albumin was present just before the injection. In this case transient albuminuria occurred after each injection.

Hersheimer's reaction occurred in 2.3 per cent. These were all early and previously untreated cases of secondary syphilis, and in most of them the primary sore was still active. The rash became more prominent a few hours after the first injection, and subsided again almost as quickly as it arose.

Herpes labialis occurred in one case. This was an early and previously untreated secondary case, with an active primary sore. As was to be expected, the immediate reaction was severe. The temperature rose to 103.5°, and was accompanied by a rigor, headache, and diarrhoea. He felt quite fit next morning, and the herpes did not appear until forty-eight hours later. Herpes does not occur apart from pyrexia. In the days when impure saline was used its occurrence was far more frequent.

Thrombosis of the vein at the site of injection occurred in 0.5 per cent. In two out of the three cases the needle had frequently to be readjusted, as the fluid flowed in very slowly and at times stopped altogether. It is a question whether this slow rate of flow, in conjunction with the local injury to the vessel wall due to the needle, caused the thrombosis, or whether the thrombosis was due to the irritation of the fluid injected. The former seems the more probable, as one would expect to get a higher percentage of these cases if the latter was the explanation. The amount of sodium hydroxide used in each case was the normal.

Dermatitis occurred in one case only. The rash was of a very mild character; it was limited to the limbs, and required no treatment. It started forty-eight hours after the second injection, and cleared up within a fortnight. It recurred after a third dose—this time a half dose (0.3 gram)—and subsided as before.

A reaction due probably to an abnormal arsenical toxicity in a particular batch occurred in 0.5 per cent. This reaction, which came on towards the end of, or a few minutes after, an intravenous injection, consisted in slight oedema of the lips and eyelids, a sense of fullness in the throat, and epigastric pain. Two patients fainted as they walked to bed. The localized oedema subsided almost as quickly as it arose, but the epigastric pain lasted longer. In addition there might be a rise of temperature, headache, and diarrhoea. In Case A the reaction occurred after an injection with 0.6 gram of batch No. 85. This was the third injection, and it was given twenty-five days after the second. The batch used for the first and second injections was No. 82, the dose in each case being 0.6 gram. These injections were not followed by any such reaction.

In Case B the reaction also occurred after an injection with 0.6 gram of batch No. 85. This was the second injection, given twenty-seven days after the first, when 0.6 gram of batch No. 82 was used with no ill effects. A third injection with 0.6 gram of batch No. 91 was given in this case, fourteen days after the second, with no ill effects.

The occurrence of this reaction on both occasions with batch No. 85 naturally made this batch suspect. I find I have used it forty-eight times, and, besides the two cases mentioned, I find only one case which showed any special symptoms. This man turned pale and fainted as he was walking to his bed. His pulse was soft, but the rate did not rise above 72, and he was well again in a few minutes. He had no oedema or epigastric pain. The injection was his first, and the full dose was given. When an injection gives rise to a reaction out of the ordinary, the question is apt to arise whether or not the addition of the alkali, to the drug in acid solution, was omitted. There is no chance, however, of this error having been committed in any case in this series, as a point has always been made of tabulating in the reaction scheme the amount of alkali required for each dose before injecting it. Some such precaution as this is necessary, as it is a mistake made more easily than might be supposed.

I have gone into detail over these cases, not because they caused any real anxiety, but because they showed a reaction out of the ordinary; a reaction, in fact, which cannot be put down to the stage of infection of the patient or to faulty technique in the administration of the drug. Neither can it be put down to "cumulative action." The reaction was too sudden for this; moreover, the interval

between the successive doses was in the two cases A and B twenty-five and twenty-seven days respectively, and in Case B a subsequent full dose, though from a different batch, was given fourteen days later with no ill effect.

Nor can these patients be said to have shown an idiosyncrasy for arsenic as given them in the usual form of the disodium salt of dioxydiamido-arsenobenzol, as they did not show any toxic symptoms to full doses given with any other batch than batch No. 85.

