

**"606" in theory and practice / by Paul Ehrlich and J.E.R. McDonagh.**

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IN THEORY AND  
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EHRlich AND Mc DONAGH

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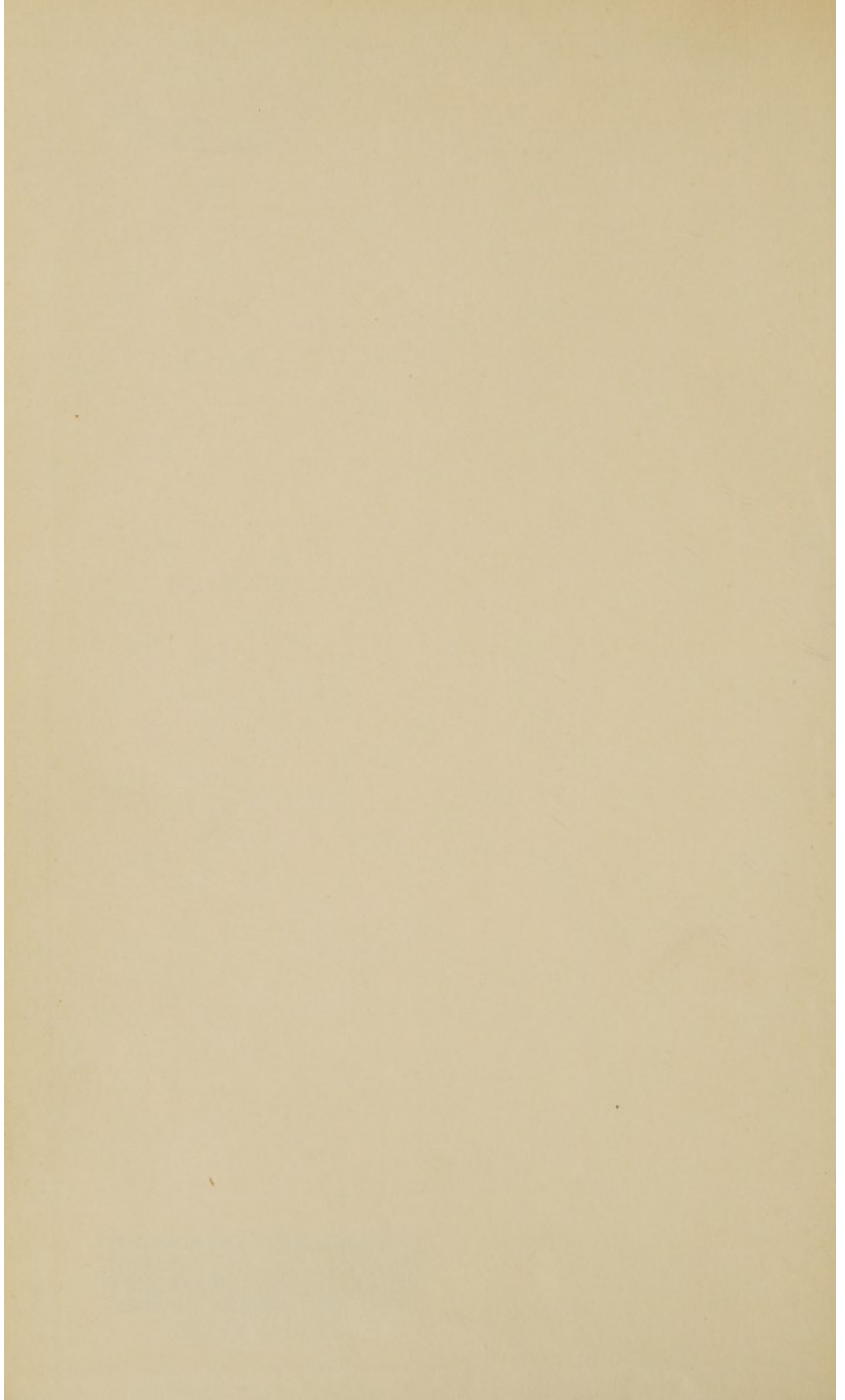
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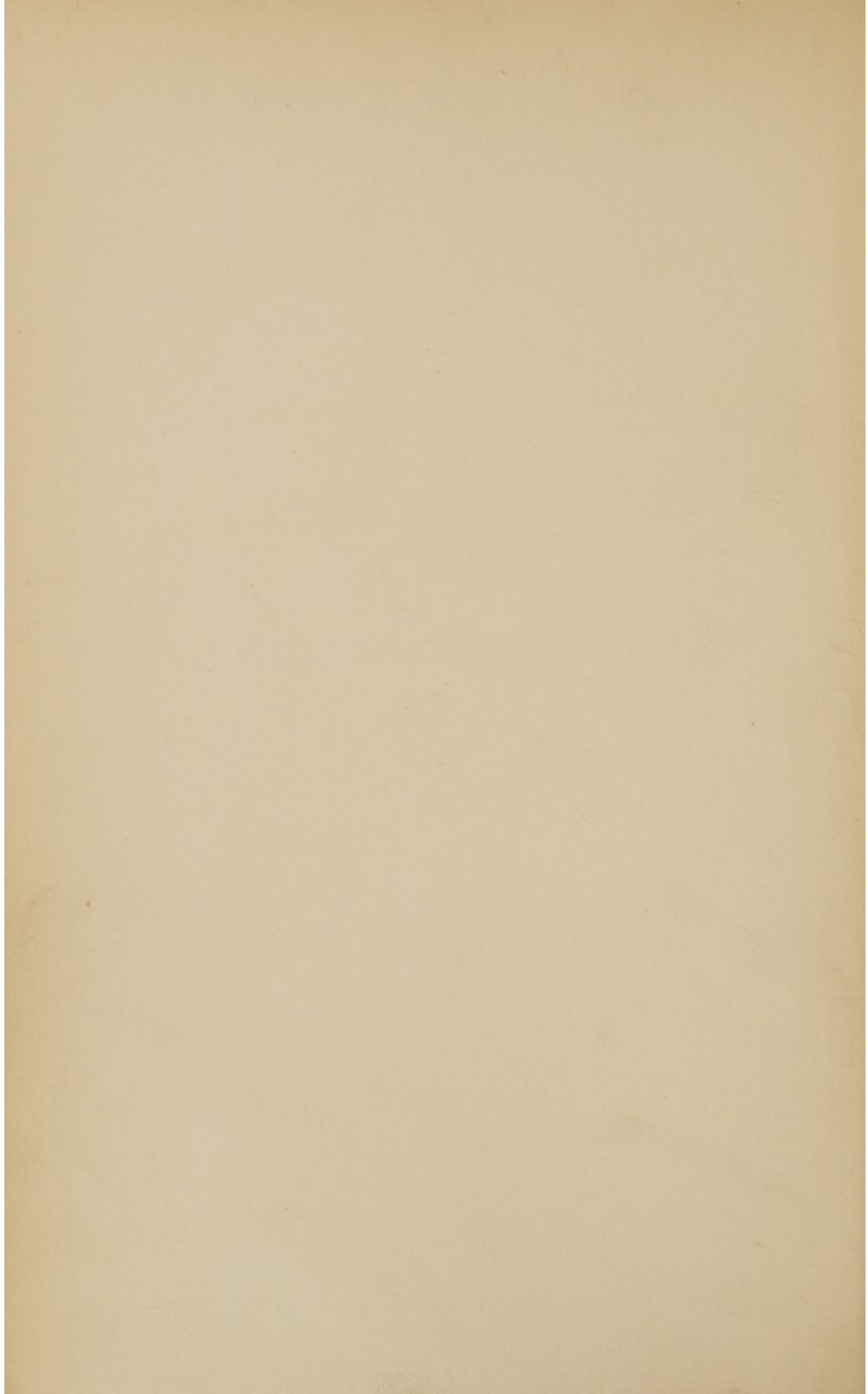


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“606”

IN THEORY AND PRACTICE



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OXFORD MEDICAL PUBLICATIONS

“606”

IN THEORY AND PRACTICE



BY

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## PREFACE

I AM glad to have the opportunity of writing the introduction to this book, since Mr. McDonagh from the beginning, as the first observer in England, has devoted the greatest attention to treatment of syphilis by 'Salvarsan', and has succeeded in obtaining some most excellent results.

The practical application of every experimental piece of work is beset with difficulties, and this was especially the case with 'Salvarsan', owing to its physiological and chemical peculiarities.

It required the painstaking observations of many to determine the best method of administering the drug, whether it should be intramuscular or intravenous, and if intramuscular whether the solution should be acid or alkaline, or in the form of a neutral emulsion.

Then again, the great difficulty had to be overcome of fixing the proper dose, proving the possibility and advisability of re-injection, and the important question of the influence of a combined treatment.

Equally important, although not so serious an undertaking, was to settle the contra-indications, and as regards these I do still maintain, as I have from the beginning, that severe and advanced disease of the central

nervous system and circulatory system is a contra-indication to this treatment. In no drug does the beneficial action stand in so close relationship with its method of administration as in 'Salvarsan'; this has been clearly shown by reports of recurrences and especially the effect on Wassermann's reaction, which varies enormously. If the very best results have not always been obtained, it is only what might have been expected to occur when neither the best method of giving the drug nor the proper dose were yet determined.

Every real advance in medical knowledge can only be obtained when a few pioneers will set to work to break down the barrier and give to others the results of their experience, so that the failures which they themselves have had may be avoided by those that follow after.

On this account I believe that this short work, which sets forth very clearly Mr. McDonagh's large clinical experience, should prove of the greatest value to every reader, since I have always considered him as one of the most successful pioneers in establishing the best method of administering the drug, its dosage, as well as when it should be repeated, so that the very best results may be expected by following his advice.

P. EHRLICH.

FRANKFURT AM MAIN,  
*March 10, 1911.*

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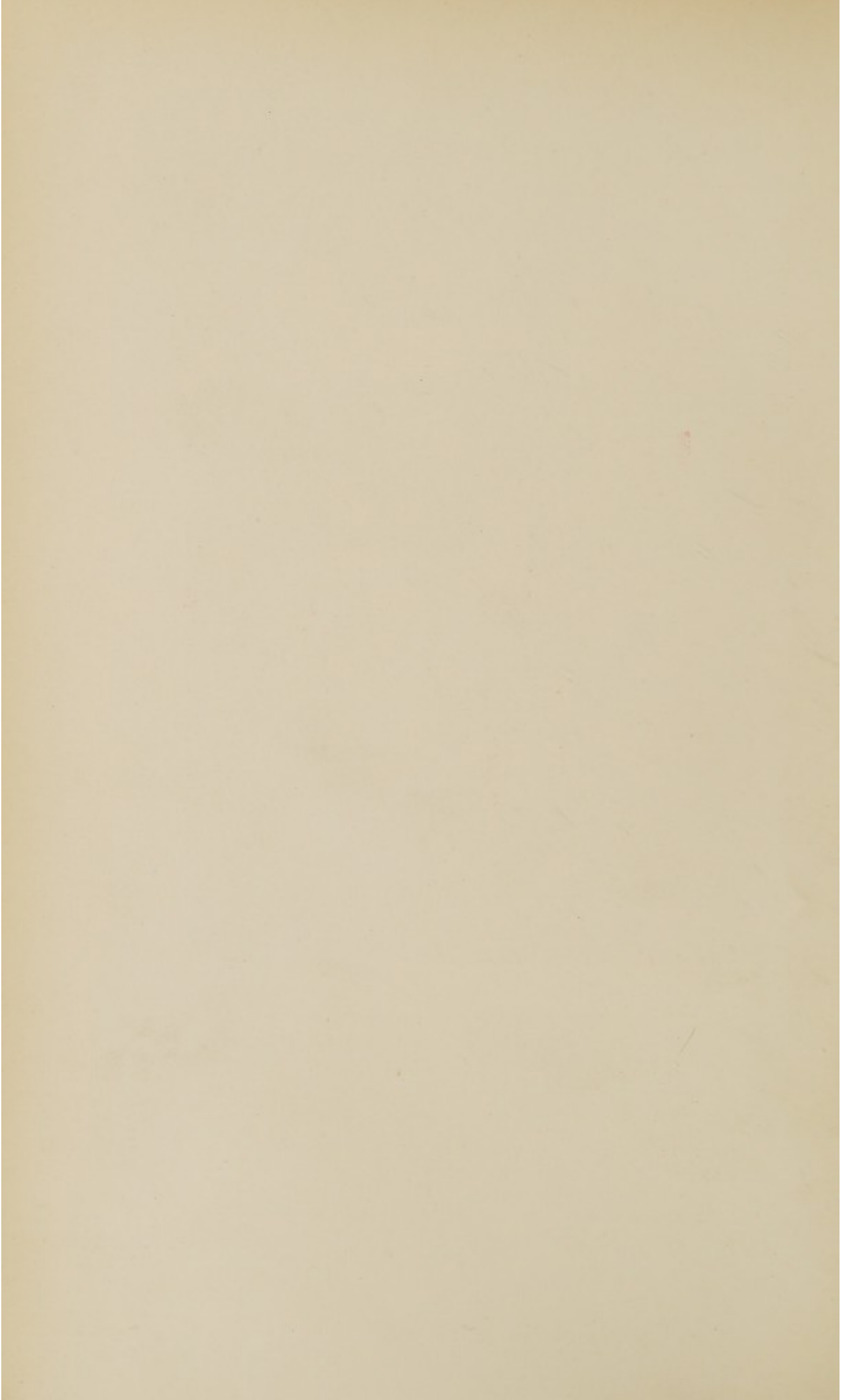
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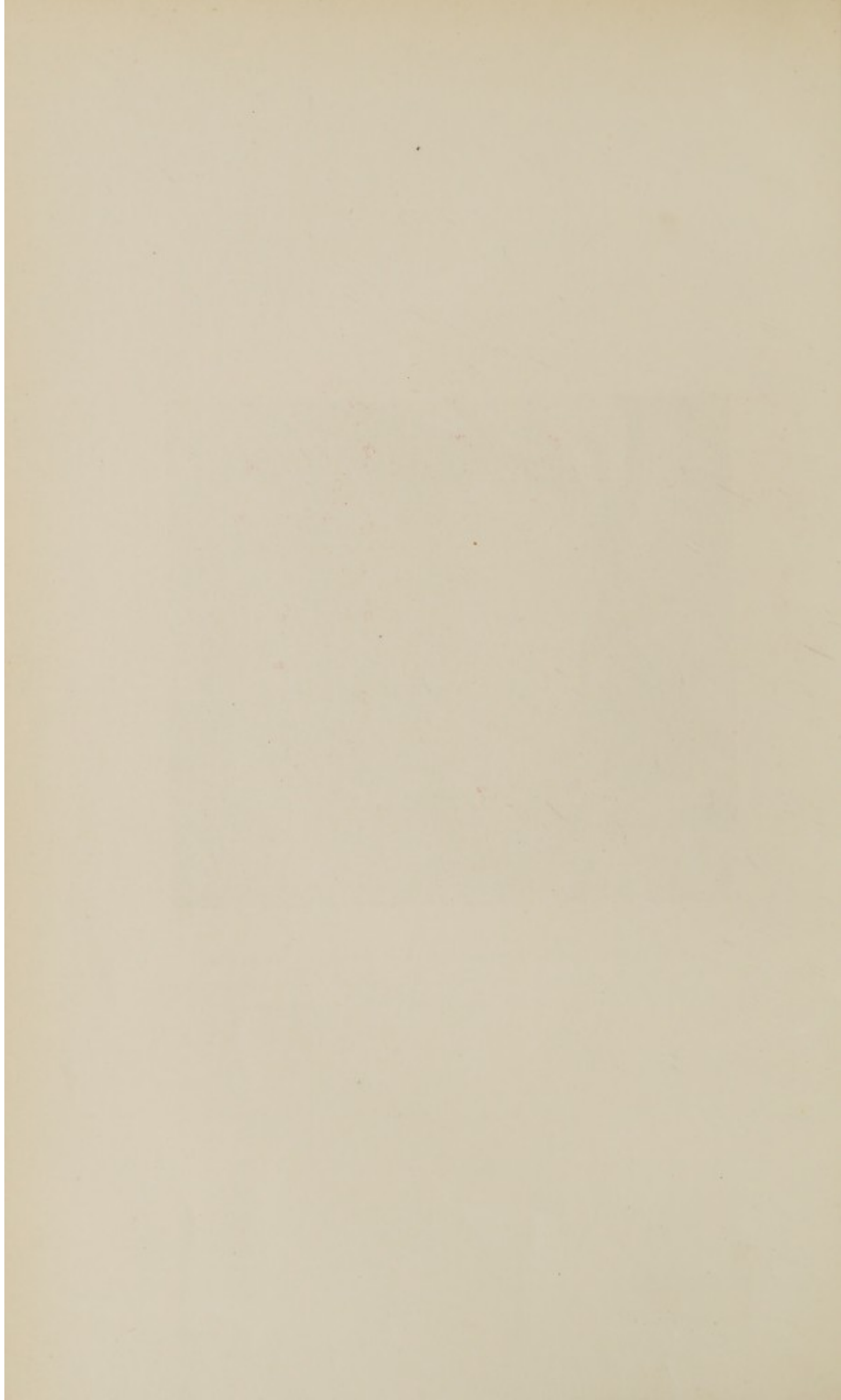
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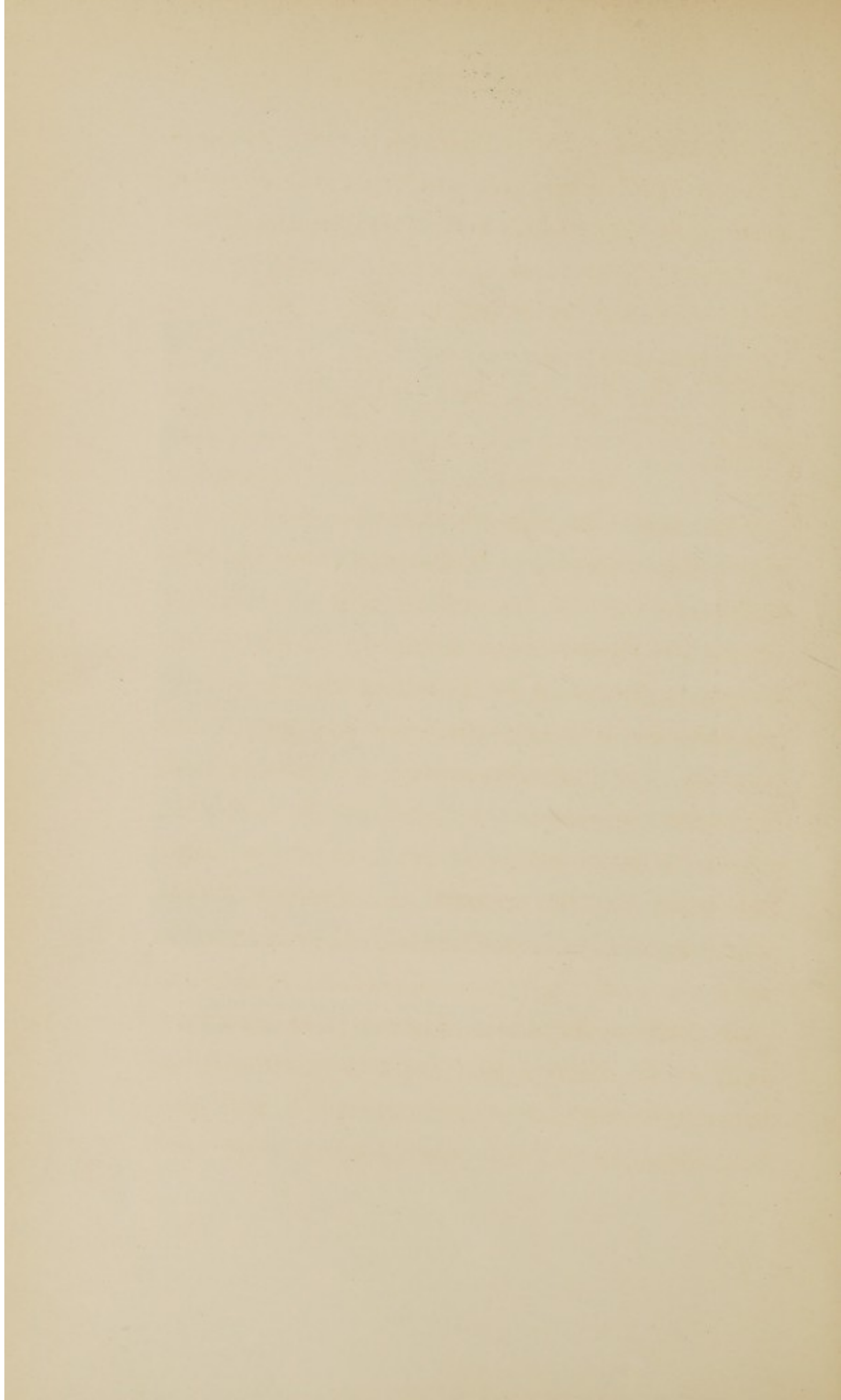
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## CHAPTER I

### THEORY OF THE ACTION OF '606', LEADING TO ITS CHEMISTRY, DISCOVERY, AND CONFIRMA- TION BY BIOLOGICAL EXPERIMENTS

*Introductory.*—The rôle which chemistry is likely to play in the future will no doubt surpass even the wonderful discoveries of bacteriology; not only will the chemistry of the different organisms and the poisons they produce, be ascertained, but the factors, which go to make immunity and which form the basis of the tests we now have, will no doubt in some cases be capable of synthesis. For instance, anti-bodies have been shown by Landsteiner to belong to the group of lipoids, so it is more than likely that before long the empirical and laborious Wassermann's reaction will come down to a simple chemical test.

