the later months might exclude the drug. Age and Cachexia would also exclude its use, if elimination is deficient or if kidney trouble were suspected.

The contraindications must always be fully considered before the drug is administered but every case must be judged on its own merits.

The untoward effects arising from dosage and technique will now be briefly considered.

1.DOSAGE.

The dose to be given is important . In healthy males .6 - .5 grams may be given on the first injection. In women .3 - .4 grams is a suitable dose. Children of 12 years may be given .2 grams. Too large a dose given on the first injection may be followed by unfortunate sequelae.

TECHNIQUE.

Subcutaneous injections have now been given up. Neutral suspensions and alkaline solutions are irritating and have been followed by persistent oedema, infiltration, suppuration and necrosis at site of injection. A number of such complications have been reported and the method is no longer employed.

INTRAMUSCULAR INJECTIONS.

Owing to the greater efficiency of the intravenous method intramuscular injections have been practically given up except in cases where a depot action is desired.

The untoward effects liable to follow intramuscular injections are 1. Pain. 2. Infiltration and Necrosis at point of injection. 3. Injury to blood vessels, with Haematoma and thrombosis etc. 4. Encapsulation and retention of the arsenic . 5. Nervous derangements.

PAIN.

The neutral suspensions and alkaline solution are alike painful. Frequently hypodermic injections had to be given to

relieve the pain. In some cases the pain experienced was excessive. One patient to whom an alkaline solution was given complained of severe pain, which extended down the back of the leg, necessitating his confinement to bed for a fortnight.

INFILTRATION AND NECROSIS AT SITE OF INJECTION.

In Hata's experiments on fowls, necrosis was observed at the site of injection. In a few instances where the drug had been administered by injection into the gluteal muscles, encapsulation occurred and absorption did not take place. In some cases suppuration has occurred. Cases have also been recorded where blood vessels were injured and haematoma formed. Sciatic pains have followed where it is to be presumed the large nerve trunks were injured.

Since the introduction of the intravenous method of treatment local complications have been fewer. The action of the drug too, is much more efficient for the solution carried by the blood stream reaches so to speak tne uttermost corners of the organism. The results of treatment therefore are much more certain and uniform.

In this method however, there are certain important points to be attended to, in order to avoid untoward effects. In the first place, needless to say, everything should be thoroughly sterilised and the site fo injection painted with a 2½% solution of Tinct. Iodi.

The Salvarsan must be thoroughly dissolved in a pint of sterilised Salt Solution. The Solution must then be neutralised or rendered faintly Alkaline by a 1% solution of Sodium Hydrate.

Wechselmann[30] has pointed out that the reaction and temperature following intravenous Salvarsan injections was due to impurities in water mainly micro-organisms. Personally, where the water has been boiled for several hours, I have never known a temperature to occur after Salvarsan treatment. A Glasgow surgeon informs me that this has also been his experience.

Anotner very important point is that the solution must not be too alkaline. Cases of severe fall of blood pressure associated with shock and collapse have followed the employment of too alkaline solutions. McDonagh[20] points out that such a sudden fall of blood pressure might be of serious consequence where myocarditis or arteriosclerosis were present. Local Thrombosis and Phlebitis have also followed where the solution was too alkaline.

Care must also be taken to see that the needle employed enters the vein properly. In most cases perhaps it is best to cut down and expose the vein. The solution should be introduced at a temperature of 105° F. great care being observed that air bubbles do not enter the vein.

In all cases the patient should rest in bed for one day following the treatment. This must be insisted upon. Many patients it is true, go about and attend their usual duties. In one case on record, death followed from Cardiac Thrombosis and Embolism, the patient having engaged in garden work immediately following the injection.[3]

NEURORECURRENCES.

Complaints have been made by some observers of nerve lesions following the use of Salvarsan , which they attribute to the

neurotoxic influence of arsenic.

At the very beginning of the Salvarsan epoch, reports emanated from some quarters in France that Salvarsan had caused optic atrophy in three cases. It has been shown that these cases were reported before Salvarsan was used in France. On the other hand Wechselmann has reported a number of cases of optic neuritis and Choroiditis in Syphilis which have been greatly benefited by Salvarsan. Scott records a case of optic neuritis appearing after one injection of Salvarsan but which was cured by a further injection.

