

**"Salvarsan" or "606" (dioxy-diamino-arsenobenzol) : its chemistry, pharmacy and therapeutics / by W. Harrison Martindale and W. Wynn Westcott.**

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"SALVARSAN"

("606.")

ITS CHEMISTRY,  
PHARMACY AND  
THERAPEUTICS.

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Martindale & Westcott.

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1911.

London: H. K. LEWIS.



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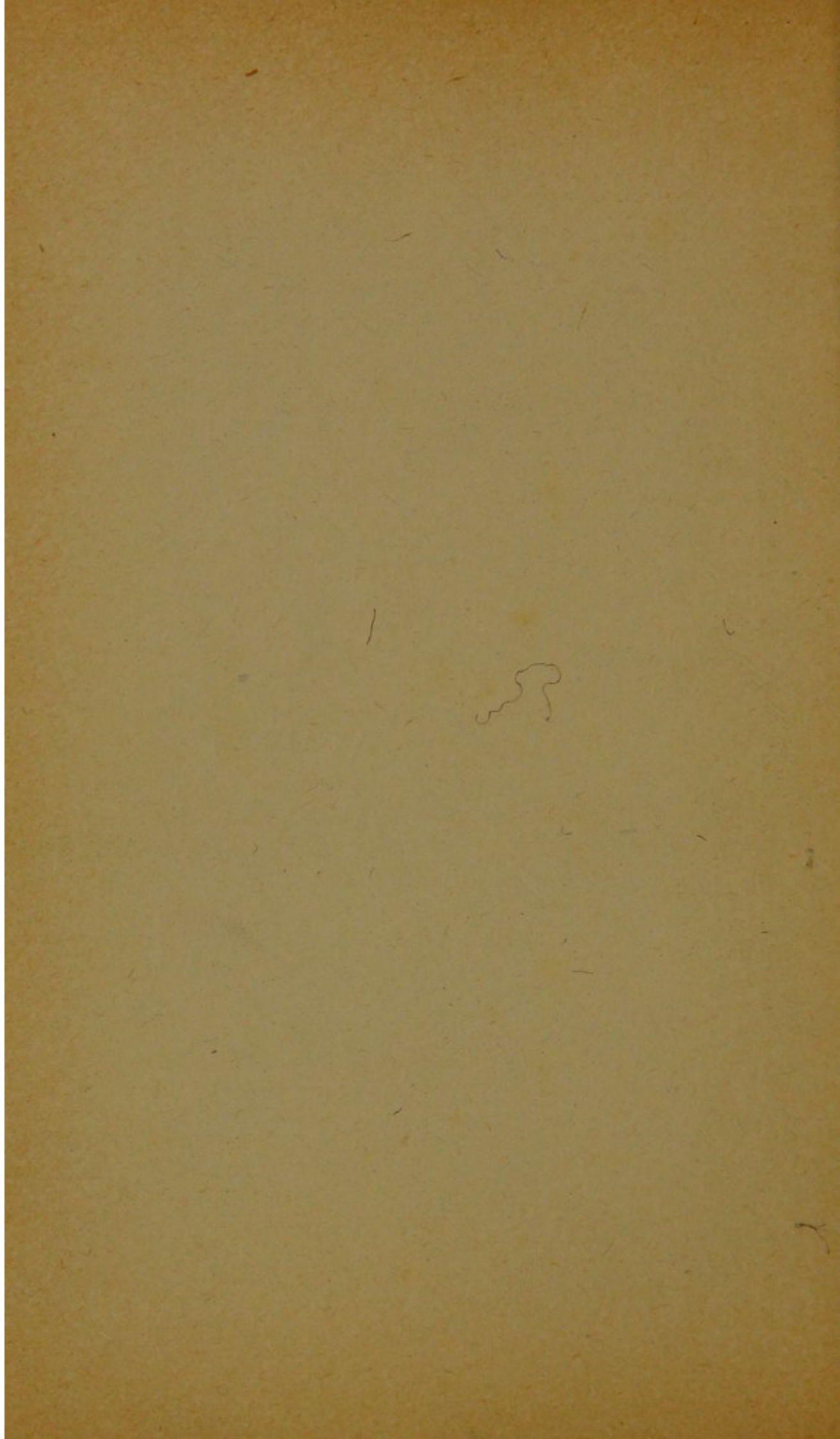


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“SALVARSAN” OR “606”



Wm.

# "SALVARSAN"

OR

# "606"

(Dioxy-Diamino-Arsenobenzol)

Its Chemistry, Pharmacy and  
Therapeutics.

BY

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LONDON :

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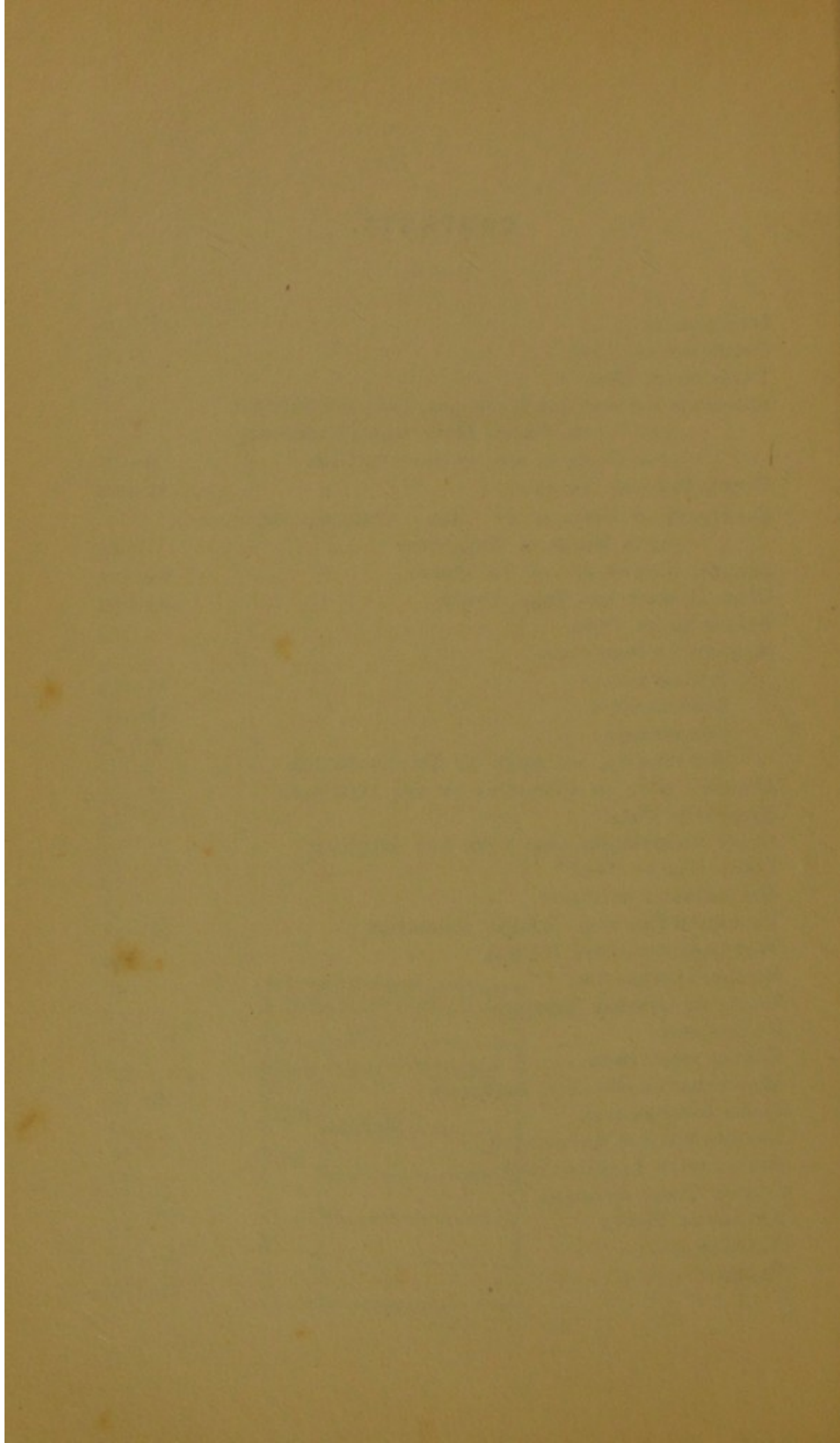
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## CONTENTS.

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INTRODUCTION	vii—xv
CHEMISTRY OF "606"	i—6
THERAPEUTIC USES	7—9
RESULTS IN PRIMARY AND SECONDARY, TERTIARY SYPHILIS AND VARIED FORMS, HEREDITARY, PARASYPHI- LITIC CASES, AS ALSO IN COMPLICATIONS	9—17
OTHER DISEASES TREATED	17—19
TREATMENT OF SYPHILIS BY "606" COMPARED WITH OTHER MODES OF TREATMENT	19
SPECIFIC NATURE OF THE TREATMENT	19—21
DOSE, HIGHEST AND TOXIC DOSES	21—23
REPETITION OF DOSE	23
METHODS OF INJECTION—	
INTRAMUSCULAR	24—29
SUBCUTANEOUS	29—32
INTRAVENOUS	32—38
INTRAVENOUS, FOLLOWED BY INTRAMUSCULAR	38
AUTHORS' NOTE ON CHEMISTRY OF THE INJECTIONS	38—42
APPARATUS USED	42
LOCAL ANÆSTHETICS USED WITH THE INJECTION	43
LOCAL USE OF "606"	43
HERXHEIMER'S REACTION	43
UNTOWARD RESULTS. ARSENIC RETENTION	44—46
WARNINGS AND AFTER EFFECTS	46
RISE IN TEMPERATURE	47
EFFECT ON GENERAL HEALTH	47
RECURRENCE	47
CONTRA-INDICATIONS	48
WASSERMANN'S REACTION, EFFECT ON	49—51
BLOOD EXAMINATIONS	51
EXAMINATION FOR SPIROCHETES	52
ABSTRACTS OF LEADING ARTICLES	52
SPECIAL COMMUNICATIONS	53—60
ANTISEPTIC POWER	60
REFERENCES	62—74
TABLES	75—77





## INTRODUCTION.

The exhibition of Mercury in some form or other has hitherto been the main routine treatment of syphilis, either by internal administration or by local use. The relative advantages and defects of the various modes of introducing mercury into the system have been the subject of discussion on many occasions. One of the principal objections to the methods of combating the disease in vogue up to the present time—and the remark applies equally to 'Iodide'—is the extremely prolonged administration or application which is necessary. The Final Report of the 'Special Advisory Board for the Army Medical Service,' for example, dealing with the treatment of Venereal Disease, after taking the opinion of experts, laid down as a basis of treatment 'a more or less continuous course of mercury by the mouth for  $1\frac{1}{2}$  to 2 years'—*e.g.* in the form of Grey Powders—one grain doses to be taken several times a day. For inunction Mercurial Ointment is ordered in the form of a 6 weeks' course, the rubbings lasting 20 or 30 minutes daily. For intra-muscular injection preparations of soluble and insoluble mercurials are largely employed.

In place of simple mercurial treatment may be mentioned Donovan's Solution, Iodides and many Organic Iodine Compounds, Antimonials, Quinine Preparations and Sarsaparilla Decoctions which have their respective supporters.

More recently Organic Compounds of Arsenic, for example Sodium - *p* - amino - phenyl - arsonate, which has as synonym 'Atoxyl,' achieved some success. It was naturally imagined that with these compounds, containing as they do large pro-



portions of Arsenic in a relatively non-toxic condition, rapid curative results could be attained with little concomitant danger, but these hopes and aspirations were by no means completely realised.

Atoxyl, according to recent trials *in vitro* has proved itself inferior to '606,' the new chemical compound, to the consideration of which this book is devoted, in power of killing protozoa. Atoxyl, in fact, was found to be incapable of destroying trypanosomes *in vitro*. With the début of Sodium-*p*-amino-phenyl-arsonate sprang up several allied substances, *e.g.*, Acetylated Atoxyl. It was thought that the introduction of the Acetyl grouping would overcome the serious effects on the optic nerve which, unfortunately, had been experienced, and render large doses of the compound safe for use in syphilitic affections, but even this body has produced toxic symptoms.

Simultaneously work proceeded in the treatment of trypanosomiasis with arsenicals and various Anilin colours, as it was found that some of the latter, for example, Trypan-red, were active against trypanosomes.

The recent discovery that a body elaborated from 'Atoxyl' (containing 34 per cent. Arsenic as against the 25 per cent. in Atoxyl) possessed parasitotropic properties greatly attracted our attention in view of the fact that in quite a humble way we had been treading in some of the earlier steps of the great synthetist a year or two ago. One of us (W. H. M.), recognising the importance of the problem, decided to prepare on an experimental scale, a large number of Organic Arsenic Compounds that were likely to prove of therapeutic value. Many of these substances were obtained in a beautifully crystalline condition and of great purity, and were demonstrated in a paper read before the International Congress of Applied Chemistry in London in 1909. The paper contained little new in the direction of synthesis of new bodies, but the physiological tests on frog's muscle by Professor Waller at the London University demonstrated that several were relatively non-toxic. We may mention for example the readily soluble Sodium-di-iodo-methyl-arsonate containing 18 per cent. of Arsenic. Several other bodies indicated their possible



value for the specific purpose. None of them, however, were tried *in vitro* or *in vivo* on spirochetes or trypanosomes. The difficulty of obtaining physiological and clinical reports in questions of this kind in this country (*c.f.* 'Medical Press,' October 19, 1910, p. 416), and stress of other work, prevented us from carrying the investigation further. The results we briefly incorporated in the 14th edition of the Extra Pharmacopœia (1910).

So much may be said in explanation of our interest in the subject, for it will be understood that we disclaim any idea of comparing our tentative efforts with the elaborate far-reaching research which has recently led Professor Ehrlich to make the bold assertion that the body Dioxy-diamino-arsenobenzol is capable of bringing about a 'sterilisation of the system.'

So far there has been no complete *résumé* in English dealing with the matter comprehensively. In our attempt to supply one we have studied the recent reports on the new compound with assiduity, and have provided concise notes which we think will assist the reader to understand its chemistry, pharmacy and therapeutics with a minimum of time and trouble. Many voluminous papers have been written regarding its clinical trials, more especially in German medical journals. A number of these are in great measure repetitions of what has been provided by others. The information here supplied has been digested and analysed under certain headings (*c.f.* 'Contents'), and though this could not possibly be done in a hard and fast manner, our digest will, we think, prove of assistance. Our information covers the period March 15th to December 17th, 1910.

Ehrlich and Hata's treatise—'Die experimentelle Chemotherapie der Spirillosen (Syphilis, Rückfallfieber, Hühnerspirillose, Frambösie)'—Julius Springer, Berlin, which has been issued quite recently, is a work to which students would naturally turn for information respecting the latest views on chemotherapy. We may therefore give a brief notice of it. Ehrlich in his prefatory remarks acknowledges the assistance of a small army of chemists, biologists and experimental therapists. Amongst these S. Hata, of Tokio, is specially



mentioned. He also thanks Mr. J. D. Rockefeller for financial aid. A new type of Therapeutic Institute, he says, has been founded, and his favourite theme of placing chemical synthesis at the service of medicine has thus been realised.

Hata conducted research with '606' and other chemicals on the spirilla of relapsing fever in rats and mice : subsequently on fowl spirillosis and the spirilla of syphilis. Aqueous or alcoholic solutions of the substance were mixed with Physiological Salt Solution or isotonic Sugar Solution and suitably diluted. These dilutions were mixed with equal volumes of blood containing spirilla diluted about 30 or 40 times with Physiological Salt Solution, and examined after an hour to determine whether they remained motile or not. Non-motility was considered to indicate their destruction. In the animal experiments a series was inoculated with spirilla-infected blood, and the following day the blood was examined microscopically to ascertain presence of the parasites. The animals were then inoculated with the substance to be examined. Blood was removed daily and examined for presence or otherwise of spirochetes. Naturally, in experiments of this kind the nature of the infection, whether virulent or otherwise, has to be carefully controlled throughout. Hata used the infecting blood diluted as a general rule to the utmost, and yet not too dilute to prevent easy recognition in the animal the following day.

Curative trials of substances under examination were conducted by injecting, usually subcutaneously, on the day following the inoculation, varying doses of the preparation—determined by previous trial on similar healthy animals. The spirillar content was then determined daily. If the substance was active the spirilla disappeared in one or two days ; if insufficiently active they, however, reappeared sooner or later. The microscopic examination has to be conducted during 60 days.

A large number of Aniline dyes were tested in this manner on spirilla of relapsing fever. Methylene Blue in dilution 1 : 6,000,000 was sufficiently powerful to cause cessation of movement *in vitro*, but when animal experiments came to be conducted it was found that about 500 times as much was



necessary as was required *in vitro*—in other words, the dye is much more strongly 'organotropic' than 'parasitotropic,' hence, indirectly, it causes an increase in the number of parasites.

With regard to Arsenicals in the treatment of relapsing fever in mice, Hata was only able to obtain curative action with Atoxyl by feeding as much as seven days in advance and seven days subsequent to infection. Similarly Arsenophenylglycin did not furnish him with satisfactory results in relapsing fever in mice, though it is active in the case of trypanosome infection. Dioxy-diamino-arsenobenzol, on the other hand, both with mice and rats infected with relapsing fever, had powerful action, both as preventive and curative. In addition, it caused no evil after-effects, which are frequently seen with other arsenical bodies.

With regard to fowl spirillosis the chemical was found to have a curative dose intramuscularly of 0.0035 Gm. per kilo body weight if treated the day after inoculation. It gave better results than Atoxyl, Arsacetin, etc.

Hata gives interesting tabulated results of treatment of rabbits inoculated with syphilis in the cornea by '606.' The injections were given intravenously in amounts varying from 0.006 Gm. to 0.04 Gm. per kilo body weight about two months later—*i.e.*, after complete corneal opacity had set in. Healing was uniform even in the case of the low dose of 0.006 Gm. The marked keratitis cleared in three weeks, and there was no recurrence. Hata, however, does not consider keratitis in rabbits very suitable for trial, as it is not possible to examine continuously for spirilla in this infection without damaging the cornea,—it is, in fact, only possible to judge progress in this instance by external appearances. Experimental research is, however, more satisfactory in the case of artificially induced scrotal syphilis when a pronounced chancre has been produced, as by this means after the injection has been given spirochetes may be searched for systematically. Between 0.015 Gm. and 0.01 Gm. per kilo body weight sufficed intravenously to promptly sterilise the animal's system sufficiently to prevent recurrence.

Hata concludes the first portion of the book by saying that if not curative clinically, at any rate '606' will point the way



to a great extent for the ultimate discovery of a specific treatment of spirochetal diseases.

Ehrlich deals with the fundamenta for the constitution of '606'—to this we make some references in the body of our work. He also deals *inter alia* with warnings as to the use of the substance. With regard to untoward results with the preparation he states that not a single case has come to his knowledge of blindness having been caused by '606'; on the contrary, eye affections, such as iritis gummosa, and optical neuritis have been wonderfully treated. He remarks that the best proof of absence of action on the kidneys with the substance is the fact that syphilitics whose kidneys are affected are as well treated as are any other patients placed under the new remedy.

The last portions of Ehrlich and Hata's treatise should prove particularly useful to those making a special study of the subject, though some points, *e.g.*, the decision as to dosage, the question as to form of injection ('acid,' neutral or alkaline), the best mode of applying the treatment, the question of gradual increase of dose, etc., are dealt with in a somewhat questioning spirit.

It may be that our book (the bulk of which was written before Ehrlich's treatise came into our possession), dealing as it does with the subject in an impartial manner, will be found of assistance to physicians, physiologists and chemists in these directions. Most of the information herein contained deals with the original communications of those who have employed the preparation clinically. Furthermore, a very large proportion of these communications was not made until the closing of Ehrlich's List of References (Oct. 5, 1910). We refer for example to the important '606' number of the 'Deutsche Medizinische Wochenschrift,' No. 41, Oct. 13, 1910, and many other papers since issued,—see List of References.

Johannes Bresler ('Die Syphilisbehandlung mit dem Ehrlich—Hata'schen Mittel,' C. Marhold Verlagsbuchhandlung, Halle) has collected the results up to the middle of August last. Our work also deals with the original important communications by Ehrlich, Alt, Neisser, Schreiber, Michaelis,



Loeb, Glück, Wechselmann, Taege, Iversen, etc., between the period March to the middle of August, 1910, but since then a veritable mass of papers has been communicated by writers of many nationalities—German, French, English, Austrian, Russian, Japanese, American, etc., and to these we have paid special attention.

In addition to the foregoing, many of whom have contributed several times further, Herxheimer, Kromayer, Zeissl, Spiethoff, Duhot, Blaschko, Bayet, McDonagh, McIntosh, Schwartz and Flemming, Lange, Anscherlik, Gourwitsch and Bormann, Treupel, Huegel and Ruete, Sieskind, Werner, Favento, Grassmann, Orth, Miekley, Uhlenhuth, Stern, Grünfeld, Lesser, Ritter, Weintraud, Lindenmeyer, Munk, Zieler, Hammer, Pick, and others have published their clinical experiences with '606.'

The 'British Medical Journal,' 'Lancet,' and other scientific journals have printed leading articles on the subject—two of these we have reproduced in a condensed form.

It may be added that the use of '606' has been extended to relapsing fever, frambœsia, malaria and leprosy with some success. We give notes on the results in each disease.

To revert again to our 'Contents,' we may briefly draw attention to a few features of our book.

In the matter of 'Therapeutic Uses' most conflicting opinions exist, though it is fair to state that those emanating from German scientists indicate a most comprehensive curative power for the remedy. With these must be read, however, the 'Contraindications,' which we classify later in our pages.

Again 'Results' leave the student in some doubt as to whether the possible success is worth the attendant risk. We are told the fact that '606' solutions kill protozoa *in vitro*; hence, with the knowledge also that the  $\frac{C}{T}$  dose ratio

$\left\{ \begin{array}{l} \text{Dose sufficient to destroy all parasites} \\ \text{Max. dose which will not kill patient} \end{array} \right\}$  for the substance is propitious, we should have sufficient confidence to submit it to trial. Exigencies of the case will necessitate careful perusal of the 'Dose' chapter, in which authoritative opinions of various workers are given. It may be



that treatment by 'Repetition of Dose' will commend itself.

The patient having been acquainted with the risks of the treatment and 'after-effects' (usually transient)—our next step is to determine the 'Method of Injection' to be employed to give the greatest likelihood of success with the minimum of 'Untoward Result,' be this in the direction of 'Local Reaction,' 'Rise in Temperature,' 'Effect on General Health,' etc.

To control our result it would be well to have the Complement—Deviation test of Wassermann conducted both before and after the injection.

We provide also a few words of 'Warning' which may be appropriate, as the whole matter may be considered *sub judice*. Quite recently C. F. Marshall (*vide* Refs.) has written in a warning tone concerning the preparation. Untoward results unforeseen by writers hitherto may, perhaps, be expected to occur. Naturally enough their note is one of enthusiasm. The 'Special Communications' of some authorities in this country, to wit, O. Grünbaum, J. Hutchinson, J. Ernest Lane, F. W. Mott, G. Ogilvie, G. Pernet, J. H. Sequeira and Campbell Williams will, we think, be read with some interest. The 'References' contain frequently additional matter which would otherwise have congested our main sections and reduced the conciseness. They are arranged as near as possible in chronological order. As the treatment has been a process of gradual development, the later references, especially those of leading authorities, should carry the greater weight when deciding modes of procedure.