My (Ehrlich) therapeutic discoveries are no chance ones; on the contrary, they are nothing more or less than a life's work, which commenced on hearing a lecture given by Heubel on lead-poisoning, in my third

semester. I wondered then how drugs distributed themselves in the body, how they entered into chemical combination with the cells of the host to produce pathological lesions. Since drugs could act injuriously on living cells, I strove to find those which would have a destructive action on the cells (organisms) which were the causes of the various diseases. Two laws were fixed firmly in my mind, viz., that for chemistry, 'corpora non agunt nisi liquida'; for therapeutics, 'corpora non agunt nisi fixata':—which means that a drug can have no action on the body, unless it enters into chemical combination with the cells thereof. The aim was to kill the organisms of the various infectious diseases by chemical products, which only entered into chemical combination with these organisms in order to destroy them and did not combine with the cells of the host. Such an action was designated parasito-tropic, but it was almost invariably found that these chemical products showed some amount of fixation with the living cells of the body, or in other words were organo-tropic. The first point was to discover chemicals which had a parasiticidal action and from these to select those which would act destructively on the organisms without giving rise to toxic effects. Drugs having a parasiticidal action are found to be capable of being classified into three groups.

(1) Arsenic and antimony ; (2) azo dyes, e.g. trypan red, trypan blue, and trypan violet ; (3) basic triphenylmethane dyes, e.g. parafuchsin, methyl-violet, and pyronin. The action of these drugs was tried mainly on trypanosomes and the spirilla of relapsing fever, since these organisms multiply in the blood, making an examination of their multiplication or their destruction an easy matter ; and as a drop of blood from an infected animal contains many protozoa, investigations *in vitro* were possible, and by these means it was found that chemoceptors could be established between any one preparation from these groups and the organisms in question. An immunity could be produced against the corresponding group, and not against any example of the other two.

Experimenting with arsenic, it was found that an arsenoceptor was only formed with the trivalent molecule. The action *in vitro* was not always the same as that *in vivo* ; for instance, *in vitro* methylene blue was a powerful spirillicide, but *in vivo* it was only so when a dangerous dose was used, owing to the fact that its action was so strongly organo-tropic, so much so that the spirilla often multiplied and flourished at the expense of the host. This phenomenon, called 'effectus contrarius', was not uncommonly met with when dealing with the products of the two dye groups. It was owing to

the organo-tropic action of these two groups that endeavours were not made to discover a drug which would be safe to use clinically, consequently attention was solely directed to the group containing arsenic.

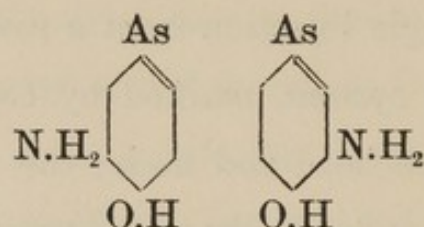
*Atoxyl.*—The first step in this direction was the discovery of atoxyl, which was only later found to have a pentavalent molecule, which explained its power of destroying protozoa *in vivo* only, since, as was known before, arsenic could only act as a parasiticide in its trivalent form. In the body atoxyl is reduced into para-amino-phenylarsenious acid, or into the trivalent and bivalent molecules; the latter being incapable of fixation, accumulated in the system as the result of several injections, thereby causing toxic symptoms in those who possessed a natural sensitiveness to arsenic, such as optic neuritis. Arsacetin, which was the next step along the line, was found to have the same unpleasant sequelae following its use. Next followed arsenophenylglycin, which was a trivalent arsenical compound. Although these three were powerful trypanicides, they exerted little or no action on the spirilla of recurrent fever. Since neither came up to my ideal or were the 'therapia magna sterilisans' which was to kill the organisms of protozoal diseases at one fell swoop by a single injection and within twenty-four hours, further experiments were instigated, with

the result that the goal was nearly reached by the discovery of arsenophenol, which killed the spirilla of recurrent fever in mice after two injections. Next came the drug which could do the same with one injection, it being called dichlorphenolarsenious acid. Fulfilling as it did my ideal 'therapia magna sterilisans', the drug could never be used clinically owing to the toxic symptoms it produced in animals; mice, for instance, suffered two weeks after a single injection from a severe disturbance of their nervous system, marked by continual shaking movements of the head and neck; the symptoms were progressive, so that finally the mice became dancing mice. Further research revealed a drug, which went by the name of dioxydiamido-arsenobenzol or '592', and its dichlorhydrate '606'. The dichlorhydrate was searched for owing to the insolubility of the mother salt, but the action of both is identical.

*Later Arsenical Compounds.*—The arsenical compounds synthesized after the discovery of atoxyl, could only be formed after the formula of the latter had been ascertained and when it was found to be an amido derivative of phenylarsenious acid; and, recognizing the range of this group, further experiments were undertaken solely with it, and after arsenophenylglycin had been synthesized, its number being '418', nearly two hundred



derivatives of phenylarsenious acid were prepared, and biologically and therapeutically tested before '606' was discovered. '606,' then, is the 606th preparation of the above-mentioned amido group, and although it is capable of being derived by a very complicated process from atoxyl, it bears absolutely no relationship to it. The formula of '606' is  $C_{12}H_{12}N_2O_2As_2$  and it is represented graphically as follows—



Although the arsenic molecule in '606' was a trivalent one and its curative dose in animals proved non-toxic, it was yet considered possible that man might so split up the arsenic ion with the result that toxic symptoms might ensue, since idiosyncrasy to drugs is more marked in man than in animals. With this surmise in view the precautionary step was advised of testing the patient's sensitiveness to arsenic by means of a Von Pirquet's cutaneous reaction or a Calmette's ophthalmic reaction such as one is accustomed to use for tuberculin; or Wolff-Eisner's intradermal reaction, which when positive is indicated by the presence of a painful cutaneous swelling, which one commonly sees when

tuberculin is injected into the corium of the skin and not into the subcutaneous tissue. Owing to the inconvenience of using '606' for such test purposes, arsacetin was advocated, but experience has since shown that these precautionary measures are unnecessary and that the tests used do not bear the same ratio to drugs, like arsenic, as they do to bacterial products, such as tuberculin.

Not only does man vary from animals in the way the body is influenced by drugs, but there is a marked difference in the behaviour of the various species of animals.

*Early Experiments on '606'.*—The first experiments undertaken with '606' were to estimate its degree of toxicity in the mouse, rat, hen, and rabbit, the animals on which future experiments were going to be tried.

The following table illustrates this point:—

Mouse	1.300	pro	20 grm.
Rat	0.2	pro	1 kg.
Hen	0.25	pro	1 kg.
Rabbit	0.15	pro	1 kg.

Each of these animals was respectively inoculated with trypanosomes injected at varying intervals with varying doses to find out how best a cure could be obtained. For instance, a dose of 1 in 700 was capable of killing the trypanosomes in an infected mouse within twenty-four

hours after the injection had been given, without producing any toxic symptoms and without a recurrence of any of the organisms in the blood. If the injection was less than this or in fact was too small, a complete cure could be obtained by giving a larger second or even third injection, but beyond this point the animals tended to show an over-sensitiveness to arsenic and the protozoa had acquired some degree of immunity. It having been shown that the protozoa could acquire an immunity against '606', it was all-important to find out that dose which would be sufficient to kill the organisms after a single or second injection. The drug was at first given only to a few medical men to use clinically so that this point could be estimated, since the ratio of body weight to toxic dose in animals could not be applied to man.

The following table shows the complete cure after the first, second, and third injections of '606' in various animals infected with pathogenic protozoa:—

Dose.	1st injection.	2nd injection.	3rd injection.
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	0 %	0 %	33 %

*Recurrences.*—In those animals which had a recurrence of symptoms owing to the dose being too small, the recurrences were always slight and never ended fatally. It will be interesting here to note how recurrences in human syphilis are affected. It must be remembered that the animal experiments were mainly on those which had been infected with trypanosomes; and since those animals chosen were extremely susceptible to infection, the trypanosomes were able to circulate and multiply in the blood, so recurrences are easily discovered. Although the rabbit, for instance, can be infected with syphilis, the disease is a local one and tends to run a course of its own, ending in resolution, so that a recurrence cannot occur; further, the spirochaete pallida has its habitat rather in the connective tissues than in the blood, so it can be seen that whatever the results obtained in animals, they had little or no analogy in man.

Cases of human syphilis which have recurred after '606' have on the whole been amenable to a further injection, and it is very rare to meet with a case in which the lesions seem to spread quicker when they recur.

In one case—a man who had a recurrence of a gumma on the nose after a second injection of '606'—when recurrence took place, it spread quicker than it had hitherto done. This patient had been previously given

several injections of atoxyl and soamin, and no doubt the spirochaetes had acquired an immunity against arsenic, and the result of giving '606' was equivalent to giving a very small dose in a patient who had never been treated, since the action of too small a dose is first to paralyse the spirochaetes and finally to stimulate them. There is no doubt the two injections used in this case were too small—0.4 gramme and 0.45 gramme respectively—and that they were given intramuscularly, so that the amount absorbed was very much less.

There are no cases on record where recurrences after an intravenous injection have proved intractable to a further one. However intractable a case may be to further treatment of '606', it does not prove intractable to mercury; theoretically this would seem to be the case, since protozoa which have become immune to arsenic do not *ipso facto* become immune to mercury and vice versa. However much mercury the patient has had, the symptoms are just as likely to clear up with '606' as if he had had none.

Some observers supplement the treatment of '606' by mercurial inunctions or injections as a routine, but such a course does not seem to be necessary because mercury can always be relied on in case of need, should '606' fail to cure the patient, and such a failure is extremely

rare when given intravenously; in fact, we have never had a case nor do we know of one. As a prophylactic '606' is valueless, but an animal injected and inoculated within twenty-four hours with trypanosomes does not become infected.

The following table is illustrative of the advantage of '606' over the rest of the arsenical synthetic products.

	C = Curative dose } T = Toxic dose. }
Atoxyl	$\frac{C}{T} = \frac{1}{2}$
Arsacetin	$\frac{C}{T} = \frac{1}{3.3}$
Arsenophenylglycin	$\frac{C}{T} = \frac{1}{3.3}$
'606'	$\frac{C}{T} = \frac{1}{58}$

*Mercury.*—For very many years mercury has been the only specific for syphilis, but unfortunately it is extremely poisonous in its curative dose, so that small doses have to be used over a long period. In consequence, many attempts have been made to discover a mercurial compound which would fulfil the 'therapia magna sterilisans', which is to kill the spirochaetes by means of a single injection. The only combination, which came to be used clinically, was atoxylate of mercury, discovered by Uhlenhuth and Manteufel. Using this drug

they were able to kill all the spirochaetes which were produced by local inoculation of the testicles in rabbits with four injections. Not only were four injections insufficient to have a like effect in man, but the doses required were much larger comparatively, and as a result toxic symptoms ensued and recurrences were frequent after its employment, so that atoxylate of mercury never came to be extensively employed.

*Arsenic Preparations.*—How it came to be that the latest specific for syphilis is a compound of arsenic and not of mercury, was owing to the well-known fact of the far greater influence the former drug exerted in sleeping sickness, and it was for this disease that atoxyl was discovered. When on March 3, 1905, the spirochaete pallida was discovered by Schaudinn and Hoffmann as being the cause of syphilis and a protozoon, which probably belonged to the same group as the trypanosomes, and since arsenic had often played an important rôle in the treatment of syphilis, the later synthetic arsenical compounds discovered, of which atoxyl was the stimulus, came to be used for syphilis as for sleeping sickness.

Although atoxyl was very largely employed, it came into disuse not only on account of its failing as the 'therapia magna sterilisans', but mainly owing to the ocular symptoms which resulted. Arsacetin again, although

more potent, also shared the same fate owing to similar sequelae following its use. Arsenophenylglycin was never extensively employed owing to the fact that '606' quickly followed its appearance. Practically the only clinical experience obtained with this drug was Professor Alt's, who chiefly used it in the treatment of paralytics. Although most of the cases did not improve, (which was scarcely to be expected), many which gave a positive Wassermann's reaction before treatment gave a permanent negative reaction after. Arsenophenylglycin was less toxic and more efficacious than either atoxyl or arsacetin, but nevertheless fell short of the 'therapia magna sterilisans'.

'606.'—Finally, as above described, came dioxydiamido-arsenobenzol, chemically discovered by Bertheim and tested biologically by Hata. As before stated, most of the animal experiments were carried out on those which had been infected with trypanosomes, but when it was found that rabbits could be inoculated with the syphilitic virus, similar experiments were undertaken. A rabbit can be inoculated with the spirochaete pallida in two ways—in the cornea and in the scrotum; by the corneal route a keratitis is produced analogous to that form met with in congenital syphilis, the cornea becomes cloudy with newly-formed blood-vessels running into it.



By means of a single injection of '606', these vessels disappear, the cornea becomes quite clear and a recurrence has not occurred in those animals so treated with that dose which was found to be curative, but not toxic. Resolution lasts for two or three weeks. By the scrotal route an ulcer is produced in the skin, which is indurated and resembles in every respect a chancre. Occasionally there is an orchitis and the inguinal glands may become enlarged; or a primary syphilitic orchitis may be produced by the direct inoculation of the testicle. As a result of an injection of '606', the spirochaetes were found to disappear within twenty-four hours and the local condition completely healed in from 2-3 weeks. Owing to the influence of '606' on both spirochaete pallida and the trypanosome, experiments were also undertaken to estimate its value in other protozoal infections, such as yaws or Framboesia, the causal agent of which is the spirochaete pertenuis, which closely resembles the spirochaete pallida; this organism has only quite recently been proved to be pathogenic to the lower animals, the ape being the only animal which had heretofore proved susceptible. Nichols succeeded in inoculating rabbits in the testicles; in the ordinary course of events, the disease lasts about 4-6 weeks and the Wassermann's reaction becomes positive in the first or second. Twenty-four hours after

an injection of '606' no spirochaetes could be found, and within a week or more the orchitis disappeared and the Wassermann's reaction became negative. Equally remarkable results were obtained in animals infected with the spirilla of relapsing fever, and in hen-spirillosis.

That 'Salvarsan' has a specific action against the spirochaete pallida there is no doubt, since its action is equally remarkable in relapsing fever, yaws, and Vincent's angina. Dschunkowsky obtained striking results in the spirillosis of geese; and Ornstein in the spirillosis of hens; Gerber has also shown its destructive effect on the spirochaetes of the teeth.

*Objections answered.*—Many authors have urged that 'Salvarsan' cannot fulfil the 'therapia magna sterilisans' so far as syphilis is concerned, owing to the fact that in syphilis the parasite has a predilection for the connective tissues, whereas in trypanosomiasis the parasites infest the blood-stream itself. This is, however, incorrect, since, in chronic trypanosomiasis in rabbits, marked connective tissue changes are common, due to the direct influence of the presence of trypanosomes, and these parasites have been shown to have been destroyed by an injection. Further, even in a chancre, before there are any secondary symptoms at all, the spirochaetes have already found their way into the connective tissue. Three days

after the injection the chancre has clinically healed, silver nitrate preparations fail to show spirochaetes, and no further symptoms of the disease make themselves manifest.

The argument that recurrences have occurred which go to prove the incorrectness of the 'therapia magna sterilisans' ideal requires analysing. When it is wished to produce such a marked effect in a chronic disease, two factors are necessary:—(a) that the dose should be sufficiently large, (b) that it should be given in a form where its action is quickest. When the drug was first used, small doses were employed, as there was no clinical experience to guide one. It has since been found that these doses were too small, therefore it is not surprising that some of the early cases recurred.

The following table drawn up by Dr. von Raven in Tokio illustrates the action of arsenophenylglycin in sleeping sickness:—

## GROUP 1.

1.	1 times the dose	1-10 mgr. pro Kg.	1=100.00% failure.
2.	36 "	" 10-20 "	" 20= 55.56% "
3.	21 "	" 20-30 "	" 7= 33.33% "
4.	23 "	" 30-40 "	" 5= 21.70% "

## GROUP 2.

5.	29 times the dose	40-50 mgr. pro Kg.	0	failure.
6.	20 "	" 50-60 "	0	"
7.	3 "	" 60-70 "	0	"
8.	1 "	" 70-80 "	0	"

*Importance of Size of Dose.*—It is obvious from this table that the best results are dependent upon the size of the dose ; another reason why some of the earlier cases recurred was owing to the fact that the injection was given either intramuscularly or subcutaneously. In many such cases the arsenic no doubt became encapsuled, which prevented its complete absorption, and experience has since taught us that the intravenous injection is the best means of prescribing the drug. That syphilis can be cured by a single or two injections is undoubted, since six cases are already on record of a fresh infection of a typical chancre ; again Neisser has proved that a second inoculation of apes was possible after the first infection was cured.

## CHAPTER II

### HARMFUL RESULTS WHICH WERE EXPECTED TO FOLLOW THE USE OF '606' AND CONTRA-INDICATIONS TO ITS EMPLOYMENT

#### A. NERVE LESIONS

*Supposed Toxic Effects.*—Owing to the fact that amaurosis has occurred after the use of atoxyl and arsacetin, there was first a very strong suspicion that the employment of Salvarsan might be followed by the same serious results. In September 1910 a notice was sent round to those to whom the drug had been entrusted, to ascertain if any severe eye lesions had occurred, and from the 8,000 cases which were collected there was not one of optic atrophy, those of optic atrophy which Hallopeau reported—not from his own personal experience—never really existed. Since that time there has been one single case in which optic atrophy followed an injection of '606'. A female aged 22, under the care of Prof. Finger, received on July 6, 1910, 0.4 gramme of Salvarsan in an emulsion for a malignant form of syphilis of long duration. On October 5, that is, three months later, the patient complained of dimness of vision in both eyes; the pupils were unequal, and there

was bilateral early optic atrophy. It should be mentioned that this patient throughout the previous year had been rigorously treated with organic arsenical compounds. She had received thirty arsacetin injections and sixty-nine injections of 'Enesol' (salicyl-arsenate of mercury). It is a well-known fact that an oversensitiveness to arsenic, inso-much as the eyes are concerned, can easily occur after continuous treatment with the organic synthetic compounds, and it has been shown that arsacetin has a greater influence in producing optic atrophy in cases which had been previously treated with atoxyl than in fresh cases ; so it is more than likely that this single case was determined by the previous arsenic treatment. When a patient has been previously treated vigorously with atoxyl, arsacetin, or arsenophenylglycin, or shown any visual disturbance after injection, he should not be given '606'. The advice at first was to exclude all patients suffering from ophthalmic lesions from treatment, but when it was found that the iritis and irido-cyclitis which may occur in the secondary period of syphilis completely disappear under an injection without optic neuritis ensuing, cases of syphilitic optic neuritis were treated with the same remarkable improvement. So many such cases have been treated that the rule can be laid down that so long as the eye lesion is of syphilitic origin, there is

no danger of the patient having an injection, and only those cases should be excluded in which syphilis is not the cause. Cases have been reported in which other nerves have been affected and some reports are current that the recurrences after treatment show a special predilection for the nervous tissue and the neurotropic action of '606' has more than once been alluded to. How far, then, is this borne out in actual practical experience. Out of 17 recurrences which Finger reported, 3 suffered from an affection of the acoustic nerve; following this, a similar report was sent round, and out of 7,000 cases in only 9 was there any affection of the 8th nerve. In all these cases the patients had received a single subcutaneous injection of a small dose. In not one of these cases was the syphilis more than eight months old, and, oddly enough, nearly all gave a negative Wassermann's reaction. At first sight it appears that a toxic lesion of the 8th nerve had resulted from the use of 'Salvarsan', an opinion which seemed all the more likely since similar cases had occurred after the use of arsacetin and hectin. Against this must be taken into account the cases of affections of the sense organs which Finger had reported as occurring in the early stages of syphilis after the employment of quicksilver. Urbantschitsch also reported similar cases after the use of injections with soluble mercurial

preparations. Against the toxic action is the fact that all these cases have improved on antisyphilitic treatment, and, further, affections of the eye and ear, when of syphilitic origin, are markedly benefited by the treatment; so one can regard such a catastrophe as being a neuro-recurrence and not a toxic one. As without exception these accidents have occurred in fresh syphilitic cases, it shows the importance of giving the largest dose possible at this stage, and in its most potent form, which is intravenously.

Some of the cases of a neuro-recurrence affecting the 8th nerve have been successfully treated by a second injection of '606'. In the cases of neuro-recurrence the nerve affection was the single lesion, and, as stated before, the Wassermann's reaction was negative. It is probable that a few spirochaetes had found their way into the nervous tissue, which is badly supplied with blood, but they were not able to multiply and liberate toxins, with the result that a negative Wassermann's reaction was obtained, and that their destruction was not complete, owing to the fact of a too small dose having been given. If this theory is correct, that the organisms do not multiply, in the ordinary course of events they would die out, a fact borne out in practice, since some of these cases have improved without any treatment whatever, while



others quickly responded to mercury and potassium iodide.

#### B. FATAL CASES DUE TO '606'

Every one is familiar with the reports of cases of death which have found their way into medical journals, not infrequently second or third hand, without a description of the case. There is practically no drug which has ever been used in medicine at whose door some severe toxic manifestations cannot be laid. Chloroform, when used on perfectly healthy individuals, has one victim in 50,000; taking all cases, 1 in 2,070; but it is still being largely employed. So far, the death-rate as the result of '606' is 1-5,000. Now in the year 1906 seventy deaths were recorded as being directly due to injections of mercury, and 110 cases of severe injuries following its use.

Before 'Salvarsan' was ever used clinically, disease of the heart and great vessels, nephritis and diabetes, were all considered as contra-indications, and some of the deaths are due to this rule not having been followed. Again, several injections have been given as a last resource with the hope of saving the patient. Five known cases of death, in which the employment of '606' was discussed, have taken place without the injection being given; had the exitus occurred after injection, '606' would have been given the credit.

