case of patients who are unable to afford the expense of such.

8. That more specialized lectures for practitioners, students, and nurses should be given on venereal diseases, and opportunities for clinical and laboratory research:

REFERENCES.

¹C. Browning, *BRITISH MEDICAL JOURNAL*, January 10th, 1914.
²W. W. Sanger, *History of Prostitution*, 1913. ³Amand Routh, *BRITISH MEDICAL JOURNAL*, January 24th, 1914. ⁴R. W. Johnstone, Report on Venereal Diseases, Local Government Board, 1913.

ARSENO-THERAPY IN SYPHILIS, WITH MORE PARTICULAR REFERENCE TO "GALYL."

BY

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ALMOST since the introduction of syphilis into Europe, three of the heavy metals—mercury, arsenic, antimony—and their salts have been used in its curative treatment. Of these, mercury has until recently held pride of place, because the *dosis curativa* of both arsenic and antimony was so much greater than the *dosis tolerata* as to render them too dangerous for continued use. For this reason, therefore, they held until recently the mere secondary position of adjuvants; and it was not until it was shown that relatively enormous doses of the organic salts of arsenic could be tolerated in the successful experimental treatment of spirilloses and trypanosomiasis that the possibility of using these synthetic preparations in the analogous disease—syphilis—occurred to clinicians.

Naturally the idea, once mooted, was eagerly acted upon. In the last six years, therefore, a considerable number of these organic preparations have been tried successfully, and already an enormous literature has arisen therefrom. At the London Lock Hospitals we have had experience of a number of these—atoxyl (soamin), orsudan, arsacetin, arsenophenylglycin, hectine, salvarsan, neo-salvarsan, and lately galy. All of these have had rapidly curative effects in certain of the lesions of syphilis, particularly in those occurring on mucous surfaces—primary sores, condylomata, mucous plaques—less markedly on some of the secondary eruptions and tertiary lesions, least of all on the general adenitis of the secondary stage.

All these substances have one characteristic in common—the presence in their molecule of one or more benzene chains in which one of the hydrogen atoms has been replaced by an atom of arsenic; and it is to that their efficacy was and is due.

Therapeutically, most of these earlier substances were excellent; but the selective action on the optic nerve, producing amaurosis after the use of some of them, has caused all before salvarsan to be rejected, and many are now almost forgotten, although some of us who used them still remember how exceedingly rapid and gratifying the clinical results following their administration were.

SALVARSAN AND NEO-SALVARSAN.

Remembering these former disasters, when salvarsan was introduced syphilologists were naturally chary of using it at first; but the accumulated experience of the last four years has largely calmed this fear, and now several hundred injections a month are given at the London Lock Hospitals, with practically no fear of any disturbance; complications. Nevertheless, a study of the literature shows that, although no such spectacular catastrophe as total blindness is likely to follow the use of salvarsan, yet the substance is not without danger, even in competent hands.

Mouneyrat,¹ the discoverer of "hectine," states from the results of experiments on animals, that in acute salvarsan poisoning death is due to an "intense congestion, with minute haemorrhagic foci in the brain, liver, kidneys, spleen, and lungs," and that both salvarsan and neo-salvarsan can produce haemorrhagic meningo-encephalitis.

Delayed salvarsan poisoning, he states,² is due to the substance being "*un corps neurotrope*," since, in spite of assertions to the contrary, a certain proportion of each injection, varying with the individual, becomes fixed by the nervous tissues. The toxicity, however, he maintains, is not due to the arsenic content, but rather to the presence in its molecule of functional groups rendering it vasodilator, and allowing it to fasten on nervous tissue—"acting towards the nerve nuclei in exactly the same manner as the basic dyes, fuchsin, thionin, methylene blue, and vesuvian—bodies whose basic character is due to the same functional group present in salvarsan." That there is considerable clinical support for these statements is undoubted. We have seen an acute nephritis, almost fatal, set up by one injection, and we now refuse to use either salvarsan or neo-salvarsan in any case with albuminuria which will not yield first to mercury. Moreover, evidence is slowly accumulating showing that salvarsan and neo-salvarsan occasionally have a special affinity for the eighth nerve. Several cases of stone deafness have occurred within our knowledge after an injection; and any tendency towards deafness is now, therefore, looked upon at the Lock Hospitals as a distinct contraindication to their use.

Galy.

Although, then, our experience with salvarsan and neo-salvarsan, extending now to some three thousand cases, has been exceedingly fortunate as regards complications, yet, recognizing that most of our patients are drawn from young and otherwise healthy lives, and that it is in older lives that delayed symptoms are more likely to occur, we are always ready to try any improvement offered which has any claim to be free from such risks.

Mouneyrat has synthesized two such bodies, "galy" and "ludy," which he claims to be without vaso-dilator tendencies, and less neurotropic than salvarsan. By his courtesy a small supply of galy, sufficient for ten cases, was sent to us in July, 1913.