I believe this reaction to be an indication that the particular batch used contains a rather higher percentage of arsenic in a toxic form than should be the case. The symptoms suggest a toxic action on the vascular endothelium, with effusion of serum in certain localities where the tissues are lax, and a general lowering of blood pressure. In view of the fact that only two, or possibly three, patients out of forty-eight injected with the batch in question—which was one of the earlier ones—showed a toxic reaction, it cannot be said that the increased toxicity in this case was very marked.

It is known that different samples of salvarsan and neo-salvarsan vary slightly in their toxic (organotropic) properties. The total toxicity of these complex arsenical preparations can only be tested by experiments on animals. By this means batches which are found to be distinctly toxic are prevented from reaching the public, but it must happen occasionally, and more particularly when a preparation is first brought out, that a rather doubtful batch is passed, and I think this is a case in point. Certainly I have had no such reaction with any of the later batches, all of which have proved highly satisfactory.

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THE HISTORY OF ORGANIC COMPOUNDS OF ARSENIC IN THE TREATMENT OF PROTOZOAN DISEASES.

By BENJAMIN MOORE, D.Sc., F.R.S.

THE man who welds the last link in the chain, especially if he assigns a name to the link, often gains the reputation of having forged the whole chain, and this is especially true in regard to the series of discoveries which have led up to salvarsan and neo-salvarsan.

But the pioneers are the real discoverers, and it appears necessary to make some attempt to keep history correct in this field at the present moment, or the labours of the pioneers may become forgotten. The whole history of the therapeutics of organic compounds of arsenic revolves around the discovery and applications of atoxyl, the first of these compounds to be synthesized and applied in the treatment of protozoan diseases.

Salvarsan and neo-salvarsan are simply derivatives of atoxyl obtained in attempts to suit the original discovery more accurately to treatment.

It is noteworthy that the contributions of the observers of France, Britain, and Germany towards the evolution are just those which might have been expected from experience in the scientific history of these nations.

Atoxyl, the mother substance of the group, was discovered by the famous French chemist A. Béchamp in 1863. Béchamp was the author of a long series of papers on organic chemistry and bio-chemistry, and in 1863, when the properties of aniline and its coloured derivatives were attracting much attention, and shortly after the first of the aniline dyes had been obtained by Perkin, he obtained atoxyl by heating a mixture of aniline and arsenic pentoxide to a temperature of about 190° C. In his original paper Béchamp stated how he had isolated atoxyl, and accurately described its properties and those of its more important salts. By an error easily excusable in a first paper at the date 1863, he described his newly-discovered compound as an anilide of arsenic acid.

The discovery lay dormant for many years until the compound was exploited as a remedy for cutaneous infections by the Berlin firm called the Lanolinfabrik Martinikenfelde. The substance, now labelled atoxyl, was made by Béchamp's process, and misleadingly described as an anilide of arsenious acid. The process of manufacture

was entirely concealed, and the description as a compound of arsenious acid, which is not used at all in the manufacture, was obviously introduced in order to throw chemists off the track. The formula published—namely, $C_6H_5NH.AsO_2$ —is entirely erroneous and misleading. The name atoxyl was given because the compound was found to be many times less poisonous than inorganic arsenical compounds.

The substance was first recommended in Germany as a therapeutic agent in skin diseases—an obvious application from the known properties of the inorganic arsenical compounds.

The new remedy, however, entirely failed in this field; it became discredited as a remedy in skin affections, not merely from its failure as such, but because it caused in certain cases optic atrophy and blindness.

If no fresh research had been made at this point atoxyl would have become forgotten, the whole development of organic compounds of arsenic in therapeutics would have been delayed, and there would have been no salvarsan ("606") or neo-salvarsan in our generation.

The first movement, it will thus be seen, arose in France from Béchamp's discovery, the next step came from Britain; it was not made by Koch, as erroneously stated in a recent paper in this JOURNAL. Thereon arose the whole harvest of the later therapy of organo-compounds of arsenic in the treatment of syphilis and other protozoan diseases. This is a point worth emphasizing at a moment when many are lauding German scientists as the discoverers of the remedy for syphilis and related protozoan diseases.

