fact that hydrogen peroxide appears to exert a similar action to eusol suggests that the reaction is of the nature of an oxidation process.

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THE THERAPEUTIC AND REACTION EFFECTS OF KHARSIVAN.

A RECORD OF 600 INJECTIONS.

BY

H. C. LUCEY, M.D., B.S.LOND.,

TEMPORARY CAPTAIN, R.A.M.C., ROYAL HERBERT HOSPITAL,
WOOLWICH.

WHEN kharsivan, the British preparation of the same chemical constitution as salvarsan, was introduced last year, the Medical Research Committee made an appeal to members of the medical profession to furnish it with accurate records of the results, both as regards its therapeutic efficacy and the occurrence of any special incidental symptoms.

For such records, in the treatment of syphilis, to be value, it is necessary that (1) some definite scheme for recording results should be adopted, (2) all disturbing factors, such as errors in technique, should be eliminated.

A scheme such as that shown in the next column will be found useful.

It is convenient to keep a ledger embodying some such scheme as this, the details of which should be filled in every time a patient receives an injection.

In this way, besides noting the immediate reaction to a dose given on a particular date, a permanent record is kept of the patient's syphilitic history. The third case in the reaction scheme may be taken as an example. In the column "Previous Treatment" it will be seen that the patient had an injection of kharsivan 0.6 gram on January 19th, with two mercurial injections to follow. On referring to the page in the ledger recording injections given on January 19th, details of his condition and reaction on that date will be noted, and it will be observed what progress he has made in the interval.

At the present time, as a routine for primary and secondary syphilis, I give three injections of kharsivan 0.6 gram at fortnightly intervals, with two weekly injections of mercurial cream in the intervals. This is a short intensive course, designed to render a soldier fit for active service as quickly as is possible consistent with a reasonable chance of a permanent cure.

That this course of treatment does give him a reasonable chance is shown by Gibbard and Harrison's statistics produced at the International Congress of Medicine, 1913. On a precisely similar course, but using the German preparation "606," they found that only 3.9 per cent. of cases relapsed clinically and 19.4 per cent. serologically within a year of the suspension of treatment. It is, of course, not possible during war time to carry out systematic Wassermann tests or to examine patients at stated intervals for signs of relapse; but up to the present I have had only one man return to me, and that not for a relapse, but for a fresh infection.

I give this case with reserve as an example of re-infection with syphilis, because, unfortunately, the diagnosis of primary syphilis in the first instance, though supported on clinical grounds, was not established beyond all doubt by the finding of *Treponema pallidum*. No examination of the exudate from the sore was made on the first occasion.

D. A. was admitted into hospital on August 12th, 1915, with a sore on the glans penis. This was typical of a syphilitic chancre in this situation, being of the papulo-erosive type,

Name.	Syph. Stage.	Date.	Condition.	Previous Treatment.	Urine before Injection.	Temp. before Injection.	Preparation Used.	Dose.	Batch.	Amount of 4 per cent. NaOH.	Temp. after 4 hrs.	Temp. after 8 hrs.	Headache.	Rigor.	Vomiting.	Diarrhoea.	Urine 24 hrs. after.	Other Symptoms.
J—	Sy ¹	Feb. 2	Pr. Sore. In coronal sulcus; active 15 days. Glands. Both inguinals +. Skin. Nil. Mouth. Nil. Anus. Nil. Other Evid. Tr. pall. present.	Nil	N	98.2°	K	0.6 gm.	142	4.2 c.cm.	99°	101°	Slight	Nil	Nil	Nil	N	Nil
S—	Sy ²	Feb. 2	Pr. Sore. Under surface of prepuce; active 5 weeks. Glands. Both inguinals +. Skin. Roseolar rash on body and limbs. Mouth. Nil. Anus. Nil. Other Evid. —	Nil	N	99.4°	K	0.6 gm.	142	4.2 c.cm.	100°	103°	For 6 hrs.	Nil	Once	5 times	N	Herxheimer reaction.
B—	Sy ²	Feb. 2	Pr. Sore. Scar from sore 6 months ago. Glands. General +. Skin. Pigmentation from old rash. Mucous patches healed. Anus. Condylomata healed. Other Evid. Headache better.	K 0.6 gm. Jan. 19. Hg. ii.	N	93.4°	K	0.6 gm.	142	4.3 c.cm.	98.2°	98.7°	Nil	Nil	Nil	Nil	N	Nil
T—	Sy ³	Feb. 2	Pr. Sore. History of in 1908. Glands. Nil. Skin. Nil. Mouth. Glossitis. Anus. Nil. Other Evid. Wassermann +.	Treated with pills in 1903 and 1909.	N	98°	K	0.6 gm.	142	4.2 c.cm.	98.6°	98.2°	Nil	Nil	Nil	Nil	N	Nil