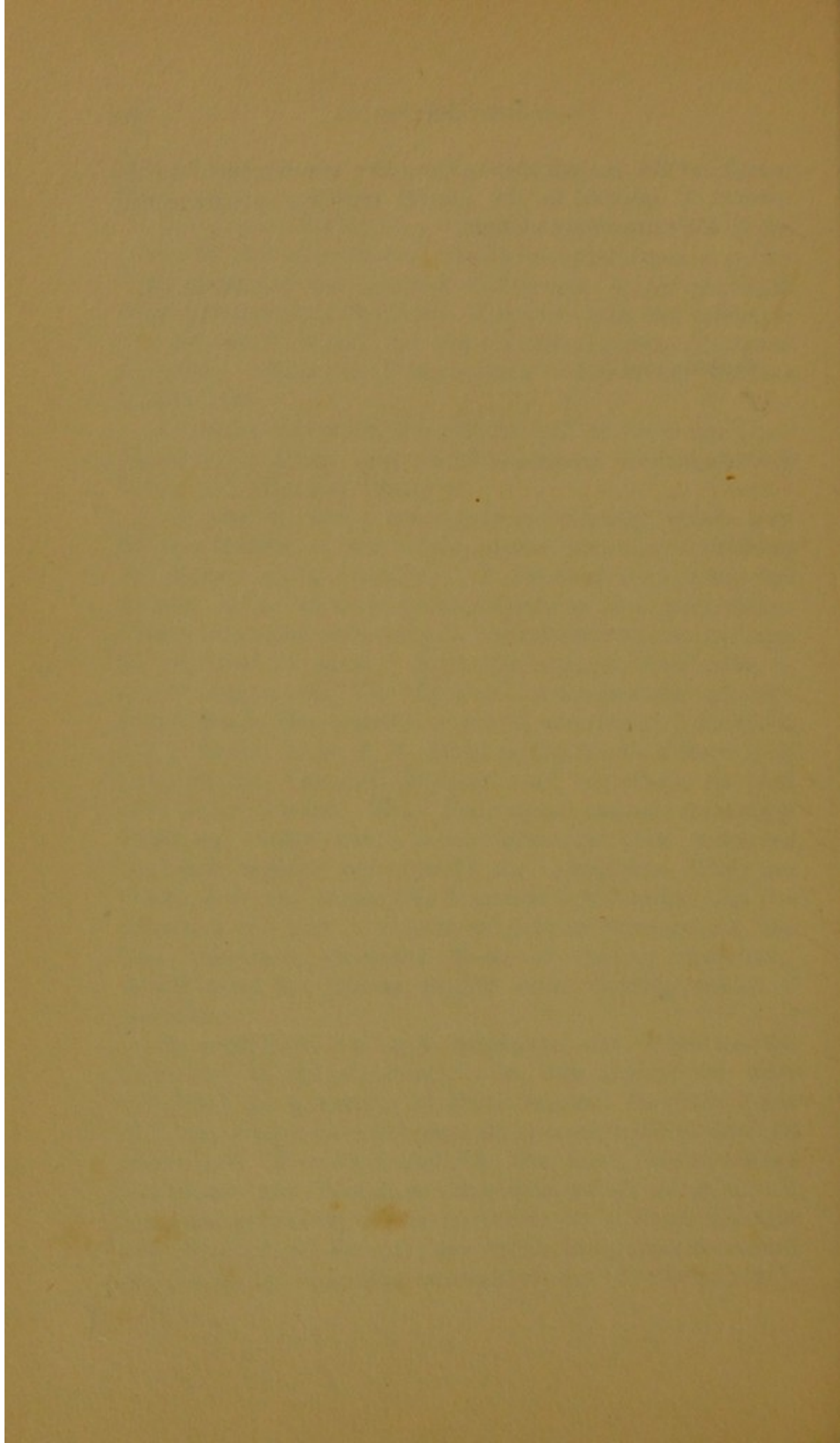
In conclusion, we may emphasise our 'Note on the Chemistry of the Injections.' In this chapter we have calculated the quantities of alkali required for given doses of Dioxy-diamino-arsenobenzol Di-hydrochloride to produce respectively 'Mono-hydrochloride,' the 'Base,' 'Mono-sodium Compound,' and Di-sodium Compound, which we think will place the Chemistry of the Injections on a more scientific basis than existed hitherto, our object being thus to reduce the possibility of adding marked excess of caustic alkali,

which would be attended with grave consequences to the patient if injected in the gluteal muscles, subcutaneously or by the intravenous method.

W. H. M.  
W. W. W.

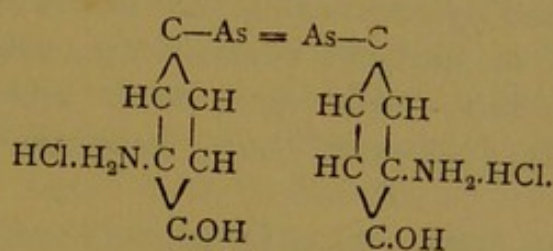
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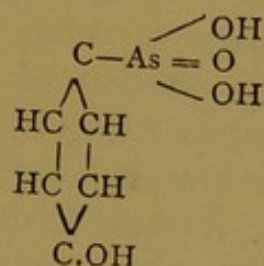


## CHEMISTRY OF '606,'

THE chemical compound  $\text{D}^*$  DIOXY-DIAMINO-ARSENOBENZOL DI-HYDROCHLORIDE, which passes under the synonyms 'SALVARSAN,'† 'ARSENOBENZOL,' 'EHRlich-HATA,' or '606,' is believed to have the constitution ;—



As this formula indicates (empirically it amounts to  $\text{C}_{12}\text{H}_{12}\text{O}_2\text{N}_2\text{As}_2(\text{HCl})_2$ —molecular weight 438.972 I.Wts.) it has for its basis *p*-oxyphenylarsonic acid.



This body by nitration, and subsequent reduction under certain conditions, is stated to produce a condensation of two molecules forming ultimately the Dioxy-diamino compound. This base is then converted into the Hydrochloride of the above formula.

\*Part I Poison—Poisons and Pharmacy Act, 1908. See Extra Pharmacopœia XIV., pp. xvi., 930.

†The preparation (which is patented) has been placed on the market under this name (a Registered Trade Mark) in hermetically sealed glass tubes, each containing 0.6 Gm.



Ehrlich, in his treatise (p. 119), explains the steps by which *p*-amino-phenylarsonic acid (the acid of which Atoxyl is the sodium salt) may be converted into *p*-oxyphenylarsonic acid by diazotising, also the reducing stages after the subsequent nitration, but there are a few difficulties which are not cleared up from the chemical point of view, and, needless to say, these are not dealt with minutely in the Patent Specification, *q.v.* Para-oxyphenyl-arsonic acid, it appears, can also be manufactured by acting upon Phenol with Arsenic Acid.

In some instances the Hydrochloride has been used therapeutically, but more often the base or the Mono or Disodium compounds have apparently been employed. Examination of the literature, however, shows that the amounts of added alkali have been most variable. We can only explain these discrepancies by concluding that the substance supplied for use was not of uniform composition, requiring various amounts of alkali — this is indeed admitted. Large amounts of alkali in excess of theory have produced excessive pain.

Ehrlich, in his book, claims for himself and his co-workers, Berthelm and Hata, priority (in 1909) in the manufacture of '606.' He shows how he proceeded from Atoxyl, which he demonstrated as inactive on trypanosomes *in vitro* to this substance by a systematic synthetic process. The 'axle' of the entire advance made by him, he says, was the correct recognition of the constitution of Atoxyl by himself and Berthelm. Atoxyl was previously thought to be Meta-Arsenic Anilide; the point is elucidated in the 'Extra Pharmacopœia,' and in 'Organic Arsenic Preparations' (W.H.M.).

'606' forms a bright yellow powder slowly but completely *soluble* in water. It contains theoretically 34.15 per cent. Arsenic with strongly acid reaction. It is supplied in glass tubes first evacuated then filled with inert gas to prevent oxidation.

'606' that has become discoloured — either grey or brownish — must not be used,

It will be easily understood that the Hydrochloride may be converted into the basic substance Dioxy-diamino-arsenobenzol (No. 592 in Hata's series) of the formula



$C_{12}H_{12}O_2N_2As_2 = 366.036$  I.Wts., by treatment with alkali. We shall deal with this later, but may here define the base as an unstable, easily oxidisable, *insoluble* substance containing 40.96 per cent. Arsenic, readily soluble however in Alkalis. Using NaOH, for example, the Mono-Sodium Compound  $C_{12}H_{11}NaO_2N_2As_2$  and the Di-Sodium Compound  $C_{12}H_{10}Na_2O_2N_2As_2$  are successively formed. These bodies are not very stable in solution.

A point enters here regarding solubility, which is of great importance in the whole treatment, and which, in our opinion, throws considerable light on the matter. Michaelis (81) states;—

If the preparation is rendered very slightly alkaline—almost neutral—the solubility is at its minimum; this amount of alkalinity corresponds very closely with that of the blood and tissues. It is probable the *relatively low toxicity in comparison with other Arsenic preparations is due to the fact that it is so insoluble in the blood*. The concentration in the blood, therefore, can never exceed this slight amount. Michaelis thinks that no matter in what form the substance is introduced the solubility is never more than 1/1000 per cent.; see also Michaelis' Injections.

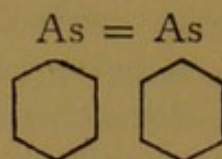
Ehrlich points out the 'parasitotropic' importance of the unsaturated trivalent Arsenic—such as we see in the formula for '606,' as also in Arsenophenylglycin,  $COOH.CH_2.NH.C_6H_4-As = As-C_6H_4.NH_2CH_2.COOH$  (compare, *e.g.*, the  $As^v$  in *p*-oxy-phenyl-arsonic Acid above, or in 'Atoxyl,' 'Arsacetin,' Cacodyl Compounds, etc.)

Pentavalent Arsenic Compounds, according to Ehrlich, should take a secondary position in spirillocide power, the reasons given being that 'large doses of them are necessary, and that they are not very active, further that there is danger of optic atrophy' (68).

He also draws attention to the OH in the para position in '606.' Arsenobenzol (we refer to the chemical with constitution as indicated on page 4) has strong spirillocidal action; but it is also powerfully poisonous, and has other disadvantages. He had years ago, he says, evolved the principle, 'you must poison above in the Arsenic radical,



below in the Benzene radicle remove poison.' Proceeding on these lines he introduced into Arsenobenzol



substitution radicles which (a) reduce the entire toxicity, (b) increase spirillicidal power, (c) produce a more stable compound.

'Intuitively to a great extent,' he says, 'he had always thought that in the case of therapeutically active Benzol derivatives containing two different pharmaco-dynamic substitution radicals, of which one acts salt-forming (*e.g.* OH, NH<sub>2</sub> group) an increased action must be produced when a third radical was introduced in the ortho-position to the salt-forming group.'

It is stated that almost 200 derivatives of Phenylarsonic Acid had to be prepared, examined biologically, and tried therapeutically subsequent to Arsenophenylglycin, which had the number 418, before the most active '606' had been synthesised.

DESCRIPTION OF THE ENGLISH (No. 13485, June 3, 1910) AND GERMAN PATENT FOR THE MANUFACTURE OF '606,' *i.e.*, FOR THE PREPARATION OF AMINO DERIVATIVES OF OXYARYLARSONIC ACIDS AND THEIR REDUCTION PRODUCTS.—DEUT. MED. WOCH., No. 37, Sept. 15, 1910, p. 1716.

Therapeutically useful bodies may be prepared by nitrating Oxyarylsonic Acids and reducing the resulting Nitro compounds. The Amino-oxyaryl Compounds are capable of curing animals infected with the *spirilla* of Relapsing Fever by a single injection. A reaction of this kind has not been possible with Arsenic Compounds so far described.

*Example 1.*—144 Gm. Sodium-*p*-oxyphenylarsonate dried at 80° C. is added in small portions to 450 Cc. Concentrated Sulphuric Acid at 0° C. whilst vigorously stirring. Continuing the stirring, a mixture of 39 Cc. Nitric Acid (Sp. Gr. 1.4) with 39 Cc. Concentrated Sulphuric Acid is added in small quantities so that the temperature does not rise above 0° C. When the addition is com-



pleted the temperature is allowed to rise to  $10^{\circ}$  C.; the mixture is then poured into 2250 Cc. water and the Nitro-phenolarsonic Acid is filtered off, after allowing to stand 12 hours in the cold. This Nitro compound is in the form of a yellowish-white crystalline powder, which on heating deflagrates. It is fairly soluble in hot water, with difficulty in cold, easily in Alcohol, Acetone or Glacial Acetic Acid.

The easily soluble alkali salts of this Nitro body form markedly yellow solutions.

Reduction leads to Amino-oxyaryl-arsonic Acids, and to the Amino-oxy derivatives of Arsenobenzol, from which the corresponding Arsonic Acids can be re-formed.

*Example 2.—Reduction by means of Sodium Amalgam.*—A solution of 31.6 Gm. Nitrophenol-arsonic Acid in 600 Cc. Methyl Alcohol is warmed at 60 to  $70^{\circ}$  C. with 840 Gm. 4% Sodium Amalgam until no further gas evolution takes place. About 450 to 500<sup>c</sup> Cc. Methyl Alcohol are distilled off; the residue is treated with 120 Cc. water, and after removing the Mercury is made acid with 150 Cc. Hydrochloric Acid (Sp. Gr. 1.19). After 12 hours small impurities which have separated out are drawn off, the liquor boiled with charcoal, filtered and 52 Cc. 10 x Normal NaOH added. In this way the bulk of the Aminophenol-arsonic Acid is stated to crystallise out in leaflets or minute prisms, decomposing at  $170^{\circ}$  C. without melting. The acid is very slightly soluble in water or organic solvents, but easily soluble in alkalis and in aqueous mineral acids. An alkaline solution gives a dark green colour with hypochlorites; an acid solution gives a strong red colour with a drop of Potassium Dichromate solution.

*Example 3.*—Reduction of Nitrophenol-arsonic Acid with Sodium Sulphide (vide Patent for details).

*Example 4.*—66 Gm. of Nitrophenol-arsonic Acid are dissolved in 1320 Cc. water with 225 Cc. 2xN.NaOH, and added to a solution of 855 Gm. Anhydrous Sodium Sulphide and 171 Gm. crystalline Magnesium Chloride in 4275 Cc. water. On warming the mixture at  $50^{\circ}$  C. *Dioxy-diamino-arsenobenzol* is stated to crystallise out as a bright yellow crystalline precipitate. To throw it out completely the solution is treated until a small filtered portion on boiling remains clear. The substance on drying forms a yellow powder soluble in dilute Hydrochloric Acid, Sodium Hydroxide Solution and Soda Solution. Acetic Acid throws the body out again from alkali salt solutions.

*Example 5.*—Dioxy-diamino-arsenobenzol can be oxidised to Aminophenol-arsonic Acid by means of Hydrogen Peroxide.

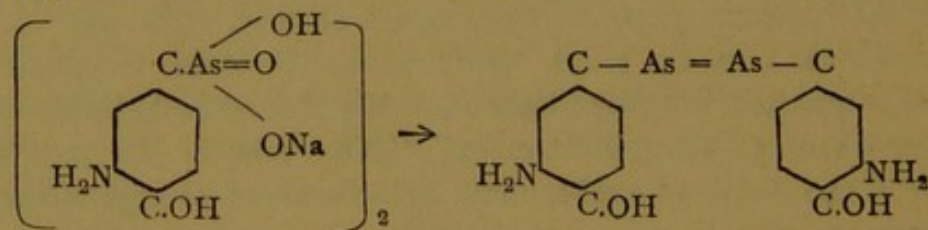


Details are also given concerning Diamino-arsenocresol and Tetramino-arsenophenol.

With regard to Example 4.—

Theoretically 263 Gm. Nitrophenol-arsonic acid require 40 Gm. NaOH for the salt or 80 Gm. for the Arsenic Hydroxyl and the Phenolic OH together, therefore 66 Gm. would require 10 Gm. or 20 Gm. respectively. The 225 Cc. of 2xN.NaOH used are equivalent to 18 Gm. NaOH, *i.e.*, 8 Gm. too much for the first case, and 2 Gm. too little for the second. As the Dioxy-diamino-arsenobenzol is stated to be thrown out, and the Sodium Sulphide is in the proportion of about 43 molecules, and the Magnesium Chloride about 3 molecules, it would be of interest to know the products of the reaction.

We have, therefore, a condensation from the Aminophenol-arsonate (containing As<sup>v</sup>) to '606':—





## THERAPEUTIC USES.

The modern treatment of syphilis according to Neisser is based on the discovery of spirochetes by Schaudinn, the discovery by Metchnikoff and Roux that syphilis can be communicated to Apes ; also that rabbits can be infected, as shown by Bartarelli and others ; and, finally, the introduction of the Wassermann-Neisser-Bruck Serum diagnosis method. The latter is, perhaps, the most important of all from the medical point of view. An immunity to syphilis does not exist ; neither immunisation nor serum-therapy are possible ; hence the value of the new 'chemo-therapy.' (Neisser, in the course of his investigations, determined that Mercury is an actual syphilis cure, that Iodine preparations are also curative, though much less so than Mercury.) Syphilitic infection, according to this authority, takes place throughout the entire system very rapidly after it is created—indeed, there is probably a saturation of the system through the blood stream at the moment of infection (68).

So far as syphilis is concerned, Neisser states Arsenophenylglycin, the immediate predecessor to '606' in popularity, and the new body are equally active, but the new body is less poisonous.

After Hata, a co-worker with Ehrlich, had demonstrated the curative power possessed by a single dose of the preparation on fowl spirillosis, on relapsing fever in rats and mice and syphilis in rabbits, Alt at Uchtsprunge received a supply (Sept., 1909) for trial on human beings. Spirochetes which were present in enormous numbers in a large chancre of the genitals of a rabbit disappeared in a day. Dogs were first injected, subsequently Alt's two assistants, Hoppe and Wittneben, injected themselves with 0.1 Gm. each and thus the treatment was extended to trials on lunatics (70). Subsequently Schreiber received a supply for trial in early syphilitic cases.

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A few phrases occur in the literature which it would be well to describe here:—

**Chemotherapy.**—'The principle of this is to employ chemical substances in infectious diseases in which the natural recuperative powers of the system, assisted by the formation of specific antibodies, are unable to bring about a restoration to health. All the early preparations made by the investigator acted destructively on the antibodies, but the new substance amongst hundreds was found in its action on *spirillosis* in animals to hinder the development of parasites whilst not being harmful to the patient, at least in the doses required to destroy the parasites' (112).

**Parasitotropic Chemicals** possess a strong avidity for the parasites and will kill them in the living being without injuring the tissues or organs in contradistinction to *organotropic* substances.

Ehrlich, in his division of chemical bodies, points out that all substances which are parasitotropic are *also poisons to the living organism, i.e.*, are also organotropic. Practically, therefore, one can only use as curative bodies those in which the *organo and parasitotropic properties* are in the right proportion.

A very large number of trials, in particular in the study of trypanosomiasis, showed a comparatively small range of chemical bodies having power of fixing trypanosomes. They fell into three classes: (1) Arsenic and Antimony Compounds; (2) certain Azo-dyes; (3) certain basic triphenyl-methane dyes, *e.g.*, Para-fuchsin, Methyl Violet and Pyronin. With a body of one group it was possible to produce a specific immunity in these protozoa against substances of the same group, but not against bodies in the other groups.

**Therapia Sterilisans Magna** is a phrase used by Ehrlich to denote the rapid killing off of all the specific germs by introducing a sufficiency of a parasitotropic chemical.

The idea of 'Therapia Sterilisans Magna' is a bold one. It is not improbable that during a lengthy treatment (with comparatively small dosage) with a poison like Arsenic that micro-organisms gradually become tolerant to it—they become in fact Arsenic-fast, whilst the tissues of the body, their host,



do not get the opportunity to recover before they are exposed to subsequent fresh infection. Alt satisfied himself as to the value of this surmise by experimenting on dogs.

McDonagh (102) has given a review of this initial work of Ehrlich's. He states the best results *in vivo* with '606' are obtained when the spirillar disease is at its height; the body is saturated with the specific organisms which produce antibodies, and obviously the more organisms the more antibody.

A. Lesser (105) provides a recent somewhat critical survey of Ehrlich's principle. He states that there is no exact proof of a direct parasitotropic action of '606' in the human organism. The claim that this is so is based, Lesser points out, on analogy with results of treating *spirillosis* in fowls and *trypanosome* infection in mice. Whether the action is spirillotropic or organotropic, '606' is, according to Lesser, the most powerful antisymphilitic so far in use.

## RESULTS.

We have arranged the results approximately in the following order:—

PRIMARY AND SECONDARY CASES OF SYPHILIS.

TERTIARY SYPHILIS AND REPORTS ON VARIED FORMS.

HEREDITARY CASES.

PARASYPHILITIC CASES.

COMPLICATIONS.

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### PRIMARY AND SECONDARY SYPHILIS.

Alt (1) states primary syphilitic sores were reduced in a few days by the administration of '606.' Indurating action was also reduced; maculo-papular eruptions of a moist ulcerating character were reduced in colour and dried up. Ulcerations on the genital labia healed in a few days; large papules on the back and side in most obstinate cases were cured, specific angina diminished—in short, the substance '606' was specific in its action with one injection.

Wechselmann (1a) first exhibited syphilitic patients who had been cured by '606' at the Berlin Medical Society, June 22, 1910. He was especially enthusiastic regarding cases of



tertiary ulcerations of palate and nose which had resisted Mercury and Potassium Iodide.

A rapid improvement in a papular crusted syphilide is reported, also the cure of a partly pemphigoid syphilide. Papules on tonsils and genital labia disappeared (4).

Papular syphilide extending over the entire body with various other signs of infection virtually cured (8), see also (75).

Equally rapid disappearance in secondary pustular squamous forms (75).

In one day induration and papules began to form fresh skin, roseola became reduced in colour, papules and condylomata appeared as if they were being dried up and drawn in by internal action. Headache and the pain of periostitis disappeared (12).

In three cases with hypertrophic papules on the tongue as large as hazel nuts these disappeared in 16 hours after intramuscular injection (14).

Several cases with initial induration showed distinct softening and cleaning of the base of the ulcer within 24 hours of the intramuscular injection. Amongst 81 cases of recent syphilis were ten with a macular exanthem. These rashes disappeared in three to five days. Of special interest was a case of syphilitic lichen in which after an intramuscular injection of 0.4 Gm. of '606' desquamation and disappearance of the trouble was complete on the seventh day. Pustular exanthem of the scalp and beard also disappeared 27 cases in which the organs of the throat were affected were successfully treated in two to seven days. Spots on the tongue, tonsils and gums disappeared. 29 cases of condylomata on genitals (scrotum and penis) cleared up in a few days; affections of female genitals were treated with equal success (14).

Superficial erosions, roseola, maculated syphilis, plaques, specific pharyngitis and angina disappeared in a few days (21). See also (49).

Primary and secondary exanthemata of the skin and mucous membrane receded in a few days (26, 75).

Results on the surface of the tonsils very similar to the effect with Antitoxin in the case of diphtheria (75).



The effect on specific lesions was frequently visible in 24 hours. A severe gangrenous case of primary syphilis, in which the prepuce was almost completely destroyed and the glans had been changed into an ulcerated surface, was specially well treated by 0.6 Gm. Disappearance of all ulceration and good granulations set in after seven days. Roseola disappeared in 10 to 20 days after 0.3 to 0.6 Gm. doses (30). See also (75).