At the Fifth National Congress of Neurlogists held at Berlin in 1911, Finger of Vienna said that in 500 cases of Syphilis treated by Salvarsan 44 examples of nervous lesions had occurred affecting chiefly the optic and auditory nerves. Out of 2,800 cases of syphilis however, treated by Wechselmann[58] only 10 cases of nervous complications were recorded.

According to Wechselmann tnese cases improved under the continued Salvarsan treatment.

In Finger's cases, the patients only received one injection of Salvarsan which was not even followed up by mercurial treatment: therefore evidence would point to Finger's cases being of the nature of neuro-recurrences of syphilis not caused by the action of Salvarsan but due to recurrence of the disease.

Knick and Zaloziec[18, 57] reported 10 cases of Auditory nerve trouble in early syphilis cases treated by Salvarsan. In every case the doses were small and on further Salvarsan treatment some improved.

Altogether the evidence that Salvarsan causes nerve lesions appears to be inadequate.

DOSAGE & METHODS OF ADMINISTRATION.

In the earlier cases .3 grams of Salvarsan were administered which corresponds to a dose of .015 grams. per kilo. weignt in rabbits. Wechselmann found that this dose could be repeated with advantage. Later experience showed that a robust adult male could tolerate a dose of .45 - .6 grams without danger.

A single dose is often sufficient to cause an entire disappearance of symptoms. In treating Syphilis however, it is not sufficient to merely cure symptoms, the case must be treated until the Wassermann reaction is rendered permanently negative. It is possible to do this in primary and in the great majority of secondary cases. Tertiary cases are much more resistant to treatment and it may be impossible to obtain a permanent negative reaction. In tertiary cases however, the Wassermann reaction is of less importance , as the infectivity of the case is slight or absent.

McDonagh 20. 21, 22 finds that it is possible to obtain a cure in the majority of cases i.e. absence of symptoms with permanent negative serum reaction, by giving from three to seven doses of Salvarsan at suitable intervals according to circumstances.

Female patients should receive doses of from .3-.4 grams according to age. Children should have .01-.1 grams. A child of twelve may have .2 grams.

In Debilitated or weakly adults the dose of .3 grams should not be exceeded.

Should there be any suspicion of renal mischief the drug should not be given. 6, 47. 48

When deficient elimination is suspected or in patients over forty years, confinement to be should be insisted on for at least three days, during which time, a daily estimate of the arsenic excreted in the urine should be made.

If it is decided to give Salvarsan in cases of general paralysis or locomotor ataxia, the dose of .3 grams should never be exceeded.

Death has followed in these cases from an injection of Salvarsan. Necropsy showed in one case a specific Meningitis of the cervical part of cord: evidently the Salvarsan injection had given rise to a sudden hyperaemia of this region, death resulting from compression and paralysis of the nuclei of the phrenic nerves.[27]

In a case of tabes, when death followed on injection of Salvarsan, punctiform haemorhages were found in the Medulla Oblongata.[27]

Salvarsan therefore, should be administered with the greatest caution in degenerative diseases of the nervous system.[38, 27, 43, 44]

METHODS OF ADMINISTRATION.

The subcutaneous method has now been given up. The intramuscular method should also be avoided except in the case of infants where it may be impossible to administer the drug intravenously. The intravenous method is undoubtedly the best, pain and risk of necrosis are avoided: better results are obtained and the injection can be repeated without fear of accumulation.

TECHNIQUE.

The patient should be kept in bed for twelve or fourteen hours previously. The skin surface should be sterilised. The veins are then rendered prominent by the application of an elastic bandage. A prominent vein at the bend of the elbow should be

selected. If the vein does not stand well out, a slight incision should be made and the vessel exposed. The best needle to use for the injection is that recommended by McDonagh which is bevelled to a point on the upper surface instead of beneath with a slightly concave plate of metal to allow it to rest on the skin.

The solution should be injected at a temperature of 105° F., and in making the injection care should be taken that no air bubbles or blood clot enter the vein.

To start with it is good practice to inject normal saline to make sure the needle is in the vein. If the needle is not in the vein and Salvarsan solution is injected it gives rise to great pain.

The injection may either be given by a syringe or by the transfusion method. The latter is simple, safe and convenient and a transfusion apparatus can always be readily improvised.