K = Kharsivan.

N = Normal.

Hg = Injection of mercurial cream.

circular, and evenly circumscribed, denuded only of epithelium and possessing a glazed surface. There was no pus. The patient had exposed himself to infection three to four weeks previous to its appearance. The incubation period, therefore, favoured a diagnosis of syphilis rather than soft sore.

The inguinal glands on both sides were discrete and enlarged, but they showed no signs of active inflammation. The nature of the glandular enlargement was, therefore, in favour of syphilis. On these grounds the case was diagnosed as primary syphilis, and an examination of the exudate for *Treponema pallidum* was not considered necessary. He received the 1.2.1.2.1 course of treatment, as indicated above. The sore rapidly healed and the inguinal glands were reduced.

On January 24th, 1916, he was readmitted with a fresh sore. This was in the coronal sulcus, and well away from the site of the previous sore, so that this could not be a case of "redux chancre." The sore was a typical Hunterian chancre. He had exposed himself to infection four weeks previous to its appearance, and the inguinal glands on both sides were enlarged. There were no secondary signs. This time the exudate was examined for *Treponema pallidum*, which was found to be present. The evidence therefore, though not complete, is in favour of this being a case of reinfection with syphilis, the previous infection having been completely cured by a course of treatment consisting of three injections of kharsivan (0.6 gram) and four of mercurial cream.

I confess, in peace time, I would prefer to give a longer course than this, especially for secondary cases, but my object in this paper is not so much to discuss the merits of any particular course of treatment, but rather to state my experience of the immediate therapeutic and reactionary effects of kharsivan.

The Immediate Therapeutic Effect of Kharsivan.

I believe kharsivan to be every bit as potent as the original German preparation. It may be objected that by adding mercurial injections to the course of treatment the effect of the drug cannot be properly determined. But the immediate effect of kharsivan given without the addition of mercury is apparently as rapid as when mercurial injections are added. The type of lesion which clears up most rapidly is, as would be expected, one in which the blood supply is good, and in which there is no breach of surface. This is particularly well marked in those cases of syphilitic infiltration met with in the later stage of syphilis, around the mouth and nose, causing great disfigurement. A patient suffering from such a lesion looks a different person a few days after a single injection.

Primary sores are rendered inactive after one injection; the time taken, however, before they become completely healed varies according to the extent of breach of surface, the degree of added infection, and the situation of the sore. Those situated on the skin as a rule take rather longer to heal than those on mucous membrane. I find the average time for all primary sores to be fifteen days, using in addition to the general treatment some local application such as lotio nigra or calomel.

The activity of a rash is immediately checked after the first injection, and it disappears in a few days or weeks according as to whether it is a roseolar or a pigmented papular rash. A very deeply pigmented rash may take months to fade completely. Condylomata and mucous patches usually clear up within a week.

Enlarged lymphatic glands are reduced at the end of a course of treatment, though, as a rule, if this has lasted only a few weeks, not sufficient time has been allowed for their complete subsidence. This is only what one would expect owing to their solid consistence. They subside completely later. That incomplete reduction of the lymphatic glands, at the end of a short intensive course of treatment, does not signify incomplete destruction of the *Treponema pallidum*, is shown by the absence of relapses in the great majority of such cases. Experimental evidence is afforded by Iversen,¹ who punctured the glands in 10 cases of secondary syphilis before and after an injection of salvarsan. He found that, whereas before the injection the organisms were present in large numbers, they could not be detected three to five days after an injection.