Macular exanthemata and disease of the mucous membranes, whether erosions, plaques or ulceration, improved. Primary cases where a chancre existed frequently healed in 48 hours. Pustular exanthemata were also rapidly treated. Large papular syphilides are, however, less amenable, two injections being sometimes necessary. Bone disease reacts promptly. Swellings in the vessels are reduced. Syphilitic anæmia always well affected. The keratitis of hereditary syphilis requires local treatment in addition with an Arsenic preparation (56).

A most extraordinary view of the benefits of the discovery is provided from a 'highly conservative' Russian paper. It commences with 'The Liberation of Whoredom.' Some of it is hardly capable of being rendered into printable English. 'No more danger! Down with the family! No need to toil in the sweat of one's brow to support it! Long live prostitution—prostitution the like of which has not been seen since the downfall of Rome,' etc., etc. (65).

The results seem to be particularly gratifying in obstinate cases of malignant syphilis where other forms of treatment have been given up as unavailing—see (2) (4).

#### TERTIARY AND VARIED FORMS OF SYPHILIS.

The action of '606' in tertiary syphilis is especially remarkable (75). The large dose seems to be the moving factor in cutting down the time of treatment. This is particularly seen in treatment of gummata (14).

In three cases of gumma on the larynx the injections were practically life-saving (14).

The substance is deemed to be specific. In all cases there was a prompt diminution in the syphilitic appearances (7).



Apparently '606' has the property (a) of causing the pathological tissues to be quickly absorbed, (b) of causing epithelium to proliferate rapidly and to form skin over ulcers (25).

The opinion is frequently expressed that with a single dose of '606' one is able to produce the same effect as by a laborious five to six weeks' inunction or injection treatment by mercury.

Tertiary skin affections were treated with useful result. A case of malignant syphilis yielded remarkably. Cases of chronic pemphigus were well treated (26).

IRITIS treated in four days, papules and gummatous processes disappeared with astounding rapidity (29). Four cases of iritis papulosa improved (56). Lindenmeyer (108) treated five cases of keratitis of syphilitic origin with intragluteal injections of '606.' In four of the cases before treatment there was great sensitiveness to light. The eyes affected were only half open. Ten to 24 hours after injection the sensitiveness disappeared. Reaction on the cornea was not determined, but the time was too short for final statement of value.

Best results in MALIGNANT SYPHILIS, particularly in those cases in which there was little response to Mercury and Iodine (80).

McDonagh found general improvement throughout. The more severe the case the quicker the action, and the earlier the case the larger the dose required (35).

Hereditary syphilis in a boy of five: keratitis improved. Difficulty in hearing disappeared almost completely after 14 days. Improvement of incontinence and pain in a sufferer from tabes dorsalis. The sugar excretion of a diabetic patient with tertiary ulcers on the tongue disappeared (40).

Sores healed rapidly, as also throat and skin affections. Cases of periostitis showed rapid signs of subsidence (52).

Some advanced cases: two syphilis maligna, another was tuberculous. Dose—0.3 to 0.6 Gm. as a rule. Never higher than the latter at one time. Syphilitic signs on the skin and in mucous membrane began to disappear, even after 24 hours. Induration, papules and condylomata commenced to dry up and heal. Rapid improvement in specific angina and roseola.



Two cases of roseola were, however, not affected by 0.4 and 0.5 Gm. A case of recurrent gumma on the nose, which had previously required 10 calomel injections, was reduced with a single '606' injection of 0.3 Gm. Cerebral syphilis was well influenced by 0.5 Gm. Progressive paralysis was not well affected.

*Wechselmann* (112) relates his remarkable case of a youth of 18, who had previously since 1906 received all possible forms of treatment. On April 2nd, 1910, he was admitted to Wechselmann's hospital ward. 'He was then suffering with a bluish red patch on the inner side of the upper part of the thigh, partly cicatricial and partly ulcerating about the size of palm of the hand. On his head a similar patch  $2 \times 6$  Cm., with slimy serpiginous ulcers; several bones showed thickening; and there was ulceration of the throat. On the penis there was an open slimy ulceration of the skin of the glans and the ventral surface of the penis down to the fascia.' April 13th he received 0.25 Gm. of '606,' whereupon rapid recovery began. After a recurrence on June 27th a further dose of 0.45 Gm. was given, and a third on August 8th. The patient was now quite recovered and fit for work.

*Wechselmann* (*ibid.*) has treated over 1,100 patients. 'Eroded chancres become clean after 12 to 24 hours. In marked sclerosis the process takes place with equal rapidity, but absorption requires longer. There were only four instances in which an exanthem appeared after the healing of the primary sore. . . . *Plaques muqueuses* of the mouth heal in 24 to 48 hours. . . Roseola fades in a few days, as also malignant ulcerative syphilides, rupia, moist papules, small papular syphilides (usually so refractory) and gummata. For large papular syphilides a second injection is often necessary. Syphilitic bone disease, also the nocturnal pains are well treated; the latter disappear like magic.'

'Visceral syphilis, gummata of the testicle, syphilitic tumours of the larynx, icterus, epileptiform attacks of syphilitic origin, cerebral syphilis, paresis of the trochlearis and abducens muscles and pulmonary syphilis were very favourably influenced. In tabes dorsalis the subjective improvement was



very great. . . whether by suggestion or by salutary properties is not yet determined' (112).

#### HEREDITARY SYPHILIS.

A case of hereditary syphilitic eye affections, keratitis and iritis. After 0.4 Gm. gradual improvement. Wassermann's Reaction, however, still + after 18 days (13).

Report of a case of a woman in her last month of pregnancy, leucoderma of the throat, extraordinarily large genital condyloma infected with countless *spirochetes*. Wassermann-Neisser-Bruck reaction strongly positive. At first it was thought desirable to treat with '606' before parturition in order that the substance might react on both mother and child at the same time. Various difficulties being in the way (uncertainty as to date of delivery, etc.), it was decided to inject after delivery. Ten days after birth of the apparently syphilitic child the mother was treated with an injection of 0.3 Gm. of '606' in simple aqueous solution into the buttocks. Result—pain was set up three days afterwards at site of injection, headache, reduction of the foul condyloma, disappearance of the spirochetes. As to the child, this improved from the fifth day after the mother had been injected. The explanation of the cure of the child is difficult. First it was thought the milk contained its supply of '606,' then  $As_2O_3$  was surmised,—both were wrong, no arsenic found by Marsh test. The surmise is that the sudden killing off of the spirochetes set free a large quantity of endotoxins. This would produce Antitoxins, and these latter may have been carried over by the milk. The case suggests a promising method of treating syphilitic infants. The suggestion is made that in future syphilitic mothers must nurse their children and from the very beginning must be injected with '606,' or if this is not practicable a syphilitic wet nurse must be obtained for the infected child, and before nursing must be immediately injected with '606'! (22)

A hereditary case—a child of two months. Papulopustular syphilide with infiltration of the lips, coryza and osteochondritis on one upper arm. Dose, 0.02 Gm. intra-



muscularly. All the symptoms of disease had gone in 12 days (30).

A similar case to that previously reported (22), viz., in Münch. Med. Woch, Aug. 16, 1910 (v. p. 14). The mother was injected, Antitoxin being believed to have developed in sufficient quantity in the milk passing to the child to neutralise toxins, but it is conceivable that spirochetes remain which are not killed off, and it is thought desirable to inject the child also as soon as it is strong enough to stand it. (Ehrlich (109) advises that both mother and child should be injected.) For every kilo body weight dose suggested for the infant was 0.008 to 0.01 Gm. Recommendation for the injection of a syphilitic wet nurse repeated (31).

McDonagh (124a) says that though children may not be completely cured in this way yet they are put in a much more favourable condition for treatment by the drug direct. Dose in such cases should range between 0.004 to 0.005 Gm. per lb. body weight.

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*Neisser* (68) advises '606' in (a) where there is an idiosyncrasy to Mercury, and in cases where patients have apparently grown Mercury-resistant. In cerebral, ocular, hereditary, ulcerative and malignant syphilis in which immediate treatment is a matter of gravest importance; in severe leucoplakia and the like, in which the treatment often acts in a magical manner. (b) To remove toxic cachexias, especially in malignant cases. Patients in the most wretched condition recover and put on weight. (c) To remove symptoms dangerous from the contagious aspect. The fact that the treatment can be carried out successfully in a few days, compared with the length of time required for the Mercurial treatment, is a valuable feature in Ehrlich's discovery. By pressing the treatment in all directions it ought virtually to stamp out the disease.

"General opinion" at recent important meeting of scientists at Königsberg "appeared to be that '606' had wonderful effect in tertiary and primary syphilis and acted well in secondary: especially active in malignant and advanced



cases. Does not affect the eye—large doses in early stages cure in one dose—permanency yet to be proved" (125).

#### PARASYPHILITIC CONDITIONS.

A useful table of results, including a few cases of tabes and paralysis. A case of progressive paralysis in which there was disturbance of speech, loss of control in various ways, received 0.8 Gm., and tolerated the dose well (52).

Parasyphilitic conditions, tabes dorsalis and the like treated. Trials in parasyphilitic affections of the nervous and vascular system will only be possible in the very earliest stages (51).

In progressive paralysis there was little or no improvement (60).

Tabes not affected (61).

Parasyphilitic disease has been well treated. There would appear to be also some hope in treatment of paralysis (73).

A case of tabes and progressive paralysis received 0.5 Gm. Patient felt better in 10 days, but objectively there was no marked benefit (100).

Results not so brilliant in parasyphilitic conditions and nerve lesions of syphilis as in syphilitic affections of other parts (116).

In short, with regard to these affections good results can only be anticipated by employing the remedy at the very commencement of symptoms of disease.

#### COMPLICATIONS.

A case of syphilis coupled with phthisis. Mercury had not been able to remove the mucous papules and plaques in the mouth completely. They disappeared promptly with the new preparation. The lungs were not affected by the injection. Another similar case which had been under mercurial treatment six times, and in which the symptoms always recurred in the mucous membrane with typical late roseola was greatly improved at time of writing (13).

With regard to heart and nerve disease, etc.—complications: according to Alt cerebral syphilis is one of the most fruitful objects for treatment with '606,' providing care be



taken with the dose. The intravenous injection, as described by his colleagues Hoppe and Schreiber, under consideration. Sufferers from tabes have been well treated by this worker (70).

Syphilis with tubercular lesions. The latter were benefited. Secondary infection with streptococci and staphylococci often cured simultaneously. Gonorrhœa with syphilis: '606' has no effect on the *gonococci* (102).

With regard to Neisser's work, in which he was able to reinoculate apes a second time (see Specific Nature of Treatment) with syphilis, McDonagh (102) points out that a 'second attack' in man is regarded by many as impossible; this is probably due to the inefficiency of Mercury in producing a cure, therefore several such cases may be seen which have previously been treated with '606.'

Ehrlich has now details of 12,000 cases treated by physicians to whom the substance was supplied (see also Untoward Results).

### OTHER DISEASES TREATED.

It is thought that not only is the substance specific for syphilis, but also that it probably acts against *Spirillosa* in general. Indeed all diseases which are well treated by Arsenic could be submitted to '606' (12).

Relapsing fever has been treated by doses of 0.3 Gm., making up the solution to 250 Cc. or more with sterile physiological Salt Solution. This is injected into a vein of the arm. For the purpose a sterilised graduated bottle is employed, provided like a wash-bottle on one side with a rubber ball and on the other with the injection needle. The dose is quite sufficient for the treatment of Relapsing fever (21).

In malaria and relapsing fever the injection should be intravenous. The intravenous method would be preferable in all cases where rapid action is required (54).

McIntosh has experimented with '606' on recurrent fever in rats. Refers to Hata's original communication ('Verhandlungen des Kong. f. Inn. Med. Wiesbaden,' p. 235, 1910). 0.005 Gm. of '606' (subcutaneously) for a rat of



100 Gm. was found to be most suitable amount as a curative dose. The chance of any toxic effects occurring in the employment of a therapeutic dose of '606' is extremely remote, as his experiments show that the '*dosis maxima bene tolerata*' is six times as great as the '*dosis curativa*' (36).

Some further results have been obtained in the treatment of malaria. 22 cases, 11 tropical and 11 tertian infection, are reported on. Intramuscular, subcutaneous and intravenous methods have been tried. Latterly, on recommendation of Ehrlich, combined treatment, intravenous one day followed by subcutaneous the next. Tertian ague was much less resistant to '606' than the Aestivo-autumnal. Parasites disappeared from peripheral blood in all 11 cases of tertian fever promptly—three times within 12 hours, five times within 24, and three times within 48 hours of injection without reappearing except in three cases. In each of these three cases small doses (0.3 to 0.5 Gm.) had been given. Using larger doses (0.6 to 0.7 Gm.) especially combined use of this dose twice, one day intravenously and the second subcutaneously, there was no subsequent recurrence] in Tertian malaria. In the Aestivo-autumnal cases they disappeared in only five cases promptly after injection. In the other six cases it was impossible to drive away the parasites completely even with the combined dose above mentioned.

Iversen (72) has used '606' in malaria. Five slight cases of Tertian ague were injected with excellent results. He then tried it in the Caucasus—in a region saturated with malaria. 27 Tertiary, 4 Quartan, 27 Tropical and 2 Tertian-tropical received 0.45 to 0.8 Gm. intravenously and subcutaneously before, during, and after the paroxysms. Results—Tertian cases about 70% cured after intravenous injection of 0.5 Gm. Parasites disappeared from the blood in about 12 to 24 hours. There were no further paroxysms. In about 30% paroxysms ceased, but parasites did not disappear so rapidly.

Quartan and Tropical cases not treated so well, but there was improvement. Arsenobenzol is not specific for malaria.

Ehrlich (69) gives a résumé of these cases.

Concerning Relapsing Fever. \* Dose used 0.3 Gm. This



was rapidly curative. The spirochetes disappeared from the blood in five to ten hours. Simultaneously with their disappearance clinical symptoms improved (72).

Framboesia in the West Indies had been well treated with '606.' Vincent's angina cured in four days (109).

Leprosy in Russia (113) has been treated with '606.' Two young men (20 years of age) who had been lepers for ten years and were both severe sufferers from *photophobia* received injections. There was little pain, their fear of light disappeared, and temperature had fallen about a degree. The reduction remained permanent. Ulcer on the leg of one patient showed signs of cicatrisation.

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#### THE TREATMENT OF SYPHILIS BY '606' COMPARED WITH OTHER MODES OF TREATMENT.

*Alt* (1) employed Atoxyl and Arsenophenylglycin prior to working with '606.' Dose of Arsenophenylglycin was 0.8 Gm.—results with the latter were on the whole satisfactory, but the new body is more active and produces less objectionable after-effects. He compares results (70).

Cases have frequently been demonstrated of good effect of '606' after Mercury, Atoxyl, Iodide, and Decoctum Zittmanni had produced little beneficial result, see (8).

*Neisser* (68) recommends that every case should be treated twice when possible, *i.e.*, the dose especially when using less than 0.6 Gm. should be repeated after three to six weeks and supplemented by a Mercurial course in addition, as he does not rely completely on a single dose of '606.'

#### SPECIFIC NATURE OF THE TREATMENT.

Of 12 infected monkeys treated with '606' some time after the initial symptoms had disappeared, five could be reinfected some months later with human syphilitic material, and after the usual incubation period they presented typical primary lesions, although they had certainly been originally healed (16); but there is evidence that re-inoculation with syphilis may take place before the first infection cured (128).



A. Loxton (48) writes pointing out that to him the point demonstrated by Neisser is the most hopeful record of all so far with '606.'

*Ehrlich* (69) writes concerning the *specific action* of '606.' With a sufficient dose the *spirochetes disappear* in 24 to 48 hours, if longer it is due to the dose being insufficient or insufficiently absorbed, or that the type of spirochetes to be dealt with are Arsenic-resistant. A *second fact* proving the specific action of '606' is the formation of SPECIFIC ANTI-BODIES (*c.f.* in particular the formation of these in the case of the cure of a syphilitic child through the medium of the mother's milk). The *serum of patients* cured by '606' has been shown to have a curative action by injection, especially in the case of hereditary infantile syphilis. This Serum action is insufficient to act as an absolute cure. If one out of 1,000 spirochetes remain behind, this is quite sufficient to produce recurrence (see also ref. No. 79). A *third point* to show the specific action is the result with the WASSERMANN TEST, which in 90% or more of cases becomes negative after the injection; but, in some cases, early stages in primary affection and occasionally in malignant affections the result is exactly in the opposite direction, negative before and positive after the dose. Ehrlich explains this fact thus, in such cases the number of spirochetes is too small to bring out the reaction, but after the extinction of the spirochetes by the injection the entire amount of endotoxins is absorbed, and hence produces a + reaction. Wassermann's reaction is therefore a reaction of the organism on the absorbed contents—assimilation products, endotoxins—of the spirochetes. As a *fourth proof* of specificity Ehrlich draws attention to the *extraordinary rapidity* with which the medicament acts. A patient with a gumma on the tonsils, which had been treated for a couple of months without success, had an injection of '606'; within five hours' time the patient could eat a slice of bread and butter. A patient with iritis exudativus could only see a finger at a metre's distance three hours after 0.4 Gm. of '606' he could see himself in the glass at 5 metres, and could read small print 20 hours afterwards. One has to assume, in the specific removal of pain



which '606' exercises, that the pain is due to secretions of the spirochetes which are neutralised by '606' in a manner like toxin is neutralised by antitoxin.

## DOSE.

In opening a tube of '606' it is a convenient plan, having previously shaken the contents into the opposite end, to warm the neck of the tube in a flame and then snap off with a piece of moistened gauze (106) or, to simplify, employ a small file.

*N.B.*—The basic substance (prepared by precipitation) is not stable. Again, the Di-Sodium Compound in solution is unstable (similarly, the Mono-Sodium body should be regarded with caution—W.H.M.). *Suspensions or solutions for use must, therefore, be freshly prepared, or grave consequences may result.*—Quoted from the Manufacturers of '606.'

0.5 Gm. may be taken as a rule as a sufficient intramuscular or subcutaneous dose, but larger amounts (0.6, 0.7, 0.8 Gm. up to even one Gm.) are advocated by the Manufacturers in the case of strongly built adult males according to nature of the case. In the case of women, 0.45 up to 0.5 Gm. is generally sufficient. For exceedingly weakly patients a dose of 0.3 to 0.4 Gm. is suitable. For children 0.2 up to 0.3 Gm. is suitable, and infants have received injections of 0.02 up to 0.1 Gm. with good result (see also page 32).

Trials have been made with *minute* doses of the substance. Even with these small doses improvement was to be seen (26).

Experiments on animals have demonstrated that trypanosomes may accustom themselves very rapidly to an *insufficient* dose of '606,'—therefore as large a dose as possible must be given to permanently cure the animal (77).

The fact that there was great difficulty in producing Arsenic-fast forms in spirilla-infections points to the fact that repeated doses can be given in these diseases without evil result to the patient. A *Therapia sterilisans fractionata* could indeed be employed, in which one would kill off with each injection a portion of the parasites (77).



It is a difficult matter to determine a dose for '606' that shall be active and yet safe. Ehrlich (109) says Alt, to whom he first gave the substance for trial, is still (Oct., 1910) using only 0·3 to 0·4 Gm. The original trials by Alt (1) were with 0·3 Gm. of the substance. This quantity (see Alt) (1) is well mixed with about 10 Cc. of sterile water. 2 to 2·3 Cc. sterile  $N/1$  NaOH Solution are added so as to leave a small portion undissolved. It is then diluted to 20 Cc. with water, adding a small quantity of Eusemin as anæsthetic, the dose being 10 Cc. into each gluteal muscle—*c.f.* 'Methods of Injection' and 'Local Anæsthetics.'

The **highest dose** employed by Schreiber & Hoppe (7) in 300 cases was 0·0096 Gm. per kilo body weight. (Note, a 12-stone man would, therefore, receive, according to these authorities, at most 0·8 Gm.) It is doubtful, according to them, whether 0·6 to 0·7 Gm. suffices to cure in one dose—so far this was used without danger. Much higher doses than 0·8 Gm. have been used.—*Vide infra.*

The **toxic dose** used subcutaneously for rabbits is said to be 0·15 Gm. per kilo, *i.e.*, approximately 10 to 15 times the highest dose used in man. An average rabbit weighs about 2,000 Gm., therefore, toxic dose for these animals would be about 0·3 Gm. (see also 129).

Statements have been made to the effect that 0·3 Gm. for a human being should not be exceeded.

0·4 to 0·5 Gm. was employed in a number of cases, the dose being given in 20 Cc.—a half into each gluteal muscle (14).

In cases of *primary* affection, in view of the virulence of the spirochetes, 0·5 to 0·6 Gm. is necessary, whilst for later affections 0·4 Gm. suffices (17).

McDonagh (102) also finds that a much larger dose of '606' has to be used to heal an early chancre than to cure completely an extensive gummatous ulceration.

Neisser mentions that 1 Gm. doses (single injection) have been given to adults (68); Ehrlich says 0·6 to 0·8 Gm. is safe (102).

A report on some cases of syphilitic skin disease includes 47 males and 28 females, 6 children (4 male and 2 female).



The latter received dose 0.05 to 0.1 Gm. up to 0.2 Gm. if necessary. Adults 0.3 Gm. to start with, and later 0.4, 0.6, 0.8, and even up to 1.2 Gm. 52 received one injection only, 17 received two, and 6 received three (26).

*Alt* does not advise more than 0.5 Gm. for a dose, this being suitable for especially strong adults. A higher dose than this has occasioned, especially in recent syphilis, a rise in temperature approaching  $39.5^{\circ}\text{C.}$ , has also disturbed heart action, created a tendency to sickness, etc. (27). (See also 'Rise in Temperature' and 'After-Effects.')

Dealing with cases which will not react to the substance, Stern's conclusions are that 0.5 Gm. is too small a dose in many cases, that even with 0.7 to 0.8 Gm. some Arsenic-resistant spirochetes may form, and that, thirdly, the general idea that it is possible to cure syphilis with a single dose is not correct. The future will show to what extent a repeat dose can be safely given (in view of the cumulation of arsenic in the muscles and the local action). (See also 'Intramuscular Method of Injection.')

*Ehrlich* in a recent communication (69) says *in the case of nerve diseases 0.4 Gm. should be considered a maximum, but in ordinary syphilitic affections, especially primary cases, 0.7 to 0.8 Gm. should be given*, and even higher than this, or by repeated dose—the main issue is to counteract infection as rapidly and completely as possible. (See also 'Methods of Injection.')

**Repetition of dose** (see also *Intravenous followed by Intramuscular Injection*, under 'Methods of Injection').

The question as to safe time limit for repeating the dose naturally came up for very careful consideration.

In some cases there seemed to be an arrest of improvement after 0.3 Gm.,—hence these authors (26) adopted an increased dosage at fortnightly intervals—*e.g.*, 0.4 Gm. as first dose, then 0.6 to 0.7 after 14 days, then 0.9 to 1 Gm. after a further fortnight's interval.

An intravenous injection was given four weeks after an intramuscular, and was well tolerated (7).

*Wechselmann* states that contrary to the fear of possible danger with regard to the repetition of dose of '606' it is quite



safe to reinject, if necessary, eight days after the first dose; obviously it would be better to wait if possible for three or four weeks, so that the centres of attack may be in a quiescent state ready for the fresh dose (46).