Too much care cannot be taken in the preparation of the Solution: it should be made neutral or faintly alkaline: it must not be too alkaline or too acid.

The powder should first be dissolved in a pint of sterilised water prepared from freshly distilled water. The solution is then rendered neutral or faintly alkaline by the addition of 10 c. c. of 8% caustic soda solution, when the neutral base is precipitated which is dissolved on the further addition of 8 c,c. of the soda solution.

On the completion of the injection saline solution should be used to wash out the vein. This frees the tissues from the Salvarsan solution and lessens the liability to local Thrombosis.

Having completed the injection, the patient should then be put to bed, to remain there for a further six hours.

Neosalvarsan. 40, 41, 42, 43 47.

In the Munch. Med. Wochenschrift of April 23rd. 1912 E, Screiber reported on this substitution product of Salvarsan. Sreiber tested the drug on 230 patients and gave 1,200 injections some intramuscularly and some intravenously. In his opinion he found the drug, more active, better tolerated in large doses, and more suitable for intramuscular injection than Salvarsan.

Since, then the drug has been widely tried and the results appear to be in no way inferior to those obtained from the use of Salvarsan, Neo-Salvarsan is specially commended by its greater solubility and freedom from untoward effects: sickness vomiting, diarrhoea etc. after its use have been but rarely noticed. 40. 42.

At Chatham the Naval authorities have adopted Neosalvarsan exclusively and have noticed no fall in their percentage of cures. McDonagh finds that many cases of tertiary syphilis can be cured by Neosalvarsan which failed to be cured by Salvarsan.

The great advantages of Neosalvarsan are that it is rapidly and completely eliminated from the system and there can be little chance therefore, of toxic symptoms arising from an accumulation of the drug: for this reason it can be administered intravenously and the dose repeated as required: owing to its neutral reaction there is little or no local reaction, troublesome infiltration and oedema do not occur if properly injected.

The only disadvantages appear in the instability of the drug: it is very readily oxidised: great care must therefore be taken in the preparation of the solution for injection.

As soon as the drug is completely dissolved it should at once be injected. On no account must the solution be allowed to stand; each dose should be freshly dissolved for each individual patient. The solution must never be heated , the temperature should not exceed 71.6° F. There would appear therefore, to be some risk in using the drug in hot climates.

A sterile saline solution may be used to dissolve the drug, the strength should not be greater than .4%. The solutions must not be unduly agitated. By observing these points the formation of toxic products by oxidation will be averted.

CHEMICAL COMPOSITION.

The active constituent of Neosalvarsan is dioxydiamido-arsenobene-mono- methane-sulphinate of Sodium, - ($C_{12}H_{11}O_2AS_2N.CH_2O.SO_2Na$) . It is a condensation product of Formaldehyde sulphoxylate of sodium and Salvarsan, bearing the number 914 in Ehrlich's laboratories. The formaldehyde sulphoxylate of soda is fixed to one of the two amido groups of the arsenobenzol. It is a yellow powder of peculiar odour freely soluble in water with neutral reaction.

DOSAGE.

As the formaldehyde sulphoxylate of soda is approximately 1/3 of the compound, the dose of neosalvarsan is .75 grams to correspond with .5 grams of Salvarsan. For adult males the dose .6 - .75 grams which may subsequently be increased to .9 grams. The dose for females is .45 - .6 grams.

Screiber employed the drug in larger doses giving 1.5 grams to men and 1.2 grams to women.

CHEMOTHERAPEUTIC TESTS.

Neosalvarsan had more marked spirillicidal action and less toxicity than Salvarsan in mice inoculated with relapsing fever and nagana. Rabbits would tolerate doses three times larger than Salvarsan.

UNTOWARD EFFECTS.

Sickness and vomiting are rare with Neosalvarsan. The neutral reaction as previously mentioned renders it specially suitable for intramuscular injection.

CONTRAINDICATIONS.

It should not be administered in cases of cerebral syphilis if meningitis be suspected. Epilepsy is also a contra-indication. There is a risk in such cases of local Hyperaemia, congestion and haemorrhages. Death has been recorded from Haemorrhagic encephalitis.

TECHNIQUE.

Personally I prefer to give the injection intravenously but it may be given either intramuscularly or intravenously.