The following cases are of practical importance:—

1. A well-known case of Spiethoff:

A female, aged 28, very anaemic and extremely emaciated, was admitted on account of tertiary syphilitic ulceration of the pharynx and larynx. Three years previously she had undergone a course of atoxyl injections. She was given an injection of 0.5 gramme intramuscularly and was found dead in bed next morning.

P.M.—Tertiary syphilitic ulceration of the pharynx and larynx with stenosis of the larynx. Gummata in the liver, hypoplasia of the heart and the aorta. It is quite possible that death in this case was due to shock in a very ill-nourished person, produced by the pain of the intramuscular injection, or still more likely to the diseased condition of the liver and heart.

2. A case reported by Auton and Halle of death occurring in a patient who was given an intravenous injection of 0.4 gramme for a gumma in the left parietal region of the brain, which had lasted for five years. The intravenous injection was acid. Hering had previously shown that acid solutions are extremely toxic when given intravenously.

P.M.—Softening of the left temporal and parietal region. Hydrocephalus internus. Anaemia and oedema of the brain. Chronic leptomeningitis, hyperaemia, and

oedema of the lungs, flabby heart with muscular atrophy, and fatty degeneration, especially on the right side. Cirrhosis of the left kidney, swelling of the spleen, and hyperaemia of the liver. Death was probably due in this case to the toxic action of the acid solution on a degenerated heart muscle.

3. A male, aged 39, had complained of cardiac trouble for some months. The heart was enlarged to the left; there was a diastolic murmur over the aorta, but the compensation was complete. The pupils were unequal and did not react to light. The patient received an intravenous injection of 0.5 gramme, but before this he had been given an injection of scopolamine-morphia and he died five hours after the first injection.

P.M.—Hypertrophy of both ventricles. Chronic aortitis. Sclerosis of the coronary arteries, diffuse myocarditis with thinning of the heart muscle at the apex. There is no doubt that the cardiac lesion was the cause of death in this case.

4. A woman, aged 26, who gave a history of two abortions but had no signs of syphilis, was admitted complaining of pain in the cardiac region, and because a Wassermann's reaction was positive 0.4 gramme was given intravenously. She died three days later, with signs of increased difficulty in breathing. In the meantime

she had carried on her work in the garden against orders.

P.M.—Thrombosis of the vein at the site of injection and an embolus of the pulmonary arteries. There was syphilitic aortitis, sclerosis of the coronary arteries, and degeneration of the heart muscle. The death in this case was due to the thrombus, which became dislodged, probably owing to the fact that the patient returned to work too soon. It is undoubtedly a mistake to allow a patient out of bed under three days after an intravenous injection has been given.

These four cases, which have been cited as deaths due directly to the injection, can be seen to belong to that class of case in which from the start there was considered to be a strong contra-indication, the cardiac lesion being more or less severe in all.

#### C. CONTRA-INDICATIONS

A class of case where great care should be exercised is where jaundice is a complication of syphilis. Provided that jaundice occurs in the early secondary stage, and provided also that there is no evidence of degeneration of the liver, or acute atrophy ascertained by the presence of leucin and tyrosin in the urine, it is perfectly safe to give an injection; but the

injection should be intravenous, since, when given intramuscularly, the continued action of the arsenic may have some injurious effect on the liver cells, whose resistance is already lessened.

The other contra-indications to 'Salvarsan' are diabetes, nephritis not of syphilitic origin, advanced pulmonary tuberculosis, aged and very emaciated individuals, and also in advanced cases of nervous diseases.

## CHAPTER III

### CLINICAL USE AND METHODS OF ADMINISTRATION

WHEN '606' was first used clinically, the pain produced was often too severe for a patient to stand, and on this account its further use seemed to be somewhat limited. The pain was most severe when the solution was injected in either an acid or an alkaline medium.

Owing to the severe reaction, intravenous injections became preferable, until Michaelis and Wechselmann found a means of producing a neutral emulsion which had the effect of largely diminishing the pain.

The injection, then, can be given either intravenously or intramuscularly.

#### A. INTRAMUSCULAR INJECTION

The yellow powder being acid, alkali must be added before it can be injected. Sodium hydrate is the alkali most frequently employed, excess of which can be neutralized or not; if it is neutralized, the pain is not so severe, but an emulsion is formed, which has the distinct disadvantage of not being so quickly absorbed,

consequently it may become encapsuled by the tissues and an arsenic dépôt formed. Schreiber cites a very interesting case of a man who had insoluble mercurial injections; several years after the last, he met with an accident, which resulted in letting loose the mercury which had been encapsuled by fibrous tissue, with the curious result that the patient suffered from mercurial stomatitis. As the pain produced by the injection of the salt in solution is so severe, the method will never be generally employed. This method has another objection in that the bulk of fluid is large, so that two sites have to be used. Dissolve the powder in alcohol—ethyl alcohol for choice—not methyl alcohol, as has been advocated, since this, unless absolutely chemically pure, may give rise to unpleasant symptoms, probably dependent on the presence of formaldehyde, which is not an infrequent impurity. 0.5 c.c. of alcohol is used for every 0.1 gramme of powder, and 20 c.c. of ordinary sterile warm water are added, and the mixture stirred with a glass rod until every trace of the powder is dissolved, then add slowly, mixing thoroughly while adding, 1 c.c. of decinormal sodium hydrate solution to each 0.1 gramme of powder used, and inject equal quantities into each buttock, at the junction of the outer and middle third of a line drawn from the top of

the greater trochanter to the middle line of the body ; the needle employed should not be less than two inches in length. The preparation which is now on the market as 'Salvarsan' requires no alcohol to dissolve it, thereby the pain is considerably modified. If the solution is intended to be neutralized, the best plan of procedure is as follows :—

The powder is put into a mortar and to it is added 1 c.c. of a saturated solution of sodium hydrate, mixed and then dissolved in 4 c.c. of very hot water ; as an indicator 3 drops of the standard alcoholic solution of phenolphthalein are added, which colour the solution a bright red ; then just so many drops of glacial acetic acid are added, till a yellow emulsion is produced, and finally one or two drops of sodium hydrate are put in until the emulsion assumes a rose-pink tint. This emulsion is taken up in the syringe and the residue left in the mortar can be obtained by adding another 1-2 c.c. of hot water. The injection need not necessarily be made in the glutei ; especially is this the case with male patients, who take to bed badly. Further, the pain is often more severe in this situation when the patient is in a recumbent posture than when he is up and about, consequently, movement excites the local reaction, with the result that the injection mass tends to gravitate downwards on to the



sciatic nerve, producing bad sciatica, which necessitates a prolonged stay in bed.

A favourite place for an injection is under the trapezius muscle, midway between the scapula and the vertebral column, just below the angle of the scapula, on the left side in right-handed individuals and vice versa.

Not infrequently, immediately after an injection into the shoulder, especially in plethoric persons, there is a great difficulty in breathing, owing to a spasm of the intercostal muscles on that side. This difficulty in breathing, which may be accompanied by coughing, does not usually last more than a quarter of an hour, and in only one case did the patient become somewhat cyanosed; and as the difficulty in breathing persisted for some time—pleurisy developed in this particular case—it is better to inject emphysematous patients in the glutei.

*Results of Intramuscular Injection.*—Intramuscular injections must always be preferred to subcutaneous, as the pain in the latter is more severe, the swelling produced by local reaction is greater and there is more liability of the skin necrosing over it. If complete aseptic precautions are taken, an abscess should not result from an intramuscular injection. Directly after the injection the pain is very acute, due to the sudden distension of the tissues. This

persists for about 10 or 15 minutes and is followed by a dull aching pain which varies in its duration from 1-3 weeks. The third day a large tender swelling may form due to toxic oedema, which is best relieved by alternate applications of an ice-bag and hot fomentations. When the swelling gets smaller, nothing gives the patient more relief than the application of a belladonna plaster, which at the same time aids absorption. Morphia may or may not be necessary. Pain is less in women than in men, but in any case varies enormously with the individual; for a few nights after the injection, sleeplessness is not uncommon. There may be a rise of temperature the first night, but this is more frequent on the second and third, on the fourth day it usually falls, or it may persist for another day or two. Occasionally the temperature rises as high as  $103^{\circ}$ , and although the rise in temperature seems to be in direct ratio with the severity of the infection, it is by no means the rule, so that the rise of temperature cannot be taken as an absolute indication that the drug is acting. Sometimes on the second or third day the patient complains of a sore throat. Constipation after the injection is more often the rule than not, so it is advisable to order a laxative the evening after the injection. Although several out-patients have been injected, it is best to keep the patient in bed from four

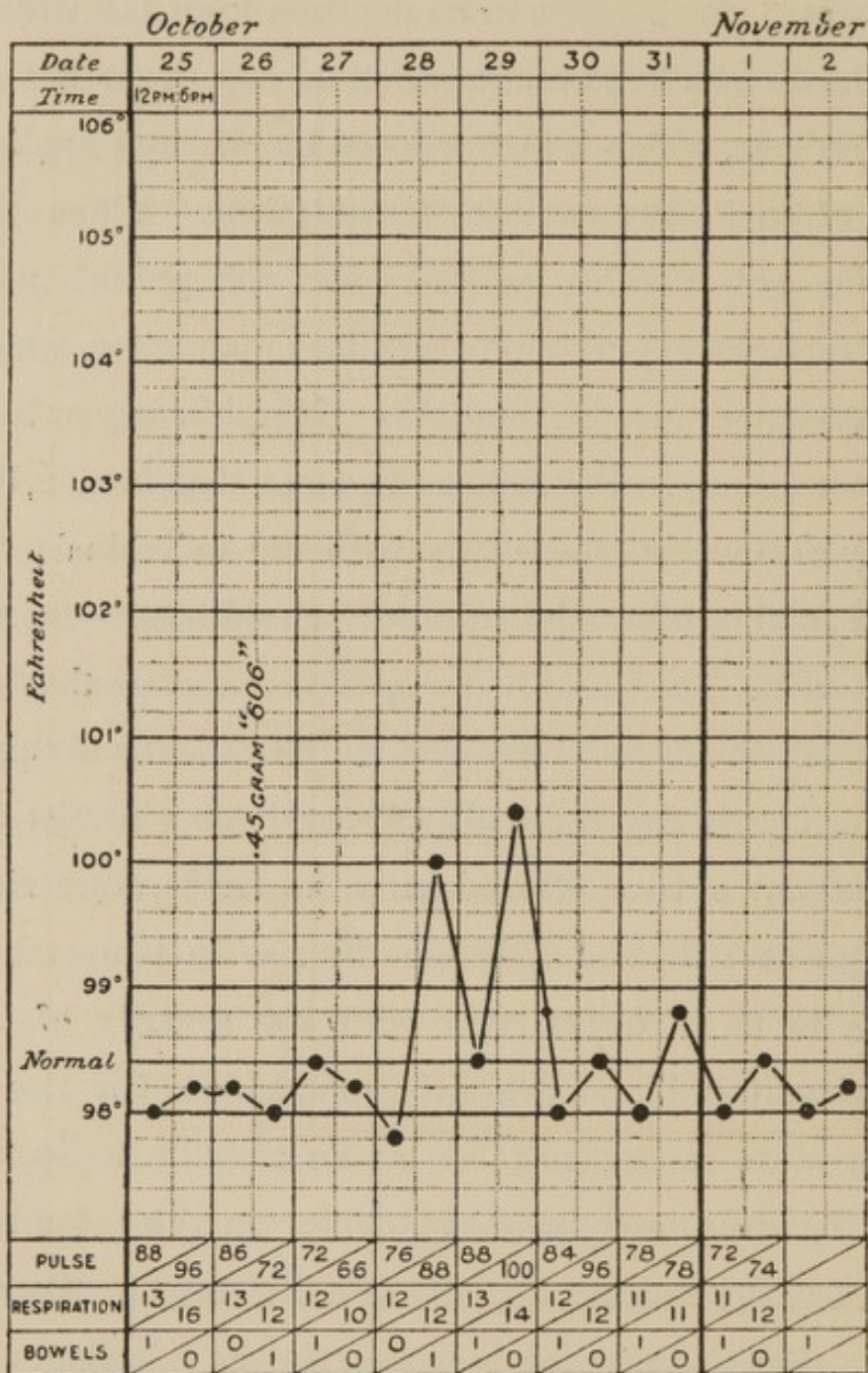


FIG. 1. TYPICAL CHART AFTER AN INTRAMUSCULAR INJECTION.

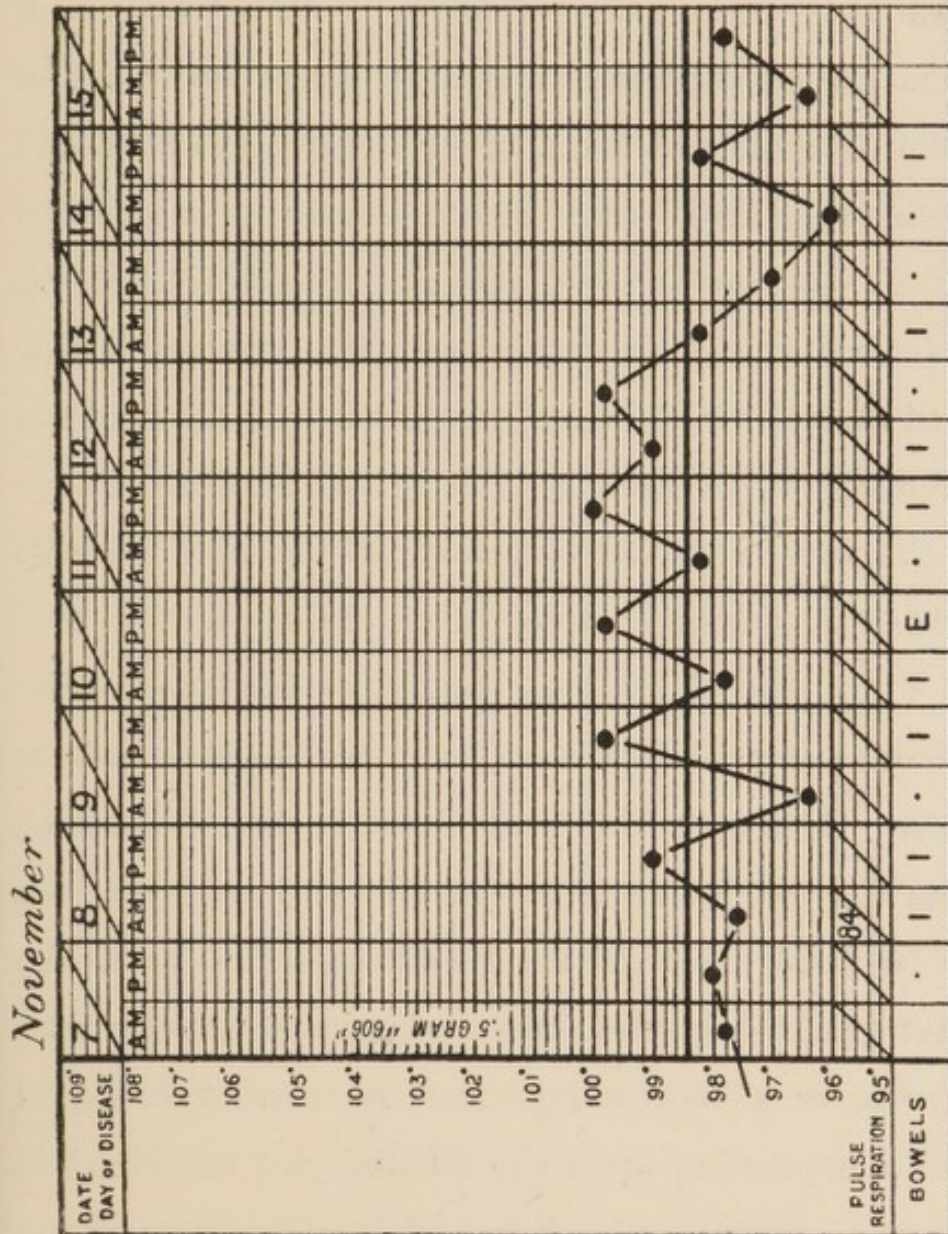


FIG. 2. TYPICAL CHART AFTER AN INTRAMUSCULAR INJECTION.

days to a week. The following is the best method of preparing a neutral emulsion :—

*Neutral Emulsion (Citron's Method).*—The contents of a tube are emptied into a syringe, and then 1 c.c. of absolute alcohol and 5 c.c. of hot water are added and the mixture stirred until all the powder is in solution. Next 40 drops of a 10 % solution of potassium bicarbonate in normal saline are added. The mixture is now stirred carefully with a glass rod until a liquid emulsion is produced. The piston is then pushed into the syringe and the latter inverted to get rid of the air. As this emulsion is sometimes thick, a needle as stout as that used for a pleural effusion, should be employed. For preference one should use platinum needles with iridium points. Although the pain is very much lessened, unless the patient remains quiet for a few days, there may be a very painful toxic oedema. The great disadvantage of this method is that recurrences are common.

Kromayer advocates injecting the powder in liquid paraffin, depending upon the alkalinity of the blood to produce a mono- or bi-sodium salt. Such a preparation is painless, but not so efficacious.

The injection should always be employed fresh and preferably made at the bedside. A tube should never be opened and half used one day and half another,

as this procedure has in some cases resulted in toxic symptoms supervening, such as anuria, inflammation of the bladder, and atony of the large intestine.

*Clinical Course after an Intramuscular Injection.*—However the solution be prepared, and however carefully it may be given, one can never say beforehand how much pain the patient is going to suffer. Some patients have little or none, whilst others, on the other hand, have excruciating pain which may last as long as a week. Needless to say, the very greatest precaution should be taken in sterilizing everything before its use; since if an abscess forms, the pain will necessarily be severe. Even when the strictest antiseptic precautions are taken, swelling, softening, and necrosis of the part injected may take place. The swelling is of the nature of a toxic oedema. It comes on about the third day, diminishes in size at the end of a week or ten days, after which time its diminution is very gradual and a small amount of infiltration may be perceptible for months after. As a rule the swelling is not painful; it gives the appearance of fluctuation, but under no circumstances should it be opened, unless an obvious abscess forms, when the swelling becomes acutely painful. The skin over it is usually of normal hue; when the swelling first appears, the skin may be red, but if the skin becomes red for the first time

at the end of a week, an abscess must be feared. The redness which appears with the swelling is analogous to that met with in urticaria, and quickly disappears under an application of the following lotion :—

R. Plumbi subacetat. gr. x.  
 Liq. Ammon. Fort. ℥ v.  
 Spir. Vini rect. ℥ i.  
 Solut. alumin. acetat. 3 % ad ℥ i.  
 m. f. lot.

When the swelling appears, alternate hot and cold applications give the patient the most relief; and when the patient gets up and about, wearing a belladonna plaster helps to diminish the pain and aids in increasing the absorption. Even after two or three weeks, the swelling may be so perceptible as to be visible through the patient's clothes.

Occasionally the swelling resolves into fluid, and in such circumstances it is either best left alone—since it causes the patient no inconvenience—or the sterile pus may be aspirated; under no circumstances should an incision be made, since a sterile abscess is almost certain to be converted into an infected one.

Necrosis to a slight degree occurs after every intramuscular injection, but a necrosis of the overlying skin only occurs when an injection is given subcutaneously,

or when some of the mass is allowed to get into the subcutaneous tissue, when the needle is withdrawn from the muscle.

One of the most important points in giving an intramuscular injection, is to avoid the entrance of any of the emulsion into a vein; the needle should be first inserted and from 30 seconds to a minute should elapse before the syringe is fastened on to it.

One case, where this precaution was not taken, resulted in the patient's getting hemiplegia, and this case was described as being due to the toxic action of '606'.

*Toxic rashes* may supervene and usually make their appearance about a week after the injection; the exanthem not uncommonly resembles that met with in measles, or scarlet fever; it may be a true urticaria, and in a case of congenital syphilis the child developed an angio-neurotic oedema of the face.

The commonest rash is an erythema iris which occurs in one or two parts of the body. Herpes of the face and genitals have occurred. These toxic rashes must not be confounded with an increase in the specific eruption, which is called Herxheimer's reaction, and which usually appears when the patient receives his first or second inunction of mercury, the action of which is to



temporarily stimulate the spirochaetes. Herxheimer's reaction after '606' only occurs when the dose given is too small.

*Necrosis.*—Deep in the muscle or the superficial layers, in some cases extending into the subcutaneous tissue, lies a hardish mass of brownish yellow colour, in the centre of which is a dark brown horny mass, which spreads out here and there into the tissues. The central portion is due to a chemical destruction of tissue, the structure of the tissue usually not being maintained. Around there is usually a capsule and marked signs of chronic inflammation. Microscopically, the necrosis is found to affect muscle fat and connective tissue, the nuclei of which do not stain. The vessels in the immediate neighbourhood of the necrosis are thrombosed. In the outer zone the thrombosis is often only partial, or the vessels are found to contain collections of leucocytes. The nerves in the necrosis also degenerate. Arsenic is almost invariably to be found, often as late as three or four months after the injection was given.

Necrosis is undoubtedly due to the poisonous action of the preparation. It is impossible yet to estimate whether a destruction of the tissues in any way breaks up the arsenic molecule or harms the individual.

Necrosis only occurs when a large quantity of the

preparation is injected in one spot, and not when several small points in both buttocks are chosen; they are more common when the injection is given in the thoracic region than in the glutei.

There is no doubt that one or two of the cases described, in which peroneal atrophy set in after an injection, were due to an inflammation or even a degeneration of the sciatic nerve by the necrosis, and not due to a neuro-tropic action of the drug. Moreover, some of the bladder and colon troubles, which have more frequently occurred after an intragluteal injection, may be reflex owing to an implication of the pudendal plexus which lies in close relation to the sciatic nerve.