*Neisser* (68) says 'in four weeks a total of 2.4 Gm. in three doses may be reached, but on account of the slow elimination there is possibility of cumulative toxic effect.'

### METHODS OF INJECTION.

There are various methods of injecting the preparation:—

**Intramuscular Injection**, *i.e.*, into the gluteal muscles. This was the first method of use.

**Subcutaneous Injection** into the tissues adjoining bases of the shoulder blades.

**Intravenous Injection**.—In this method, which is said to be painless, the 'dose' is given in much greater dilution—about 200 to 250 Cc. of diluent being employed.

**Intravenous followed by Intramuscular Injection** to prolong or intensify the action.

Whichever mode of procedure is adopted, the solutions must be freshly prepared:—

### Intramuscular Injections.

*With the deep intramuscular injections it is important to wait and see that blood does not escape from the puncture before injection. The injection must be made slowly and absolutely intramuscular—none of the alkaline liquid must escape into the surrounding tissues. Adequate antiseptic measures must be adopted, e.g. sterilising the skin with Iodine Tincture. The part may be massaged afterwards to spread the injection over as large an area as possible.*

**EHRlich's 1% INTRAMUSCULAR INJECTION** (in Schreiber and Hoppe's communication) (7).

Dissolve 0.6 Gm. of the substance in Glycol\* 3 Cc. by rubbing with a glass rod—addition of a few drops of water will assist solution. Now add water 12 Cc., shake and add (in one portion) 10.3 Cc. of  $N/5$  NaOH. Shake (a clear liquid is now formed) and make up to 60 Cc.—the entire

\*Ehrlich referred to Ethylene-Glycol  $CH_2 OH. CH_2 OH$ .



process may well be done in a graduated cylinder. This solution has been superseded by later formulæ. It contains insufficient alkali to completely set free the base.

#### A SUBSEQUENT FORMULA BY EHRLICH.

0.4 to 0.5 Gm. of '606' is mixed with  $\frac{1}{2}$  to 1 Cc. of Methyl Alcohol, dissolved in water with addition of 5 to 8 Cc. of  $N/_{10}$  NaOH (or *q.s.* to saturation) and diluted to 25 or 30 Cc. with water. This produces a clear yellow solution, half to be injected into each gluteal muscle. Said to be less painful than former (12), but still contains insufficient alkali.

#### SCHREIBER & HOPPE'S INTRAMUSCULAR INJECTION (7).

Moisten 0.6 to 0.7 Gm., the single dose, with about  $\frac{1}{2}$  Cc. of Methyl Alcohol in a 150 Cc. Cylinder. Add about 10 Cc. of sterile water and shake thoroughly, then add Sterile  $N/_{1}$  NaOH Solution in sufficient quantity to almost completely dissolve the substance with thorough shaking. Shaking is important to promote reaction and prevent excess being added. About 3.5 to 4 Cc. will be required. Add water *q.s.* to 60 Cc. and inject this solution, 30 Cc. into the right gluteal muscle and 30 Cc. into the left, using as fine a needle as possible with the slightest possible amount of pressure. (A brownish insoluble portion rapidly settles to the bottom of the solution and may be rejected before use; by so doing there is no danger of blocking the needles). This injection would be alkaline to test paper (see also p. 41).

#### WECHSELMANN'S INJECTION.

Wechselmann (4) employed intragluteal and subcutaneous injections. First of all he used the Dihydrochloride dissolved in a little Methyl Alcohol or Glycol, this was mixed with 10 Cc. of water, and then 1 to 2 Cc.  $N/_{10}$  NaOH added and finally made up to 25 Cc. with water. The 'strongly acid' solution was injected. Later he added enough alkali to form the Monohydrochloride—(i.e., until slight opalescence was visible), and finally he has utilised a *neutral* suspension. For this he adds  $N/_{10}$  NaOH until the reaction is *alkaline* to Phenol-



phthalein. He then neutralises with Acetic Acid. This forms a slightly opalescent neutral painless injection.

A still further modification by Wechsellmann and Lange, Deut. Med. Woch. No. 30, July 28, 1910 (see also 112) is to dissolve the dose in 1 to 2 Cc. Commercial Sodium Hydrate Solution (P.G. is 15% by weight), to precipitate with Glacial Acetic Acid added drop by drop, to collect the precipitate and *suspend* it in 1 to 2 Cc. Distilled Water, adding either N/10 NaOH or 1% Acetic Acid, whichever is necessary to neutralise, to litmus paper. This is quite painless for intramuscular use (49) and for subcutaneous injection below the shoulder blade.

When used as a deep intramuscular injection one patient reported a feeling of local tension at site of injection. In 24 hours this reached as far as the calves of the legs (49).

The suspension may also be *centrifugalised* (19), the liquor rejected, and the yellow precipitate suspended in Physiological Salt Solution. This is then ready for injection. The injection often causes inflammation, which heals with induration and thickening. The danger attending its use is small (112).

Alt does not approve of the addition of Methyl Alcohol, the use of Phenolphthalein as indicator, and the suggestion to dissolve in excess of alkali and titrate back with Acid, etc. All this, he says, had been tried by Ehrlich long ago. Acid solutions are *poisonous* (not 'non-poisonous') (27).

### ALT'S INTRAMUSCULAR INJECTION.

Alt's more recent directions are to place 30 moderate sized glass beads\* in a 100 Cc. stoppered graduated cylinder, to add 10 Cc. of Distilled Water and then the powder. By slight shaking the substance is easily dissolved. For every 0.1 Gm. of the substance add about 0.5 Cc. Normal NaOH and shake again energetically for about half a minute. This forms a perfectly clear and slightly alkaline solution which can be diluted as desired (20 to 30 Cc.). The preparation does not always require *the same quantity of NaOH*. By this method the smallest quantity of NaOH is used, and hence

\* The glass beads are hardly necessary.



one produces the least pain. Using more than 20 to 30 Cc. of Solution for 0.3 Gm. of substance the feeling of tension is greater on the first day on account of the greater pressure, but disappears more quickly. According to Alt's studies of Arsenic elimination by the intramuscular injection of a suspension of '606' much less of the substance produces a reaction than when an alkaline solution is used (27). The amount of alkali used approximates theory for forming the base.

INTRAMUSCULAR INJECTION OF MICHAELIS (*modified by Spiethoff*).—An emulsion of 0.6 Gm. in 9 to 10 Cc. of vehicle. First a hot solution of '606' in about 8 Cc. Physiological Salt Solution is prepared. This is made alkaline with Concentrated NaOH Solution (about 3 drops), in presence of Phenolphthalein—then the excess of alkali is removed by a drop or two of strong Acetic Acid, finally rendering alkaline again with  $N/1$  NaOH at the bedside immediately before use. An important point in this method is the reduction of the volume of the injection to about 9 or 10 Cc., which is said to have a good deal to do with keeping down the pain (30). The injection may be made for the patient's comfort on *one side only* into the gluteal muscle, selecting the side on which patient is not in the habit of resting.

Michaelis (81), in recommending this *practically Neutral Suspension*, says he cannot believe that the action with this can be slower than with the alkaline injections. He injects now in preference a little deeper than before into the muscles of the back, somewhat at the side of the spinal column and below the thorax. Patients in this way can recline with more comfort.

As a general rule, after an intramuscular injection the patient should remain lying on his stomach for a while. The pain produced—some feel it more than others—can be diminished by use of the sitzbad (26).

Another operator (84) did not find the pain caused by the use of intramuscular injection of the alkaline solution to be a great difficulty. The subcutaneous or intramuscular use of a neutral emulsion is generally less painful, but not always so.

Pain after intramuscular injections, which usually lasts several hours, depends in great measure on the rate of



injection, and whether the injection has been made in vicinity of a nerve. Patient should rest for three or four days, even after pain has ceased. If allowed to walk about pain may return after three or four days, though not so severely (7).

Intramuscular injections into the *arm muscles* have also been practised.

A **Suspension in Liquid Paraffin** has also been used—injected into gluteal muscles. This requires a needle with fairly large lumen (52).

Taege (98), on the other hand, says **Oil Suspensions**, like those used in mercurial injections, are unsuitable—they are too thick, unless one uses large quantities of oil. See also *Neisser*,—*Subcutaneous Injections*.

#### INJECTIONS OF 'ACID' PREPARATIONS.

Duhot (97), concerning the technique of the preparation of the injection, points out that the processes of Wechsellmann and of Michaelis (solution in Alkali and adjustment to neutrality by means of a few drops of Acetic Acid) is tedious and not easily applied. Reports on 325 cases in which a modified and simpler method is used. He prefers a complete solution of the substance to a suspension, as this is more likely to produce the '*Complete Sterilisation of the system*.'

Pain is kept down by reducing the volume of the injection from 8 Cc. to 5 Cc., also by injecting high up in the outer hip region, in place of the deep injections into the buttock. His directions are simply :—

Rub the powder with  $\frac{1}{2}$  Cc. of Methyl Alcohol in a glass mortar, then add 4 to 6 Cc. Normal Saline. He injects the dose with a 5 Cc. 'Record' Syringe, which is provided with a Platinum Needle 2 to 4 Cm. in length. To find the best spot for injection he draws a line from *the spina oss. il. anter.* to the point of the gluteal fold. The most suitable place to inject is a region about the size of a two-shilling piece situated in the border between the upper and second third part of this line. Has used 1 Gm. doses as an average for a 70 kilo patient. Rest of two days after the injection, warm compresses to the part and warm bath necessary. Intramuscular injections found more active than intravenous, and preferred. Advan-



tages over Suspensions are (a) not more painful; (b) never produce pustulation or swellings; (c) more potent and rapid; (d) the injections take 5 minutes; and no danger of bacterial infection whilst preparing the solution.

Taege (98) prepares his solution as follows:—The contents of tube is shaken into a dry sterilised test tube. Glycerin is added in proportion of two drops to each 0.1 Gm. of the substance. Mix intimately, breaking up particles at the same time. To this add a sufficiency of freshly boiled (hot) water from a test tube, and dissolve with aid of a glass rod. Injection is then ready for use. Inject in one spot only deeply into the gluteal muscle.

The pain with this 'Acid' preparation is not marked, providing the outside of the needle be free from solution and the tissue through which the needle passes is not contaminated with it. There must be good muscle formation present. Pain was considerable in three emaciated women.

The solution must be freshly prepared—an old solution, on adding  $H_2S$ , becomes darker, showing decomposition.

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*N.B.—The manufacturers in their printed matter have thought fit to advise only one, i.e., a neutral suspension for either intramuscular or subcutaneous injection. We provide a résumé of their directions on page 31. In view of the great diversity of opinion expressed as to the relative values of the different forms of injection, physicians may nevertheless favour a complete solution as distinct from a suspension, be it either slightly alkaline or have the acidity inherent to the compound as supplied for use. Cf. Sequeira page 59.*

### Subcutaneous Injections.

The subcutaneous method has been coming more into vogue latterly—it is said to act more rapidly, and to be more completely absorbed. Statements occur to the effect that the subcutaneous is even more painful than intramuscular injection (21), but if made perfectly neutral there is little pain, and in any case pain in the back is better borne than



in the buttock muscle (55). The best place for this method of injection is about midway between spine and lower end of the shoulder-blade. Neutral suspension of Wechsellmann used (50). Injections in the chest are also made—in man into a fold of tissue below the nipple, in women below the mammary gland.

Subcutaneous injection is not so suitable as intramuscular where the skin is taut—e.g., in young people or in emaciation—for these the intramuscular dose would be preferable.

#### BLASCHKO'S METHOD (a).

Acetic Acid to neutralise excess of alkali, if used, produces a hypertonic solution of Sodium Acetate, which itself is not free from pain. The more correct procedure is to add just sufficient alkali to throw out the base. 0.5 Gm. of the Dihydrochloride requires 0.45 Gm. of 20 per cent. by weight NaOH solution = 0.36 Cc. (assuming Sp.Gr. 1.25.—W. H. M.). By use of only the necessary quantity of Alkali, and finally a drop or two of Acetic or Hydrochloric Acid, one produces a more satisfactory injection. Dilute the dose to only 8 or 9 Cc. This is said to produce a Salt Solution approximating that of Physiological Salt Solution in which the base is suspended, or even 5 Cc. will suffice, as the NaCl solution so made is said to be not too hypertonic to be painful. Such suspensions could be put up in sealed ampoules (51). *This is a suspension of the base.*

The following (b) given (52) amounts to the same thing. To every 0.1 Gm. of '606' 0.072 Cc. of 20 per cent. NaOH is added (e.g., 0.432 Cc. to a dose of 0.6 Gm.). The powder is rubbed to a paste with the Alkali in a mortar. 1 to 2 Cc. of water are added, and the mixture again triturated; finally 5 Cc. of Physiological Salt Solution is added to make the suspension for use. It is neutral and contains correct amount of alkali to precipitate the base. Site of injection usually just below lower angle of the scapula. The injection is made fairly deeply into the subcutaneous tissue to avoid unpleasant results. Almost the entire length of the needle which is moderately coarse is introduced and gradually withdrawn as the fluid enters. About the third day infiltration is seen, and this



increases for several days until a hard mass can be seen and felt, which gradually disappears after several weeks.

McDonagh (102) prepares his injection by rubbing the powder with 1 Cc. saturated NaOH Solution, adding 3 to 4 Cc. *hot* water, then 3 drops Phenolphthalein Solution and enough Glacial Acetic Acid to make a fine yellow emulsion. Finally a drop or two of the Soda—*i.e.*, sufficient to produce a pink colour.

Subcutaneous injections (according to *Neisser*, (68) produce slow and protracted action. The injection is painful if excess of alkali be used. He suggests that combined treatment by Intravenous Injection (of 0.4 Gm.) and Subcutaneous (0.5 Gm.) will probably prove useful. He, himself, has had good effect with an *Olive Oil Suspension of the Hydrochloride*. These are decidedly *non-irritating* if freshly made each time, and are to be preferred to Paraffin emulsions, as being more readily absorbed. The bulk of the injection should be kept down, *i.e.*, an emulsion of not more than 6 Cc. may preferably be used.

As to *the site of the injection*, McDonagh (102) injects "under the trapezius on a line with the spine of the scapula midway between the scapula and the vertebral column—on the left in right-handed individuals, and *vice versa*." Not infrequently difficulty in breathing occurs, especially in plethoric individuals, owing to a spasm of the intercostal muscles. Emphysematous patients should have the injection into the gluteal muscle.

Most patients hardly notice the subcutaneous injection between the shoulder-blades at the time (two male patients, however, fainted with it), but all complained of great pain two hours after the dose (106).

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INTRAMUSCULAR OR SUBCUTANEOUS SUSPENSION (Neutral)  
as advised by the Manufacturers of '606' in their German  
Directions.

Place the contents of a 'Salvarsan' tube (0.6 Gm.) in a small porcelain dish and rub it carefully with about 9 to 10 drops of Sodium Hydrate Solution 15% by weight (Sp. Gr.



1·17) then add, whilst continuing to rub with glass rod as at first, drop by drop the required amount of sterile water for making the injection—about 5 to 10 Cc.\* By this means one produces a fine suspension which is to be neutralised to Litmus Paper by the addition of either more Sodium Hydrate Solution or of Dilute Hydrochloric Acid of the P.G. strength. Obviously if less dose than 0·6 Gm. be desired one uses proportionate amount of alkali :—

For a dose of 0·2 Gm. 3 to 4 drops of 15% Sodium Hydrate.

" " 0·3 Gm. 4 to 5 " " "

" " 0·4 Gm. 6 to 7 " " "

" " 0·5 Gm. 8 drops, and so on in proportion—but

it might be preferable to dissolve the full quantity in the tube and reject a proportionate volume.

The firm of W. Martindale prepares a '606' Outfit containing 'Record' syringe with platinum needles, porcelain dish, glass rod, sodium hydrate solution, hydrochloric acid, test papers, directions for use and a tube of 'Salvarsan.'

### Intravenous Injections.

The advantage of the intravenous method is that it is practically painless (21, and others) and there are seldom objectionable local effects at point of injection. **Dose** :—As a rule less of the preparation is used than by the other methods, the average being 0·3 for women to 0·4 Gm. for men, diluted to about 200 to 300 Cc., repeated in three or four weeks. Larger doses than 0·5 Gm. are not advised.

Intravenous Injections must be suitably diluted. On two occasions out of three described (using a superficial vein in the elbow) all went well, but on the third (giving 0·4 Gm.) the dose was insufficiently diluted, *i.e.*, it was injected in only 15 Cc. of water instead of 150 to 200 Cc. This killed the patient in 3½ hours (26).

Ehrlich defends the intravenous method. He says 300 intravenous injections in general cases have been made, and as much as 1 Gm. had been safely used intravenously. Even 0·45 Gm., intravenously, in a case of severest tertiary syphilis, where there existed extreme emaciation, had been used with success. By intravenous injection elimination is

\* A little more water we found on trial necessary.



rapid—intramuscular injections are more lasting and intensive (33).

'DILUTE SOLUTION' Ehrlich (Intravenous). In Schreiber and Hoppe's paper (7):—

*Solution A.* 0.6 Gm. of the substance, 0.3 to 0.5 Cc. Methyl Alcohol or 3 Cc. Glycol.

*Solution B.* 240 Cc. or more Physiological Salt Solution. 10.3 Cc.  $N/5NaOH$ . Solution *A* is poured into *B* with thorough stirring.

Neisser in an early communication (3) states that he employed the intravenous method wherever possible. In a much later communication (68) he pointed out that intravenous injections of '606' (max. 0.5 Gm. in 200 Cc.) are energetic and rapid, but the action on spirochetes is correspondingly lessened.

Schreiber and Hoppe (7) used an Alkaline Intravenous Injection, diluting the equivalent of a dose of 0.45 Gm. to about 80 to 100 Cc.

Intravenous Injections are, in a manner, more trustworthy, *i.e.*, the dose given is known. Elimination is comparatively rapid—it may be complete about the fourth day.

#### SCHREIBER AND HOPPE'S INTRAVENOUS INJECTION.

(From a further communication.)

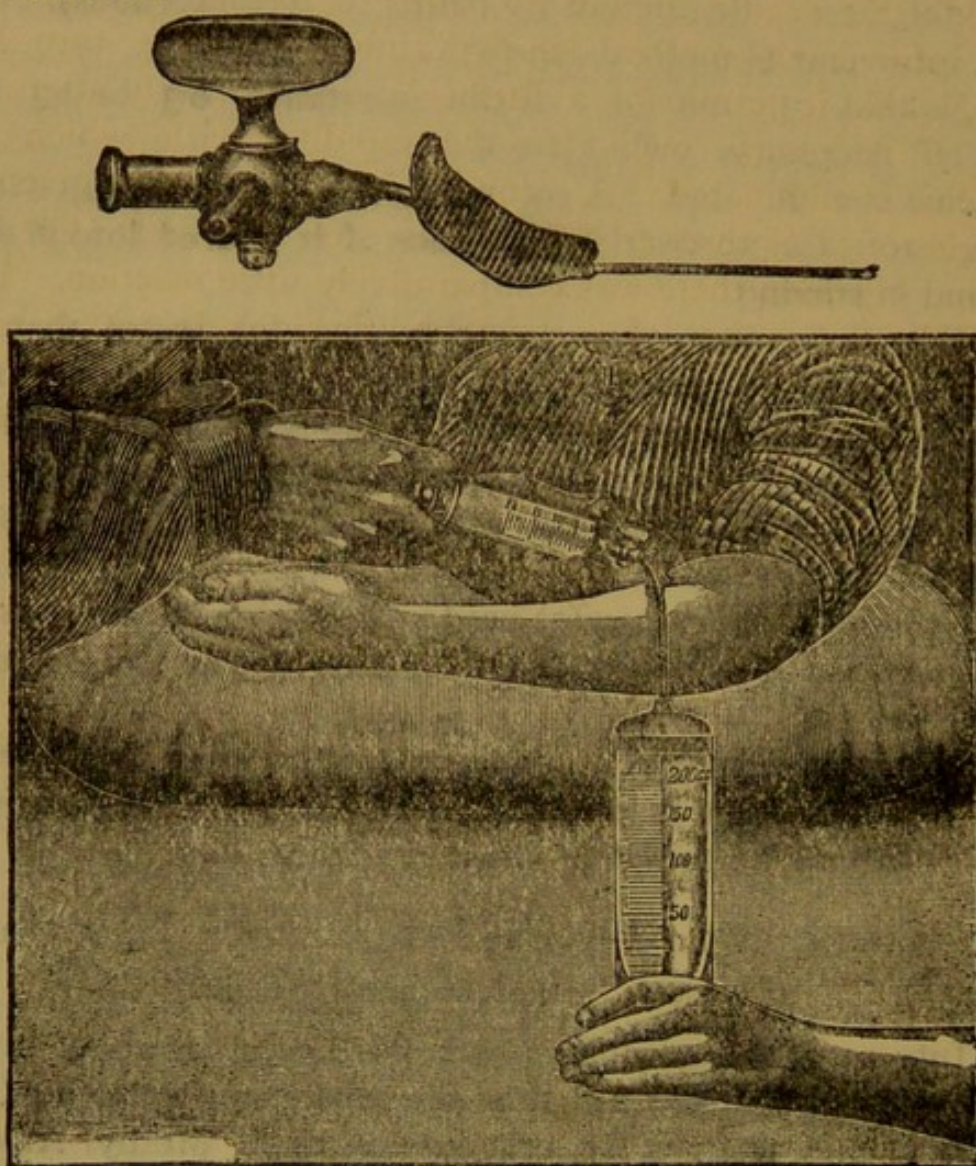
Into a 200 Cc. graduated stoppered cylinder about 10 to 20 Cc. of water are placed, then the substance (0.3 to 0.5 Gm. is shaken in and 0.3 Cc. or a few drops of Methyl Alcohol added to dissolve. To this about 1 Cc.  $N/1NaOH$  to every 0.1 Gm. or *q.s.* is added to dissolve, and sterile Physiological Saline *q.s.* to 180 Cc., finally making up to 200 or 250 Cc. (15). This is slightly alkaline.

#### ALT'S INTRAVENOUS INJECTION.

By means of glass beads and a Cylinder or Separator, previously described (see page 26), one can produce a *suspension* rapidly. Place 8.5 Cc. of water in the cylinder, then the substance and for every 0.1 Gm. of it about 0.3 Cc.  $N/1NaOH$ . Shake well for half a minute. Such a suspension is evenly distributed (27).