INTRAVENOUSLY.

.3 grams are to be dissolved in 200-250 c.c. of sterile water or preferably in .4% sterile saline solution. The solution is then transfused with the usual precautions into a vein. It may be injected by syringe as recommended by Duhot, in a concentrated solution of .6 grams dissolved in 10 c.c. of sterile water. I have given it in this way on two occasions.

INTRAMUSCULARLY

A.5% solution is employed, .6 grams should be dissolved in 22 c.c. of water. It is an advantage to lessen the sensibility at the point of injection with a .5% novococain or cocain solution.

METHODS OF TREATMENT.

As with Salvarsan three to seven injections may be employed in the treatment of Syphilis, or as recommended by Neisser, two or three injections of Salvarsan or Neosalvarsan may be combined with a thorough mercurial treatment. Duhot of Brussels employs a combined Salvarsan and Neosalvarsan treatment. In his opinion Salvarsan by whatever method administered has a depot action, the bicarbonates and albumins of the blood causing a precipitation of the neutral base dioxydiamido arseno-benzol. The action of the drug is on this account less widespread but more continuous, as the precipitated base is retained for a period in the organs of the body. On the other hand, the more soluble Neosalvarsan acts more diffusely, but less continuously as it is more quickly eliminated from the body.

ANTILUETIN.

A combination of Antimony oxide with potassium bitartarate and ammonium has been introduced by Tsuzuki[56] for the treatment of syphilis. He reports ten cases treated to the German Medical Journal 1913 Page 985. Neisser has recently stated that Antimony might be of possible value in the treatment of Syphilis: but years ago it was employed in the treatment of syphilis in the well known Plummer's Pill. In "Antiluetin" the arsenic of Salvarsan is replaced by Antimony and the benzol ring by

tartaric acid thus we have:-

$$S.B\,O\,(C_4H_4O_6)\,K\,(NH_2)\,H\,O$$

It is supposed that the Hydroxl groups of this compound combine with the corresponding haptophore groups of the parasites, anchoring them like the arsenic combination Salvarsan.

DOSAGE.

It has been administered in doses from .025 - .05 grams. subcutaneously , given every other day.

No further cases have been reported as treated with antiluetin and until further details are obtained , it is not likely that the drug will be put on the market.

TREATED BY SALVARSAN OR NEOSALVARSAN.

During the past three years twenty-six cases of Syphilis treated by the above preparations have come under my observation These include primary, secondary, tertiary and parasyphilitic cases. In nearly every instance the Salvarsan injections have been followed by a course of mercurial treatment but apart from this treatment, the effect of one injection of Salvarsan has been very striking.

PRIMARY CASES.

Eight cases were treated where the only lesion present was the chancre. In three of these cases (private patients) where the nature of the lesion was doubtful , bacteriological examination revealed tne presence of the spirochaetes.

The treatment given was to administer intravenously .4 grams of Salvarsan in dilute alkaline solution. In every case the chancre healed up within three weeks. Recently however, in treating early cases I have dissected out the chancre in addition to the Salvarsan injection.

In one case where I injected the alkaline solution of Salvarsan into the gluteal muscles, the pain and tenderness following the injection were very severe. The pain lasted a fortnight and as the patient was thereby confined to the house I did not again risk administering Salvarsan intramuscularly. Recently however, I have employed the neutral neo - salvarsan for intramuscular injection: in no instance has there been any severe pain or discomfort following the neosalvarsan injection.

In none of these eight cases have secondary symptoms developed. One patient has recently gone abroad but all the others report well. Following the injection a mercurial course of treatment was carried out.

SECONDARY CASES.

Ten cases have been treated by Salvarsan or Neosalvarsan. The characteristic symptoms were present in every case, sore throat, mucous patches of tongue and gums, glandular enlargements, and the characteristic roseolar rash. The symptoms entirely disappeared within three weeks after in injection. In six cases a second injection was given. In every case a subsequent mercurial course of treatment was adopted.