#### B. INTRAVENOUS INJECTION

The contents of one tube of 'Salvarsan' should be slowly dissolved in 3 or 4 ounces of warm physiological 0.9% saline which has been prepared with distilled water, in a graduated measure up to 10 ounces.

When the powder has become completely dissolved after sufficient stirring with a glass rod, 10 c.c. of double decinormal<sup>1</sup> sodium-hydrate solution should be added, with the result that a precipitate forms; this pre-

<sup>1</sup> Double decinormal NaOH or  $\frac{n}{5}$ NaOH = 0.8%, or 8 grammes to the litre of distilled water; normal sodium hydrate being a 4% solution.

precipitate is dissolved by a further addition of sodium hydrate, usually about 7 c.c.—this may be either more or less, according to the actual acidity of the powder. The 7 c.c. should be added slowly, and the mixture stirred thoroughly. By using a weak solution of sodium hydrate we avoid the risk of making the solution too alkaline, and the exact quantity required is more easily estimated.

If normal sodium hydrate is preferred, i.e. 4% solution, 0.7 c.c. is required for every 0.1 gramme of the powder used. When the solution is quite clear after adding the sodium hydrate, the measure should be filled with saline up to 10 ounces, and once or twice filtered through muslin or several layers of plain gauze, so as to be absolutely sure of avoiding the smallest solid particle getting into the vein, which can either cause a pulmonary embolism or hemiplegia.

9–9½ ounces must be considered the maximum dose.

To bring the solution up to the body temperature a hot jacket should be placed around the measure and the whole placed in a water bath; the jacket of gauze, muslin, &c., is to prevent the glass vessel from cracking.

Another vessel filled with saline is placed by the side of the one containing the '606'. The patient comes to the side of the bed and hangs his arm over, then a

tourniquet<sup>1</sup> is placed on the arm, and the limb made to rest on a table in as comfortable a position as possible for the patient. The bend of the elbow is then sterilized by first rubbing with acetone and then ordinary tincture of iodine.

When a vein cannot be seen it can often be felt, and should be marked out with a blue pencil to indicate its course. If this cannot be done, a vein should be exposed by an incision, either under a local or a general anaesthetic.

The solution can either be injected or transfused, injection being far preferable, as :—

(1) The needle is not so easily dislodged, for if this should occur while the solution is flowing in, by the transfusion method some must escape into the tissues before the flow can be stopped; with the syringe merely a few drops need escape, as the tap can be turned off at once.

(2) The operator has more control over the proceedings.

(3) There is no danger of air or a solid particle gaining access to the vein. Air is easily seen in the syringe and remains at the top, never coming over the centre unless

<sup>1</sup> The simplest and best tourniquet is some rubber tubing, which should be wound tightly around the arm and the two ends fixed with pressure forceps, which can be removed without disturbing the limb.

the piston is pushed right home. A solid particle is also seen; it falls to the bottom of the syringe and is not disturbed provided that the solution is injected slowly and steadily.

(4) The operation is pleasanter from the patient's point of view, because it is so much quicker.

(5) The risks which are alleged to follow injection and not transfusion, do not in actual practice exist.

A good syringe is one invented by Schreiber, and made by the firm B. B. Cassell, Frankfurt a. M. The cannula is bayonet-shaped, bent, and fixed to a three-way metal stop-cock, so that the fluid can be sucked up from the vessel and injected directly into the vein. The needle has also a plate at its base upon which a finger can rest to keep it steady. The one disadvantage of this syringe is that the whole apparatus is rigid; therefore the slightest movement of the syringe may be sufficient to dislodge the needle.

To overcome this difficulty, Allen and Hanbury have constructed for one of us (McDonagh) a needle, which is  $1\frac{1}{4}$  inches in length, behind which is a slightly concave metal plate which rests on the arm and is fixed by a piece of tape which runs under a metal bridge above, or a piece of elastic fastened with bull-dog forceps. This piece is fixed by means of a bayonet-catch to the

three-way stop-cock; but the connexion between the needle and the bayonet-catch is made by a piece of thick rubber tubing, so that every movement of the stop-cock or syringe behind is broken at the loose connexion and does not affect the needle.

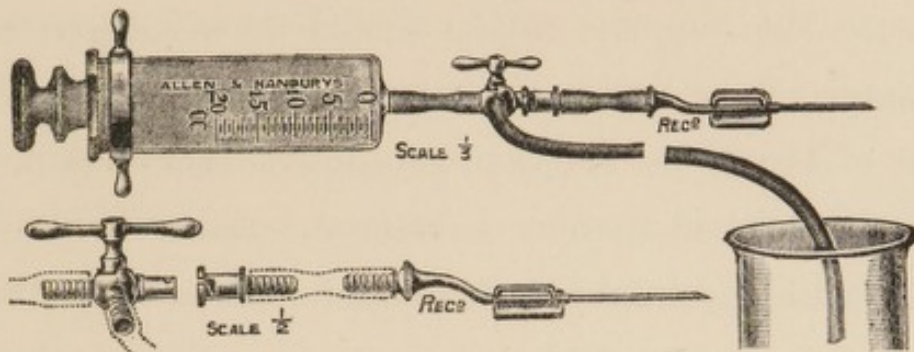


FIG. 3. McDONAGH'S SYRINGE.

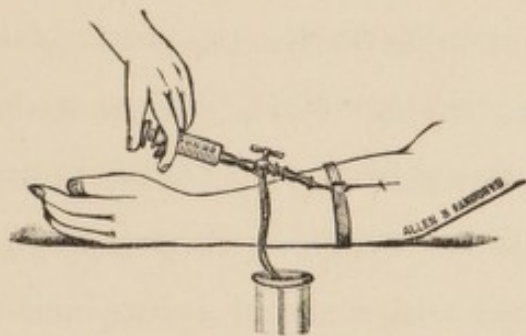


FIG. 4. THE SAME IN USE.

The all-glass syringe, which should hold 20 c.c., fits on to the stop-cock by means of a piece of stout rubber tubing, instead of being inserted into a metal tube, which may not fit every syringe.

The syringe is first filled with saline solution and all air expressed both through the tubing and the needle, then the needle is inserted into the vein, and fixed with

the stop-cock open. If the vein has been pierced, which can at once be told by touch, or by blood flowing back into the syringe, the tourniquet should be removed and some saline injected. If the cannula is not completely in the vein, the saline will produce an infiltration; should this be the case, the needle should be withdrawn and another vein chosen, as it is most important to prevent any of the '606' solution getting under the skin, as the pain caused thereby is intense. If much escapes there will be painful induration and oedema of the best part of the arm, and the swelling often takes weeks to disappear. When the solution has all been injected, some saline should finally be used to avoid leakage of a drop or two of '606', which is done by transferring the tubing from the '606' vessel to the one containing saline. Suppose, during the injection, that the needle slips and some of the solution escapes, the patient complains at the same moment of a burning sensation. One should immediately take the needle out, apply a tourniquet to the arm and allow the vein to bleed, which will often prevent an infiltration forming. If the injection is skilfully done, the patient has no pain.

Under no circumstances must the preparation be injected in a concentrated form, and great care should be taken not to inject the solution too quickly.

*Clinical Course after an Intravenous Injection.*—While the solution is being injected, patients often complain of a tingling or numbing sensation at the tips of the fingers and toes, also a fullness and swimming of the head; the face, or in fact any part of the body, may become lobster-coloured as a whole or in patches. The eyes appear very bright, the patient complains of a peculiar metallic taste in his mouth and very rarely of a tightness in the chest. Mucous membrane lesions immediately after the injection may swell up, but this is more often the case when the solution is injected cold.

A few hours after the injection there is a rise of temperature to  $101^{\circ}$  or  $103^{\circ}$  F., the patient may have one or two rigors, usually feels very sick, and there may be vomiting. For the rigors, recourse should be had to hot-water bottles, blankets, &c.; if the vomiting is incessant, draughts of soda water will usually stop it. The vomiting can be practically eliminated if the patient is prepared beforehand, as he would be for a surgical operation.

The rise of temperature is usually greatest in patients who are suffering from syphilitic nervous disease and in those patients who have had malaria. In such cases, a rise to  $105^{\circ}$  or  $106^{\circ}$  must not be considered alarming.

There exists no ratio between the rise of temperature



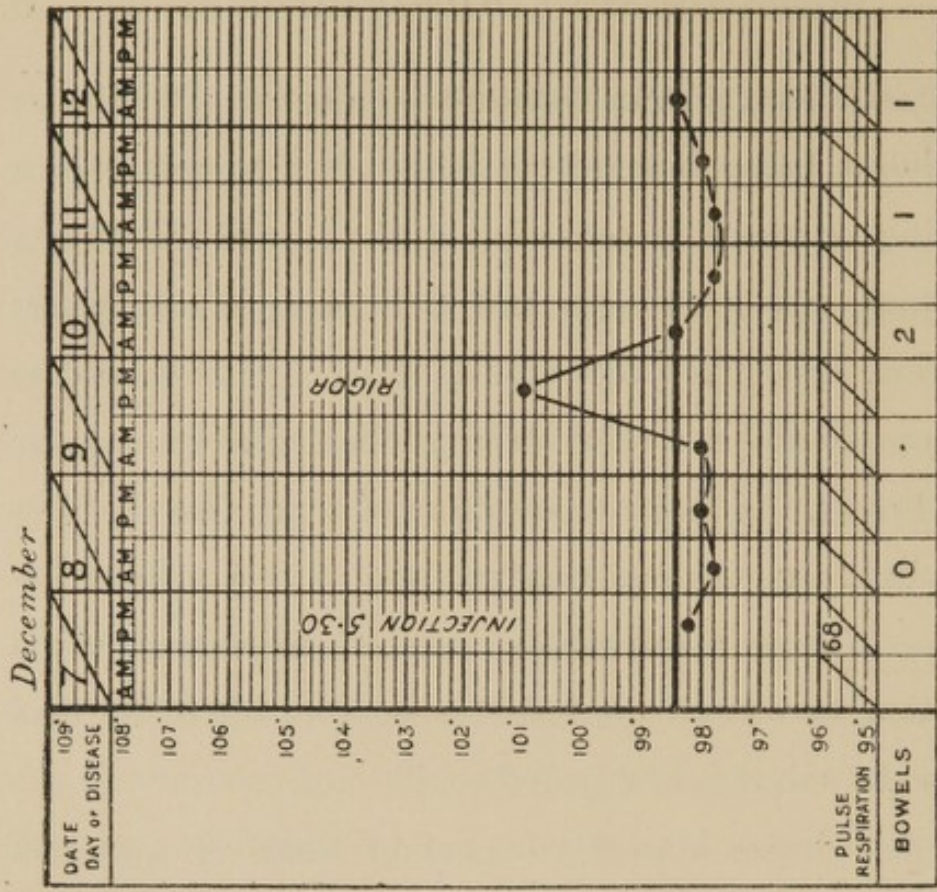


FIG. 6. DELAYED RISE OF TEMPERATURE.

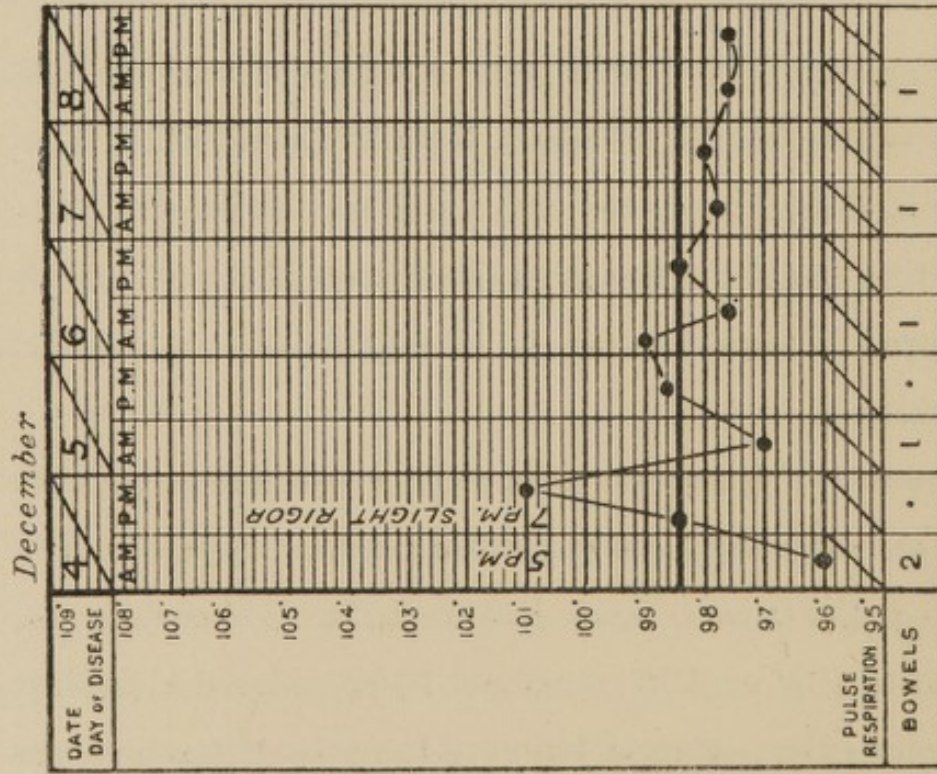


FIG. 5. TYPICAL CHART.

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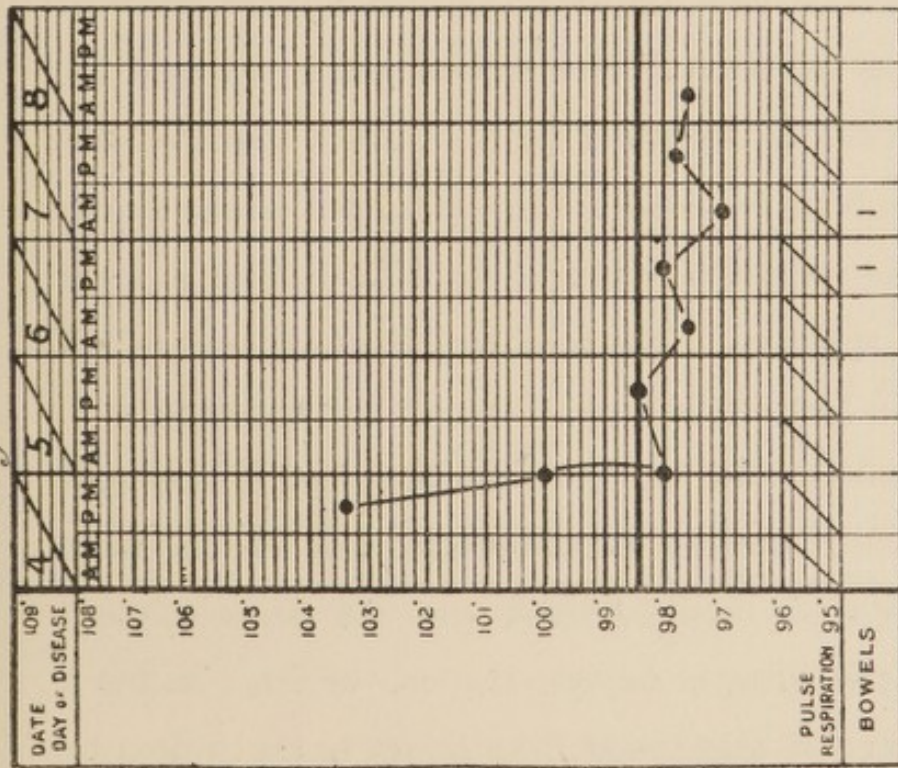


FIG. 7. CASE OF HEMIPLEGIA CAUSED BY THROMBOSIS.

In this case every afternoon before the injection the patient had a rise of temperature to 102° or 103° F., due to malaria; since the injection the malarial symptoms have also disappeared, but malaria will recur because '606' seldom has a permanent effect in this disease.

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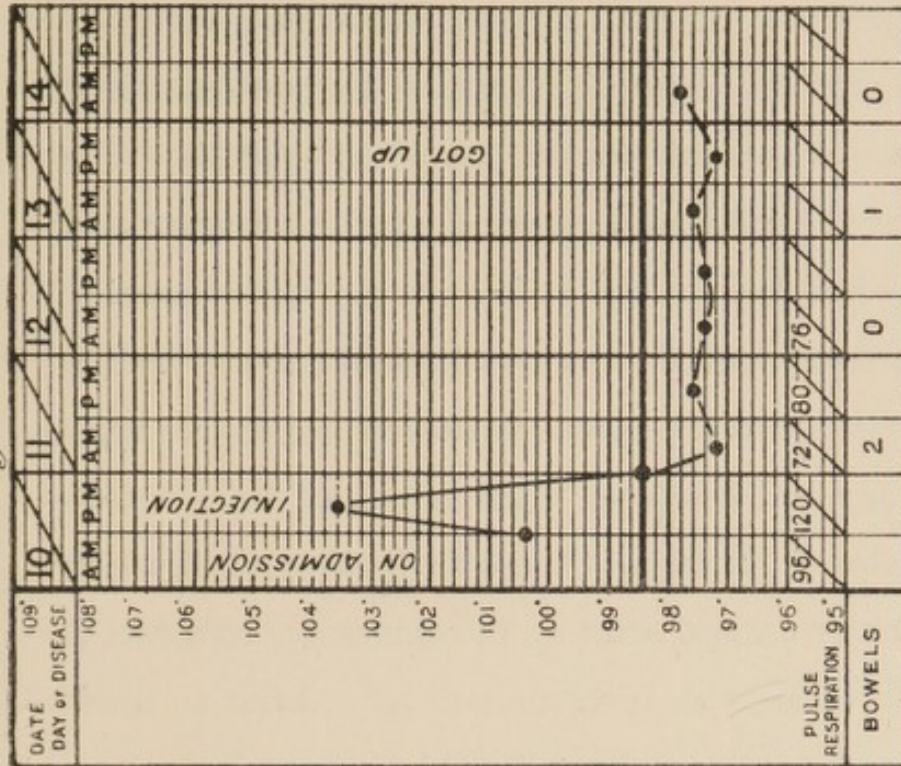


FIG. 8. CASE OF MALARIA COMPLICATING SYPHILIS.

and the severity of the disease, since patients with secondary syphilis may get no rise of temperature, and, vice versa, patients who have never had syphilis. The same night the injection is given the patient may or may not sleep, but he usually wakes up the next morning feeling perfectly well. It is very seldom for any feeling of malaise to last as long as the second day, except in some cases of nervous diseases, when a rise of temperature may be delayed till then. The constipating effect which is occasionally noticed after an intramuscular injection is not met with after an intravenous one. After an intravenous injection the patient should be kept in bed for three days.

In only one case did a toxic rash appear after an intravenous injection. The patient was a boy aged 17, who received an injection for a primary chancre; the usual symptoms followed the injection, but on the fourth day the temperature went up to 105° F. and a toxic erythema appeared. The next day the temperature fell and within forty-eight hours the rash had vanished.

Occasionally after an intravenous injection the vein injected may become thrombosed; this occurs most commonly when distilled water and not saline solution was used; it always follows the use of too alkaline a solution, and it may occur from injury to the intima by

the movements of the needle. In the ordinary course of events it is of no moment ; it is only likely to make the arm stiff for a time, but both this and the tenderness soon disappear. Unless absolute asepsis is the régime, the thrombus may be septic.

Some temperature charts after intravenous injection are given on pp. 46 and 47.

#### C. ADVANTAGES OF THE INTRAVENOUS METHOD

There is a distinct advantage in the intravenous injection, since a second injection can be made within a short interval without there being the slightest risk of producing intoxication, because the arsenic is excreted in a few days. An over-sensitiveness to arsenic by the second injection does not occur, as Ehrlich has feared. On the contrary, patients generally show less reaction after the second than they did with the first. The following chart is from a case where the reaction was great after the first injection, with little or none after the second. The second injection is made in every case in which the symptoms do not promptly disappear, or when the Wassermann's reaction is still positive after the fourth week.