A Canadian observer, H. Wolferstan Thomas, working in the School of Tropical Medicine at Liverpool, found that arsenical compounds had a distinct therapeutic value in the treatment of various diseases due to trypanosomes, and was searching for an arsenical compound less toxic to the host and more fatal to the protozoans. He applied atoxyl, and found that this drug, the first organic arsenical compound to be thus utilized, had a wonderful effect in prolonging life in infection with several different types of trypanosomes.

This paper was published long in advance of Koch's report on the treatment of sleeping sickness, and in it Thomas distinctly advocated the use of atoxyl in human trypanosomiasis.

Therein lay the germ of all future discoveries as to the application of organic arsenical compounds in the therapeutics of protozoan diseases. The future lay in the detailed experimentation as to the best compounds of the organo-arsenical compounds to be used.

Although the origin of atoxyl and its chemical constitution had been concealed, Ehrlich himself at a later period acknowledged its discovery by Béchamp and the priority of the English in its application; thus he writes in *The Experimental Chemotherapy of Spirillosis*, translated by Newbold and Felkin (Rebman, Limited, 1911):

I myself, at the very beginning—January, 1903—of my trypanosome researches, employed atoxyl in conjunction with Dr. Shiga, but abandoned it because it did not exercise any destructive action on the parasites in the test-tube. Therefore directly I became acquainted with the positive result obtained by the English authors, I again took up the study of atoxyl in the summer of 1905, and set myself the task of finding out new preparations which belonged here, and which were of greater curative power and less toxicity.

This somewhat self-protective acknowledgement is all very well at such a late period, but it is to be remembered that nothing regarding the application of organic arsenical preparations of arsenic in trypanosomiasis or other protozoan diseases had appeared in Germany till long after Thomas had published his paper, and that atoxyl, discovered in France, was only exploited in Germany as a secret proprietary drug and described under a most misleading formula. It is again to a French chemist, M. E. Fourneau, that the world owes the merit of having shown that atoxyl was the substance discovered by Béchamp in 1863. He stated this quite clearly in the *Journal de pharmacie et de chimie* in April, 1907, in a passage which may be translated as follows:

According to a circular sent out by the manufacturers of atoxyl "atoxyl is the anilide of meta-arsenic acid; its constitutional formula is $C_6H_5NH.AsO_2$, and consequently it contains 37.69 per cent. of arsenic."

The formula assigned to atoxyl by the manufacturers, probably with the object of defeating competition, is false.

Atoxyl is not a new product, but a product which has been known for a long time. It was not discovered by a German, but by Béchamp in 1863; he obtained it by heating arseniate of aniline.

This is established by the analysis of atoxyl, by the examination of its properties, and by a comparison of atoxyl of German origin with ortho-arsenanilide prepared according to Béchamp's method, the two bodies being identical.

It was only some time after this exposure by Fourneau of the identity of Béchamp's original compound with atoxyl that any publication of the real constitution of atoxyl appeared from any German laboratory.

As the use of atoxyl in the treatment of protozoan diseases had been introduced from the Liverpool School of Tropical Medicine, it was natural that the constitution and mode of action of the drug should interest other workers in the school, and in 1906 the present writer, in collaboration with Nierenstein and Todd, commenced work upon the subject.

It was soon discovered that it was not an anilide from its resistance to hydrolysis and general stability to reagents. No modern chemist capable of producing the substance and experimenting on its properties could possibly make such a gross error as to its nature, and one is driven to the view that, like the concealment of the process of manufacture discovered by the French chemist, the formula given and the statement that it was an anilide of arsenious acid, were both meant to deceive and lead away from any use of arsenic acid in the process of synthesis.

The substance is obtained by the simple process of heating molecular proportions of arsenic pentoxide and aniline above the boiling point of aniline and separating from other products in the melt. In their work, Moore, Nierenstein, and Todd showed that:

The substance atoxyl is in all probability not an anilide, but a sodium salt of an organic acid containing an amidogen group and an arsenic radical directly united to a benzene ring.