The following cases are of special interest:-

1. A lady, recently married, developed in June 1912 a rash all over her body. She complained of a sore throat and that she had severe headaches at night. She was confined to bed and appeared obviously very ill. An examination of the throat revealed the sharply defined intense redness characteristic of syphilis, mucous patches were present on tongue and gums. There was general glandular enlargement. ~~On the skin there was general glandular enlargement~~. On the skin there was present a typical macular syphilide eruption. Treatment by a pill containing Hyd. g. Creta Gr. 1, Pulv. Opii gr. 1/8 given three times in the day, was first adopted.

The headaches however increased in severity and the patient could get no sleep at night. A varied analgesic treatment failed to give relief.

For a fortnight the temperature continued to go up at night

to 101° F. and to fall to subnormal in the morning.

After consultation it was considered advisable to try Salvarsan. A dose of .3 grams was given intravenously and the immediate effect was remarkable. The headaches which had lasted for weeks were relieved at once, and the temperature remained normal. The rash faded within a week, and entirely disappeared in a fortnight. The sore throat cleared up and the mucous patches disappeared. Within a week the patient was able to rise from bed and go about again.

A subsequent injection of Salvarsan was given followed by a mercurial course.

The patient has since remained well. This case illustrates the very rapid effect of Salvarsan in relieving distressing symptoms.

2. A man aged forty (Hospital case) sent by his Doctor to the Royal Infirmary Dispensary in August 1915; four months previously he had contracted Syphilis and had been treated by mercury for two months without improvement. His body was covered by a large and small papullar eruption - see coloured photograph plate taken by Dr. Faulds. .4 grams of Salvarsan was administered intravenously and within a month the rash had entirely disappeared. A further injection of Salvarsan .5 grams was then given and mercurial treatment continued: recently the patient was reported as keeping quite well.

This case demonstrates the great rapidity with which a troublesome rash disappeared, after two months of mercurial

treatment had failed.

3. Woman aged 35 (Hospital case) pregnant at 7th month macular syphilitic rash on trunk and arms. Glands generally enlarged. Mucous patches on tongue and gums .4 grams of Salvarsan given intravenously. Mercurial treatment then given; child born at full time apparently healthy and has since remained in good health.

4. Male aged 30 consulted me in February 1912 about a mucous patch on tongue. After further enquiry it was found he had a scaly papullar rash on arms and anal Condylomata. He admitted infection and stated that he had treated himself for six months with a proprietory blood mixture. He received .4 grams of Salvarsan intravenously: the symptoms disappeared immediately. The patient received subsequent mercurial treatment.

TERTIARY CASES.

Three tertiary cases treated with Salvarsan have come under my notice.

1. Mrs. B, aged 37 pregnant at eighth month consulted me in 1912 in regard to large tertiary syphilitic ulcers of right leg. She had been treated for some months with Pot. Iodide and Citrate of Iron in large doses without much benefit. .4 grams Salvarsan were given intravenously and at the time of delivery the ulcers had practically healed. Photograph shows ulcers cicatrised six months after delivery. At the present time she is quite well and child perfectly healthy.

2. A.S. Male age 40 perforation of hard palate and syphilitic ulceration of larynx. Patient speaks with a hoarse aspirated voice:.4 grams Salvarsan given, followed by considerable improvement.

3. Mrs. R. age 50 (Hospital case) red gummatous ulceration below ear on right side about size of a florin: white scars on brow and below ear on opposite side. Patient received .3 grams of Salvarsan intravenously and a pill containing Hyd. G, Creta gr. 1. Quin. Sulph. gr. 1 and Pulv. opii gr 1/8 t.i.d. Patient disappeared for six weeks but returned with the ulcer perfectly healed.

PARASYPHILITIC CASES.

Locomotor Ataxia

1. man previously reported, treated with Salvarsan: .3 grams given twice within a month: no obvious improvement.

2. Woman slightly ataxic and partially blind: Optic atrophy present in both eyes: one dose of .3 grams giving no

improvement.

GENERAL PARALYSIS.

Four cases in Hawkhead Asylum treated in 1911 by one dose of .3 grams. Patients slightly improved, but such improvement might have occurred apart from the Salvarsan treatment. In three of these cases the Wassermann reaction which was positive before treatment, continued so after treatment.

CONCLUSIONS.