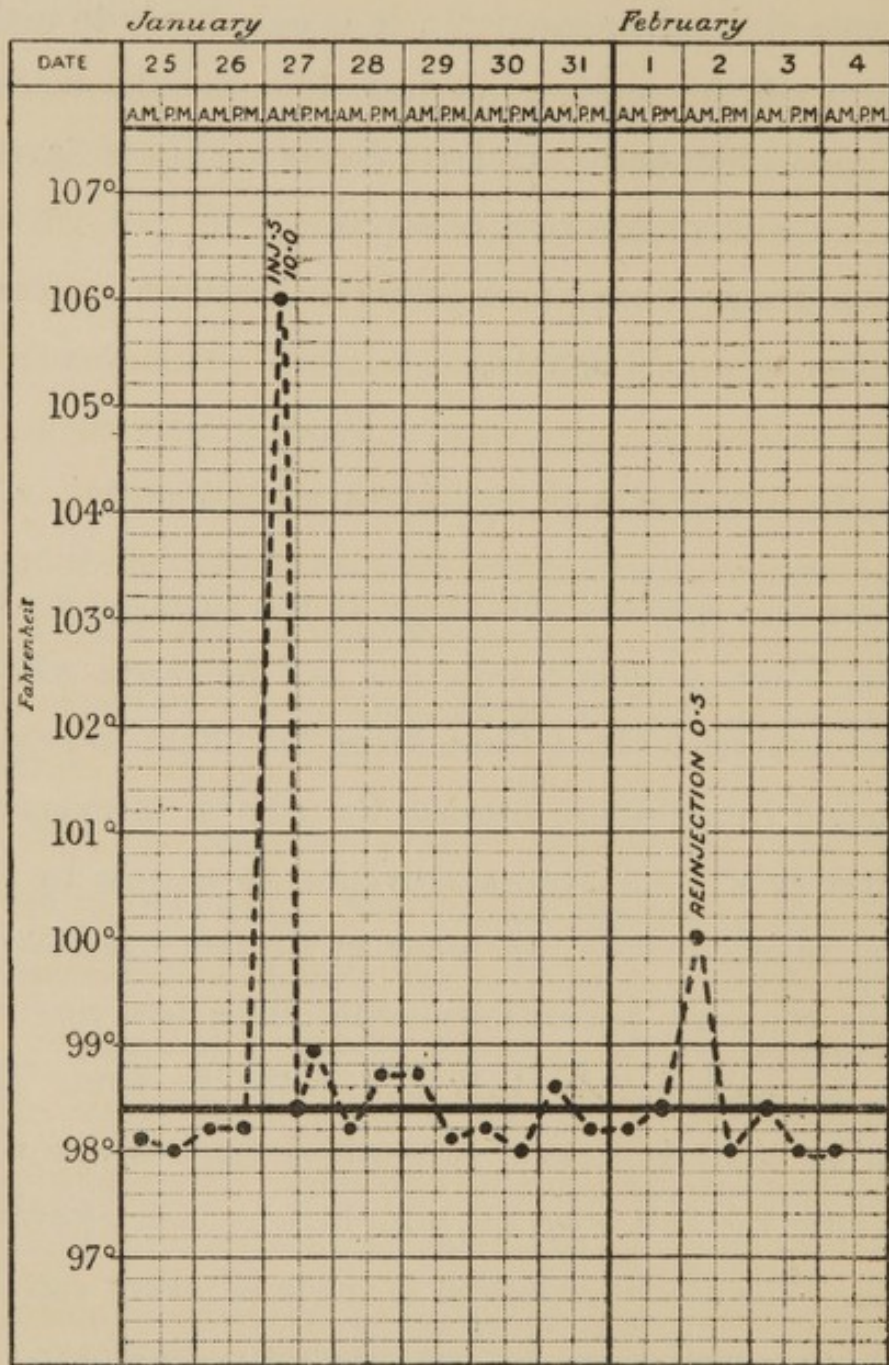


FIG. 9. CASE OF MARKED REACTION AFTER THE FIRST INJECTION WITH ONLY VERY SLIGHT REACTION AFTER THE SECOND.

## D. CHOICE OF METHODS

The question will naturally be asked as to which is the most efficacious of all the methods described for injecting '606'. Everything considered, intravenous injections are to be preferred. The pain after an injection is practically nil, although not infrequently in a few hours the patient has a rigor and a rise of temperature, which becomes normal the following day and he feels perfectly well. In syphilitic diseases of the central nervous system, the rise of temperature may be delayed to the second or third day; a small majority of patients have attacks of vomiting a few hours after the injection and complain of headache and weakness. The symptoms are very rarely worse than these.

In about 3% of all cases, either directly or within an interval of an hour or two after the injection, the patient may go deathly white, and the pulse become very feeble; this is followed by either a severe attack of vomiting or diarrhoea.

The patient may have acute spasmodic abdominal pain, and during each spasm the pulse increases in rate and becomes very soft. Under such conditions he should be surrounded with hot-water bottles and have the bed-clothing piled on, and a subcutaneous injection of ether

(15 minims) or camphorated oil (15 minims containing  $1\frac{1}{2}$  grains) should be given. If the vomiting persists, it may often be stopped by a drink of soda water.

Two or three hours later, except for a headache the patient is perfectly well.

The greatest advantage of the intravenous route over the intramuscular, is that an arsenic *dépôt* is avoided, which becomes a danger when a second injection has to be given, since the arsenic may be liberated and, together with that which is now injected, produce a toxic dose.

Schreiber's figures, which are far and away the most important, as he has been using the drug since September 1909, show the very distinct advantage of the intravenous over the intramuscular route. 152 cases were injected intramuscularly with 18 recurrences. 565 cases were injected intravenously with only one recurrence, which could have been avoided if another injection had been given four weeks later, after a positive Wassermann's reaction.

Unfortunately very few workers on the continent have employed the intravenous route, therefore, before criticizing the reports, one should ascertain how the drug had been prescribed.

## E. DOSAGE

The patient should first have an intravenous injection of 0.5–0.6 gramme for a man and 0.4–0.5 gramme for a woman. The injection should in all cases (except nerve cases and some tertiary lesions) be repeated on the fifth or sixth day, and only a third injection given when Wassermann's reaction is positive between the fourth and sixth week. If a third injection is necessary it may be given either intravenously or intramuscularly.



## CHAPTER IV

### OTHER CONSIDERATIONS

*Amaurosis. Comparison between Atoxyl and 'Salvarsan'.—* Igersheimer showed that atoxyl-amblyopia was found to be a simple progressive atrophy of the optic nerve, which can occur early or late after treatment; in only two cases was the amblyopia stationary and it did not advance further than a retro-bulbar neuritis. Nonne, who was fortunate enough to have the opportunity of studying the condition post-mortem, found that the chief changes occurred in the nerve fibres themselves and in the neighbourhood of the chiasma. The changes were purely parenchymatous. The same changes, as above described, could be produced artificially in the eyes of rabbits by means of a local application of atoxyl, and in dogs and cats after subcutaneous injections. In cats cell-changes were also to be found in the brain and spinal cord, the part most affected being the optic thalamus. Wechselmann, who has injected over 1,400 cases, has not once met with a case in which amaurosis has occurred after the use of '606'. All these cases were examined both before and after the injection was given by Fehr. It was found

that 2% of cases of syphilis in the eruptive stage had lesions of their optic nerves, such as neuritis and retrobulbar neuritis, which did not give rise to any subjective symptoms.

There is no doubt that papillitis in the secondary stage of syphilis occurs more often than might be believed; it is usually unilateral, and, unless vigorously treated, may quickly lead to atrophy and loss of vision. Two such cases have occurred in my experience during the last six months. If the lesion had occurred after '606' had been given and not before, there is no doubt that 'Salvarsan' would have been held responsible. Of the 270 cases one of us (McDonagh) has injected, in one only has optic neuritis supervened. Five weeks after an intravenous injection the patient complained of a haze in front of the right eye. He was in the early stage of secondary syphilis when the injection was given. Wassermann's reaction was negative at the time the papillitis appeared. The condition improved under vigorous mercurial treatment and must be looked upon as being a recurrent syphilitic manifestation and not as a sequence of using 'Salvarsan'.

Igersheimer (*M. M. Woch.* No. 51, 1910) by experiments on dogs and cats showed that the toxicity of the arsenical synthetic compounds was not due either to the

arsenic or the aniline, but to the phenylarsenious acid molecule, since the simple sodium salt of phenylarsenious acid will produce the nervous symptoms in both dogs and cats which are known to occur after the continual use of atoxyl.

Experiments were then undertaken with 'Salvarsan', in order to ascertain whether a derivative of phenylarsenious acid developed in the body. Although almost poisonous doses were used, and even in cats, which are remarkably sensitive to arsenic, no toxic symptoms were observed, provided that the injection was a single one, or at most two, and no phenylarsenious acid could be demonstrated in the body after death. Whether the same holds good for repeated small doses is another point, since, if an animal is killed a short time after the injection, arsenic is found in the optic nerve. Under these circumstances, giving repeated small doses may prove dangerous. No arsenic is found in the optic nerve when therapeutic doses are employed.

The action 'Salvarsan' has on spirochaetes is a definite chemical combination, since in syphilitic keratitis produced in rabbits by inoculation after an injection of 'Salvarsan', arsenic can be found in the enucleated cornea, but no arsenic is found in the cornea when the keratitis has been produced by a bacillus coli infection.

*Effect on Wassermann's Reaction.*—Although the reports are very conflicting as to the influence of 'Salvarsan' on Wassermann's reaction, it may be broadly stated that a positive reaction can be converted into a negative one. The change from a positive into a negative reaction is gradual, since, if a serum is tested week by week, the amount of complement capable of being fixed by a given serum gets less and less every week, until—usually between the fourth and sixth weeks, when none is absorbed—there is a negative reaction. In a few cases, where a chancre was the only clinical manifestation when the injection was given, and where the reaction was negative, the effect of an injection has been to cause a positive reaction within a week, which became negative again two or three weeks later. Such cases have always been those where the chancre was far advanced, but where no secondary symptoms were clinically manifest.

A few cases of recurrent and malignant syphilis, which gave a negative Wassermann's reaction, continue to give a positive reaction after the injection; Wechselmann reports five such cases, in which the change to positive was gradual to a point of complete fixation, followed by a gradual diminution in the amount of complement absorbed until it became negative. Theoretically this

phenomenon has been explained as being due to a destruction of the spirochaetes.

In cases which have recurred after an injection of '606' a positive reaction is always obtained, and this again becomes negative when the injection is repeated. In congenital syphilis the tendency is for the Wassermann to remain positive in spite of the patient being clinically cured. Opinion is still divided as to whether repeated infections can alter the reaction. Some cases of late syphilis likewise persist in giving a positive Wassermann's reaction after treatment. Why this is, cannot satisfactorily be explained, since we are still in the dark as to the causal factors of Wassermann's reaction, and the question whether a positive reaction is invariably indicative of active syphilis cannot at present be answered.

Some cases which continue to give a positive Wassermann's reaction between the fourth and sixth week after injection may some weeks later even without the repetition of an injection become negative, this being especially the case after an intramuscular injection.

A single intramuscular injection is more often capable of producing a negative reaction than a *single* intravenous dose, but a negative reaction following intravenous injection is much more permanent. A recurrence after an intramuscular injection can in most cases, provided

the patient has not undergone treatment by other arsenical compounds, be changed; after a second intravenous injection it is the rule; and finally if the two intravenous injections follow one another within a week, a negative reaction generally follows, but whether it is in every case permanent cannot at present be determined.

Pregnant women at any stage of pregnancy stand the injection well, and in only one case, reported by Glück, did an injection result in abortion. A sufficient number of cases has not yet been injected to allow of an opinion being given as to the curative action on the future offspring, and we are always hampered by the fact that syphilitic mothers may give birth to healthy children. Fortunately cases of tuberculosis which develop syphilis do well with '606', whereas a patient the subject of both diseases usually responds to mercury very badly, and both diseases are often aggravated by it. Diseases or conditions which have a tendency to haemorrhage should not be treated with '606', since arsenic causes dilatation of the small arteries and capillaries. Where inflammatory processes, other than syphilitic, are present at the time when the injection is given, the discharge may become haemorrhagic. This occurred in a case of otitis media reported by Wechselmann and also in a case of nephritis. A case of pulmonary tuberculosis, with

evidences of a cavity, had a severe haemoptysis forty-eight hours after an injection. In a hernia which had recently been operated on, the wound bled freely.

*Excretion of Arsenic.*—Fischer and Hoppe (*M. M. Woch.* 1910, No. 29) did some experimental work in connexion with the excretion of arsenic after an injection.

The following table indicates the excretion of the arsenic in the urine of a paralytic patient, who received 0.1 gramme (0.04 As) subcutaneously.

1 day	0.0033	gram.	Arsenic
2 "	0.0018	"	"
3 "	0.0022	"	"
4 "	0.0026	"	"
5 "	0.0034	"	"
6 "	0.0021	"	"
7 "	0.0018	"	"
8 "	trace	"	"
9 "	trace	"	"
10 "	Free from Arsenic		
Total	0.0172	gram.	Arsenic

In several cases of paralytics, who had received 0.3 gramme, the urine was carefully examined. In every case the excretion came to a close between the twelfth and the fourteenth day, but the total amount of arsenic excreted varied between 0.02 and 0.07 gramme.

Cases other than paralytics, whose renal function was

better, showed no trace of arsenic in the urine five days after the injection.

After an intravenous injection, the excretion was very much quicker. In paralytics, on the fourth day no arsenic was to be found, in other individuals the excretion was complete on the second and third days. Even after rectal injection of 'Salvarsan', arsenic was demonstrable in the urine, showing that some absorption had taken place, but obviously only very little, since the urine was free from arsenic the third day.

Atoxyl and arsacetin are very quickly and completely excreted in the urine, but arsenophenyglycin and Ehrlich-Hata's preparation are partly excreted in the faeces; for instance, in three days after an intramuscular injection of 0.3 gramme the faeces contained 0.0062 gramme of arsenic, and its presence could be demonstrated up to the tenth day. After an intravenous injection, it was found to be present up to the fifth or sixth day. In cases where a post-mortem examination was performed after an intramuscular injection, the presence of arsenic could be proved only in the muscle into which the injection had been made, but not in any of the internal viscera, proving the truth of Ehrlich's original statement, that the action of '606' was not organotropic. Even some weeks after the injection, arsenic has been found at the site of injec-



tion, clearly showing that an arsenic dépôt had been formed which had prevented the complete absorption.

Another action of 'Salvarsan' is to cause a leucocytosis, which may sometimes be as high as 30,000; the increase is chiefly in the neutrophile leucocytes, although occasionally there is an increase in the eosinophiles. The usual count is about 17,000, but the rise is always of short duration.

## CHAPTER V

### PRACTICAL USE

#### A. IN THE PRIMARY STAGE

IN no period of syphilis is 'Salvarsan' more strongly indicated than when the chancre is the sole symptom, since with a single injection the chances are that no further manifestations of the disease will appear. If the second injection is given within a week a cure is practically certain. The prognosis is best when the patient gives a negative Wassermann's reaction, because a positive reaction means that the infection has become generalized; although there may be complete absence of clinical signs.

Naturally, the sooner the sore is diagnosed the better the outlook, and the lymphatic glands being enlarged does not in any way militate against the cure, since they become enlarged and hard some time before the disease becomes generalized. The enlarged glands must be looked upon as a battle-field, where some time is being spent in a fight between the spirochaetes and the gland-cells; if the former are victorious then they spread all over the

body, and the time this takes varies enormously, which accounts for the delay often seen before secondaries make themselves manifest. In many cases, no doubt, the spirochaetes invade the blood-stream direct from the local lesion, then the rash, &c., quickly appear.

Very rarely the lymphatic glands are victorious, resulting in a complete destruction of the organisms and thus rendering the patient liable to a fresh infection. Recently I (J. McD.) have had two such cases, in which a year or more ago the patients had a single sore—an undoubted chancre at the corona, with inguinal adenitis but with no further symptoms; both patients developed within the last two months another chancre—not on the site of the original; from this spirochaetes were demonstrated and Wassermann's reaction was negative.

Both sores healed up within four days after an intravenous injection of 'Salvarsan' and the Wassermann's reaction has remained negative since.

Too much weight cannot be laid on the importance of diagnosing a syphilitic sore as soon as possible, and this can so easily be done by looking for the specific organism, either by means of the dark-ground illumination, or better still, the indian-ink method.

We should certainly not wait for secondaries to develop, or until the Wassermann's reaction has become positive.

I have now injected fourteen cases in the primary stage of syphilis, where inguinal adenitis was the only symptom besides the sore.

Not one of these cases has developed any further symptoms, and at the time of writing all give a negative Wassermann's reaction.

The first case is now eight months old, and one may say that if secondaries were to appear they would have done so before this.

Two of these cases gave a positive Wassermann's reaction one week after injection, which again became negative and was found to remain so about two weeks later.

In both these cases the injection was followed by a swelling of the inguinal glands, even to the size of bantams' eggs, a phenomenon which more often occurs in the early secondary stage, shortly after the rash has made its appearance.

The enlargement is probably due to, first, stimulation of the gland tissue of the organisms, and secondly, to their subsequent complete destruction, with liberation of endotoxins, which may also account for the positive Wassermann's reaction. The enlargement of the lymphatic glands and the occurrence of a positive Wassermann's reaction, always followed an intramuscular

and never an intravenous injection; the latter mode of administration, provided the maximum dose was used, would never stimulate the organisms, which might easily ensue from the slow absorption from an intramuscular injection. When giving '606' in this stage, the maximum dose should invariably be used, because destruction of the organisms by antitoxins, such as occurs in the later stages, takes no part owing to the paucity of organisms; therefore the action must be direct and vigorous.

Without going into the pro's and con's of removing the chancre when possible or of cauterizing it, instead of resorting to these measures, experience has shown that rubbing in mercurial ointment certainly expedites healing.

The local sore not infrequently remains indurated for several months after the injection; whether this has any significance or not has not yet been determined, but local applications during treatment prevent this to some extent.

That the 'therapia magna sterilisans' effect is obtained is proved beyond doubt, because six cases are already on record where the patient has come under observation with a fresh attack of syphilis, after having been cured of his first with '606'.

This was also shown experimentally to be the case in apes by Neisser, who was able to inoculate the animals for the second time, after having cured the first attack with a single injection.

This being the case, it behoves all to diagnose the sore as soon as possible and without delay give the patient a maximum intravenous injection and follow this by a second injection on the fifth day for safety.

*Case 1.* A man, aged 35, came up on July 26th with a sore on the penis, which he had had for three weeks; with the exception of enlargement of the inguinal glands there were no secondary symptoms.

Spirochaetes were found on examination, Wassermann's reaction was negative.

On July 27th the patient received an intramuscular injection of 0.45 gramme.

After twenty-four hours the chancre showed marked signs of healing, no spirochaetes were demonstrable, and four days later the sore had become completely covered with epithelium. Wassermann's reaction is still negative and no further symptoms have developed.

*Case 2.* A similar case to the above except that 0.5 gramme was given intravenously in the evening. The next morning the chancre began to show signs of healing, and no spirochaetes were found. (If films are made

before the spirochaetes have completely disappeared, they are found to be swollen, broken up, and the curves not so numerous, indistinct, and irregular.)

*Case 3.* A Japanese, aged 26 years, came to the Lock Hospital with seven chancres on his penis and inguinal adenitis. The patient received an injection of 0.5 gramme into his shoulder and was sent home. When he came up a week later the chancres had completely healed, but the glands were larger. Eight days after, not a trace remained of the initial lesions, and the glands had returned to their normal size. In several cases we have noticed this enlargement of the glands after the injection, but the increase in size is not permanent.

The following is a very interesting case, showing the influence '606' exerted upon a primary lesion which had become phagedaenic owing to secondary infection with streptococci.

*Case 4.* The patient, 35 years of age, developed a chancre in January, 1910. The sore became phagedaenic and when he was admitted to hospital in July the penis had almost disappeared, the urethra opening under it as a separate structure; there were also two offensive ulcers above the pubes. Owing to the extremely septic condition an injection of '606' was given to see if it would have any influence in checking its further course.

Seven days after the injection the condition ceased to spread, and fourteen days later the ulcers had cicatrized and the stump of the penis had completely healed.

Since the injection the patient has put on  $2\frac{1}{2}$  stones in weight, and is now heavier than he has ever been before. The patient has no difficulty in passing his water, and there has been no outbreak of anything since.

'Salvarsan' exerts no influence on soft sores and the gonorrhoea which not infrequently accompany syphilis.

It does not seem to matter at all in what locality the chancre is situated, with regard to its improvement under the treatment; but the glands which enlarge as a result of the infection, although they regain their normal size, remain somewhat harder than those on the opposite side. The dorsal lymphangitis of the penis and its analogous condition in the female, namely the lymphatic non-inflammatory oedema of the labia, quickly resolve under treatment.

Balanitis erosiva et gangraenosa, a condition usually mistaken for syphilis, but caused by Gram-positive, vibrio-shaped bacteria and Gram-negative spirochaetes, the same organisms which are characteristic of Plaut-Vincent's angina—a septic condition of the throat—improve under 'Salvarsan'.



## B. SECONDARY STAGE

Provided the dose is large enough the manifestations of the secondary stage disappear quickly or slowly according to the particular form present. If the dose is too small, the first result of the injection is to aggravate the lesions; this corresponds with the Jarisch-Herxheimer's sign, which so frequently occurs when a patient is first put on a course of mercurial inunctions. This phenomenon occurs more frequently after intramuscular than intravenous injection.

The macular syphilide disappears in a few days and has already faded considerably within twelve hours after an intravenous injection. The papular syphilide is practically the slowest of all the skin lesions to vanish, and it may be a matter of weeks before the big infiltrated lesions completely disappear. Curiously enough, recurrent papular syphilides, such as lichen syphiliticus and corymbose syphilides, disappear quickly.

The squamous syphilide or psoriasis syphilitica is also slow in becoming absorbed, but it must be remembered that the scaling is itself a sign of retrogression and invariably occurs on syphilitic papules, especially those which are densely infiltrated. The first sign we have of the disappearance of a papule is the

presence of scales in the centre. The orbicular seborrhoeic syphilide disappears in a few days.

Pustular and rupial syphilides improve rapidly, especially when the crusts are removed and the ulcers cleansed with antiseptic lotions.

*Leucoderma syphilitica* is absolutely uninfluenced by treatment.

The secondary lesions that disappear most rapidly are mucous membrane papules and condylomata, probably owing to the excellent blood supply of the part; often within a few hours of the injection the sore throat vanishes, and the mucous papules on the lips, cheeks and tongue have completely gone in a few days, and if there is a recurrence at this stage the mucous membrane of the mouth is usually first affected. Papules on the palms of the hands and soles of the feet are the most stubborn of all except when tertiary manifestations.

In syphilitic alopecia the hairs stop coming out within a day or two after the injection, and it is only a matter of time before the bare areas are covered again.

Nail affections certainly improve, but very slowly.

The pains in the joints and bones which patients not infrequently complain of, due to inflammatory changes of the synovial membrane or the periosteum, vanish in a few hours; likewise is this the case with the nocturnal

headaches, which probably depend upon hyperaemia of the meninges.