The only known organic arsenical compounds showing a similar stability to the action of alkalis are those containing the arsenic directly united to the benzene ring—such as phenyl-arsenic acid and its salts $[C_6H_5.As(OH)_2]$ and $[C_6H_5.As(OH)(ONa)]$.

Its toxic properties are neither those of arsenic nor of aniline, even when pushed to excess, and its therapeutic action is rapid; from this and its high conductivity showing high dissociation the conclusion is drawn that its activity must be ascribed not to free inorganic arsenical ions or to free aniline, but to a complex organic ion containing both the arsenical and aniline radicals.

Before the introduction of atoxyl into the therapy of trypanosomiasis by Thomas a great deal of research had already been expended on the subject by observers all over the world. Ehrlich and his school were at work upon the subject, and had been experimenting with aniline colours, usually with negative results, except in one or two instances. One colour which produced the greatest effect, but still only acted feebly, being named "trypanroth" on account of its action.

As soon as Thomas published his results, Ehrlich and his collaborators set to work, as recorded in Ehrlich's own words earlier in this paper, and, practically simultaneously with the paper from the Liverpool school described above, Ehrlich and Bertheim published a paper showing that atoxyl was para-amido-phenyl-arsenic acid.

From this stage onward to salvarsan and neo-salvarsan the experimental work consisted in experimenting with various derivatives of atoxyl to find those most suitable for therapeutic use.

These are all aniline derivatives, containing, like atoxyl, an arsenical group directly attached to the benzene nucleus, and hence atoxyl may be regarded as the mother substance for them all. Salvarsan was originally obtained by using atoxyl as a starting point and condensing so as to obtain two derived amino molecules united by the arsenical groups.

Neo-salvarsan is obtained by the introduction of a simple side-chain group giving a substance with more favourable solubilities for administration.

This last stage in experimentation requires a battery of working chemists and therapeutists producing a large number of small variants and testing them patiently in a large number of experiments.

The rôle here is exactly that which suits Teutonic talent, and it was here that the combination of the chemical staff of the Höchst Anilinfabrik and the Frankfurt School of Therapy achieved the success which repaid them commercially and gave them the credit of

naking a discovery when they had really only succeeded in exploiting at the concluding stages the pioneer work of others.

Soon after the publication of the constitution of atoxyl the writer met Ehrlich in Liverpool on his way to receive a medal at a sanitary congress being held in Douglas, Isle of Man, and congratulated him on his recent paper with Bertheim establishing the constitution of atoxyl, remarking that he had an able and energetic young man in Bertheim. The Geheimrath laughed heartily and said: "Energetic young man! Why he is a director of the Höchst Anilinfabrik, one of the greatest aniline dye works in Germany, and turned the whole staff on to the work."

It is in this combined team work, dealing with minute details, that Germany excels, and the history of the production of organic arsenical therapeutic agents is very similar to that of the aniline dye industry.

SUMMARY.

To conclude this brief sketch of the history of the therapy of protozoan diseases by the use of organic arsenical compounds, a history which only pretends to present the salient points and not to give any complete account of the literature, the following summary may be given:

Atoxyl, the mother substance, was discovered in France, the application to protozoan diseases was made by a Canadian working in a British laboratory, and the chemical nature of atoxyl was shown simultaneously in England and Germany; then German observers finessed amongst the derivatives to find the compounds best adapted for therapeutic use.

The details of production of the compounds were not revealed by Germany, and it is a matter for congratulation that these can now be manufactured in Britain.

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THE PREVENTION, SYMPTOMS, AND TREATMENT OF TETRYL DERMATITIS.

BY

ENID SMITH, M.B., B.S.LOND.

FOR the past nine months I have acted as medical officer to munition works employing about 250 women, where tetryl (tetra-nitro-methyl-anilin) is used.

This note, on the means used to avoid the dermatitis and other troublesome symptoms caused by handling this explosive, is written at the suggestion of Dr. Legge, H.M. Medical Inspector of Factories.