Drawn from cases personally treated:-

1. That the earliest cases of syphilis ought to be invariably treated by Salvarsan: that the results of a combined Salvarsan mercurial treatment are very satisfactory.
2. The action of Salvarsan is remarkably rapid and effective in secondary cases.
3. That unless otherwise contraindicated all cases of pregnancy suffering from syphilis ought to be treated with Salvarsan.
4. Tertiary cases are greatly benefited by Salvarsan.
5. The benefits resulting from Salvarsan in parasyphilis are doubtful.
6. That Salvarsan-mercurial treatment is the best method so far as knowledge goes at present.
7. That syphilis ought to be otherwise treated as a notifiable disease.

A D D E N D U M.

ENCEPHALITIS HAEMORRHAGICA.

Reference has already been made to this grave but fortunately rare condition following the injection of Salvarsan or Neosalvarsan. Since writing this thesis ~~numerous~~ several reports of fatalities have been published. Milian and others have described the condition: few cases however have occurred in this country.

The symptoms have set in with convulsions followed by coma forty-eight hours to three days after an injection of Salvarsan (usually a second injection). The condition has generally occurred in patients in the early secondary stage of syphilis. The earliest cases were recorded by Fischer, Kannengiesser and Almkvist (Munch. Med. Woch. No. 34 - 1911). Mentberger has given in his book an analysis of a series of cases collected by him: he attributes the cause of death to arsenic intoxication. Surgeon Scott R.N. B.M.J. of Nov. 22 1913 refers to two cases where death appears to have been due to acute cerebritis. Recently a case has been reported in Guy's Hospital. Post Mortem a great dilatation of the cerebral and meningeal blood vessels with oedema of the brain is found. On section punctiform haemorrhages are present: microscopically there is congestion, endarteritis and extravasation of blood.

Similar conditions it is to be noted are found after poisoning with organic and inorganic substances, e.g. in alcholic poisoning.

Enrlich[6] in an interesting letter to the British Medical Journal May 9th 1914 points out the complex origin of

encephalitis following Salvarsan injection. According to him there are several factors including possible deficient adrenalin secretion which probably contribute to the condition, these may be summarised as follows:-

1. Liberation of endotoxins by the destruction of parasites.
2. The formation under certain circumstances,—possibly deficient elimination—of a toxic product paramidophenylarsen-oxide from Salvarsan.
3. Deficient elimination by the kidneys.
4. Deficient adrenalin secretion resulting in a wide dilatation of the bloodvessels with a consequent great fall in blood pressure.

In this letter Ehrlich refers to the value of adrenalin injections as employed by Milian in accidents following Salvarsan injections.

Further he insists on the importance in always beginning treatment with small doses, and on the observance of the most careful technique in the preparation and injection of the solution.

As most cases of encephalitis Haemorrhagica have occurred after a second injection of Salvarsan, Ehrlich alludes to the contra-indications to a second injection where a first injection has been accompanied by untoward effects. These contraindications have been described by Meirowsky and Kretzmer[45] and also by Milian.[47]

Lastly in his letter Ehrlich refers to the value of preliminary mercurial treatment in secondary cases. This has been recommended by Scott[54] & Gennerich: large numbers of

spirochaetes are thereby gradually destroyed and according to the endotoxin theory the risk of encephalitis would be materially diminished.

ALPHABETICAL LIST OF REFERENCES.

1. Alt. Munch Med Wochenschrift 1909 P. 1457.
Munch.Med. " 1910 P. 501.
Berlin Klin. " 1910 P. 1293.
Deutch Med. " 1910 P. 1896.