Rarely these headaches may be intense. We had a patient who could rest neither day nor night and who nearly went off his head with pain, and was continually begging his relations to throw cold water over him ; he lost his headaches completely three days after the injection ; this patient had had six intramuscular injections of grey oil, without receiving any benefit. So severe was the pain that on two occasions he threatened to commit suicide.

The following case shows the benefit of '606' in iritis occurring in the secondary stage of syphilis :—

*Case 4.* A man, aged 26 years, was infected middle of May, 1910, but owing to severe iritis of the right eye Dr. Huey sent him up to the Lock Hospital for admission. The patient had a chancre on the fraenum and corona glandis, polyadenitis, a papular rash on the trunk and thighs, nocturnal headaches, ulceration of the left tonsil, and iritis (the photophobia was too intense to allow of a proper examination). 0.45 gramme 'Salvarsan' was injected ; on the following day the patient was able to dispense with his eye-shield and within four days any one examining the eye for the first time would have diagnosed a slight conjunctivitis, the pupil being circular and reacting normally, and there were no synechiae ;

before ten days were over all symptoms had practically disappeared. At no time did the patient receive any local treatment. On August 25th, Wassermann's reaction was positive only with the barium prepared serum.

On January 19th, 1911. Patient still without symptoms, gave a negative Wassermann's reaction, and it would be impossible to say which eye had been affected. In a somewhat similar case where the iritis was complicated with scleritis, although the improvement was in the end remarkable, it was quite fourteen days before the signs of inflammation had disappeared.

*Case 5.* A man, aged 22 years, came for treatment at the end of August with a urethral chancre, general glandular enlargement, and a diffuse maculo-papular rash. An injection of 0.5 gramme 'Salvarsan' was given and within a week all signs of the disease had disappeared except for slight enlargement of the inguinal glands, which have since gone back to their original size. Ten days after the injection Wassermann's reaction was positive; in fact, the serum had the power of fixing more complement than it did before the injection was given. On September 29th, Wassermann's reaction was only just positive.

*Case 6.* The patient, a woman, aged 38 years, was admitted, under the care of Dr. P. Abraham, to have an

injection of '606'; of this she received 0.6 gramme on September 3rd, for lichen syphiliticus on the face and other parts of the body, which had persisted for fifteen months and in spite of continuous treatment had never improved. On the third day the patient had delirium tremens; she had never had an attack before, but she was an alcoholic and was under the influence of alcohol when admitted into the hospital. In a short time the patient recovered and the syphilitic lesions completely disappeared, leaving only slight pigmentation behind. Just as the patient was going to be discharged she developed erysipelas on the forehead from a case in the same ward; as a result of the rise of temperature her mental balance again became affected, but regained itself when the temperature fell. The patient has now quite recovered, is fully *compos mentis*, and there are no scars at the sites of the lesions. No recurrence had taken place up to the end of January, 1911.

The most striking results so far obtained in the secondary period have been in cases of malignant syphilis, of which the following is an excellent example.

*Case 7.* A man, aged 32 years, contracted syphilis in April, 1910, and as soon as the nature of the sore had been ascertained he was put under mercurial inunctions (*ung. hydr. oleatis*  $\bar{3}$  i. nocte) and took *hydr. c. cret. in-*

ternally. A rash then appeared, but the patient did well under treatment for two months, when stomatitis, ulceration of the pharynx, and gummata of the skin and scalp developed, which became worse the further mercury and iodides were pushed. The patient was so weak from dysphagia and anaemia, having lost two stones in two months, that he was admitted into the West London Hospital under the care of Dr. H. Pritchard, to whom we are indebted for notes of the case, and received an injection of '606'. Two days after the injection the throat was not so sore and on the third day there was no difficulty in swallowing, and the sores on the body showed marked signs of healing. Within a week the mouth and throat were normal, and within a fortnight every gumma had cicatrized, and the patient remarked that he had never felt better in his life. Five weeks after the injection Wassermann's reaction was negative, but towards the end of January a large gumma broke out on the back of the right thigh. *What then?*

Another case of malignant syphilis was essentially the same as the last, except that there was the additional complication of pulmonary tuberculosis. After an injection the patient's cough subsided, there were no more night sweats, and although the physical signs were still present they did not appear to be so obvious.

*Lesions of the Ears.*—To look upon a special form of otitis media as being due to syphilis is impossible, since examination of the pus would never reveal the spirochaetes, but that such cases can occur is undoubted, and the pathological lesion *present* to account for it would probably be mucous papules, which are almost certain to be present both in the external auditory meatus and in the pharynx in the region of the Eustachian tube. Beck reports (*M. M. Woch.* Nov. 3, 1911) an interesting case from Ehrmann's clinic of a patient who had a discharge from the middle ear, with condylomata of the meatal canal, which commenced when the secondary rash was at its height. There were also numerous mucous papules in the mouth.

As a result of an injection of 'Salvarsan', within nine days the discharge stopped, the patient recovered his hearing, the condylomata had disappeared and the perforation of the drum was absolutely dry.

Nerve affections of the auditory apparatus in the second stage of syphilis are undoubtedly rare, but they warrant our careful attention, owing to the fact that cases have been recorded of deafness occurring after the employment of '606'. Although one of us (McD.) was especially on the look-out for cases of nerve deafness in the secondary stage, within the last six months at

the Lock Hospital, he only came across two, in which there was a lesion of the cochlear nerve occurring within 2-3 months from the date of infection. In both cases one ear was first affected, then the other, and in neither case was there any involvement of the vestibular nerve.

One of the cases was treated with '606', with the result that the deafness completely disappeared, and three months have already elapsed without there being recurrence or aggravation of the symptoms; the other case remained uninfluenced.

The following two cases where there was involvement of the cochlear and vestibular apparatus reported by Finger are worthy of mention.

Both cases received an injection of '606' when the chancre was the only symptom present.

Three months elapsed since the injection without any secondaries having developed.

One patient seven weeks after the injection, the other nine weeks, had a sudden attack of giddiness and became somewhat deaf. The Wassermann's reaction in both cases was negative. Four weeks later one developed trouble of the facial and trigeminal nerve on the affected side, a polyneuritis cerebri meniereformis (Frankl-Hochwart), and at the same time as this polyneuritis appeared the blood test was positive.



A third case—where both the cochlear and vestibular apparatus became affected on one side early in the secondary stage, where no treatment had been adopted—cleared up on an injection of '606'; but five weeks later the patient complained of deafness in the other ear, felt giddy and could not walk straight, and vomited after every meal.

The patient on examination was found to have nystagmus; with eyes closed and feet together, he always fell to the right (the side affected). Wassermann's reaction was negative.

The affections of the auditory nerve which have been reported as ensuing from the use of '606', have nearly all occurred early in the secondary stage, which again corresponds to the most usual time for the lesion to make its appearance as a secondary syphilitic manifestation. We have had one case only where deafness followed '606', and oddly enough most of the cases reported have come from Vienna. The case was that of a patient who was given '606' (0.6 gramme) intramuscularly early in October 1910 for a secondary syphilitic rash. The rash disappeared all but a few papules, but a second injection could not be given as he had to go abroad.

Every symptom ultimately disappeared, but towards the end of December he developed symptoms of both

cochlear and vestibular affections on one side, with a swelling of one knee-joint. The Wassermann's reaction was positive, so the patient was put on mercurial treatment, with what result we have not as yet heard.

Urbantschitsch is of the opinion that the deafness after 'Salvarsan' is a true toxic neuritis, and that the drug has a neurotropic action.

He describes five cases in which the vestibular nerve was alone affected, giving rise to symptoms such as giddiness, nystagmus, and vomiting, which usually appear suddenly a few hours or days after the injection, to disappear, with one exception, in a few weeks.

In four cases the cochlear division was alone affected; this gave rise to deafness, which disappeared in a short time.

In two cases the auditory nerve itself was affected.

On the other hand Urbantschitsch has reported cases of deafness of some years' standing which have been cured by an injection.

Affections of the vestibular division he has also noticed after mercurial injections, especially of the soluble salts.

It is also a curious fact, and so far no explanation seems to be forthcoming, that in the cases which recur after 'Salvarsan', lesions of the optic nerve and auditory

nerve are never present ; affections of these nerves have been the only symptoms and have always occurred in those cases who were injected in the early secondary stage.

Few as the cases reported are, the benefit they obtain under mercurial treatment, as well as the improvement they show even when left alone, enable a good prognosis to be given.

Nearly all the cases described have been those in which a subcutaneous or an intramuscular injection was given, and the feeling is very much towards the view now, that the arsenic pent up in the tissues undergoes a chemical change, resulting in the compound formed being more toxic ; this may or may not be the case, but it is a fact that toxic symptoms are extremely rare after an intravenous injection, while their occurrence is more often seen after intramuscular and still more often after subcutaneous injections.

Both the lesions of the optic and auditory nerves are probably caused directly by the syphilitic toxins in a structure the resistance of which has been lowered by the continued action of 'Salvarsan'.

*Phlebitis* is a rare manifestation of syphilis, but from the clinical interest of the following case and the way it improved under '606' it should be recorded.

*Case 8.* S. W., aged 38, came up to the hospital on September 4th, 1909, with a typical secondary specific eruption.

Under treatment with injections of mercury salicylate the rash quickly disappeared.

On December 1st the patient complained of severe pain on the inner side of the thigh; there was nothing to see, but on palpation one could feel, along the course of the internal saphenous vein, about  $1\frac{1}{2}$  inches above the knee, a hard, tender, spindle-shaped swelling, roughly 1 inch in length; a diagnosis of syphilitic phlebitis was made. As time went on this swelling came nearer to the surface, the skin became red over it and very painful to the touch; finally it ulcerated, with the clinical picture of a gumma. Papules appeared along the course of the vein, both above and below the ulcer. 'Nodules' of phlebitis also appeared on both legs and ulcerated when they came to the surface.

The patient had bad varicose veins. 'Salvarsan' was given in August, 1910, with the result that all the ulcers have healed; no fresh ones have appeared, a result which was not obtained even after twenty-seven mercurial injections; pain has completely disappeared and the patient feels a new woman and is free from any symptoms at the time of writing.

*Papulo-pustular Syphilides.*—*Case 9.* W. G. was infected in April 1910 and when the rash appeared the patient took pills and continued them for three months; the rash got worse and when the patient came up to the Lock Hospital his face was covered with papulo-pustular lesions, both tonsils were ulcerated, there were mucous patches in the mouth and on the tongue, there was also a gumma on the right thigh, and the primary chancre had not healed.

Early in September patient received an injection of '606', and within a fortnight all the lesions had disappeared.

The buccal lesions had vanished within a week; we have already noted that in all cases they are the first symptoms to disappear, probably owing to the free blood supply of mucous membranes. This patient is still free from recurrence and has gained two stones in weight.

*Early Meningitis.*—*Case 10.* H. H. Infected in July 1910. The patient came up to the Lock Hospital with a large chancre, ulceration of both tonsils and mucous patches inside the mouth, there was also a rash over the trunk.

The rash was a peculiar one, of the small papular type, a type very resistant to ordinary syphilitic treatment;

the papules appeared in the centre of the macules. The symptom the patient most complained of was excruciating headache, which was not improved by five injections of grey oil. At last the headaches became so severe that the patient often begged his relatives to throw cold water over his head. The fourth day after an injection of '606' the headache disappeared, three days later the throat was normal and the rash fading. No recurrence has yet appeared.

#### C. TERTIARY STAGE

Clinically speaking, no syphilitic lesion seems to respond so quickly to '606' as a cutaneous gumma, and although of course one sees plenty of instances of a miraculous 'cure' under potassium iodide, these cases heal as a rule up to a certain point only and advance no further; a large number are quite uninfluenced, while recurrences are almost invariable, even when the treatment is supplemented with mercury.

Under 'Salvarsan' it is the exception for a gumma not to respond to treatment. We have had cases where the ulceration had remained for four weeks unaltered, and yet the patient gave a negative Wassermann's reaction.

The explanation probably depends upon two factors: (a) the presence of fibrous tissue, (b) secondary infection.

One remarkable case of an ulcer on the thigh only began to heal after four weeks, when potassium iodide was given—a drug which has no influence on Wassermann's reaction and therefore cannot be regarded as a specific for syphilis. Another case healed the moment hydrogen peroxide was used to overcome the secondary coccal infection.

In view of these two cases it seems advisable to supplement the 'Salvarsan' treatment with iodides internally and local antiseptics externally. Two cases of gummatous ulceration were undoubtedly made worse with '606', but we have not seen this happen since employing the intravenous method; both cases healed under mercury and iodide. The most striking thing about an ulcer which has healed under '606' is the character of the scar left; it is more superficial, its edges are not so pigmented, it is thin, soft, and easily wrinkled, therefore not adherent to the subjacent structures. This is a most important point, since ulcers over bone, especially ulcers over the tibia, when they heal up under ordinary treatment, leave the skin so firmly bound down to the bone that the slightest injury may lead to further extensive ulceration.

In such a case treated with '606', after the ulcer had healed, it was not adherent to the bone.

The skin under ordinary circumstances heals slower when bone is directly subjacent to it than where it covers soft parts only, therefore an ulcer so situated may take some time before it is completely closed; the formation of scales at the margin should be avoided, and the continuous application of some emollient to both edges and surface, with an occasional touch of lunar caustic, will often tend to promote healing. When gummatous ulceration is in the neighbourhood of joints, contraction is often an undesirable result of healing; in such cases '606' is strongly indicated, because practically little or no contraction ensues, owing to the suppleness of the scar.

A patient who was unable to completely extend her knee and walk properly, had no difficulty some days after an intravenous injection of 'Salvarsan' had been given.

The most striking effect of '606' in tertiary cases is the improvement it brings about in the general condition.

Several patients who had been unable to earn their livelihood, purely from weakness and general malaise, have returned, and are doing more work than they have been accustomed to for years—feeling, as more than one patient has expressed it—ten years younger.

The improvement in the 'well-being' of the patient is



extraordinary and is usually the first sign which he draws your attention to.

Colour returns to the face, the patient sleeps and eats well, feels better in every way, takes a greater interest in life, and gradually puts on weight.

Without there being any gross nervous lesion allowing of a diagnosis, it is not uncommon to find that patients who are suffering from—let us say tertiary cutaneous manifestations, complain of headaches, inability of applying mental power, perhaps also slight feelings of giddiness, symptoms to which one's attention is not usually drawn, but the disappearance of which strike the patient most.

Another very common group of subjective symptoms are precordial pain and 'heaviness', palpitations, irregularity of the heart-beat—a pseudo-angina. These symptoms are most likely dependent upon an insidious and early general arterio-sclerosis.

So frequently have we observed these symptoms, that they are proving of great value in diagnosis, where there are no objective symptoms to guide one, and the history of syphilis is of very little value.

*Cutaneous Gummata.*—*Case 11.* A housewife, aged 42 years, was admitted with gummatous ulceration and elephantiasis of the left leg, the condition having been

gradually getting worse since 1908. Syphilis was contracted in 1904. For this case I am indebted to Dr. H. G. Adamson. The affected leg was red and swollen from below the knee to the ankle-joint, there were several scars from old gummata, ten recent septic ulcers and a few abscesses filled with pus, which were just on the point of breaking down. The circumference in the thickest part was 12 inches. The ankle-joint was swollen and too painful to move, the patient could not bear pressure on the leg, and the pain was very acute when standing on it. The patient's general condition was not good, she was anaemic, felt ill, and had no appetite—in fact, looked as if she was under the influence of septic poisoning. On August 18th the patient received in the glutei 0·4 gramme of 'Salvarsan' in an emulsion; the next night the temperature rose to 101·4° F., and the pulse-rate increased to 104; two days later both the temperature and pulse were normal. There was a slight trace of albumen after the injection. On the 21st the circumference of the leg had diminished by half an inch; the ulcers were quite clean and commencing to granulate, and the patient could move the ankle-joint. No albumen was present. On the 23rd the ulcers had healed. The leg measured 11 inches. The patient got up, and was

able to put the foot to the ground without it causing any pain. On the 26th the leg measured  $10\frac{3}{4}$  inches. The skin had regained its normal colour, there was no pain, the abscesses referred to above had aborted without discharging their pus, and the patient declared that she had never felt so well in her life.

Beyond the great improvement in the general condition the most important point in this case was the way in which the septic material, pus, &c., had disappeared without any supplementary treatment. On September 15th, Wassermann's reaction was negative.

The future course could not be followed, as the patient was lost sight of.

*Serpiginous Syphilides.*—Case 12. W. J. C. Infected, May 1907, and was treated internally with mercury for two years. In October 1909, serpiginous syphilides appeared on the head, scrotum, and arms, which improved under eleven injections of grey oil, but did not vanish under further treatment with internal administration of mercuric chloride and potassium iodide. As the patient had chronic superficial glossitis, which did not improve, an injection of '606' was given in September 1910. Within a week the skin lesions had completely vanished and the tongue was markedly improved. Curiously enough, '606' has very much

increased the acne on the back; the appearance of acne pustules has not uncommonly followed the intramuscular injections.

No recurrence has so far appeared.

*Ulceration of Nose with Bone Necrosis. — Case 13.*  
F. M. Infected seven years ago. Two years ago the throat became sore, and it was on this account that she came under Dr. H. J. Davis at the West London Hospital.

The patient was found to have extensive ulceration of the mucous membrane of the nose, mouth, palate, pharynx, and larynx; necrosis of the vomer, ethmoid, both maxillae and nasal bones, and a gumma on the bridge of the nose. The ozoena was very marked.

On October 25th the patient received an injection of '606'; within a week the difficulty in swallowing had almost left her, the voice was better, and the ulcers had healed, except for the one on the bridge of the nose. Within a fortnight after, some bone had come away, the gumma healed, and the ozoena was much less.

The improvement has been maintained.

*Gummatous Ulceration of Throat. — Case 14.* The patient was a housewife, aged 23 years. The date of infection was not quite clear, but there had been four pregnancies with evidence of syphilis. She came

for treatment a year ago with a sore throat and difficulty in speaking and swallowing solids. She was under the care of Dr. H. J. Davis, who very kindly asked me to give her an injection. The diagnosis of syphilis was unmistakable, there was ulceration of the pharynx, the larynx, and the posterior nares ; the uvula and part of the soft palate had gone. For one year the patient was treated with anti-syphilitic remedies without avail ; her general condition became so bad, and the ulceration tended to advance, that she received as an out-patient 0.5 gramme in an emulsion of 6 cubic centimetres, which was injected under the left trapezius. For three or four days the patient was extremely ill, had high fever, and sweated profusely. The further course will be best explained by a letter received seven days later :—

For twelve long months I could not eat anything solid, and even found it difficult to swallow liquids. But a few hours after your injection I found relief, much to my delight. Although it is only a week since you did it I feel a new woman and can eat almost anything.

The improvement in her general condition was really remarkable, her speech was no longer a whisper, and the ulceration had completely healed eleven days after the injection. There has been no recurrence.

Where there is already stenosis of the larynx, which

has necessitated tracheotomy, '606' has proved unavailing.

*Gummatous Ulceration of the Larynx.*—Case 15. M. N. Woman, aged 22, primary lesion on the left tonsil about October 1909. In December there was enlargement of the cervical glands, some of which broke down and suppurated. The suppuration extended into the cellular tissues of the neck, so that a form of angina appeared which hindered the patient from swallowing; there was also extensive ulceration of the pharynx. The patient lost flesh rapidly and was unable to take mercury. Treatment with soamin resulted in a marked improvement at first, but the lesions quickly recurred and did not respond to continued treatment with this drug. In all thirty-six injections were given, owing to signs of optic neuritis appearing in the left eye; the drug was then discontinued. Inunctions of mercury and iodide of potassium were tried, but the patient became still more emaciated, the ulceration spread up to the naso-pharynx and down to the larynx, and the pain was intense on swallowing. Meanwhile, gummata appeared on the thighs and buttocks, arms and face; an ulcer also appeared on the nasal septum and symmetrical effusion occurred in both wrist joints. By September 1910, the patient had become almost aphonic,

and the ulceration of the pharynx had spread. There was also great difficulty in breathing, so that a tracheotomy appeared necessary. She was given an injection of '606' on September 29th. On October 5th the temperature rose to 103°F.; next morning it was normal and she felt very much better. A week later she was able to get about, the pain had disappeared, she was eating well and with a good appetite. Dr. Penny saw her on October 22nd and writes the following: 'Patient was extremely well, the ulceration has completely healed; patient is gaining steadily in weight and admitted to have never felt better in her life. She still has blurred vision in the left eye, but states that she could see with it much better than before. The voice is natural and the patient is once more resuming her daily routine.'—This improvement has been maintained.

*Glossitis.* A late syphilitic lesion—and, perhaps one might add, the most obstinate to treat, and the occurrence of which must always be looked upon with gravity, owing to it being a forerunner of carcinoma—is chronic superficial glossitis.

In England the condition is extraordinarily prevalent; in countries where mercury is not administered per os it is correspondingly rare; the frequency of carcinoma of the tongue bears the same relation.

Undoubtedly there are other factors at work, but mercury in the form of pills and medicine undoubtedly increases all intrabuccal lesions; patients at the Lock Hospital have frequently asked for injections, owing to the fact that the tongue and mouth get sore the moment they take pills.

If patients are examined who take pills regularly oedema of the tongue will very frequently be observed; this in time leads to atrophy of the papillae, a smooth mucous membrane, which becomes covered with white patches and is studded with fissures—in fact chronic superficial glossitis.

When once this condition has set in, mercury even in the form of inunctions and injections seldom causes improvement, and the same may be said of the local applications of bichloride of mercury and chromic acid, and how often do these cases end in carcinoma!