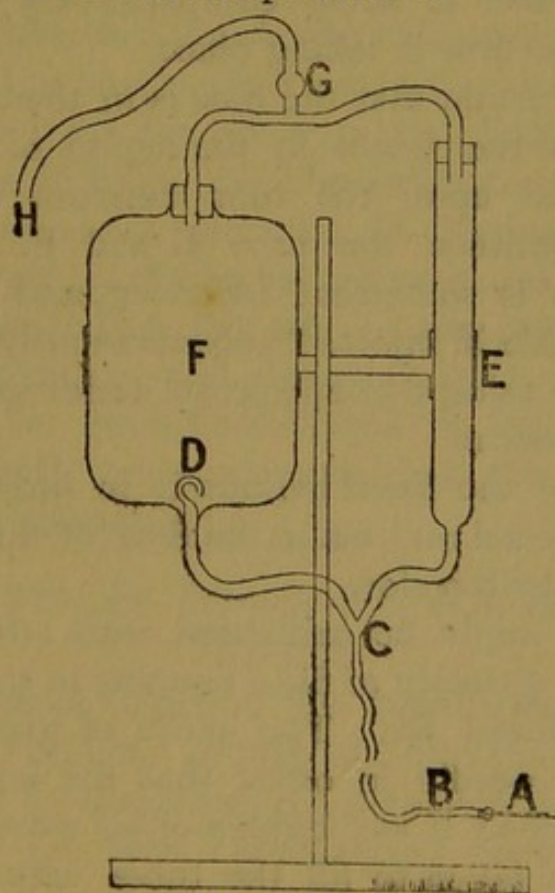
With regard to technique of the intravenous injection Schreiber (54), writing again on the subject, gives following information :—



A special syringe is recommended by him provided with an attachment and three-way cock, so that the solution for injection can be sucked up and then on turning the tap can be injected direct into the vein. A preliminary injection is first made with Normal Saline Solution to make certain that the needle actually rests in the vein and that it has not gone through the other side of it. Further, when the injection is made every care must be taken to prevent the injection passing into the tissues, as this is liable to set up painful infiltration. After the injection of the '606' a further small quantity of Normal Saline is injected as a precaution. Should



the needle have come out or have damaged the vein elsewhere one immediately notices that the injection is causing swelling and pain, otherwise if all goes well, excepting for the prick of the needle, there is no pain. A further advantage of the intravenous method, though involving more care and skill, is that it permits of a further injection shortly after the first if necessary, owing to the rapidity with which the Arsenic is eliminated. A second injection has been given in a series of cases three to four weeks after the first. On this second injection there was comparatively little reaction. It is given by this author when the syphilitic signs do not abate, or when the Wassermann test remains positive after four weeks. With regard to reaction following intravenous injection where the central nerve system is attacked, as in tabes, the rise in temperature often occurred somewhat later than in syphilis. Even on the second day vomiting and diarrhoea have been observed as sequels to injection, as also headache, and on one occasion urticaria. In the case of weakly syphilitic persons it is well to inject a small dose as a trial and then to repeat if the trial is satisfactory. Where prompt action is required the intravenous method is to be preferred.



GRÜNBAUM'S INTRAVENOUS APPARATUS.



## GRÜNBAUM'S INTRAVENOUS INJECTION

From a private communication. (See also page 54.)

The apparatus which I have used for the injection of '606' into the veins, consists of an exploring needle A, connected by a short piece of rubber tube with a piece of glass tubing B, this in turn by a long piece of rubber tubing with a three-way tube C. Between B and C an ordinary clip is placed. C is connected with two vessels E and F. F is of 400 Cc. capacity. The outlet from the lower end of the vessel F should be something of the shape represented in the diagram D, in order that any small heavy particles such as minute fragments of glass shall not pass out of it into the tube. E is a smaller, narrower vessel. Clips are placed between C and F and between C and E. The vessels are closed above by rubber corks through which tubes pass to connect to the three-way tube G. In G is a filter of cotton wool, and the tube passing from it to H is connected to small hand-bellows. The object of this somewhat complicated apparatus is to permit of the injection of a small quantity of normal saline first, in order to be certain that the needle is in the vein. The vessel E being comparatively narrow allows one to see that the flow is taking place.

When one is certain that the flow is in the vein, and there is no distension of the tissues in the region of the vein, then the clip is placed upon the tube between C and E and removed from between the tube C and F. The alkaline solution of '606' is somewhat irritating, and would lead to considerable trouble if injected subcutaneously in the region of a vein, and by using this apparatus accidents of that kind are not likely to occur.

The object of the hand bellows is in order to raise the pressure of the vessel and make the flow of fluid more rapid in case it should be too slow.

The vessel F might be calibrated with advantage. It is true that a small quantity of fluid remains in the vessel F, but that can be allowed for. The piece of glass tubing B is inserted near the needle in order that the injection may be immediately stopped if any bubble of air were to appear. If all precautions be taken to fill the tubes with normal saline



before the beginning of the injection this should not occur, but it is a precaution which is worth adopting.

*Schreiber* (71) says Methyl Alcohol is no longer necessary to assist solution, as the substance is now comparatively easily soluble in water. He adds after solution  $N/1 NaOH$  2·8 to 3 Cc. for 0·4 Gm., or a little more if necessary, if on shaking a clear solution is not formed. The solution is then diluted for use. It is slightly alkaline—consisting of Mono-Sodium compound. An ordinary syringe is used, but the needle has a bayonet-shaped attachment, etc., as already described. Four hundred cases treated with this method without severe consequences, but doses of 0·5 Gm. may produce diarrhœa and sickness. Acid Solutions must not be employed. The preparation is suitable for use locally to primary affections and condylomata.

*Weintraud* (107) employs a vein canula,  $1\frac{1}{2}$  metres of rubber tubing and a cylindrical funnel. The dose is first dissolved in 30 Cc. hot water, and this solution added to a sufficiency of physiological salt solution warmed to blood heat containing enough  $NaOH$  to redissolve the basic 'Arsenobenzol' which is thrown out from the Dihydrochloride on neutralising. (This sounds simple, but obviously to produce a fairly neutral solution *one must know beforehand* how much alkali is required—and samples are stated to vary. The amounts required by theory for the Mono-Sodium and the Di-Sodium compound are given on page 39). 0·8 Gm. as a dose has not been exceeded. There is no reaction at the site of the injection, but rise in temperature, sickness and diarrhœa may occur in the first few hours. The remarkable signs of healing appear even more quickly with the intravenous than the intramuscular or subcutaneous methods.

#### MANUFACTURERS' DIRECTIONS FOR INTRAVENOUS INJECTION.

For intravenous injection the manufacturers advise for a 0·5 Gm. dose 1·09 Gm. = 0·94 Cc. of 15% Sodium Hydrate solution. To be dissolved in a porcelain dish and made up to 100 to 250 Cc. with Physiological Salt solution (0·9%) and filtered.



The manufacturers *also* advise proceeding on the *following* lines. Add 'Salvarsan' 0.6 Gm. to about 30 or 40 Cc. Physiological Salt solution contained in a 300 Cc. stoppered cylinder provided with about 50 sterile glass beads. Dissolve by shaking thoroughly, add 1.308 Gm. = 1.14 Cc. (about 23 drops) of 15% Sodium Hydrate solution. A precipitate is formed which redissolves. Dilute the clear yellow solution to 300 Cc. with Physiological Salt Solution. One or two more drops of Sodium Hydrate may be required.

Each 50 Cc. of this solution contains 0.1 Gm., *i.e.*, 150 Cc. form an average dose for women, and 200 Cc. for men.

A 250 Cc. Burette divided into 50 Cc.'s with rubber tubing, pinch clip and canula is suitable for use.

#### **Intravenous followed by Intramuscular Injection.**

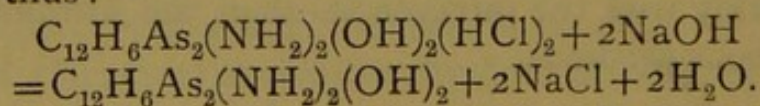
It has been found useful to employ first 0.4 to 0.5 Gm. intravenously, and after 48 hours to inject 0.3 to 0.4 Gm. intramuscularly (21).

Alt (27) states this will probably be the method of the future.

The recommendation is repeated to inject first intravenously and then intramuscularly so as by this means to increase the dose. It may be that by a single intramuscular injection one does not kill all the spirochetes—possibly a resistant form remains (54).

#### **AUTHORS' NOTE ON CHEMISTRY OF THE INJECTIONS.**

The reaction which takes place on bringing Sodium Hydrate in contact with Dioxy-diamino-arsenobenzol may be indicated thus:—



438.972 Gm. require 2000 Cc. N/1 NaOH. approx.

∴ 0.3	"	"	1.37 Cc.	"	"	"
0.4	"	"	1.82 Cc.	"	"	"
0.5	"	"	2.28 Cc.	"	"	"
0.6	"	"	2.73 Cc.	"	"	"
0.7	"	"	3.19 Cc.	"	"	"

We see from the above that the **basic substance** is formed and may be precipitated from solution.



By the use of *half the amount of* Sodium Hydrate in the above it will be evident that a body of the formula  $C_{12}H_6As_2(NH_2)_2(OH)_2HCl$  can be formed.

In this case—

0.3 Gm. of the { Di-hydrochloride } 0.68 Cc. N/1 NaOH approx.  
would require

0.4 " " " 0.91 Cc. " " "

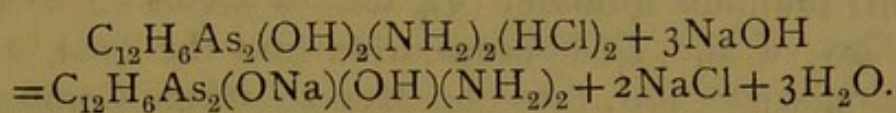
0.5 " " " 1.14 Cc. " " "

0.6 " " " 1.36 Cc. " " "

0.7 " " " 1.59 Cc. " " "

to produce **Mono-hydrochloride**.

Again, it is possible to replace one or two Hydrogen atoms of the Phenolic Hydroxyls (after saturating the HCl radicals), producing Mono- and Di-Sodium compounds as follows :—



In this instance

0.3 Gm. of the { Di-hydrochloride } 2.05 Cc. N/1 NaOH approx.  
would require

0.4 " " " 2.73 Cc. " " "

0.5 " " " 3.42 Cc. " " "

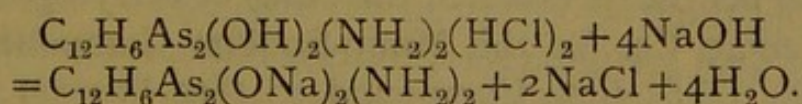
0.6 " " " 4.1 Cc. " " "

0.7 " " " 4.78 Cc. " " "

to produce the **Mono-Sodium** Compound.

The Mono-Sodium Compound is, at any rate, conceivable theoretically—we have not observed any reference to it in the literature.

Carrying the reaction into the final stage we have :—



i.e., 0.3 Gm. { Di-hydrochloride } 2.73 Cc. N/1 NaOH approx.  
of the { would require

" 0.4 " " 3.64 Cc. " " "

" 0.5 " " 4.56 Cc. " " "

" 0.6 " " 5.47 Cc. " " "

" 0.7 " " 6.38 Cc. " " "

to produce **Di-Sodium** Compound.



An important practical point has now to be considered. We see from the above that 1.0 Gm. requires 4.56 Cc.  $N/1$  NaOH to form the base, and 2.28 Cc. to form the Mono-hydrochloride. Hata states that 1.0 Gm. dissolved in 10 Cc. Methyl Alcohol and 90 Cc. water produces a permanent opalescence with 2.2 Cc., i.e., approximating the amount necessary for making the Mono-hydrochloride, which is, therefore, less soluble than the Di-hydrochloride. On adding 5.4 Cc. in place of this 2.2 Cc., the precipitate of the base, he says, is just re-dissolved.

From this we note that 0.84 Cc. are added in excess of that demanded for the precipitation of the base, so that in making solutions where an excess of Alkali is to be avoided (and using Methyl Alcohol, which may affect solubility slightly), we must carefully bear this proportion in mind.

Note that this quantity (5.4 Cc.) is about *q.s.* to convert 0.632 Gm. of the Di-hydrochloride into the base, and the remaining 0.368 Gm. into the Mono-Sodium Compound to form a *soluble compound*.

Regarding the use by Alt—*vide* page 22—of '2 to 2.3 Cc.'  $N/1$  NaOH for 0.3 Gm. of the body, note that this quantity of the Di-hydrochloride would require 1.37 Cc. to set free the base and 2.05 Cc. to make the Mono-Sodium Compound, and also 2.74 Cc. to make the Di-Sodium Compound. This Injection therefore, *chemically* speaking, does not contain any uncombined alkali.

Regarding the use by Ehrlich (7) of 10.3 Cc. of  $N/5$  NaOH to 0.6 Gm.: this quantity should require 13.66 Cc. of  $N/5$  NaOH to neutralise (set free the base) or carrying the matter further, 20.49 Cc. for the Mono-Sodium Compound or 27.3 Cc. for the Di-Sodium Compound, so that here on all counts there is insufficient of the alkali to form these compounds. There is slightly more than *q.s.* to convert into Mono-hydrochloride.

In a subsequent formula by Ehrlich (12) 0.4 to 0.5 Gm. theoretically (on same formula) require 18.2 to 22.8 Cc.  $N/10$  NaOH to set free the base, but the operator uses only 5 to 8 Cc. for this purpose. For the Mono-Sodium Com-



pound 27.3 to 34.2 Cc. would be wanted, and for the Di-Sodium body 36.4 to 45.6 Cc. Obviously, according to Hata the amount used is also insufficient to dissolve precipitate.

*Re* Schreiber and Hoppe's (7) use of 3.5 to 4 Cc. of  $N/1$  NaOH for 0.6 to 0.7 Gm., 0.6 Gm. obviously from our chemical-formula would require 2.73 Cc. only to neutralise (set free the base) and 4.1 Cc. for the Mono-Sodium body by substituting Na for the H in OH or 5.5 Cc. to make the Di-Sodium Compound. According to Hata's data, however, 3.24 Cc. only is necessary, hence they approximately agree.

For Blaschko's injection (52 b). To use 0.072 Cc. 20% (w/w) NaOH to 0.1 Gm. is the same as 2.25 Cc.  $N/1$  NaOH to 0.5 Gm. This is approximately correct for precipitating the base.

The use by Alt (27) of 0.5 Cc.  $N/1$  NaOH to each 0.1 Gm. of '606': this is near theory for precipitating the base.

The use by Schreiber and Hoppe subsequently (15) of 3 Cc.  $N/1$  NaOH to 0.3 Gm. (1 Cc. to each 0.1 Gm.) is slightly more than necessary to make Di-Sodium Compound.

The use by Schreiber (71) of 2.8 to 3 Cc.  $N/1$  NaOH for 0.4 Gm. approximates the amount necessary for producing the Mono-Sodium Compound (2.75 Cc. is correct). Hata would employ *only* 2.16 Cc. for this amount, using Methyl Alcohol.

The direction by the manufacturers to employ in the Intravenous Injection 1.308 Gm. of 15 per cent. NaOH to 0.6 Gm. Di-hydrochloride, i.e., 4.9 Cc.  $N/1$  NaOH, is a little more than the amount necessary to make the Mono-Sodium Compound—see formulæ *antea*.

In any case where not indicated the amount of the Mono- and Di-Sodium Compounds can be found by working on the basis that for the Mono-Sodium Compound 0.5 Gm. requires 3.431 Cc.  $N/1$  NaOH, and for the Di-Sodium body 0.5 Gm. of the Di-hydrochloride requires 4.58 Cc., as previously described. The reader will be able to see at a glance which body is formed in any formula by reference to the figures on p. 39, bearing in mind the important point shown by Hata.

*Briefly, the minimum of Alkali should be employed as found experimentally sufficient to dissolve.*



Anomalies of this kind seem also to have struck Blaschko (51), who gives a useful paper. He commences by demonstrating that the alkaline solutions of Schreiber should be rejected by reason of the pain they produce, and the use of Methyl Alcohol is to be avoided on account of its being poisonous. For further details see Subcutaneous Injections—Blaschko.

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In general, Ehrlich (69), in his latest report, says the alkaline injection, as used by Alt (34) and Iversen, *appears to possess the strongest action, though they are more painful than the neutral emulsion of Michaelis or Wechselmann. The neutral injection might well be used in the case of neurasthenics and those who feel pain greatly. In other cases the alkaline solution may be the more active* (but the general opinion favoured Wechselmann, (125). Combined intravenous and subcutaneous injections will probably be the most effectual, e.g., 0.4 to 0.5 Gm. intravenously, and then two to four days later a subcutaneous or intramuscular injection (69). We would emphasise these remarks by impressing on the user the necessity of not making his solution too alkaline, otherwise serious, if only transient, consequences may be expected.

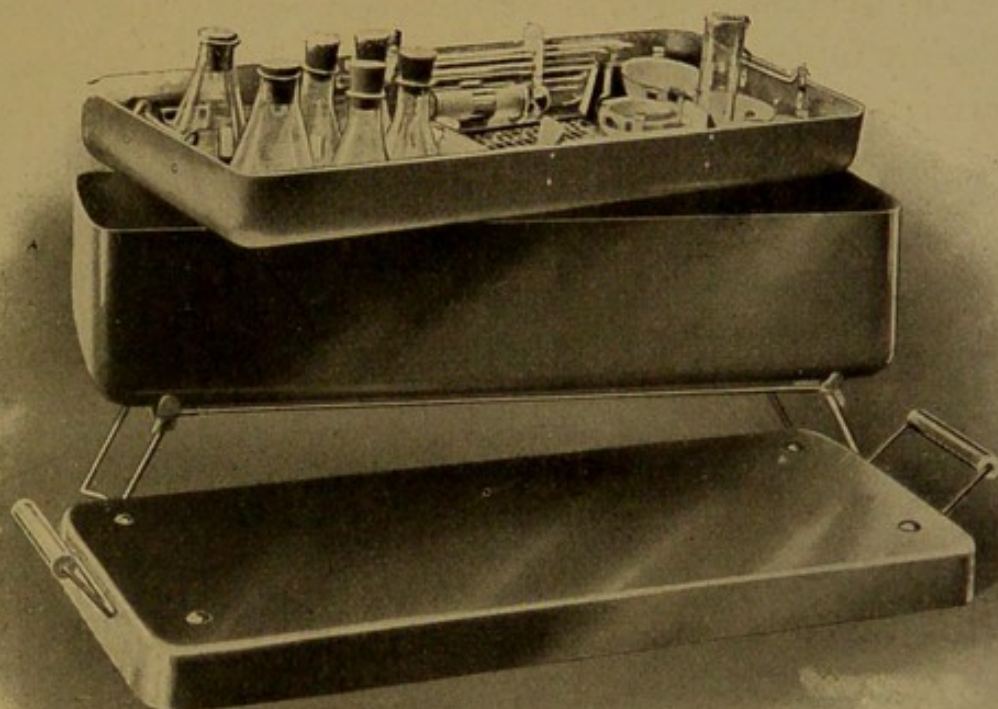
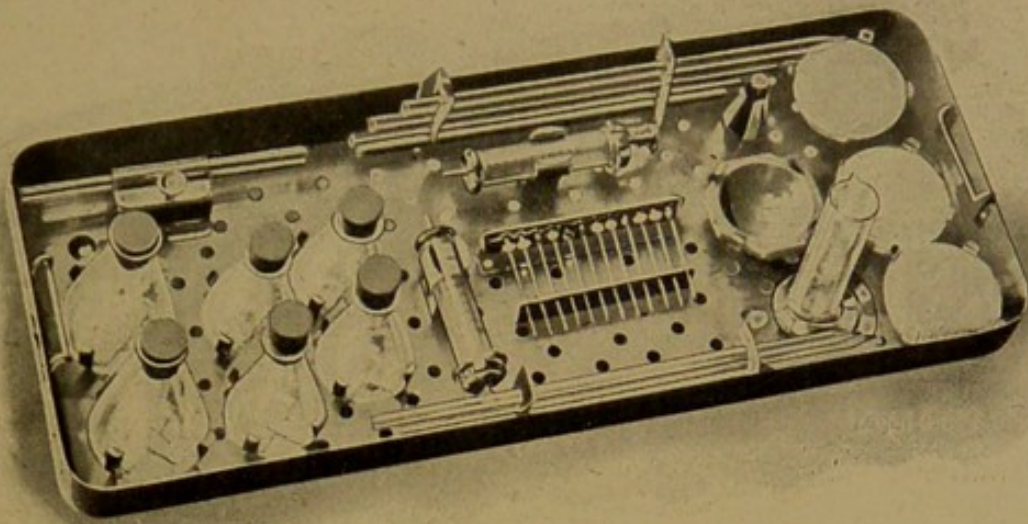
#### APPARATUS USED.

For *intramuscular injection* a 10 Cc. sterilizable syringe with 10 Cm. needle may be employed (14). For subcutaneous use 5 to 6 Cm. needles are sufficiently long.

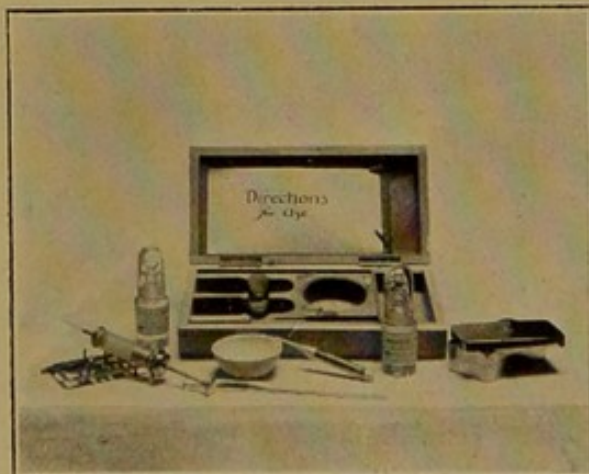
An account is given (110) of a complete apparatus for carrying out the Injection. The Outfit contains mortar, pestle, pipettes, measure, syringe, needles, flasks, etc., Concentrated Soda Solution, Glacial Acetic Acid  $N/_{10}$  NaOH, 1% Acetic Acid, Sodium Chloride, etc. It is complete for Wechselmann's method or that of Michaelis. See also Martindale's Outfit, p. 32.

For *intravenous injection* a special syringe with handy finger grip and three-way tap is designed. See page 34.





A COMPLETE OUTFIT FOR VARIOUS METHODS OF  
INJECTING '606.'



MARTINDALE'S OUTFIT FOR INTRAMUSCULAR AND  
SUBCUTANEOUS INJECTION OF '606.'







also the Apparatus of Grünbaum, p. 35. In the absence of these a length of rubber tubing, vein canula and funnel should operate satisfactorily. See page 38.

### LOCAL ANÆSTHETICS.

Alt employed Eusemin to alleviate the pain. (Eusemin: a solution of 5 of Adrenalin Chloride, 1 in 1,000, Cocaine Hydrochloride 0.75, in Physiological Salt Solution 100—Extra Pharmacopœia, Edition xiv. p. 829.)

Morphine in dose of 0.01 Gm. used with advantage where pain excessive with subcutaneous injections (50).

Previous injection of 2 Cc. of 1% Novocain Solution has also been advised, and is said to render the injections absolutely painless. Ethyl chloride has also been used.

### LOCAL USE OF '606.'

For condylomata a powder containing '606' has been used, as also a 50 % Ointment: strongly caustic when used in this manner and hence curative (71).

### HERXHEIMER'S REACTION.

*Skin Eruptions.*—Urticaria and erythema frequently follow the intramuscular injections, sometimes extending over the entire body (14). See also (75).

'Herxheimer's Reaction,' in which the eruption increases temporarily soon after the injection (it becomes darker and appears to have spread) was given in most marked manner, even in two hours after injection, reaching its highest point in 12 hours, and disappearing in two to four days (12).

Herxheimer observed the reaction both with small (0.3 Gm.) and large (0.5 Gm.) dose (20).

The reaction was observed in three cases. It is believed to be due to the fact that in these cases an insufficient curative dose had been given (21).

One gets a similar effect at the commencement of Mercurial treatment. Ehrlich deals with the subject (69). He confirms that it is due to an insufficient dose, especially when it occurs 24 hours or more after injection.



## UNTOWARD RESULTS—ARSENIC RETENTION.

Arsenic Retention may well be viewed as the principal untoward result. This is likely to occur by the intragluteal method of injection, the intravenous method has therefore been thought more 'accurate' (6 and 7).