Reactions following Injections of Kharsivan.

I am in the habit of injecting six to a dozen cases in one morning. It is useful to do them in groups like this, because each case serves to control the others. Thus the technique, dosage, and batch of kharsivan being the same for all, if only one or two cases show a marked reaction of the usual febrile type, it is only reasonable to look for the cause in the individual rather than the solution injected.

If all, contrary to the rule, show marked reactions, then it is only reasonable to suppose that some common disturbing factor has been introduced—for example, bacterial contamination of the saline. Similarly one is able to test one batch of kharsivan against another.

Saline fever can be ruled out of this series, as freshly distilled water has been used throughout.

Except in a few cases where it has been thought safer to go gently, the full dose (0.6 gram) dissolved in 200 c.cm. of saline, has always been given, and in no case has one full dose followed another at a shorter interval than fourteen days.

No breakfast is allowed previous to the injection, and bed for twenty-four hours and no food for six hours after the injection has been the rule.

The absence of any unpleasant symptoms in the great majority of cases is very striking; 72 per cent. of the injections were followed by no symptoms whatever. The figures given below, relating to the various reactionary symptoms, must not be taken to indicate the number of patients who react, but only the frequency of the symptoms, a combination of which may occur after a single injection in one individual.

Pyrexia—The two chief factors (the saline being pure) which determine whether or no an injection will be followed by a rise of temperature to 100° F. or more are: (1) The absence of previous treatment; (2) the stage of syphilitic infection.

To catch a rise it is necessary to take the temperature four and eight hours after the injection. It is often not marked until after the first four hours. There are two types of cases in which after the first injection a reaction of the usual febrile type can be predicted.

(1) A previously untreated case of primary syphilis which is two weeks or more old.

(2) A previously untreated case of early secondary syphilis, particularly when associated with an active primary sore.

In reality these two types represent one stage, that is, generalized infection in the host who is fresh to it, only in (2) this is more advanced and apparent, and is usually marked by a more severe reaction. The temperature in such a case may rise as high as 103.5° F., and this may be associated with any or all of the following symptoms—rigor, headache, vomiting, diarrhoea, and occasionally a Herxheimer reaction. (See Case II in the reaction scheme.) Very often, however, and especially in primary syphilis, the reaction is limited to a temporary pyrexia, and no symptoms whatever are complained of.

It is most unusual for a reaction of this type to take place after a second injection given a fortnight later. It is rare for very early primary, and later secondary, and tertiary cases to show much of a reaction.

It would seem, therefore, that the freshness of the patient to the infection is a factor as well as the degree of infection in determining whether a reaction takes place or not. It is interesting, when injecting a group of men, to pick out beforehand those who are likely to react, and it is surprising how accurate it is possible to be. It must be remembered that a patient who has an acute superadded infection, such as a tonsillitis or influenza, may show a febrile reaction after an injection. As a result of the administration of the drug some of the pyogenic organisms are probably killed off and their toxins set free, hence the sudden rise in temperature.

Douglas and Colebrook² have recently shown that the blood possesses a marked bactericidal power an hour after an injection with neo-salvarsan, but that this diminishes rapidly in a few hours. The bactericidal power was not so marked when salvarsan was used.

Headache occurred in 17 per cent.

Rigor occurred in 5 per cent.

Vomiting, usually only slight but occasionally severe, occurred in 7 per cent.

Diarrhoea occurred in 10 per cent. This varied from two to eight motions in twenty-four hours. It is possible that in a few of these cases the looseness of the bowels was aided by a purgative given on the previous night.

Transient albuminuria developed on the day following the injection in 0.3 per cent. The urine was always tested before and twenty-four hours after. One of the cases gave a history of previous kidney trouble, though no

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

Hershheimer'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