Mercury given internally injures the tongue; an injured organ has its resistance lowered and thereby becomes an easier prey to any parasite. Almost without exception these cases of chronic superficial glossitis give a positive Wassermann's reaction, and the tongue lesion may as often as not be the only clinical symptom of syphilis; these patients are then actively syphilitic. Where there is already scar tissue '606' cannot work wonders, but



when we had injected several tongue cases, the results produced by this treatment far outreached our expectation.

Here is the case of a man who, for two years after the condition had been diagnosed, came up regularly to hospital for treatment without any benefit.

*Case 16.* M. B. Infected 1902, and has taken mercury internally for eighteen months. Three years later the first recurrence came in the form of a papular rash, which disappeared under six weeks' oral administration of mercury. In January, 1908, the patient came to St. Bartholomew's Hospital, under the care of Mr. Bailey, complaining of a sore tongue, which caused pain on swallowing; the condition had been getting worse since the middle of 1907. The patient had had chronic superficial glossitis. Since January, 1908, till the end of August, 1910, the patient was treated with hydr. perchlor.  $\bar{c}$  pot. iod. and local applications of chromic acid without producing any great improvement.

An injection of '606' was given and patient said within a week his tongue felt as well as it used to be, and so it remains up to the present.

*Case 17.* A soldier was injected whose tongue was twice the normal size, deeply fissured and ulcerated, his condition having gradually got worse during the last

five years. As in most of these cases of chronic glossitis, mercury had little or no influence upon it. One week after the injection the tongue had nearly regained its normal size, there was no ulceration, and the fissures were not nearly so deep, and the patient says that he has had more ease than he has had for some years.

*Case 18.* Another patient with chronic superficial glossitis and two swellings on the tongue, which might have been either gummata or malignant disease, was given an injection as he was most anxious not to lose the anterior two-thirds of his tongue. The lumps completely disappeared and he said that he felt very much better.

*Lymphatic Enlargement.*—The following is an interesting case of recurring enlargement of the lymphatic glands in late syphilis.

*Case 19.* A patient developed syphilis some years ago and had the usual symptoms, for which he was treated thoroughly. The symptoms never completely disappeared and a rash would appear periodically and there would also be attacks of malaise and great enlargement of the glands in the neck (size of a hen's egg). Potassium iodide in large doses caused temporary improvement. I gave an injection of '606', and a fortnight later received the following letter from the patient, who had suffered very considerable pain:—

I can hardly express my delight in being able to inform you that I am beginning to feel my old self again. Every day I can note an improvement in the feeling of well-being. The rash has gone and the glands are going; those at the angle of the jaw are still a little enlarged but seem to be getting smaller each day; those in the neck are reduced to the size of small peas and shot, and there is now no pain or tenderness in them. The awful depression and shooting pains are relieved, and once more I am beginning to feel there is some pleasure in being alive.

*Auditory Symptoms.*—Menière's symptom complex, deafness, giddiness, and tinnitus, although an uncommon sequence of syphilis, is met with occasionally in the tertiary stage and some of the cases reported have improved under '606', but as this has only been in the minority of the cases, too good a prognosis should not be given.

*Joint Affections.*—Joint affections in syphilis are not so common as to refrain us from reporting a most interesting case shown in the Gesellschaft der Aerzte in Vienna by Schlesinger.

The patient suffered from periodic acute polyarticular arthritis which had never had any tendency to supuration.

Each exacerbation was ushered in with a high temperature, swelling, and pain in several joints, which had resisted thorough mercury and iodide treatment. The

recurrences were so frequent that the patient's general condition was becoming markedly affected; in consequence '606' was prescribed during an acute attack. Within a few hours the temperature fell, the swelling and pain disappeared, and a few days later the patient was able to walk about.

Owing to Wassermann's reaction remaining positive another injection was given, which had the desired effect in producing a negative reaction, and the patient is still free from any recurrence.

*Pulmonary Syphilis.*—The following case, reported by Lesser, of pulmonary syphilis is worthy of mention, owing to the rarity of the condition.

The infection was of eight years' standing, and the patient was admitted into the hospital with a temperature of 103° F. and 6% albumen in the urine. The attacks of coughing which caused the patient to seek advice began to disappear within twenty-four hours after the injection; on the fourth day the cough had left the patient and there was only 0.5% albumen in the urine. The physical signs of bronchitis had completely cleared up within ten days.

This case has a double interest, from the way the albumen disappeared, thus showing the beneficial action of 'Salvarsan' on syphilitic nephritis.

## CHAPTER VI

### SYPHILIS OF THE NERVOUS SYSTEM

WHERE nerve fibres in the brain and spinal cord have already been destroyed, no regeneration is possible, therefore no benefit can be expected to follow treatment with 'Salvarsan.'

Clinically, at any rate in the early stages of nerve affections, it is impossible to say whether there is degeneration, or whether the symptoms of degeneration may not be caused by pressure, as from meningitis or some perivascular syphilitic infiltration, or to the direct action of a syphilitic tonin.

When pressure is the cause much may be expected from an injection, but unfortunately there are no means of distinguishing.

Supposing the lesion to be even a chronic one, or one of primary nerve degeneration, an injection, without causing regeneration, may stop the progress of the condition, and arsenic, although it is capable of causing neuritis, has an undoubtedly tonic effect on nerve tissue.

Provided everything else is in order and the lesion

*Improvement  
manifest lesions  
propagation  
new case to  
open. Corroborated:  
syphilis diagnosed.*

X

is not of too long standing, with marked degeneration, the patient should be given the benefit of the doubt. Although the arsenic in '606' is roughly forty times the toxic dose of arsenious acid, neuritis following its employment is practically unknown.

Cases of peripheral neuritis have been cited as occurring after an intramuscular injection, in the limb injected, but these cases are far more likely to be dependent upon nerve implication in the necrosis at the seat of injection than to a pure toxic neuritis.

*Locomotor Ataxy.*—That the pains in tabes are sometimes made worse is only too true; this occurred in two of our cases out of a total of nineteen, and both cases were unfortunately medical men, who had had the trouble for ten and more years, with an unusual excess of lightning pains.

In both cases an intramuscular injection was given, the pain of which would undoubtedly tend to aggravate the condition, but whether an intravenous injection would be capable of doing the same, remains yet to be seen.

In five cases the pains vanished after the injection and so far have not recurred.

The other twelve remained *in statu quo*.

The five cases of tabes which improved included three where pain was the chief symptom complained of;

the ataxia and other signs were present but not, so far as the patient was concerned, troublesome.

Two cases recovered their knee-jerks and in these two the Argyll-Robertson pupil disappeared; one of these was a case where the ataxia was very slight and this also vanished; whether there will be a recurrence or not, it is impossible to say, as barely four months have elapsed since the injection was given.

The other case is given below in detail, but unfortunately after a four-months interval the bladder symptoms are beginning to return, and the patient has once wetted his bed.

*Case 20.* The patient, aged 36 years, developed syphilis ten years ago, for which he was treated with mercury internally for three years. Owing to impotence and loss of control over the bladder and rectum of four years' duration he consulted Mr. Arthur Shillitoe, who found that he had unequal pupils (the inequality being due to an old iritis of the right eye) which did not react to light, and there were no knee-jerks. As he gave a positive Wassermann's reaction Mr. Shillitoe very kindly asked me to give him an injection of '606'. Within a week after the injection the control over the rectum had been regained, and the inability of starting the act of micturition had disappeared. The knee-

jerks were slight, the pupils reacted sluggishly to light, and the very slight ataxia which was present before had now disappeared. The patient was seen again on October 12th : the notes state that the vision in the left eye is greatly improved and that glasses can be dispensed with. Erections returned ; he could do exercises and walk without getting tired. There was no indigestion nor precordial pain. The knee-jerks have now returned and the pupils react to light. Wassermann's reaction was negative.

In January, 1911, the bladder symptoms began to return, and quite lately on more than one occasion the patient has had nocturnal enuresis. At the time of the bladder recurrence the pupils reacted better to light than ever before, and the knee-jerks were brisker. Wassermann's reaction is now positive, so an intravenous injection was given, with the result that the symptoms have disappeared and the patient reports that he has been dancing !

The one other case which improved was one in which a perforating ulcer of the big toe was the main complication ; the ulcer healed up slowly under an injection of ' 606 '.

There have been many cases reported where the ataxia has disappeared and where perforating ulcers



have healed, but most of these cases have recurred after a period of a few months, many to be again improved by a second injection.

Undoubtedly the intravenous route is the one to choose, and—(a rule which may stand for all nervous cases)—only half a dose should be given, and if there is any improvement, which will be noticed within a week, either a full injection may be given, or the usual <sup>?</sup> time allowed to elapse and a re-injection given only if there is a positive Wassermann's reaction.

So far as tabes is concerned, the ratio of improvement which may be expected to follow provided that Wassermann's reaction is positive or negative cannot at present be determined.

If any improvement has taken place after mercury, a better prognosis can be given and the patient advised to have an injection ; but on the whole there is practically nothing which guides one in giving a prognosis, so, under the circumstances, an injection should never be strongly urged, and the possibility of an aggravation of symptoms should be mentioned to the patient.

Optic neuritis in tabes verging on atrophy has never been improved, and such cases should not be treated.

Bulbar symptoms in tabes absolutely negative an

injection, as the risk of death from respiratory failure is very great.

*General Paralysis.*—What influence has '606' on general paralysis of the insane?

When the symptoms are so far advanced as to make a diagnosis obvious, the case is too late; on the other hand, when the symptoms suggest the diagnosis, improvement is often remarkable.

Such a case as the following is illustrative of this point:—

*Case 21.* A man, aged 45, who had been infected fifteen years ago, had for the last year complained of headaches, inability to work, which was made still more difficult owing to loss of memory and slow cerebration; further, the patient was very irritable, and had periodic attacks of diplopia and facial paralysis. Mercury in no form benefited him. Since an injection of 'Salvarsan' which was given four months ago, the patient has been able to return to work and transact business as usual, his family admit that he is a changed man, and the parietic symptoms have completely vanished.

When dementia has once set in, an injection is not only valueless, but dangerous.

The following early case of G.P.I. reported by Marcus (*M. M. Woch.* 2, 1911, 76) is worthy of note. The

patient had fibrillary tremors of the lips and lower jaw when he spoke, the facial expression was fixed, the pupils were unequal, and the knee-jerks were increased. The speech was in monotone, there was literal atony and amnesic aphasia. The writing was hardly legible. The memory was failing.

A few days after the injection the speech had remarkably improved. Within three weeks all the tremors had vanished and the aphasia was no longer noticeable; the improvement was so marked in every way that he was able to undertake his duties again as an engineer.

*Ophthalmoplegia.*—In cases of ophthalmoplegia externa and interna, which are probably always syphilitic in origin, '606' should always be given, and the improvement varies, according to how much nerve-tissue is destroyed; therefore, although complete recovery may result, prognosis should be reserved for a week after the injection. If the recovery is going to be complete, the diplopia will have disappeared and the pupil will react to light; if the diplopia remains, although there may be marked improvement, it points to nerve degeneration, and a second injection is useless.

*Meningitis.*—In no form of nerve syphilis is the improvement more marked than in gummatous meningitis, the basal form of which is by no means uncommon.

*Case 22.* S. S., female, aged 47, married. Date of infection uncertain but probably twenty-four years ago, when after her second marriage she had five consecutive miscarriages. Nervous symptoms began in 1901, when the left arm and leg were noticed to drag, and there was giddiness, also disturbance of vision; in the patient's words, 'things went suddenly black.' She was admitted into the Great Northern Hospital for seven weeks; four years later she complained of partial paralysis of the left arm and leg, cramps in both legs, double vision, and loss of memory for minor events. This time she was admitted into King's College Hospital for sixteen weeks and left much better. A year later she was re-admitted for eleven weeks, because she had occasional attacks of unconsciousness, during which she squinted. During the past year there were further attacks of faintness and giddiness, which have been very much worse for the past three months; three weeks ago she dropped down unconscious in the street, since then she has complained of continual dizziness and headache, and a marked tendency to fall to the right side when walking. On admission, patient was found to have double optic neuritis, the right pupil was smaller than the left, but both reacted to light and accommodation. There was paralysis of both external recti, paresis of the lower

half of the left side of the face and deafness on the right side. The patient could not hear a watch held within an inch of the ear, nor when it was placed on the temporal bone ; the tongue was protruded to the right, the other cranial nerves were normal.

*Arms.* Muscular power and sensation good and equal, tendon reflexes increased, there was inco-ordination.

*Lower limbs.* Muscular power and sensation good and equal on both sides. Knee-jerks present and equal, no clonus, plantars brisk and flexor, co-ordination impaired ; other systems normal.

On October 24th patient had an injection of '606'. On October 26th the paralysis of the external recti had completely disappeared, and there was less headache ; inco-ordination was less, the hearing on the right side had improved to the extent of hearing a watch held within one inch of the ear. The paresis of the lower half of the left half of the face and the protrusion of the tongue to the left side of the face were still present ; by the 8th of November the facial paralysis had almost disappeared, the tongue was protruded in the middle line, and when the patient walked about the ward it was noticed that there was no tendency to fall to either side ; when she left on November 16th one would not have known that there had been anything the matter with her.

Mr. Etherington Smith kindly examined the case on January 24th, and sends the following note :—

Her improvement has been maintained, and she has now no symptoms at all; the optic neuritis has gone, leaving, of course, post-neuritic changes, and the vessels are markedly degenerate. She has slight facial weakness on the left side, but all the other paralyses are gone. The left pupil reacts fairly well, the right is small and does not, which is probably due to old posterior synechiae. She now does all her ordinary work.

The next case is one of extreme interest, as the patient was suffering from syphilitic meningitis and had double optic neuritis; the case was very kindly sent by Mr. A. W. Hare of Newquay, and for the notes of the condition before injection we are indebted to Dr. F. E. Batten, who kindly saw the case.

*Case 23.* The patient, a man, aged 40 years, developed syphilis eleven years ago, but had no secondaries, and only took mercury internally for six months. In 1908 gummata developed in the skin and some of the cranial nerves became involved. Some improvement was obtained after several injections of soamin and potassium iodide internally. In January 1910 the patient had diplopia and was much troubled with headache and vomiting. In March he first noticed weakness of the

right side of the face and was treated with mercury and iodide, with only temporary improvement. When seen on September 12th the condition was as follows: 'There is an internal strabismus with diplopia due to paralysis of the right external rectus and weakness of the left external rectus. The movements of the eye dependent on the third nerve are good. The pupils react well and the vision is good. There is some swelling of both optic disks. There is paralysis of the right side of the face and both motor and sensory portions of the right fifth nerve are involved. There is deafness on the right side, but the tuning-fork is audible when placed in contact with the mastoid. There is some unsteadiness in gait, but this would seem to be dependent on the diplopia. Romberg's sign is absent and there is no weakness of the limbs. The knee-jerks are active and equal; the plantar jerks could not be obtained, and the abdominal were difficult to obtain, but were equal. The articulation is somewhat nasal, but no weakness of the palate can be detected, although there is some difficulty in deglutition. The movements of the tongue are good. It seems probable that there is a circumscribed syphilitic meningitis at the base of the brain involving the right fifth, sixth, and seventh cranial nerves, and probably also the right eighth and ninth and the left sixth to a lesser

degree. There is no evidence of any affection of the pyramidal tracts.' An injection of 0.5 gramme of '606' was given. The patient was very ill for a few days, but on the third day the temperature returned to normal and he declared that his hearing had improved. Within a week he could walk without a stick, all the affected nerves had regained some of their power, the improvement in the sixth and seventh being very striking. The injection was given on September 12th and on September 28th the following letter was received from Mr. Hare :—

Optic neuritis is still present, but the patient says his visual power has improved daily, especially during the last four or five days. The third, fourth, fifth, sixth, and seventh nerves all show signs of improvement in function, but I cannot find any increase of hearing on the right side, though the patient says there is. Swallowing, respiration, and heart's action all improved. To-day the heart beat was perfectly regular at 78, whereas I have often found marked irregularity both as regards rate and strength. I am very glad you have so successfully carried out the treatment and I must congratulate you on its probable successful issue, as I think there could hardly be a worse case than this to test the treatment upon.

Another letter, dated October 12th, states that the optic neuritis has almost gone, the eyesight greatly improved, and that the patient can walk 100 yards



without staggering. The hearing has also greatly improved.

In this last case, although there was no return of symptoms, the patient had an idea that a further injection would possibly aid in completely getting rid of the symptoms; consequently a second was given, with dire results. Soon after the injection the patient became cyanosed and had great difficulty in breathing; this as well as another similar attack passed off, but they were followed on the third day by another, which proved fatal.

This case is exceedingly instructive, because in all intracranial affections this difficulty in breathing is not uncommon, especially after an intramuscular injection; in fact we have not seen it occur after the intravenous method; whether this is due to the advantage of the latter method, or to the fact that in all nervous cases only half a dose is used, cannot definitely be decided; the employment of the small dose, which can always be repeated when considered necessary, certainly minimizes the danger.

In these late cases, where the disease is local, the danger of increasing the lesion due to stimulation of the organisms does not arise, since this phenomenon only occurs in the early stages of syphilis, when the

organisms have got their own way, and are particularly brisk.

The dyspnoea is undoubtedly due to a further raising of the intracranial pressure, caused by reactionary inflammation around the diseased focus, which has the effect of inhibiting the respiratory centre, which may and does lead to complete failure of action.

Should such a thing occur, either a lumbar puncture should be resorted to, or the skull opened.

*Thrombosis.*—Cases which offer more difficulty than any others are those of hemiplegia from syphilitic thrombosis; because there is not only the risk of the reactionary inflammation raising the intracranial pressure, but there is also the danger of haemorrhage setting in, from softening of the thrombus, and rupturing of the already damaged vessel walls, which must resist the rise of blood-pressure caused by the injection, plus the tendency to haemorrhage which occurs with arsenic.

When the case is recent, '606' should not be given, and in such cases the patient should undergo a course of inunctions, after which the improvement is often wonderful; only when mercury seems to have no further action should '606' be advised and then only half a dose should be given, which can be repeated again if necessary.

*Case 24.* G. R., man, aged 33, had a chancre in 1902, but no symptoms till August 1910, when he had a paralytic seizure in bed, which woke him, when he felt as if he was being torn in pieces and found he could not move his right arm nor his right leg, the sensation being also completely blurred in the parts affected.

He was first seen at the beginning of December 1910, with a view to doing a Wassermann's reaction, which was positive.

Examination showed that his voice was weak, he spoke in a monotone and slowly, the face was expressionless, with signs of right-sided paralysis.

Movements in the right arm and leg were good and the patient was able to write and walk well. The reflexes were increased and there were tremors on several occasions; '606' was begged for, but refused, because, although the improvement was remarkable, it had of late remained stationary; finally, at the patient's own risk, I gave 0.25 gramme of 'Salvarsan' intravenously.

No untoward symptoms followed the injection, the patient was up and about within a week, feeling ever so much better.

The facial paralysis was decidedly less, the grip in the right hand was stronger, the gait was better, and the tremors, which so troubled the patient before, were

now only slight; the fingers had completely recovered their sense of touch and only the thumb remained *in statu quo*.

So great and unexpected was the improvement that the patient is returning to the Gold Coast to take up his duties.

## CHAPTER VII

### CONGENITAL SYPHILIS

GLÜCK reports a case of a woman aborting after an injection, but whether the abortion was *post hoc* or *propter hoc* cannot be said; my own experience has led me to believe that the injection will not produce abortion and it is safe to give it in any month of pregnancy. What influence such an injection is going to have on the child must be a question reserved for a future answer, because a syphilitic mother may give birth to a healthy child irrespective of treatment, therefore it is impossible to say whether the child is non-syphilitic because of the injection or for other reasons. Where the mother contracts syphilis while pregnant, it stands to reason, if the infection is diagnosed before secondaries appear, an injection would prevent the child from becoming infected.

We injected a woman <sup>\*</sup> 6½ months pregnant with five chancres on the labia, from which *spirochaete pallida* was obtained. She said she had only had the sores for two weeks; there were no secondary symptoms at all.

*dose recommended is 1/4 gm.*

An intramuscular injection of 0.6 gramme quickly healed the sores up, the patient went to full time and was delivered of a healthy child.

When the patient has already reached the secondary stage, she should certainly receive an injection, but there are not yet sufficient cases on record to allow any statements to be made as to the condition in which the child will be born; this also applies to women who are syphilitic and who have borne syphilitic children, although they themselves show no clinical signs of the disease.

If a mother gives birth to an infant which presents syphilitic manifestations the child should not be injected, as the risk of death is too great.

Wechselmann injected five cases of specific pemphigus neonatorum, the ordinary sequence of which is death; two recovered, but the other three died some days following the injection, when post-mortem examination revealed visceral disease.

Wechselmann ascribes the death to be due to the dissolution of the spirochaetes, resulting in an enormous dose of endotoxins, which poison a marasmic and weakly infant.

A child who is born with symptoms should be suckled by its mother, when she has received an injection; the

effect of this is to heal the child's lesions, owing to the antitoxin which results from the death of the mother's spirochaetes, which is conveyed to the child through the milk.

That the curative effect is due to the antitoxin and not to arsenic, is proved by none of the metal being found in the milk; another proof we have of the antitoxic action of '606' is that the symptoms of an adult are markedly improved by an injection of the serum from a syphilitic who has been treated with '606', in whom no arsenic is found either in the urine or faeces.

However much improved the symptoms may be by this procedure, a cure cannot be said to have been produced, and it is always becomes necessary later, when the child's condition is better, to give an intramuscular injection.

The dose should range between 0.004 and 0.005 gramme per pound weight of the child, and an intramuscular injection is best given in the glutei in solution.

In children about three or more years old an intramuscular injection must be given, owing to the difficulty of getting into a vein; the immediate reaction from an injection in a child is not severe, but a toxic dermatitis accompanied by a second rise of temperature, occurring

usually a few days later, is on the whole more commonly met with than in adults, while, on the other hand, the pain of the injection is generally very much less.