2 Boas. Die Wassermannsche Reaktion 1911.

3 Browning & Mackenzie . Recent Methods in the Diagnosis and Treatment of Syphilis 1912.
B.M.J. 1911 Sept. 23.

4 D'Arcy Power. B.M.J. June 22 , 1912.

5 Ehrlich & Hata Chemotherapy 1910.
Ehrlich Abhandlungen Uber Salvarsan.

6. B.M.J. May 9th 1914.

7 Fordyce New York Medical Journal 1911 May 6th.

8 Fournier Leçons sur la Syphilis 1881.

9 Gauchier Bull. de l'Acad de Med. 1911 Nov.21.

10 Goldenberg & Kaliske American Journal of Med. Sciences, March and April 1911.

11 Gibbard & Harrison B.M.J. 1913 Nov. 22.

12 Géronne Berlin Klin. Woch. 1910 P. 1032.

13 Hoppe Screiber Munch Med. Woch. 1910 P. 1930.

14 Hoffmann Die Aetiologie Der Syphilis Berlin 1906.

15 Huggenburg Med. Klin. 1910 P. 1400.

16 Iversen Munch Med. Woch. 1910 P. 777
Munch Med. Woch. 1910 P. 1723.

17 Jeanselme et Vernes Paris Medical 1912 March.

18 Knick & Zaloziecki Berlin Klin. Woch. 1912 April 8th.

19 Levaditi Compt. rend. de la Soc. de Biol. 1911 1908.

20 McDonagh Salvarsan in Syphilis Oxford Med. Manuels.

Lancet 1910 Sept. 3

21 B.M.J. 1912 June 8.

22 B.M.J. 1913 Dec. 6.

23 McIntosh & Feldes Syphilis from the Modern Standpoint.

London 1911.

24 McAlister B.M.J. 1913 Dec. 13.

25 Meirowsky and Kretzmer Die Salvarsan tnerapie der Syphilis

Wiesbaden Bergmann 1914.

26 Metschnikoff Annales de l'inst Pasteur-XXI 1907

27 Mentberger Entwicklung und Gegenwärtiger Stand der Arsenotherapic

der Syphilis 1913.

28 Morris B.M.J. 1912 Mar. 30.

29 Neisser Deutch Med. Wochenschrift 1910 P. 1212.
Berlin Klin. Wochenschrift 1910 P.1485.

30 Oppenheim Deut. Med. Woch Band 43.

31 Oui Echo Med. 1912 Mar. 24.

32 Screiber Muech Med Woch. 1912 April 23.
Munch Med Woch 1910 P 2026.
Munch Med Woch 1910 P.1430.

33 Sieskind Munch. Med. Woch. 1910 P. 2027.

34 Scott B.M.J. 1913 Nov. 22.
35 Truffi Centralbl. of Bakt. 1 abt. Bd 48.
36 Tsuzuki Deut. Med. Woch. 1913 P. 985
37 Uhlenhuth Arbeiten aus. d Kaiserl. Gesundheitsamte xxxiii Heft 1.

38 Wechselmann & Ehrlich Handbook of Syphilis 1911.
Berlin Klin. Woch. 1912 April 8.

39 Zeissl Wein. Med. Woch. 1910 P 2203.

REFERENCES IN RECENT LITERATURE.

40 Salvarsan and Neo-Salvarsan - Sabatie (Progrès Médical Jan. 24 1914)

41 Scarlatiniform Rash produced by Neo-Salvarsan - Bullard (Annales de Dermatologie et Syphilis, 1V, 8 and 9).

42 Neo-Salvarsan - Heredde (Journal des Praticiens, 1912, XXV1).

43 Neo-Salvarsan in General Paralysis - Scredde (Bulletin de la Societe Francaise de Dermatologie et Syphilis, No. 7, July 1913).

44 Cerebritis following Salvarsan - Caesar (Dermat. Zeitschr. XX no. 7).

45 Hemiplegia and Death after Neo-Salvarsan - Curle (Annales des Maladies Vénerales, April 1913).

46 Salvarsan in Lichen Ruber Planus - R. Polland (Wien. Klin. Woch.).

47 Toxicity of Neo-Salvarsan - Milian, Girand and Duret (Bulletin de la Societe Francaise de Dermatologie et Syphilis May 1913).

48 Deaths after Salvarsan and Neo-Salvarsan - Burnier (Annales des Maladies Venerales Feb. 1913).

49 Mercurial Preparations in Spirachaetosis - Abelin (Deut. Med. Woch. Sept. 26, 1912).

50 Nervous Symptoms after Salvarsan - Ravaut (Annales de Dermatologie et Syphilis, 1913).

51 Rectal Administration of Salvarsan - Rajat (Annales des Maladies Vénerales Nov. 1912).

52 Cranial Nerve Disease after Salvarsan - Alex. Zaloziecki and R. Fruhwald (Wein. Klin. Woch. 29 and 30 1912)

53 Salvarsan in Diseases of the Eye - Benda (Wien Med. Woch. 26,27,1912).

54 Relapses after Salvarsan in Syphilis - Gauchier and Levy Franckel (Annales des Maladies Vénerales, July 1913).