In the use of an intramuscular injection after 36 days it was possible to find a very large proportion of the Arsenic still in the muscles. Inflammation may hence occur (7).

*Death.* A case of death after 0.5 Gm. is reported. The case in question was the subject of much complication, bad nutrition and respiration, *hypoplasia* of the heart (30).

Ehrlich says that the case of death referred to in 'Münch. Med. Woch.,' Aug. 23rd, p. 1771, see Intravenous Injections (26), was a matter of idiosyncrasy (33).

A death (99) is reported with 0.5 Gm. injected by Wechsellmann's method in the scapular region without any local reaction. Patient had had two apoplectic attacks. Poisonous symptoms developed in nervous system. Tremor, sweating, loss of strength,—no symptoms in the digestive organs. Temperature rose to 39.8, died on the fifth day with appearance of advanced heart paralysis. Post-mortem examination showed acute parenchymatous degeneration of the organs.

Death of a child 10 days after 0.02 Gm. (100).

**Estimation of the Arsenic** excreted in the urine from paralytics who received various doses—0.1, 0.3, 0.4 Gm., etc., by intramuscular injection, showed that upwards of half the total Arsenic was excreted in about ten days. The elimination is very gradual in these cases. With epileptics with normal kidney function the elimination was complete in four or five days, but there was greater absorption also. In general it appears the excretion is much slower with '606' than with Atoxyl or Arsacetin or Arsenophenylglycin when injected subcutaneously; also that whilst Atoxyl and Arsacetin are excreted quickly and almost completely by the urine in the case of Arsenophenylglycin and '606,' the Arsenic is largely to be found in the fæces (10). See also (64).



Some unpleasant experiences with the preparation are recorded (1). Urine retention which lasted some days; Albuminuria also seen as an effect of the injection; disappearance of patellar reflexes; marked tenesmus and constipation. These symptoms thought to be very similar to those which accompanied Atoxyl (11).

*Alt* lays stress on the fact that the cessation of Arsenic output in the urine does not necessarily mean that there is no more Arsenic in the body; on the contrary, there may be a considerable deposit of Arsenic in the muscles which may lead to poisoning, especially if the dose be repeated (27).

Suppuration seen five times in 375 cases (56).

*Ehrlich*, in a recent communication (69) deals with poisonous results. He points out that one may chloroform 50,000 soldiers without a death. (As a matter of fact, the mortality in general, he says, has been one in 2,060 or 2,080.) If patients suffering from heart disease were chloroformed the mortality would be 1 or 2% or more. Mortality with Chloroform is, therefore, dependent on the type of patients—so, also, with Arsenic bodies—indeed, all bodies. There has been no report of the slightest eye trouble with the preparation. The cases of death (about 12 in 12,000 cases), refer almost exclusively to cases of severe affections of the nervous system, tabes complicated with cystitis and cachexia, bulbar manifestations, patients with extensive epidermal softening and the like (69, 75).

Two cases of necrosis of the gluteal muscles after injection have been recorded. In one case death occurred ten days after the injection, in the other six weeks. Description of the specimens (74).

A death (a case of supposed cerebro-spinal syphilis) was hastened by a dose of the substance (102). Important to conduct a 'Wassermann' before injecting with '606.' Unless this is done it is prophesied 'several' non-syphilitics will be treated with '606.'

With regard to danger of injurious action upon the optic nerve, animal experiments show there is little fear with the new synthetic. The preparation has, indeed, been used in cases where there existed optic atrophy without ill effect. Optic



neuritis may have to be treated with '606' as being of syphilitic origin.—*Wechselmann* (112).

### WARNINGS.

Apart from the questions of toxicity of dose and Arsenic retention and other untoward results (see 'Contra-indications'), *Idiosyncrasy to Arsenic* may exist. It may be desirable to try a cuti-reaction with an arsenical solution in advance (7). Indeed it has been recommended to employ the substance '606' for the purpose.

Intravenous injections must be suitably diluted. See Intravenous Method.

### AFTER EFFECTS.

Headache and sickness have been observed (1 and 3). Pain in limbs after injection (26).

Intramuscular injections prepared by Alt's slightly modified method are usually painful at the time. There is subsequently a feeling of heaviness, also of numbness in the legs, later swelling and infiltration at the point of injection. In spite of narcotics, the pain is so severe that patients lie on their stomachs and are unable to sleep. After eight to fourteen days the swollen gluteal region has become somewhat reduced, but sometimes, even for weeks, lumps as large as pigeon's eggs remain. Pain ceases as a rule in about a week. Dose used was 0.3 to 0.6 Gm. (75).

*Sequelæ to treatment* in the order of frequency of occurrence—headache, shaking in the legs, sense of cardiac oppression, difficulty in breathing, nausea, loss of appetite. To abstract this paper at length would occupy more space than this book can allow, but one can confidently recommend it to those seeking a temperate account; indeed it is in great measure contrary to the exaggerated views of many who have written on the subject (114).

### AFTER EFFECTS ON THE KIDNEY.

The general opinion seems to be that the introduction into the system of the new Arsenical Compound produces no irritation of the kidney (7).



In a number of cases no kidney trouble, except that in one case albuminuria followed (patient had double inflammation of the lungs) (26).

Action on kidney *nil* (30, 75).

### RISE IN TEMPERATURE.

Alt (1) observed a rise in temperature after the injection, 'but not higher than  $38.8^{\circ}\text{C}.$ ' Neisser (3) found rise as high as  $39.5^{\circ}\text{C}.$ , but it 'soon falls again' (see also 7). Schreiber (7) found as a rule rise not above  $38^{\circ}\text{C}.$

Rise in temperature up to  $37.5^{\circ}$  to  $38.5^{\circ}\text{C}.$  was noticed in most cases, usually dropping after second or third day (12),—(see also 106).

Temperature went up to  $40^{\circ}\text{C}.$  (26).

A larger dose than 0.5 Gm. may occasionally cause temperature to rise to  $39.5^{\circ}\text{C}.$ —should not be given (27).

In addition to the first customary fever stage, a fresh fever period was observed, viz., mostly at the end of the second or third day (30),—see also (49).

'Usually rises to  $39^{\circ}\text{C}.$  After 24 hours usually normal again' (50).

### EFFECT ON GENERAL HEALTH.

Metabolism, in particular Lecithin-metabolism, is stated to be well influenced by the injection (5, 7).

No disturbance of digestive function seen (7).

The statement is frequently made that the heart action is not upset by the treatment (14).

Patients' weight increased (26, 106).

General health is considerably affected; patients become pale and lose appetite. Recovery in one or two days (75).

### RECURRENCE.

Whether a dose of 0.6 to 0.7 Gm. suffices to prevent recurrence could not be stated—it is not known with certainty whether the dose will kill off all the spirochetes 'at one shot' (7).

Recurrence was observed in one case which had been treated with a small dose (0.14 Gm.) intravenously (12).



No recurrence in any cases treated (81 recent cases) (14).

Several advanced cases recurred (55).

A case of roseola, another of nasal gumma, another of specific angina, each with dose 0.3 Gm., and another a tubero-serpiginous syphilide of the upper lip (dose, 0.5 Gm.). See also 'Results.'

Eight recurrences in 375 cases (56).

It is possible that second larger doses will not be of much avail, the parasites may have become immune (102). For this reason the first dose should be adequate. An adult should receive not less than 0.5 Gm. A safe dose according to Ehrlich is 0.6 to 0.8 Gm., see also (115).

Some of the relapses may be due to encapsulated foci of the disease not accessible to the remedy (112).

### CONTRA-INDICATIONS.

Where serious disease of the organs of circulation or of the kidneys exist; also all general diseases and cachexias (7).

Heart affections, eye diseases, optical anomalies, putrid bronchial catarrh (20). This author also views infantile congenital syphilis as a contra-indication.

Bad nutrition must be considered in particular, especially where there are severe non-specific changes in organs of circulation (30).

Ehrlich says patients with very advanced degenerative processes of the central nervous system form a group which must not be treated with the preparation either intravenously or intramuscularly. Brain diseases, arterio-sclerosis, heart disturbances, especially angina pectoris, must be regarded as danger signals (33).

Contra-indications:—

- (a) Severe non-syphilitic retinal and optic disease.
- (b) Severe heart and vascular disease.
- (c) Severe lung affections.
- (d) Severe non-syphilitic kidney affections.
- (e) Advanced degenerative processes of the central nervous system.
- (f) Those suffering from angina and fever.

The treatment should be procrastinated (56)



Patients who have had one or two attacks of hemiplegia, advanced cases of tabes, general paralysis of the insane, should never have the injection. Cardiac disease, marked arterio-sclerosis, and Bright's disease are contra-indications (102).

A paper dealing with the forms of heart disease which form a contra-indication to '606,' states that Spirochetes exercise more often than is usually thought a dangerous power over the organs of circulation. In the action of spirochetes, even in the early periods of syphilitic disease, numberless disturbances occur which are either of clinically slight importance, or may amount to marked insufficiency of heart beat. Marked bradycardia in a syphilitic of late degree points to a strict contra-indication to the use of '606.' Fresh inflammatory heart affections naturally afford a strong contra-indication. The most difficult phase to decide upon will be chronic insufficiency of heart action. When one discovers that degenerative changes of the parenchyma have commenced in the heart muscle, Arsenic injections must not be conducted. Arsenic injections, it is well known, have a pathological influence on parenchyma. A number of other forms of heart trouble are discussed, but the article concludes with the remark, 'Experience is necessary, and some of it will be serious experience' (66).

There is often a fall in blood pressure after the injection, which in cases of cardiac debility may occasionally be very dangerous (112). Contra-indications, according to Ehrlich are 'heart affections and vascular disease' (69).

#### WASSERMANN'S REACTION, EFFECT ON.

Results with regard to Wassermann's Test, subsequent to injection, vary.

Alt, per Schreiber (1), states four out of 27 primary cases were negative to the test after injection, whilst in the case of 23 paralytic cases giving + reaction, a comparatively small proportion gave negative subsequently. In a larger proportion there was reduction in extent of response to the test.

Neisser (3a) 'was struck by the fact that only 10% of the cases treated showed a transition from a + to - Wassermann,



while recurrences were also observed in some cases. He has however, no doubt as to the specificity of the drug.'

Fifty out of 52 cases lost their positive reaction to the test in fifty days. It is believed that the arsenical body has no action on the test. Experimentally it was found to neither hinder or favour hæmolysis (7). It is well known to be otherwise with Mercury.

The reaction was little affected, but the time which had elapsed was too short to express an opinion, and doses relatively small (12).

In five out of 20 cases, 35 to 40 days after injection, reaction negative. In the remaining cases tested, eight to 21 days after injection the reaction still remained + (14).

*Rapid Results.*—In one case, for example, Wassermann's test changed to negative in 40 hours (15).

A table is given showing the gradual appearance during eight weeks of the negative sign in 15 cases treated with various doses (30). A similar table is given (114).

Results not uniform. Fact was noted that five cases of tertiary syphilis which prior to treatment were—after injection gradually became + (39). *Vide also infra.*

The detection of spirochetes in the blood, as also a positive serum reaction, permit of early recognition of syphilis; indeed, these two aids enable cases to be placed under treatment which previously had not been recognised as syphilitic. A negative Wassermann reaction in the early stages is, however, not to be looked upon as final proof of absence of syphilis. The treatment should be begun as early as possible.—*Neisser* (68).

With the aid of serum diagnosis it will be possible, *Neisser* (68) thinks, to separate the latent and hopeless cases from those which can be rapidly treated by the new chemical, but the division is not easy in practice, as it is found that even after several negative reactions have been obtained one finds recurrence and positive indication.

*Ehrlich* (69) dwells on the importance of the Wassermann reaction. He states that a + reaction occurring after — subsequent to injection is analogous with recurrence without external symptoms, and hence is an indication to inject again. It will be of great value to conduct the reaction systematically



from time to time on cases which have been treated with '606' so as to ascertain whether an actual cure has been established. A simplified Wassermann test suitable for the medical man to carry out would be of great service in this direction. (See also 'Specific Nature of Treatment,' Ehrlich. 69.)

Munk (111) states that the formation of the substances giving the Wassermann reaction in serum is not caused by living spirochetes, but possibly by their decomposition products. '606' has no direct action on these substances. Wassermann's reaction cannot give conclusive result with regard to success of the substance until six or eight weeks after the injection.

The reaction, according to Wechselmann (112) usually disappears after the injection, a time from eight to 40 days being required, according to its primary severity.

Reaction changed from + to — in six to eight weeks as result of treatment (116).

### BLOOD EXAMINATIONS.

Blood examinations showed remarkable leucocytosis after injection in some cases (26). May be as high as 30,000 (102), the increase being chiefly in the neutrophiles and occasionally in the eosinophiles. Usual count is about 17,000 (McDonagh).

Similar result, to be viewed as a result of reaction between the bone marrow and the Arsenic body. Leucocytosis occurs either with or without the use of Methyl Alcohol (30).

Leucocytosis in general not marked. The highest count observed was an increase of 13,700 (114).

In a case of syphilitic anæmia—whether by coincidence or not is not known—there was an increase of about 500,000 red cells, the hæmoglobin content remaining as before—but the patient died (30).

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Some histological investigations in two cases of congenital syphilis. In cases of this kind (the infants were each two months old) the spirochetes are present in enormous numbers, and for this reason, on account of the large amount of endotoxins which would be liberated by their destruction, the



method of treatment is subjected to the severest test. The examination, made two and four days respectively after 0.04 and 0.025 Gm. intravenous injections of '606,' showed that the spirochetes had been killed off in all the organs of the infants except a few remaining in the lungs—possibly they are able to hold out there longest on account of the oxygen present. Those remaining were agglutinated and highly degenerated. The results tend to show the remarkable power of the preparation (57). See also 'Specific Nature of the Remedy,' p. 20.

#### EXAMINATION FOR SPIROCHETES.

The spirochetes disappear from the blood in 24 to 48 hours after injection. Almost every secondary case was examined. In a sclerotic even after 16 hours (dose 0.5 Gm.) no spirochetes could be found (14).

Spirochetes disappeared after 0.6 Gm. in 24 to 48 hours (30).

See also (65) in which the following is given:—

In 64 cases of most varied kinds spirochetes were found before injection; in 16 cases they were not found.

In 49 patients disappearance of the spirochetes was determined after various lengths of time, *e.g.*,

In 4 cases disappearance on the 2nd day

6	"	"	"	3rd	"
4	"	"	"	4th	"
9	"	"	"	5th	"

And so on to

2	"	"	"	14th	"
---	---	---	---	------	---

The preparation, according to Favento, is not harmful, on the contrary, it is strength-giving and causes patient to increase in weight.

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#### ABSTRACTS OF LEADING ARTICLES.

'Lancet,' September 3rd, 1910, p. 740. A leader on '606' refers to the serious cases of optic atrophy which have resulted from Organic Arsenic treatment recently in the past. Draws attention to the contribution to the 'Deut. Med. Woch.' of



August 11th, 1910, by Wechsellmann, concerning '606,' which was employed in 503 cases. General health improves, marked feeling of well-being the day the treatment is begun. There is prompt relief of pain. Sore throat which may have lasted for years, or pain in the mucous membrane of the mouth, may disappear almost magically. Primary sores of the mouth heal within a few days, mucous plaques of the mouth disappear in 24 to 48 hours. In one case, however, while a primary sore of the tongue healed and enlarged submaxillary glands diminished rapidly, the papular syphilide also present was unaffected. A second injection was necessary. Though action on the spirochetes is so marked there is obvious chance that some remain unaffected. Note that Wassermann's test becomes negative, but later may again become positive. Five of Wechsellmann's cases were women near the end of pregnancy, but in none was the pregnancy interfered with, but the capabilities and limitations of the drug have yet to be learnt.

In a leader in the 'B. M. J.,' Sept. 17th, 1910, p. 798, we read 'it is practically certain that in the most desperate cases of syphilis in which Mercury is of no value, and which otherwise tend to run a rapid course, ending in death, health can temporarily at any rate be restored almost miraculously by a single injection.'

With regard to the Wassermann reaction and the fact that in only 10 % of cases Neisser found + to be changed to —, it is pointed out that the reaction cannot decide whether the cure is permanent or not. If Wassermann's reaction depended on presence of syphilitic antibody in the serum of syphilitics it would be reasonable to expect a persistence of this antibody after complete cure. It is a question, however, in any case whether one may correctly speak of the reaction becoming negative—it may be more correct to regard it as a weakening of the + reaction.

The article concludes with a special reminder as to possible effect on the optic nerve in view of experience with other Arsenic derivatives. It will be necessary to wait for years to determine whether the injection affects the virus in such a way as to render it refractory to a subsequent application should recurrence of symptoms occur.



## SPECIAL COMMUNICATIONS.

Several Specialists have been good enough to provide us with their personal experiences with, or their opinions on, the use of Ehrlich's preparation.

*Otto Grünbaum* (see also page 35 *et seq.*) writes:—

My experience as to the value of treating syphilis by injecting the 'Ehrlich-Hata' preparation '606' is of too short duration to permit me to state whether relapses are common or not, but I can relate my observations on patients whom I have injected intramuscularly with a slightly acid solution.

My custom has been to dissolve the preparation in the least possible quantity of pure Methyl Alcohol—this must be of a purity which one finds only in samples which have been specially prepared for analytical purposes; I then add 25 Cc. of sterile distilled water, then a sufficiency of sterile decinormal Sodium Hydrate Solution. Half of this solution is injected intramuscularly into each side in the region of the buttock.

The substitution of normal saline for distilled water, in my experience, leads to greater pain, and the injection of a hypotonic solution is better than that of hypertonic. The amount of pain during the time of injection varies tremendously. It has been one's experience that very often those cases who suffer most at the time of injection have least pain after; this is not invariably the case. As a rule, within three or four days the patient is able to walk about with comfort, but in two cases the pain has persisted for three weeks. I might add that these two cases were suffering from neurasthenia as well as an infection of the *spirochaeta pallida*.

The actual intravenous injection is practically painless, and it has been carried out by so many experimenters abroad that one cannot help thinking it is free from danger, and one trusts that it will be found that the percentage of people who have an idiosyncrasy for the drug is negligible.

As regards the results after the injection, I can only corroborate the statements made by all other observers—namely, they are a little short of miraculous. Gummata,



condylomata and rashes disappear extremely rapidly, whilst the Wassermann reaction usually becomes negative within five weeks of the injection.

The doses I have used vary from 0.45 to 0.7 Gm., and so far I have no record of relapses, but, as I have stated, this observation is of but little value because the period over which the observations have been made is of too short a duration.

*Jonathan Hutchinson* writes us as follows in answer to an inquiry:—

The unfortunate conditions under which '606' has been brought forward make it difficult in England for anyone to yet say much about it that would be of serious value, but the following facts have come out:—

1. When the alkaline solution is injected by the intragluteal method in doses of 0.4 Gm., there is, as a rule, little or no trouble to be feared from it as regards pain, etc., provided the patient lies up for a few days and that strict aseptic precautions are observed by the surgeon. I believe if '606' comes into general use that serious accidents will be numerous, owing to neglect of these precautions.

2. When used in the secondary stage of syphilis the main symptoms, *i.e.*, induration of chancre, cutaneous eruption, ulcerated throat, etc., certainly improve rapidly. I have not been able to convince myself that this effect is much more rapid than that which would follow the thorough internal administration of Mercury. The inguinal buboes especially yield just as slowly to '606' as they do to Mercury.

3. As regards a cure resulting from one injection of '606' it is now thoroughly established that recurrence of symptoms is common, although sufficient time has not elapsed yet to enable us to estimate in what proportion this occurs.

4. As regards the value of '606' in tertiary syphilis there will probably be most conflicting opinions. Sometimes a brilliant success will be obtained, but for a large number of tertiary lesions and remote results of syphilis it appears to do little or no good, and to be



distinctly inferior to treatment with Iodides and Mercury.

5. The danger of producing optic atrophy (arsenical neuritis) by the injection of '606' is a most important question. It is difficult to believe that there is no such danger when cases of partial or complete blindness following the injection of Soamin, Arsacetin and other arsenical preparations have been so numerous and deplorable that to continue using these arsenical compounds in the treatment of syphilis is almost criminal in view of the admirable results obtained (without any risk of producing optic neuritis) from the careful oral administration of Mercury.

6. The intravenous injection of '606,' if adopted on any considerable scale, will be *certainly followed by a number of deaths directly the result* of such injections.

I have already seen one patient who nearly died from such intravenous injection. She was comatose for several hours there was temporary hemiplegia, and though she was just pulled out of the jaws of death, the systemic shock that remained was most severe.

The amount of '606' injected in this case (a young, healthy woman with primary chancre of the lip) was, I understand, not excessive. It was given in divided doses into the veins of both arms.

The drawbacks and dangers inseparable from direct intravenous injections of any strong chemical (*e.g.*, a mercurial or arsenical salt) are now so well known that I cannot understand any practical surgeon caring to put his patient in such grave jeopardy for a problematical advantage.

7. There is no doubt that the intragluteal injection though far safer than the intravenous method, is sometimes followed by intense pain, which may last for a week or more. It is not improbable that in such cases wasting of the gluteus maximus may result.

*J. Ernest Lane* writes :—

My experience of '606' does not agree with the opinions of the majority of those who have tried that preparation, and I am not at all inclined to advocate its use. I shall be reading a paper at the Harveian Society on the subject on



Thursday, December 8th, and this will give you my views *in extenso* (see L., Dec. 17th, 1910).

*F. W. Mott* writes:—

I have, personally, had very little experience of the therapeutic effects of '606.' I am doubtful whether it will prove of much value in general paralysis of the insane,—it is probable that it would be very beneficial in the early stages of gummatous meningitis and arteritis. It cannot be expected that any therapeutic agent will restore nervous tissue that has been destroyed by ischamic softening by arterial occlusion. I have been unable to obtain any of the drug to try its efficacy, but I consider the best test of its influence on diseases of the nervous system would be by the examination of the cerebro-spinal fluid before and after administration. If the lymphocytes were greatly diminished it would indicate an improvement, likewise a negative Wassermann reaction when previous to the injection there was a positive reaction. The disappearance of lymphocytes from the cerebro-spinal fluid in active syphilitic meningitis is striking when Mercury injection or inunction is practised; it is probable that the new drug would have even a more pronounced effect.

*George Ogilvie* (who can speak highly of Donovan's Solution) very kindly sent us a copy of 'L'Auto,' dated November 22nd, 1910, a Parisian paper, containing a column by Louis Jullien, a Parisian authority on venereal diseases.

*Jullien* writes in a chatty manner, commencing by saying that, however little Professor Ehrlich may possess in the direction of sensitive hearing power, his ear must have tingled considerably during the last week or so. L'Académie de Médecine, the Société de Dermatologie et de Syphiligraphie, French Medical Journals, etc., have all been busy hammering at the subject. Although 'Arsenobenzol' has shown itself wonderfully powerful in certain ulcerations, both superficial and deep-seated, nevertheless there are internal lesions which are unaffected by its action,—cases known as Parasyphilitics, and which are always 'insensible to Mercury' (*sourds au mercure*),—in these there is such destruction of tissue, such degeneration against which therapeutic agents are useless.

Let us also remember that the slight manifestations with



which the *début* of the infection is characterised are most difficult to treat.