When the child reaches the age of six or seven an intravenous injection can be given, but it may prove a difficult task and necessitate cutting down upon a vein.

The following is a case reported by Taege, which demonstrates well the antitoxic action of 'Salvarsan'.

A girl, aged 19 years, with condylomata, from which spirochaetes were obtained, and who gave a positive Wassermann's reaction, gave birth on July 4th to a marasmic child, which weighed  $4\frac{1}{4}$  lb. On July 13th pemphigus bullae on the soles of the feet and paronychia of the fingers developed; the following day the mother was injected with 0.3 gramme of '606'. On the third day the mother's lesions showed improvement, and no spirochaetes were to be found in the condylomata.

The child was suckled straight away by the mother, in consequence of which, on the second day, the symptoms increased in severity, but they suddenly disappeared with such extreme rapidity that on the fifth day the greyish colour had been replaced by the normal rose-tint of the skin, the paronychia had vanished, the bullae became almost imperceptible, the child cried instead of



whimpering, and took the breast eagerly. On July 29th the child weighed 8 lb., and showed no symptoms.

Only the merest trace of inorganic arsenic was discovered in 100 grammes of milk, therefore one cannot believe that the improvement of the child was due to the arsenic, but rather to the endotoxin which resulted from the destruction of the spirochaetes in the mother, and which was conveyed to the child through the milk.

Duhot reports an almost similar case, in which the child increased more than a pound in weight the first week, a pound in the second, and three quarters of a pound in the third. In the milk Van Keerberghe could not find the slightest trace of either organic or inorganic arsenic.

*ethos?*  
A case of a girl, aged 28, with stigmata of congenital syphilis, had for the past few months been unable to do her work owing to acute pain in the arms and legs. Both arms and legs had swellings over the parts of the bones which were subcutaneous, the skin over them was red, and extremely painful to the touch; the swellings were obviously due to periostitis. Within a fortnight after the injection the patient returned to work, the pain and tenderness had completely disappeared, although the swellings were still present owing to the great amount of new bone which had formed.

The patient had also syphilitic dactylitis with a painful swelling of the first interphalangeal joints of the middle two fingers of the left hand.

The pain soon disappeared, and the movements were excellent, but some swelling still persisted owing to the enlargement of the ends of the bones.

The following case is of a boy, 20 years of age, the subject of congenital syphilis, who was suffering from extensive gummatous ulceration of the nose and its neighbourhood.

The boy had been under the care of Mr. R. H. Woods, Dublin, whom we have to thank for the notes, for fourteen years, and in spite of vigorous treatment the disease continued to progress.

The facial portion of the nose was gone, also the septum, turbinal bones and a large part of both ethmoids, and quite recently a large ulcer had made its appearance on the upper lip and another on the posterior pharyngeal wall extending from the naso-pharynx above to the epiglottis below.

Within a fortnight the ulceration had completely healed and the dacryocystitis which had developed on the right side had disappeared.

*Case 25.* W. H., aged 10, normal birth, third child in family, all other children (three) have never been ill.

When  $3\frac{1}{2}$  years old the glands on both sides of the neck became greatly enlarged and suppurated, and as soon as one opening healed up, another formed, so for some years the child had sinuses in his neck from which pus never ceased coming. The diagnosis of tuberculosis was made and the child was admitted into St. Mary's Hospital for opsonic treatment with tuberculin, which had practically no effect.

*eff.?*  
Both eyes showed signs of an old keratitis, so a Wassermann's reaction was done with a positive result, and '606' advocated. At the time of injection the child was dull, listless, apathetic, always irritable, and never cared to play with his fellow-creatures.

The glands were enlarged more or less all over the body, especially in the neck, where there were one or two sinuses.

The abdomen was swollen, tender on pressure and contained free fluid, there was also a faint rash on the trunk which resembled in every respect lichen scrofulosorum.

The patient suffered from diarrhoea and the motions were always clay-like and evil-smelling. The child had also a constant discharge from the nose.

The effect of '606' was really remarkable, for within twenty-four hours the abdominal pain had disappeared

and the free fluid vanished. Within a week the diarrhoea stopped, the glands diminished in size, the sinuses closed, and the nasal discharge ceased.

The general improvement was just as rapid, because the whole character of the boy changed, he looked better, put on weight, was cheerful and intelligent, and took part in games. The symptoms in congenital syphilis disappear rapidly, with the exception of the rhinitis, possibly owing to a superadded infection which is almost bound to occur and gain entrance by way of the nostrils; therefore the nose should be washed out daily with weak boracic lotion.

There have been some very interesting cases recorded of complete recovery in a few days from pseudo-paralysis or syphilitic epiphysitis.

In older children the following is an excellent example of improvement in a case of gummatous ulceration.

*Case 26.* A girl, aged 15 years, kindly referred to me by Mr. R. C. Elmslie, developed the usual signs of congenital syphilis soon after birth, the mother having acquired the disease two years previously. Later the child had double interstitial keratitis, which disappeared under treatment, to be followed by cutaneous gummata over the left thigh and leg, which had resisted prolonged oral administration of mercury. The gumma on the

thigh was deep, circular, and about  $2\frac{1}{2}$  inches in diameter ; on the anterior surface of the tibia were multiple sores, the base of some reaching as far as the periosteum and bone ; there was a great deal of evil-smelling discharge, and it was almost impossible to keep the ulcers clean.

The patient was injected with 0.3 gramme of 'Salvarsan' in an emulsion. Except for a little pain and a rise of temperature to 100° F., which lasted till the next day, the patient suffered no inconvenience.

On the second day the ulcers already showed signs of healing, and within ten days they had completely healed, no other treatment having been employed. This patient also says she feels very much better. The Wassermann's reaction is still positive.

The persistence of the positive Wassermann's reaction in congenital syphilis requires much more light to be thrown upon it before a satisfactory explanation is forthcoming. One of us (McD.) has examined women who have borne healthy children and presumably had no active disease, but whose sera were capable of fixing an unusual quantity of complement, and the fixation power was not lessened by treatment.

It yet remains to be seen what influence '606' exerts in congenital nervous diseases, but although the following

case recurred, its mention is of sufficient interest as it shows the usual course after an intramuscular injection.

*Case 27.* D. K., aged 10, was admitted into St. Bartholomew's Hospital on September 28th, under the care of Dr. Morley Fletcher, complaining of attacks of cramp and loss of power in the right arm and leg. First attack—sudden onset—November, 1909: recurrent attacks at intervals of 2–8 weeks since, becoming less frequent. Patient became incoherent in the early attacks, not in the more recent. Owing to a Wassermann's reaction being positive, an injection of '606' was given (0.4 gramme). She was a full-grown child, labour was normal, breast-fed for six months, walked at eighteen months, began to talk at two years, but was said to have been backward at school. Family history nil. The child was healthy-looking, lively, and talkative. The right pupil was larger than the left and both were irregular in outline, especially the right. Reaction both to light and accommodation was feeble. There was no optic neuritis or chorioiditis. The incisor and canine teeth were ridged and notched. The liver and spleen were not palpable. The reflexes were very active, there was no ankle clonus, and the plantar reflexes were flexor. On September 29th an injection of '606' was given; October 2nd and 4th there was a rise of temperature to 99° F., and although

there was some swelling, the patient did not complain of pain. On October 6th the child woke suddenly at 1 a.m. and complained of feeling sick; temperature was  $101.6^{\circ}$ , pulse 144. She soon slept again until 4 a.m., then woke feeling sick and vomited bilious fluid, but talked as usual. By six o'clock she could only say yes or no; at seven, temperature was  $102^{\circ}$ ; the child was very restless, and when asked if she had pain she pointed to her chest with her right hand. Movements were natural, subsequently she vomited several times and refused to take any food. She lay curved up on the right side and was very irritable when disturbed; the buttock was rather less swollen but a diffuse erythema had appeared, which spread around the swelling and especially down the thigh, and there was a red papular rash round the edge of the erythema. Both knee-jerks were active, the right plantar reflex was extensor and the left flexor. The next day the child was still drowsy and irritable and unable to speak. The face was red and swollen, in fact there was some angio-neurotic oedema, the tongue was furred, and the temperature  $102^{\circ}$  F. On October 8th the temperature fell to  $97^{\circ}$ ; the child was able to talk fairly well, but still unable to express her meaning at times; over the trunk and limbs there was a scarletiform rash. By October 10th the temperature was

normal, the patient had returned to her former condition, and the rash had completely disappeared. Five days later the child was discharged. Six weeks later a positive Wassermann's reaction was still given, and the attacks have recurred.

The following case is illustrative of the influence '606' may have on deafness as a result of congenital syphilis, a symptom which is usually markedly resistant to mercury. The case is reported by Joseph and Siebert (*Dermatologisches Zentralblatt*, 1910, xiii, 3). Three days after the injection a patient, 14 years of age, was able to hear well.

The common condition of interstitial keratitis is very unfavourably influenced by '606'. Cases have been described of the cornea clearing up, but no improvement occurred in seven cases we injected, beyond a slight diminution of the photophobia; no further improvement could be obtained by a second injection. Such cases should also receive instillations of 10% paraoxyphenyl-sodium arseniate.

Is it possible of explanation why the syphilitic keratitis produced in rabbits should improve so remarkably under '606' while its analogue in congenital syphilis remains practically uninfluenced? Clinically the two conditions are identical; the entrance of blood-vessels into the cornea is the same, that both are due to the actual presence of the



specific organisms has also been proved, and it can only be that the spirochaetes in both corneae behave differently. In the human cornea, for instance, the spirochaetes have probably been present since foetal life, and after many years, from causes unknown, they have led to inflammation, because spirochaetes have been found in the clear corneae of stillborn foetuses.

If the spirochaetes are present for years in a cornea in which there are no blood-vessels, there is no doubt that their biological and chemical capacities must be different from those which live and multiply in the cornea of a rabbit, which very soon after inoculation becomes vascularized.

## CHAPTER VIII

### WARNINGS

WHERE disease of the vessels is present the greatest precautions must be taken in using '606', because reactionary inflammation might cause the closure of a vessel which was already constricted, which would undoubtedly prove fatal in the case of the aorta and coronary arteries.

A breaking-down of the syphilitic products or a sudden rise of the blood pressure causing aneurysms or rupture of vessels might have bad consequences when the cranial vessels are diseased.

In such conditions either the injection should not be given at all, or only half a dose used.

In the late stages of syphilis the analogy to the Herxheimer's sign in early secondary syphilis is not to be expected after using small doses, owing possibly to the few organisms present in tertiary lesions.

In all syphilitic nervous diseases, especially intracranial affections, only half the usual dose should be prescribed, as the reactionary inflammation may cause sufficient

rise of the intracranial pressure to inhibit the respiratory centre.

Patients the subjects of intracranial mischief not infrequently have attacks of dyspnoea after an injection, and one of my cases died from respiratory failure. (See case 23, p. 110.)

Tertiary lesions of the liver and kidney should undoubtedly be excluded from treatment, because not only are these organs necessary for the excretion of the arsenic, but also, if the excretion is inhibited, the arsenic produces degenerative changes on the liver and kidney parenchyma, which is already diseased, with the result that the patient runs the great risk of succumbing to an acute degeneration of these viscera.

Concerning re-injection. It has been frequently stated as a general rule that a second or even third injection must be given, but no consideration has yet been given to the widely differing manner in which syphilis affects people even in European countries. Race plays a great rôle in the method of attack by syphilis; whether race immunity is the main factor, or whether it be the environment and the way the people live or the diet they live on, is unknown. For instance, in Bosnia visceral syphilitic disease is comparatively rare; the way all syphilitic symptoms respond to mercury is

remarkable, and the recurrences after '606' compare more favourably than all other reports from Europe.

The natives of India, again, are remarkably immune from tabes and general paralysis.

In Vienna, worse cases of syphilis are seen than in London, so even from these few remarks, a further elaboration of which would form a most interesting study, it can be seen that each case must be judged upon its own merits.

The numbers of recurrences reported from continental cities vary enormously, as also do the effects of '606' upon Wassermann's reaction; of course, the dose employed, the method of administration, and the way the blood test is done may largely be held to account for the variance.

## CHAPTER IX

### REVIEW OF CASES

THE drug has been in use for too short a time to allow of any absolute statements being made, and again one is always hampered by the difficulty of not being able to follow up all the cases treated, so that at this early stage general impressions are more to be relied upon than figures.

We therefore propose to give merely a short review of the series of cases injected by one of us (McD.) in England.

Of these 270 cases, 180 received the injection intramuscularly and 90 intravenously.

Of the 180, two died, one a case of disseminated carcinoma and the other a case of syphilitic basal meningitis. After the first injection eight cases have recurred, three of which have not been seen since. Four were given a second injection, resulting in a disappearance of the symptoms, with the exception of one man who is now improving under mercury. Two cases were made worse, and 25 cases, twelve of which were tabes, remained *in statu quo*; two of the thirteen remaining were

cases of general paralysis, one was a case of cerebral disease in a congenital syphilitic, seven were cases of interstitial keratitis, while the remainder were ordinary cases of secondary syphilis.

*Review of 270 Cases.*—Statistics are seldom of much use, and in the present instance still less so, owing to the fact that many of the cases injected have been lost sight of, and many have been treated too lately to allow of complete examination; and again, not quite eight months have elapsed since the first injection was given. In a few years' time we shall no doubt be in a position to give some kind of idea of the frequency of recurrences, and the permanent effect '606' exerts on Wassermann's reaction.

*Primary Stage.*—Chancre only, or with inguinal adenitis, 14 cases—

8 intramuscular,

6 intravenous.

Sore heals quicker after the intravenous method and the spirochaetes disappear more rapidly; the healing is certainly hastened by local applications. All cases now give a negative Wassermann's reaction.

*Secondary Stage.*—116 cases—

71 intramuscular,

45 intravenous.

In about 60 % of cases a negative Wassermann's reaction is obtained between the fourth and sixth weeks ; occasionally it is longer than this before the reaction becomes negative. Recurrences are impossible to estimate, because it has been the rule to repeat the injection on obtaining a positive Wassermann's reaction about the fifth week after the first dose, irrespective of the presence or absence of symptoms.

Over 90 % of the cases which come up for a second injection give a negative Wassermann's reaction about a month later. In just less than 3 % of cases, either the optic or auditory nerve becomes involved, in the form of a neuro-recurrence, which usually disappears under a second injection of '606', or vigorous mercurial treatment.

This neuro-recurrence is usually unilateral, both nerves have not been in the same case affected, no other symptoms of the disease are present, the cases generally have a negative Wassermann's reaction, and in all cases the date of infection was always under three months.

The small number of cases which still give a positive Wassermann's reaction after the second injection should receive a third, but the influence this has upon the reaction remains yet to be established.

The quick manner in which mucous membrane lesions

clear up is a strong indication for treatment with '606', owing to such cases being infectious. One does occasionally see cases in which fresh papules come out during treatment, this indicates an immediate re-injection.

*Tertiary Stage.*—98 cases—

61 intramuscular,

37 intravenous.

Rapidity of healing is often remarkable, and is hastened by giving potassium iodide internally and using antiseptics locally.

5 % were refractory, unless the above measures were adopted.

Previous arsenical treatment diminished the efficacy of 'Salvarsan'.

6 % have so far recurred, and with the exception of one case, the lesions healed after the second injection.

The second dose must always exceed the first. When recurrences occur Wassermann's reaction is always positive, although it may have been negative before.

Roughly speaking, 60 % give a negative Wassermann's reaction after one injection, and of the 30 %, 82 % become negative with a second injection. The injection, as in the secondary stage, should be repeated on obtaining a positive reaction after a month's interval. Nine of these cases have been late tongue lesions, all of which have im-



proved without any recurrence. Five were cases of gummatous ulceration of the throat: four were cured with no recurrence, and one case (stenosis of the larynx) was unaltered.

*Tabes.*—19 cases; all intramuscular with one exception—

2 were made worse,

12 remain *in statu quo*.

5 improved, pain disappeared, reflexes returned and pupils reacted to light, &c. Three of these recurred with a positive Wassermann's reaction, and unfortunately too short a time has yet elapsed to mention the effect of the second injection.

Whether there is any relationship between a positive Wassermann's reaction and the improvement, cannot be definitely stated.

*G. P. I.*—5 cases—

3 remain *in statu quo*,

2 have improved.

Unfortunately the Wassermann's reaction has not been done.

*Mothers.*—5 cases      { 4 while pregnant.  
   { 1 during lactation.

Influence on future offspring unable to be estimated from so few cases.

Improvement in child when suckled by its mother is great.

*Congenital Syphilis.*—13 cases—

2 cases with nervous symptoms uninfluenced.

7 cases of keratitis practically uninfluenced.

1 case of acute periostitis cured.

1 case of general enlargement of the glands cured,

2 cases of gummata cured.

In only one of these cases did Wassermann's reaction become negative; in no case was a second injection given.

Meagre as these cases are, certain conclusions can be drawn from them.

First and foremost, a patient must if possible be caught in the primary stage, and every attempt must be made, in the event of a doubtful sore, to find the spirochaete pallida.

In the early secondary stage, on account of the small risk of getting a neuro-recurrence, the question arises as to the advisability of advising an injection; it may be said that these nerve-lesions have almost invariably occurred when 'Salvarsan' was given into the muscle or subcutaneously, and again, that a unilateral optic neuritis, or a unilateral or bilateral affection of the auditory nerve, may occur in the ordinary course of events, when the patient has received no treatment whatever.

The risk of infection being great at this stage is highly in favour of administering '606', and when for some reason it is required to heal the lesions in the shortest space of time possible, '606' must take first place.

As a neuro-recurrence may appear, the possibility should be laid before the patient, and if the injection is not decided upon, a six-months course of mercurial inunctions or injections should be given to tide over the danger period, and the employment of '606' deferred till later.

In all cases of malignant syphilis, and especially when tuberculosis is feared, 'Salvarsan' should be strongly recommended; this applies with equal force to chancres which fail to heal or become phagedaenic, for in a very short time it is possible for a man to lose his penis.

In the tertiary stage '606' is to be highly recommended, especially when it becomes necessary to heal the ulcers as quickly as possible, to avoid contraction from occurring in an important organ, such as for instance in gummatous ulceration of the nose, pharynx and larynx.

It may always be remembered that the scar tissue following '606' is not only soft but far less in amount than will be expected or could be obtained from other

lines of treatment; this is of extreme importance when a vital organ is under consideration.

Chronic superficial glossitis, renowned for its resistance to mercury, should certainly be treated with '606'.

In tabes and general paralysis, and in short in all nervous diseases, a guarded prognosis must be given; and no case should be treated unless it is early; the prognosis is best in cerebral syphilis.

In all intracranial and vascular lesions the risk of death following an injection must be borne in mind—infinitesimal as it is; at any rate during the experimental stage, which we have not yet passed.

Pregnant or puerperal women should certainly be injected, and so should all cases of congenital syphilis in which a good prognosis can be given, except in cases where the central nervous system is involved, or the patient has interstitial keratitis; but these points want a great deal more working out.

Any new line of treatment is met, and rightly so too, with scepticism, since sound arguments both for and against only can place the drug in its right position, but as is always the case, critics oppose its use on every ground, and such critics are usually those who have neither used the preparation nor even seen it; *a priori* their remarks are to be disregarded.

The disappointment which followed tuberculin, which by the way was given to the world before its discoverer intended, cannot be expected to happen with '606', because more than a year's trial by the most experienced observers in syphilology has shown that such results as can follow no other treatment have occurred after 'Salvarsan', and that the risks when only suitable patients are chosen for treatment and the proper technique is employed, are nil.

That since the drug came on the market unsuitable patients have been treated, and errors in technique have occurred with disastrous results, is only too true, but fortunately '606' cannot be given the blame, as would otherwise have been the case.

That the drug is the greatest specific for syphilis we have cannot be denied, and its superiority over mercury must be seen from the foregoing pages, where several cases are cited of 'clinical' cure after 'Salvarsan', when mercury was quite inefficacious.

We are not yet in a position to foretell how many cases will recur, and whether late lesions, especially parasyphilitic affections, will supervene, but this much can be said, that the lesions are healed in a shorter time than can be the case with mercury, thereby diminishing the risk of infection, which is an important factor in

patients who have mucous papules in the mouth, or in a woman who has a chancre on her cervix.

Again, cases are accumulating where a cure has been proved, owing to the fact of a reinfection.

The rapid improvement in the well-being of the patient, to which too little attention has been drawn, seldom follows mercurial treatment.

The advantage of '606' in pregnant women and congenital syphilis has only to be mentioned, as the action of mercury is most unsatisfactory in both these stages.

Still further, only too many cases of recurrence are recorded in which the mode of administration is not discussed or made to blame.

Acid emulsions injected into the muscles or beneath the skin have not such a powerful action as when a faintly alkaline emulsion or alkaline solution is injected, and no intramuscular or subcutaneous method is as potent as an intravenous.

Each case needs to be treated on its own merits, but experience has shown that as recurrences do occur, and as it is perfectly safe to repeat the intravenous injection after the fifth day from the first, this second injection should always be made, except in the case of a nervous disease, when a month should elapse, and then only a

second injection given on obtaining a positive Wassermann's reaction.

In every case a serum diagnosis test should be carried out within six weeks after the last injection, and if still positive, a third injection should be given.

The first intravenous dose should be 0.5-0.55 gramme for a man, and 0.4-0.5 gramme for a woman, the second intravenous should be the same; while the final intramuscular should not be less than 0.6 gramme or more than 1.0 gramme or an intravenous of 0.6 gramme.

The final remark can only be that the experimental stage is not yet over, that much more is yet to be learned about the most wonderful advance in therapeutics that the world has ever seen; another few years' work will add much more light.

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