I. SELECTION OF WORKERS.

Experience showed that women with obvious eye or skin diseases should be excluded, and all workers should be taken on probation. It is quite impossible to foresee who will prove susceptible.

II. PROPHYLAXIS.

On entering the factory the workers remove their outdoor clothes, put on special overalls and slippers, and pass through a toilet room, where a responsible person sees that each worker hardens her hands in spirit lotion (filtered methylated spirit 20 per cent., water 80 per cent.) and dusts her face freely with powder (zinc oxide 1, starch 3).

In the rooms the workers are warned against touching their faces with their hands. The trays and tables are regularly wiped and the floors swept and scrubbed, so that the quantity of tetryl is limited. Tetryl-laden dust, or finely divided tetryl seems to be more injurious than tetryl in bulk. Some workers use veils or muslin across the mouth to avoid inhaling the dust. The rooms should be airy and cool, but not draughty. Hot, close weather increases the trouble, so that provision must be made for keeping the rooms cool in summer.

On leaving the works, the workers should wash their hands, using olive-oil soap or bran. Each worker should

have her own towel. The face is wiped free of powder and a simple greasy preparation may be used at the end of the day.

Washing of Clothes.—It should be noted that those living with workers get affected, especially if they wash the workers' clothes. All clothes should be soaked in cold water and paraffin and rinsed before being boiled, or the steam from the boiling clothes will be very irritating.

III. SYMPTOMS.

The hands of all workers are stained yellow, and in most of them the faces and hair. They are known in the town as the "canaries." The conjunctivae are never stained, nor the covered portions of the body, but the feet may get "yellow as duck's."

Dermatitis, by which almost all workers are attacked, consists, in its mildest form, of irritation and roughening of the exposed skin. More serious is a papular eruption; in the severest cases there is acute oedema of the whole face, closing the eyes and making the features unrecognizable; any variety of eczematous eruption may be seen. The attack may occur at any time, but usually after a fortnight's exposure.

Conjunctivitis may occur with or without dermatitis.

Nasal irritation manifests itself in excessive sneezing and in epistaxis, but is never severe enough to keep a worker at home.

Pharyngeal irritation has occurred in a few cases. Asthmatic attacks compelled two workers to leave.

Constitutional symptoms are almost absent. Insomnia perhaps occurs out of proportion to the cutaneous irritation. "Biliousness" at the monthly periods has been noticed. It has not been found necessary to give the workers rest days on this account. The appetite is excellent, and the general health of some delicate women has certainly improved.

TREATMENT.

If the symptoms are slight the worker is encouraged to remain at work, perhaps changing to a room where tetryl is not used. The symptoms will then, as a rule, subside in the course of a few days and not recur.

If the symptoms are more severe—if, for example, there is oedema or a papular eruption, or conjunctivitis of moderate degree—the worker must stay at home. She should not return until quite well, as a convalescent seems unusually susceptible. If, after recovery, the worker gets a second severe attack, I advise her to find other work. In some cases, however, where the worker has remained at her own risk, she has gradually improved, and the skin, apart from pigmentation, has become practically normal.

For the dermatitis, in the severest cases, steaming the face with subsequent application of wet cloths reduces the swelling and allays the irritation. Later on, and in less severe cases from the first, calamine lotion acts well, though some prefer an ointment composed of zinc ointment, lanoline, and castor oil, equal parts. I have avoided lead lotion, as lead has a dangerous affinity for tetryl.

For conjunctival irritation colloidal silver acts well, though it smarts on application. For nasal irritation we use liquid paraffin.

RELAPSING PARATYPHOID "A" INFECTION.

BY

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SINCE the outbreak of the war paratyphoid fever has received a considerable amount of attention, and, with the extension of bacteriological laboratories, further opportunity has been afforded for its study. So far as recognized, the cases have presented more or less definite clinical manifestations, and the diagnosis is usually confirmed by the bacteriologist. That the infection may present itself in anomalous or atypical forms seems very probable, yet, so far, there has been little reported on the subject.