Under treatment with '606' plaques muqueuses had disappeared, to return again shortly afterwards. Roseola had been effaced, but new spots commenced to form, etc. Always the little troubles that resist us. The writer then throws out a warning. Clinical experiments have shown the toxic nature of the medicament. There is its tendency to cause congestion of the veins and of the lungs to be borne in mind. Note what care is necessary in treating grave lesions of the intestines, in treating nephritis, and in dealing with cerebral affections. The careful clinician must resist to the utmost too marked an enthusiasm. He doubts the possibility of a complete sterilisation of the system. Arsenobenzol will not cure syphilis—its action is superficial—more rapid than Mercury, but always momentary. The rôle of '606' should be reduced to that of an excellent desiccant, an admirable cicatricising agent. He refuses to accept indications so limited, and contents himself with restricted praise.

'And then it turns,' as Galileo said. Many of us have seen a few of the striking cases—cases which looked like miracles. He recalls a case of laryngeal and pharyngeal infection on which he had operated a month or two back, snatched from a death by hunger and angina—'Celui-là seul me suffit,' he writes. Prevent the unfortunate sufferers from hoping too much of this new remedy from what they read in every periodical they lay their hands on. The future will show whether he is correct, he concludes. It will also determine where Arsenic will cure, and the position that Mercury is to occupy. Will that be the golden age for those afflicted with venereal disease? Although not ceasing to exist entirely, these syphilitic women will be rarer, and will remain 'infinitely precious'—presumably from the scientific aspect.

*George Pernet* writes, Dec. 13, 1910:—

'From my observation of cases at home, and especially abroad, the Arsenobenzol preparation of Ehrlich-Hata is a valuable remedy in various syphilitic conditions, but that it cures syphilis with one injection is quite another story. In its application patients will have to be dealt with on their merits.



I cannot help noticing, and other English medical men I have met and discussed the subject with agree, that we have in this country been treated very differently from our colleagues abroad in the way of supply for trial purposes. Why this difference, I do not know.'

*J. H. Sequeira* writes (Dec. 9, 1910):—

*Note on the Treatment of Syphilis at the London Hospital.*

Thirty-four cases of syphilis have been treated at the London Hospital with Ehrlich's '606.' There have been no symptoms giving rise to anxiety. Pain has been severe in all the cases injected with the alkaline solution, and in several instances the patient has had pain and stiffness for several weeks after the injection. There has been no local suppuration. Injections of a neutral emulsion have been unattended with pain, but there appears to be considerable doubt as to whether these neutral injections are as valuable therapeutically as the alkaline.

Cases of primary, secondary and tertiary syphilis have been treated. In all, the eruptions have cleared up with greater rapidity than with mercury. Some of the most remarkable results have been observed in old tertiary lesions, which have resisted the usual methods. The Wassermann reaction usually cleared up in three to four weeks.

Four cases of hereditary syphilis have been treated. Two infants with well-developed eruptions were taken into the wards with their mothers, and the mothers received full doses of '606.' One infant was injected directly. These three all made rapid recoveries. An ulcerative congenital syphilide in a boy of sixteen was greatly improved, but the injection had to be repeated. His vision, which was very bad, has improved, and his hearing is slightly better. The Wassermann reaction, however, is still positive. This is the case in all congenital syphilitics, whether treated by mercury or by '606.'

*Campbell Williams* writes:—One can only describe the immediate action of '606' in inveterate syphilis as 'magical' when one sees its effects upon cases of the tertiary type, which have for years resisted the orthodox Mercurial or Iodic treatment. One injection, and in the short space of a fortnight it would outwardly appear that the patient was cleansed. But



one must bear in mind that a remedy so potent for good would probably likewise be girded with possible evil effects—immediate and perchance remote. In support of this view are the reported fatal cases which have appeared in Continental Medical papers. These one may term immediate evil effects. The treatment may still be said to be on trial, and time is yet needed in which to judge as to the permanency or otherwise of the benefits which it confers. One would deduce from Laboratory experiments upon the 'Anthropoids' that its effects were permanent, in that it has been shown that re-infection can be effected after its usage upon a formerly syphilitic subject. Whether this will hold good as regards the human being remains to be seen. It is asserted that relapses do occur in cases which to all outward or clinical observation, together with a negative Wassermann, were cured. In one case reported to me it was stated that severe cerebral endarteritis ensued in about three months after the patient was deemed to have been freed from the disease, which was that of the primary and early secondary type. Doubtless, when its use becomes more general, we shall, as with other Arsenicals, find out such weak points or dangers which exist, or are presumed to exist, in connection with its administration. Personally I would hesitate to guarantee the permanency of its curative effects until it had stood a longer test of time, nor would I at present lightly describe the treatment as being absolutely free of danger or risk. The administration of Arsenic in any form may, owing to the idiosyncrasy of the recipient, bring a surprise. One may beneficially prescribe it hundreds of times before meeting with a case which will not tolerate it, and to whom it proves injurious. Personally, I would pick my case for its employment, and eschew those debilitated and aged subjects in whom a possibly greater risk might be attendant. All retinae should be carefully examined before subjecting the patient to an injection.

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#### ANTISEPTIC POWER.

There is just one word in conclusion. It occurs to us that if this Arsenical body has the power of producing a complete



sterilisation of the system so far as *spirochaeta pallida* is concerned by a simple intramuscular injection, it must surely possess bactericidal powers of no mean order. We have not in the course of our reading come across any statement in this direction, though doubtless those advocating the preparation for use are conversant with the limits of its antiseptic powers. We shall take an opportunity at an early date to determine the 'Carbolic Coefficient' on the ordinary organisms usually employed, *e.g.*, *B. typhosus* *B. coli*, etc.

It seems difficult to realise that this rather out-of-the-way compound should be invested with specific spirillocidal powers without simultaneously being detrimental to the common bacteria.

In this direction it is interesting to note that pus removed at the site of injection where infiltration and inflammation have occurred has always been reported as *sterile*.



## REFERENCES

*These References are arranged as nearly as possible in chronological order. They range from March 15 to Dec. 17, 1910.*

(1) Alt ('Münch. Med. Woch.,' No. 11, March 15, 1910, p. 561), a nerve specialist, in introducing the new preparation which he had received from Ehrlich in September, 1909, draws attention to the connection between syphilis, early paralysis, epilepsy, and idiocy. He had taken the trouble to have young epileptics and idiots examined for indication of syphilis by the Wassermann reaction, and in 9 per cent. of the idiot children in his Asylum inherited syphilis was determined. In Berlin a larger proportion had been found. Progressive paralysis, which removes thousands of human beings at the best period of their lives in Germany, is to be traced to previous syphilis. This intimate connection being proved, there appears hope of effectually combating paralysis. Neurasthenia, again, must be recognised early, in order that the earliest signs of paralysis may be treated. With some remarks of this nature, Alt proceeds to review his results with Organic Arsenic Compounds. Atoxyl and Arsacetin are briefly treated. Arsenophenylglycin had been used on 140 lunatics and epileptics with advantage. Rise in temperature after the injection, otherwise results eminently satisfactory. In this preliminary report by Alt, 23 cases, mostly paralytic, received 0.3 Gm. intramuscularly. Alt then referred to Schreiber, at Magdeburg, to have the substance tried in early syphilis in man. Twenty-seven cases were treated. General nutrition did not suffer, on the contrary there was increase of weight in most instances. As the pain which follows the injection is so marked a disadvantage to the treatment, which is only slightly mitigated by a local anæsthetic, Alt suggested that possibly the intravenous injection might be preferable.

For further details, see '*Results*,' '*Rise in Temperature*,' '*Wassermann's Reaction*,' and '*Dose*.'

(1a) 'Berl. Klin. Woch.,' No. 27, 1910; B. M. J., ii, 10, 794, 813.

(2) Dorr, 'Wien. Klin. Woch.,' No. 26, June 30, 1910 (per Bresler), reports cases. Primary and secondary affections rapidly removed. A very remarkable case of improvement of malignant syphilis in which Mercury, Iodine and Zittmann's Decoction had been used is also reported.



(3) *Neisser*, 'Deut. Med. Woch.', No. 26, June 30, 1910 (per Bresler), provides a leading paper on the subject. There may be sickness. (Arsenic has not been found in the vomit.)

(3a) *Neisser*, *ibid.*, per B. M. J., ii. 10, 794.

(4) *Wechselmann*, 'Berl. Klin. Woch.', No. 27, July 4, 1910 (per Bresler, p. 8 *et seq.*), read a paper before the Berlin Medical Society, June 22, 1910, on 80 cases of syphilis treated with '606.' The action is so rapid that one cannot demonstrate patients.

In a case of a woman with a papular-crusted syphilide of a most severe type on the arm, a few days after the injection the crusts came away, syphilitic infiltration had completely disappeared, and only a small granulating wound remained.

A large papular, partly pemphigoid syphilide in an infant was completely cured.

Papules on the tonsils, on the arches of the palate and the genital labia disappeared. Many other similar cases are reported. In particular the author was gratified with results where Mercury, Iodine, etc. treatment, had been of little avail. Injections were intragluteal—see '*Methods of Injection.*'

(5) *Alt*, 'Berl. Klin. Woch.', No. 27, July 4, 1910 (per Bresler).

(6) *Hoppe*, *ibid.*, 0.4 Gm. of arsenobenzol administered by intravenous injection is removed in three days.

(7) *Schreiber and Hoppe*, 'Münch. Med. Woch.', No. 27, July 5, 1910, p. 1430.

(8) *Michaelis*, 'Berl. Klin. Woch.', No. 27, 1910 (per Bresler, p. 16), reports on two remarkable cases shown at the Berlin Medical Society. One (syphilitic affection in the nose and throat in which the uvula was so diseased as to be hanging by a thread and daily expected to drop off) had been treated with various remedies since 1907; the other had a papular syphilide extending almost over the entire body,—psoriasis palmaris, papules on back of the hand, small excrescences on the eyes. 0.3 Gm. effected remarkable improvement amounting virtually to a cure.

(9) *Spatz*, 'Wien. Med. Woch.', 1910, No. 27 (per Bresler), used '606' in nine cases. Temperature rose as high as 39.2° C., falling again in 24 hours. Injections intramuscular.

(10) *Fischer, and Hoppe*, 'Münch. Med. Woch.', No. 29, July 19, 1910, p. 1531. Estimation of Arsenic excreted.

(11) *Bohac and Sobotka*, 'Wien. Klin. Woch.', No. 30, July 25, 1910.

(12) *Loeb*, 'Münch. Med. Woch.', No. 30, July 26, 1910, p. 1580.



(13) *Treupel*, 'Deut. Med. Woch.,' No. 30, July 28, 1910, writes concerning 500 cases. He adopts a further slightly altered method of preparing the injection and gives directions for making, both for intramuscular and intravenous injections, preferring the intramuscular method.

(14) *Glück*, 'Münch. Med. Woch.,' No. 31, August 2, 1910, p. 1638, treated 109 cases.

(15) *Schreiber and Hoppe*, 'Berl. Klin. Woch.,' No. 31, August 1, 1910 (per Bresler, p. 42), treated 120 cases.

(16) *Neisser and Kuznitzky*, 'Berl. Klin. Woch.,' No. 32, 1910, report on 126 cases.

(17) *Zeissl*, 'Wien. Med. Woch.,' No. 32, 1910, treated 26 cases.

(18) *Spatz*, *ibid.*

(19) *Wechselmann*, 'Deut. Med. Woch.,' Nos. 30 and 32, 1910, gives his method of preparing the injection. Later, 'Deut. Med. Woch.,' No. 34, 1910, recommends centrifugalising the neutral suspension and suspending in Normal Saline. Absolutely painless injection.

(20) *Herxheimer*, 'Deut. Med. Woch.,' No. 33, August 18, 1910, p. 1518, reports on 72 cases using a solution made with addition of NaOH, and then neutralised with 2% Acetic Acid, finally making up to volume with water so that a dose is contained in 10 Cc. Results analogous with others reported.

(21) *Iversen*, in St. Petersburg, 'Münch. Med. Woch.,' No. 33, August 16, 1910, p. 1723. Results with '606' on 60 cases of relapsing fever.

(22) *Taege*, 'Münch. Med. Woch.,' No. 33, August 16, 1910, p. 1725.

(23) *Isaac*, 'Berl. Klin. Woch.,' No. 33, August 15, 1910, p. 1528, provides an account of 27 cases of a completely commendatory description.

(24) *Michaelis*, 'Berl. Klin. Woch.,' No. 33, August 15, 1910, p. 1531, treated 71 cases without unpleasant sequelæ, gives directions for preparing injection:

(25) *Kromayer*, 'Berl. Klin. Woch.,' No. 34, August 22, 1910, p. 1585, has some critical remarks to make. He writes concerning 27 cases. Immediate results, both objectively and subjectively, were better than one is accustomed to see with Mercury.

(26) *Fraenkel and Grouven*, 'Münch. Med. Woch.,' No. 34, August 23, 1910, p. 1771. Over 100 cases treated, mostly by gluteal injections. As to the solution for injection the following modification is suggested: to dissolve the dose in 1 Cc. pure Methyl Alcohol,



then add a little sterile Distilled Water,  $1\frac{1}{2}$  to 2 Cc.  $N_{10}$  NaOH (sterile) and finally to add sterile water to about 10 Cc. A further dilution than this was deemed unnecessary.

(27) *Alt*, 'Münch. Med. Woch.,' No. 34, August 23, 1910, p. 1775, communicates further on his results.

(28) *Braendle and Clingstein*, 'Mediz. Klin.,' No. 34, 1910, suggest combining '606' with small doses of Mercury. They first employed Ehrlich's method, but later on account of the pain used Wechselmann's.

(29) *Zeissl*, 'Wien. Med. Woch.,' No. 34, 1910.

(30) *Spiethoff*, 'Münch. Med. Woch.,' No. 35, August 30, 1910, p. 1822. Fifty cases reported on, including six cases in the primary stage, 16 in the secondary, 12 of secondary latent, 10 of tertiary syphilis, one of hereditary, three tabes, one each of pernicious anæmia and of severe secondary syphilitic anæmia.

(31) *Duhot*, 'Münch. Med. Woch.,' No. 35, August 30, 1910, p. 1825.

(32) *Blaschko*, 'Berl. Klin. Woch.,' No. 35, August 29, 1911, p. 1611, states that it is not quite clear that Arsenobenzol acts purely as a parasitotropic substance. This author has dealt with the chemical aspect of '606' solutions. *Vide* p. 30.

(33) *Ehrlich*, 'Münch. Med. Woch.,' No. 35, August 30, 1910, p. 1826.

(34) *Bayet*, 'Journ. Med. de Bruxelles,' No. 35, 1910 (per B.M.J. ii/10, 794) gives a résumé and his own experiences.

(35) *McDonagh*, L., Sept. 3, 1910, p. 711, at the Lock Hospital, has had remarkably good results. He reports on 20 cases. He uses 0.5 Cc. Ethyl (not Methyl) Alcohol to 0.1 Gm. of the powder to dissolve, and adds 20 Cc. sterile water, and then 1 Cc.  $N_{10}$  NaOH to each 0.1 Gm. powder, and injects in the buttock—10 Cc. into each. A neutral solution made by alkali, then titrating with Acetic Acid, is preferable.

(36) *McIntosh*, L.ii/10, Sept. 3, p. 713.

(37) *Bouchard*, at the Académie des Sciences (per B.M.J.ii/10, p. 794) is hostile to the claims of the new body.

(38) *Schwartz & P. Flemming*, 'Münch. Med. Woch.,' No. 37, September 10, p. 1933, concerning the action of '606,' Arsenophenylglycin, Potassium Iodide and Mercuric Chloride on Wassermann's Reaction. These bodies possess no hæmolytic action in any dilution whatever, and they possess hæmolysis-arresting action only in very strong concentration.



(39) *Lange*, 'Berl. Klin. Woch.,' No. 36, per 'Deut. Med. Woch.,' No. 37, September 15, 1910, p. 1727.

(40) *Ivanyi*, 'Wien. Med. Woch.,' No. 36, per 'Deut. Med. Woch.,' No. 37, September 15, 1910, p. 1727. 84 cases,

(41) *Mondschein*, 'Wien. Med. Woch.,' No. 36, per 'Deut. Med. Woch.,' No. 37, September 15, 1910, p. 1727.

A case of syphilis in which there was amyloid degeneration of the kidneys cured. No toxic symptoms.

(42) *Zeissl*, 'Wien. Med. Woch.' per 'Deut. Med. Woch.,' No. 39, September 29, 1910, p. 1822. One hundred patients, 10 of which primary cases. Best results with mucous membrane papules. In tabes and paralysis no result. In hemiplegia caution is necessary.

(43) *Herxheimer and Schonnefeld*, 'Med. Klinik.,' No. 36, per 'Deut. Med. Woch.,' No. 37, 1910, p. 1727, on 200 cases. Continue to obtain good results. Contraindications: heart affections, fetid bronchitis and non-specific ocular disturbances.

Intramuscular and subcutaneous injections of neutral suspension found best.

(44) *Michaelis*, 'Berl. Klin. Woch.,' No. 37, September 12, 1910, p. 1695, 110 cases. Best results in severe cases in which Mercury and Iodides had produced little effect.

(45) *Kromayer*, 'Berl. Klin. Woch.,' No. 37, September 12, 1910, p. 1698, recommends a 10% Liquid Paraffin suspension, for injection—the '606' being used as such, not neutralised.

(46) *Wechselmann*, 'Deut. Med. Woch.,' No. 37, September 15, 1910, p. 1692.

(47) *Grosz*, 'Deut. Med. Woch.,' No. 37, September 15, 1910, p. 1693, writes concerning '606' in syphilitic eye affections. Has not observed any of the disquieting symptoms which caused Atoxyl to be used with fear.

(48) *L.*, September 17, 1910, p. 912.

(49) *Anscherlik*, 'Münch. Med. Woch.,' No. 38, September 20, 1910, p. 1980. Forty-five cases in the Army treated, employing principally the technique of Wechselmann and Lange, as given by Glück 'Münch. Med. Woch.,' August 2, 1910, p. 1638. Average dose, 0.6 Gm.

(50) *Gourwitsch and Bormann*, 'Deut. Med. Woch.,' No. 38, September 22, 1910, p. 1750, detail their methods and results. They employed the neutral suspension of Wechselmann, *q. v.*

(51) *Blaschko*, 'Berl. Klin. Woch.,' No. 35, August 29, 1910, p. 1611. See also *L.*, September 24, 1910, p. 964.



(52) L., September 24, 1910, p. 964. A visit to Professor Treupel's Clinic at Frankfurt, and interview with Ehrlich. Notes on cases seen. In one case '606' had been applied locally where injection had not proved of much service. Official demonstrations did not give much information as to which of the several methods of use was recommended. Treupel and Weintraud read a communication to the Medicinische Verein at Frankfurt, September 12, 1910 (reported 'Deut. Med. Woch.,' September 29, 1910, 1787), containing table of results, in which Treupel recommends subcutaneous injection; Weintraud, on the other hand, prefers intravenous, as being more rapid. Treupel at the Clinic gave ample opportunities for examination of varied cases. Doses ranged from 0.3 to 0.9 Gm. *Blaschko's Method* employed, *q. v.*

(53) L., September 24, 1910, p. 981.

French doctors, one in particular, Bouchard, point out that a body of similar composition, Sodium Benzo-sulphon-paraminophenyl-arsonate made at Lyons had been tested under the name of 'Hectine.'

(54) *Schreiber*, 'Münch. Med. Woch.,' No. 39, September 27, 1910, p. 2025.

325 cases have been treated intravenously without a single case of disturbance or difficulty, but care is necessary.

(55) *Huegel and Ruete*, 'Münch. Med. Woch.,' No. 39, September 27, 1910, p. 2026.

30 cases reported on, 10 received the injection intramuscularly as directed by Ehrlich, and 20 subcutaneously into the back.

(56) *Sieskind*, 'Münch. Med. Woch.,' No. 39, September 27, 1910, p. 2027.

Writes on experience in 375 cases.

(57) *Herxheimer and F. Reinke*, 'Deut. Med. Woch.,' No. 39, September 29, 1910, p. 1790.

(58) *Werner*, 'Deut. Med. Woch.,' No. 39, September 29, 1910, p. 1792.

(59) *Wolff*, 'Deut. Med. Woch.,' No. 39, September 29, 1910, p. 1832. Ten cases in various stages. He thinks one cannot speak of a *therapia sterilisans* nor of a cure in a disease which often lasts ten years and more.

(60) *Meyer*, 'Deut. Med. Woch.,' No. 39, September 29, 1910, p. 1832. Fourteen cases, 12 of which were of progressive paralysis little or no improvement. Wassermann's Test in four cases no change; four showed reduction, and in the remainder, although at first a hæmolysis, later, after several weeks, positive again.



(61) *Torday*, 'Wien. Klin. Woch.,' No. 39, 1910, per 'Münch. Med. Woch.,' No. 41, October 11, 1910, p. 2151. Eighteen cases. Two cases of severe anæmia worse, one of leukaemia improved temporarily.

(62) *Sellei*, 'Münch. Med. Woch.,' No. 39, September 27, 1910, p. 2031. This paper is simply repetition in a general way. In tabes and incipient progressive paralysis no marked noticeable result could be reported. As to technique,—solution to be as neutral as possible on the lines of Wechselmann's Modification. Combined action with Mercury advisable in some cases.

(63) *Alt*, 'Berlin, Klin. Woch.,' No. 40, October 3, 1910, p. 1857, deals with the history of introduction of '606.' Letters between Alt and Ehrlich.

(64) *Greven*, 'Münch. Med. Woch.,' No. 40, October 4, 1910, p. 2079, on the commencement and duration of the Arsenic elimination in the urine after injection of '606.' *Conclusions* (a) the elimination begins rapidly; (b) the duration of the passing of Arsenic in the urine is longer than was thought; (c) after *subcutaneous* injection the elimination is concluded more rapidly than in the intramuscular method; (d) simultaneous use of Mercury caused delay in eliminating the Arsenic; (e) Potassium Iodide given at same time shortens the duration of the Arsenic elimination.

(65) *Favento*, 'Münch. Med. Woch.,' No. 40, October 4, 1910, p. 2080. One hundred and fifty-six cases of varied type. Technique used on the lines of that of Wechselmann, namely, as follows:—

Solution of the Powder in 10 per cent. Potassium Hydroxide, precipitation with Glacial Acetic Acid, and addition of a little Distilled water. The emulsion so obtained must be neutral to litmus. It is adjusted, if not neutral to this, with one per cent. Acetic Acid or one per cent. Potassium Hydroxide to complete neutrality.

"Subcutaneous injections of 6 to 7 Gm." (presumably of solution containing average dose—W. H. M.) between the shoulder blades. It produces less pain if injected at two points instead of one. There was no suppuration in employing two injections in this manner, which had appeared when using the single injection.

(65a) 'Münch. Med. Woch.,' No. 40, October 4, 1910, p. 2118.

(66) *Grassmann*, 'Münch. Med. Woch.,' No. 42, October 18, 1910, p. 2178.

(68) *Neisser*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1889.



- (69) *Ehrlich*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1893.
- (70) *Alt*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1896.
- (71) *Schreiber*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1898.
- (72) *Iversen*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1899.
- (73) *Wechselmann*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1901, describes his case 'W. D.,' the youth of 18 referred to in previous abstract.
- (74) *Orth*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1903.
- (75) *Miekeley*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1903, reports on 157 cases treated in hospital in Berlin.
- (76) *Uhlenhuth*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1906, recapitulates earlier work with Atoxyl, etc., Mercury Atoxylate, etc., especially his own work, and indicates how Ehrlich, by remodelling Atoxyl, proceeded to '606.' (Its chemical constitution is quite distinct.—W. H. M.)
- (77) *Margarete Margulies*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1907, describes experiments on animals—mice infected with trypanosomes, on mice with relapsing fever spirilla, on chicken with spirilla, on rabbits inoculated with syphilis.
- (78) *Stern*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1908.
- (79) *Scholtz and Beck*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1910, provide notes on their experience with 90 cases. Their results agree with the general reports of others. They refer to a case of acute syphilis in which injection of Serum of syphilitics treated 48 hours previously with '606' had done good. (See also further reference in 'Specific Nature of Treatment.')
- (80) *Grünfeld*, 'Deut. Med. Woch.,' No. 41, October 13, 1910, p. 1911, writing from Odessa, points out the extraordinary frequency of syphilis there. In a few villages 80 % of the inhabitants are syphilitics. 50 cases treated.
- (81) *Michaelis*, *ibid.*, p. 1912, *re* Arsenobenzol technique.
- (82) *Volk and Lipschütz*, *ibid.*, October 13, p. 1913, preferred Wechselmann's to Alt's method of injecting.
- (83) *Dohi*, *ibid.*, p. 1914, two cases satisfactorily treated in Japan.
- (84) *Grouven*, *ibid.*, p. 1914, 200 cases.



- (85) *Glück*, *ibid.*, p. 1915, good results in 417 cases.
- (86) *Friedlander*, *ibid.*, p. 1915, deals with 100 cases.
- (87) *Citron*, *ibid.*, p. 1917, advises the precipitation of the base from the salt in *the Syringe* by means of Calcium Carbonate.
- (88) *Königstein*, *ibid.*, p. 1917, good results.
- (89) *Blumenfeld*, *ibid.*, p. 1917, 50 cases. Inter alia, 5 cases of marked syphilitic hoarseness well treated.
- (90) *Salmon* (Paris) *ibid.*, p. 1918, points to prophylactic uses of '606.' In treatment mention is made of the fact that one may base the dose on the number of spirochetes seen. He obtained good results on severe ulcers by comparatively small doses.
- (91) *Saalfeld*, 'Deut. Med. Woch.', October 13, 1910, p. 1919, deals with 25 cases. Results similar to others.
- (92) *Ledenman*. 30 cases. Inter alia a case of facial paresis of syphilitic origin, some improvement, but not cured. Similarly with a case of paraplegia of both legs.
- The neutral suspension of Wechselmann was used.
- (93) *Joseph Conrad*, *ibid.*, p. 1921, employed a specially prepared neutral suspension free from Sodium Acetate.
- (94) *Nagelschmidt*, *ibid.*, p. 1922; *Juliusberg*, *ibid.*, p. 1923; and *Pick*, *ibid.*, p. 1924, report favourably.
- (95) *Schwartz and Flemming*, 'Münch. Med. Woch.' No. 41, October 11, 1910, p. 2140, compare the effect of 0.1 Gm. of the hydrochloride hypodermically (marked reaction, death in a few seconds), with 0.2 Gm. in 2 Cc.  $\frac{N}{I}$  NaOH as advised by Hoppe. In the latter no poisonous effects.
- (96) *Ehlers*, 'Münch. Med. Woch.', No. 41, October 11, 1910, p. 2141. In leprosy, seven cases. No marked change in the skin, but the Bacilli appeared to be degenerated.
- (97) *Duhot*, 'Münch. Med. Woch.', No. 42, October 18, 1910, p. 2179.
- (98) *Taege*, 'Münch. Med. Woch.', No. 42, October 18, p. 2180, uses either Alkaline Solutions or neutral suspensions, and had employed '606' in 80 cases without untoward effect. In some cases the pulse dropped, but not below normal in respect of age. Eighty-five varied cases are reported on,—as a general rule dose was 0.3 Gm. with 0.6 Gm. as maximum. Large condylomata and roseola disappeared quickest (two to four days); on the other hand, deep tertiary ulcers required three weeks or more. There is a lengthy description of the cases.
- (99) *Ehlers*, 'Münch. Med. Woch.', No. 42, October 18, p. 2183.



(100) 'Münch. Med. Woch.,' No. 42, October 18, 1910, p. 2214. Abstract of a paper by *Junkermann*. 25 cases.

(101) Abstract of paper by *Herxheimer and Schonnefeld*, 'Münch. Med. Woch.,' No. 42, October 18, 1910, p. 2214.

(102) *McDonagh*, 'Lancet,' October 22, 1910, p. 1198, recounts his further experiences with '606.' As *prophylactic* '606' is powerless 'since it is not broken up unless acted on by protozoa.'

Details of 13 cases are provided. Risk of optic atrophy need, we are told, hardly be considered. Gives a *résumé* of the work which led to the division of chemical bodies into organotropic and parasitotropic groups.

(103) *Kakels* 'Med. Rec.,' New York, September 24, 1910 (per 'B.M.J.E.' October 29, 1910, p. 67), reports on the first two cases treated with '606' in U.S.A. First case extensive gummatous infiltration of the liver. — Dose, 0.3 Gm. produced good effect in two days. The other, a most obstinate case, was practically given up by the physicians. Within two days of injection of 0.3 Gm. marked improvement, and within one week ulceration and pustules almost disappeared.

(104) *Fordyce*, 'Med. Rev.,' October 1, 1910 (per 'B.M.J.E.' October 29, 1910, p. 67), summarises 16 cases. In one there were serious symptoms, in another a relapse — recommends 0.6 to 0.7 Gm. as dose.

(105) *Lesser*, 'Berl. Klin. Woch.,' No. 43, October 24, 1910, p. 1975.

(106) *Ritter*, 'Münch. Med. Woch.,' No. 43, October 25, p. 2232, reports on 60 cases of syphilis of various stages.

Dose, as a rule 0.5 to 0.7 Gm. for men, 0.4 to 0.5 Gm. for women.

(107) *Weintraud*, 'Münch. Med. Woch.,' No. 43, October 25, 1910, p. 2267, reports 181 Intravenous as also 60 Intramuscular and subcutaneous injections.

(108) *Lindenmeyer*, 'Münch. Med. Woch.,' No. 43, October 25 1910, p. 2268.

(109) *Ehrlich*, 'Münch. Med. Woch.,' No. 43, October 25, 1910, p. 2268, deals with attacks which had been levelled against him accusing him of monopoly; was writing 400 letters of refusal a day.

(110) 'Münch. Med. Woch.,' No. 44, Nov. 1, 1910, p. 2327.

(111) *Munk*, 'Deut. Med. Woch.,' No. 43, October 27, 1910, p. 1992.

(112) *Wechselmann*, L., October 29, 1910, p. 1295, reports on the treatment with Ehrlich's Dioxy-diamino-Arsenobenzol,



(113) 'L.,' October 29, 1910, p. 1318.

(114) *Zieler*, 'Deut. Med. Woch.,' No. 44, November 3, 1910, p. 2040, writes concerning 50 cases. Amongst these 7 primary, 22 secondary, 13 tertiary, and 6 cases of tabes.

(114a) *Hammer*, abstracted in 'Deut. Med. Woch.,' No. 44, November 3, 1910, p. 2070. Wechsellmann-Lange Suspension used. Not invariable action on Wassermann Test. All secondary signs quickly healed.

(115) *Pick*, 'Wien. Klin. Woch.,' No. 42, having had some recurrences when using an insoluble 'Emulsion.' Ehrlich, 'Deut. Med. Woch.,' No. 44, November 3, 1910, p. 2070, has a few remarks to make in reply. Recurrence probably due to insufficient absorption of the Arsenical body. Would advise the double treatment first intravenous by 0.4 to 0.5 Gm., and then by intragluteal injection, 0.3 to 0.4 Gm. (*q.v.*).

(116) *Wolbarst*, of New York, 'Med. Record,' October 15, per B.M.J., E. November 5, 1910, p. 71, confirms general knowledge of '606.' Seven striking cases observed by him. The most potent remedy for syphilis that science has yet produced.

(117) *Fausser*, 'Deut. Med. Woch.,' No. 45, November 10, 1910, p. 2116. Neutral suspension of Wechsellmann preferred to use of methyl alcohol. In a few cases as much as 1.9 Gm. introduced without danger. Cases mostly paralytics. Marked improvement.

(118) *Fürth*, *ibid.* ex 'Wien. Klin. Woch.,' No. 43, general remarks reiteration.

(119) *Jordan*, *ibid.* thinks '606' a valuable material, surpassing Mercury.

(120) *Gennerich*, 'Berl. Klin. Woch.,' November 14, 1910, p. 2089, provides  $7\frac{1}{2}$  pages on his experiences with the substance with four tables, three of which occupy a page each. He concludes by saying, 'In order, however, to give a definite opinion as to curative action all cases must be clinically and serologically examined for years.

He says, *inter alia*, in severe cases, especially malignant syphilis, the most intensive treatment must be used, *i.e.*, two-side injection of Alt. If the heart is sound, give intravenously 0.5 Gm., and two days afterwards subcutaneously 0.6 Gm.

(121) *Treupel*, 'Münch. Med. Woch.,' No. 46, November 15, 1910, deals in the first place with Infiltrations, reactions at the point of injection. These occur whichever way one proceeds to inject, *viz.*, subcutaneously or by intragluteal injection, and it matters little which type of solution one employs—toxic action of the As. preparation,



As this necrosis, especially if it occurs in deep muscular tissue, is likely to be serious and to prove dangerous, it points the reason for Ehrlich's recent imperative recommendation of intravenous injection, coupled, if necessary, with intragluteal injection of Alt's Alkaline Injection after a few days—skin to be cleansed with Iodine tincture.

Kromayer's Paraffin and his Oil Suspension used with advantage; they are easily prepared.

With six cases of syphilis of the central nervous system four reacted rapidly and well. Doses of 0.6 to 0.8 Gm. Paralysis in the region of ocular muscles and of the body muscles, haziness, and commencing congestion of the papilla disappeared within a few days.

Pain in nerve areas, not only at site of injection, lasts two to three days, with subsequent improvement of all symptoms. Some results with progressive paralysis were such as one would expect. Naturally, the new substance will not overcome results of nerve degeneration.

(122) *Willige*, 'Münch. Med. Woch.,' Nov. 15, 1910, p. 2403, employs a solution made with the smallest quantity of Methy Alcohol, then 10 Cc. of water, and finally 2 to 3 Cc. of  $N/5$  NaOH.

This solution, he states, is nearly always slightly acid—it has little or no effect on the pain or local irritation. Intramuscular injections used; later subcutaneous. The paper is in the main a recital of cases. The conclusions on 'Value in meta-syphilitic diseases,' possibilities of improvement after treatment of paralytics, influence on Wassermann are of a general nature. Severe forms of diabetes are contra-indications. Willige intends to use '606' further in progressive paralysis.

(123) 'Berl. Klin. Woch.,' Nov. 28, 1910, p. 2212, gives a number of abstracts from other papers. In one (*Gerber*) it is stated that injection of the preparation caused decrease in mouth spirilla. Suggested method of following course of treatment.

(124) *Emery*. L., Nov. 26, 1910, p. 1543. An account of a visit to Ehrlich.

The statements, on the whole, are covered by that which is contained in this paper, and it would be mere reiteration to repeat. A few points were, however, noticed in reading the article.

Analysis of the urine essential. Injection only possible when no pathological waste proceeding.

*Primary Cases.*—Action on a chancre on the lip, which healed in three or four days. Less struck by rapidity of



action on genital lesions. A chancrous ulceration of this kind required Mercury to assist treatment—an unusual case.

*Secondary Cases*—Extraordinarily efficacious on mucous plaques in all localities and of various kinds, vulvar and penile syphilides heal more slowly. Various other types described in detail.

'606' said to be a veritable triumph over the serious secondary syphilides—'the early malignant, pustular, ulcerative, ecthymatous, and raspberry-coloured syphilides.'

*Tertiary forms.*—The action is particularly startling.

(124a) *McDonagh*, Brit. Jl. of Children's Diseases, Oct., 1910, per Med. Press, Nov. 30, 1910, p. 581.

(125) *Leader*. B. M. J., Dec. 3, 1910, p. 1796. A useful summary in condensed form of the opinions expressed at the Königsberg Meeting, Sept. 20, 1910—all of these are embodied in our text from the 'Deut. Med. Woch.,' Oct. 13, 1910.

(126) *McIntosh* and *Paul Fildes*, L., Dec. 10, 1910, p. 1684, give a general account of the Chemistry of '606'—in which there are some unfortunate slips. The contribution deals with cases treated at the London Hospital.—See *Sequeira*.

(127) "A New Neurosis." B. M. J., Dec. 10, 1910, p. 1886. A skit from Paris.

(128) *C. F. Marshall*, 'Medical Press,' Dec. 14, 1910, states it is impossible to prove that either '606' or any other drug has produced a *sterilisatio magna*—in the first place it is possible that in some cases the power of resistance of the body is sufficient to overcome the spirochetes without the assistance of any drug, and that secondly latent periods may elapse between the primary and tertiary periods. Does not think Wassermann reaction can be accepted as absolutely conclusive. Recent reports from Paris indicate that relapses are common, that some cases do not respond to the treatment at all, that it has no effect on visceral syphilis, nor on para-syphilitic lesions. Concludes with 'We should think twice before recommending '606' to our patients, and insist on a written statement if they demand it.'

(129) L., Dec. 17, 1910, p. 1770—Review of Ehrlich and Hata's book 'If a drug is to be of use in clinical medicine the ratio  $\frac{C}{T}$  i.e.,  $\frac{\text{dose sufficient to destroy all parasitives}}{\text{max. dose which will not kill patient}}$  should be  $\frac{1}{3}$  or less—this is claimed to be fulfilled by '606.'

(130) *Martindale*, 'Chemist and Druggist,' Dec. 17, 1910. A note on Preparation of Salvarsan Injections.



THERMOMETRIC CONVERSION TABLE  
BETWEEN CENTIGRADE & FAHRENHEIT SCALES WITHIN CLINICAL LIMITS.

Centigrade.	Fahrenheit.	Centigrade.	Fahrenheit.
35°0	95°0	39°6	103°28
'1	'18	'7	'46
'2	'36	'8	'64
'3	'54	'9	'82
'4	'72	40°0	104°0
'5	'90	'1	'18
'6	96°08	'2	'36
'7	'26	'3	'54
'8	'44	'4	'72
'9	'62	'5	'90
36°0	'80	'6	105°08
'1	'98	'7	'26
'2	97°16	'8	'44
'3	'34	'9	'62
'4	'52	41°0	'80
'5	'70	'1	'98
'6	'88	'2	106°16
'7	98°06	'3	'34
'8	'24	'4	'52
'9	'42	'5	'70
37°0	'60	'6	'88
'1	'78	'7	107°06
'2	'96	'8	'24
'3	99°14	'9	'42
'4	'32	42°0	'60
'5	'50	'1	'78
'6	'68	'2	'96
'7	'86	'3	108°14
'8	100°04	'4	'32
'9	'22	'5	'50
38°0	'40	'6	'68
'1	'58	'7	'86
'2	'76	'8	109°04
'3	'94	'9	'22
'4	101°12	43°0	'40
'5	'30	'1	'58
'6	'48	'2	'76
'7	'66	'3	'94
'8	'84	'4	110°12
'9	102°02	'5	'30
39°0	'20	'6	'48
'1	'38	'7	'66
'2	'56	'8	'84
'3	'74	'9	111°02
'4	'92	44°0	'20
'5	103°10		



# METRIC WEIGHTS AND MEASURES AND THEIR EQUIVALENTS IN THE BRITISH PHARMACOPŒIA.

1 Gramme (Gm.)	...	...	= 15'4323564 grains.
1 Centigramme (Cgm.)	...	...	= 0'154323 grain.
1 Milligramme (Mgm.)	...	...	= 0'015432 grain.
1 Litre...	..	...	= 35'196 fluid ounces.
1 Cubic Centimetre (Cc.)	...	...	= 16'95 minims (nearly).
1 Metre	...	...	= 39'370113 inches.

The Gramme has its decimal multiples—Decagramme, Hectogramme, and Kilogramme; and divisions—Decigramme, Centigramme, and Milligramme. The Litre and Metre have their corresponding decimal divisions—Decilitre, Centilitre, and Millilitre,—and Decimetre, Centimetre, and Millimetre.

## APPROXIMATE EQUIVALENT DOSES.

FROM THE EXTRA PHARMACOPŒIA.

### WEIGHTS. IMPERIAL TO METRIC.

grain	Gm.	grain	Gm.	grains	Gm.
$\frac{1}{100}$	= 0'00065	$\frac{1}{3}$	= 0'02	12	= 0'8
$\frac{1}{80}$	= 0'001	$\frac{1}{2}$	= 0'032	15	= 1'0
$\frac{1}{50}$	= 0'0013	$\frac{3}{4}$	= 0'05	20	= 1'3
$\frac{1}{40}$	= 0'0016	1	= 0'065	24	= 1'5
$\frac{1}{32}$	= 0'002	grains		30	= 2'0
$\frac{1}{30}$	= 0'0022	$1\frac{1}{2}$	= 0'1	40	= 2'6
$\frac{1}{25}$	= 0'0026	2	= 0'13	60	= 4'0
$\frac{1}{20}$	= 0'0032	3	= 0'2	90	= 6'0
$\frac{1}{16}$	= 0'004	4	= 0'26	120	= 8'0
$\frac{1}{12}$	= 0'0054	5	= 0'32	$\frac{1}{2}$ ounce	
$\frac{1}{10}$	= 0'0065	6	= 0'4	(av.)=15'0	
$\frac{1}{8}$	= 0'008	7	= 0'46	1 „=30'0	
$\frac{1}{6}$	= 0'01	8	= 0'52	(or nearer 28'35)	
$\frac{1}{5}$	= 0'013	9	= 0'6	1 pound	
$\frac{1}{4}$	= 0'016	10	= 0'65	=453'59	



## WEIGHTS. METRIC TO IMPERIAL.

1 kilogramme...	...	...	...	= 2 lb. 3 $\frac{1}{4}$ oz.
500 Gm.	...	...	...	= 1 " 1 $\frac{5}{8}$ "
100 "	...	...	...	= 3 $\frac{1}{2}$ oz.
25 "	...	...	...	= $\frac{7}{8}$ "
10 "	...	...	...	= $\frac{1}{2}$ "
1 "	...	...	...	= 15.43 grains.
$\frac{1}{2}$ " or 500 milligrammes	...	...	...	= 7.7 "

## MEASURES. IMPERIAL TO METRIC.

minim	Cc.	minims	Cc.	fluid oz.	Cc.
$\frac{1}{2}$ =	0.03	15 =	0.9	1 =	30.0
1 =	0.06	17 =	1.0	fluid ozs.	
minims		20 =	1.2	2 =	60.0
2 =	0.12	25 =	1.5	4 =	115.0
3 =	0.18	30 =	1.8	5 =	140.0
4 =	0.24	40 =	2.4	6 =	170.0
5 =	0.30	50 =	3.0	8 =	230.0
6 =	0.35	60 =	3.5	10 =	280.0
7 =	0.42	80 =	4.7	20 =	568.0
8 =	0.5	90 =	5.3	gallon	litres.
9 =	0.54	100 =	6.0	1 =	4.546
10 =	0.6	120 =	7.0		
12 =	0.7	240 =	15.0		

## MEASURES. METRIC TO IMPERIAL.

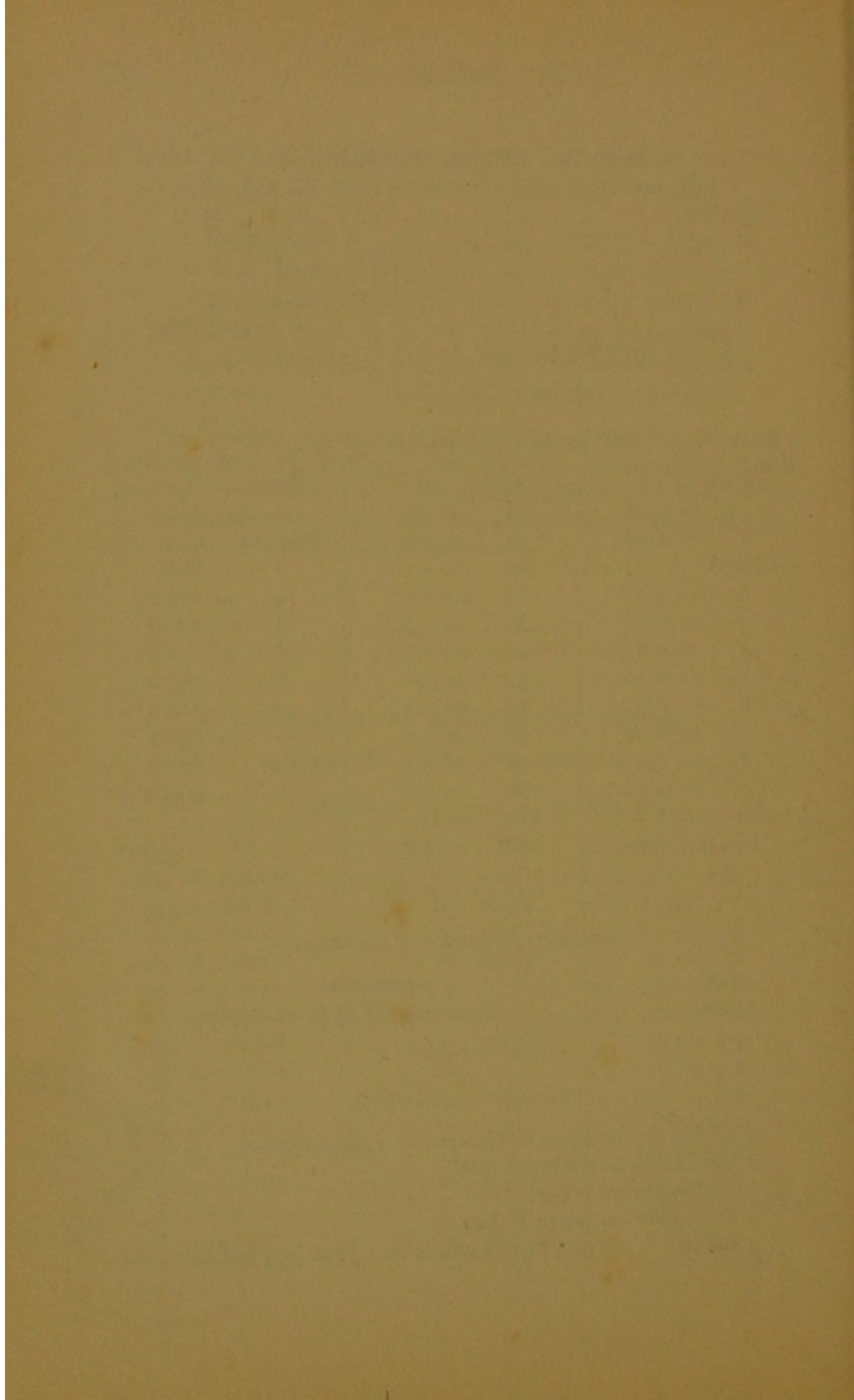
1 Cc.	...	...	= 17 minims
1 litre	...	...	= 1 pint 15 fl. oz. approx.

## MEASURES OF LENGTH.

1 micron	= $\frac{1}{1000}$ millimetre or $\frac{1}{1000000}$ metre
1 millimetre	= 0.039370 inch
1 centimetre	= 0.3937 inch
1 decimetre	= 3.937 inches
1 metre	= 39.370, 113 inches or 1 yard 3.37 inches nearly









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