Chemically, it is a rather more complex body than salvarsan. As sent out, salvarsan is the di-hydrochlorate of dioxy-diamido-arsenobenzol; and as injected, after neutralization, its formula (neglecting the "CH's" of the benzene chain) is:

Galy is "tetroxy-diphosphamino-diarsenobenzene," with the formula:

Its arsenic content is 35.3 per cent., its phosphorus content 7.2 per cent. As sent out for intravenous injection in ampoules, it is a light yellow powder consisting of galy and an appropriate amount of sodium carbonate to make it easily soluble in distilled water, forming an isotonic solution. It must be prepared immediately before use.

The average dosage for a male is 0.45 gram for the first, 0.5 gram for the second, and 0.55 gram for the third injection; for a woman 0.4 gram, 0.5 gram, 0.5 gram. The dose is calculated as being 8 to 8½ mg. per kilo of body weight in the adult male, and 7 to 7½ mg. in the female.

For solution, 30 c.cm. of distilled water per decigram is used—that is, 150 c.cm. for 0.5 gram.

It is recommended that three injections should be given at intervals of a week; and it is stated that the Wassermann reaction is generally negative one month after the last injection.

During the autumn of last year, by permission of Mr. Charles Gibbs and Mr. Arthur Shillitoe, to whom I am indebted for permission to record these cases, the supply sent was used at the Harrow Road Lock Hospital for Women.

Obviously it would be impossible on this small experience to make any wide generalizations; but it can be stated that the injections were easily borne, there were no complications at the time, the clinical results were as rapid as with salvarsan, and we have had no delayed sequelae.

Appended are short notes on the first three cases:

CASE I.

E. H., a woman aged 20, admitted July 8th, 1913, with primary sore on the left labium majus, commencing venereal warts, and amygdaloid glands in groin. No other signs. Wassermann reaction positive. Had two injections of galy, 0.45 gram, at intervals of a fortnight. Sore healed in three weeks. Was then put on weekly injections of mercury 1 grain, for nine weeks. In all, had three months' combined treatment. Condition on discharge: No signs except anaemia, and glands still marked. Refused Wassermann test.

CASE II.

G. G., aged 19, admitted July 28th, 1913, with scabies and a maculo-papular eruption, ulcerated tonsils, marked condylomata on left labium majus, and general adenitis. Wassermann reaction positive. Had two injections of galy, 0.45 gram, and sulphur baths for scabies. Condylomata, throat, and rash all gone on August 15th. Discharged herself August 24th, saying she was now quite well.

CASE III.

G. R., aged 22, admitted September 2nd, 1913, with primary sore on the right labium majus, present five weeks, condylomatous masses extending back from the labia over the perineum to the anal margin, ulcerated tonsils, and marked adenitis. Treated with pills for five weeks before admission. Wassermann reaction positive. Had two injections of galy, 0.5 gram, at intervals of a week, followed by an eight weeks' course of injections of mercury 1 grain weekly. The condylomata and throat healed in a fortnight, the primary sore in a month. The glands were markedly diminished, but did not disappear. Two months after the first injection the Wassermann reaction was doubtful. The patient discharged herself November 26th, 1913. No lesions visible.

The contraindications to galy are the same as those for salvarsan, namely, cardiac, hepatic, renal, and probably nervous diseases. The temperature sometimes rises after the first injection, and as the substance is eliminated through the bowels there is often some diarrhoea. One of our cases had a bad attack of vomiting; but as this occurred to seven patients injected with salvarsan, and eight with neo-salvarsan, on the same day, we put it down to something in the distilled water and saline used, although these were carefully prepared in our own stills on the morning of injection.

Intolerance is said to be rare; and when it does occur it is mostly in women. It is considered to be present when the temperature remains above 101° F., and is associated with vomiting. In such cases the dose must be diminished by half. Markedly cachectic or anaemic patients must be very carefully watched.

It will be noted that although, for reasons of caution, we did not at first follow the maker's suggestion of a weekly injection for three weeks, the clinical results were, nevertheless, very good. Afterwards, when we found that weekly injections appeared quite safe, we used them, with increasingly rapid results.

Unfortunately, however, it is very difficult to keep the class of patient we have to deal with in hospital after visible signs have disappeared, or to get them to return for observation when they leave; and so we have no Wassermann after-results to round off the picture. This, however, appeared to us of little consequence, because, in spite of the optimism of the discoverers, we had entertained no hopes of curing the disease by means of these three suggested injections; and so we put all the cases upon mercurial injections at once, continuing them as long as the patients remained in hospital. Indeed, we do the same now with all our salvarsan cases, since no one with an extensive experience now hopes to cure all cases of syphilis with three or more injections of salvarsan alone.

The Present Position of Arsenotherapy.

It may be possible in an early primary case to abort the disease with three or more injections of salvarsan. But even that is doubtful, as cases in which the Wassermann reaction have remained negative for a year often show a positive reaction again after that period. In the face of secondary manifestations, it is so risky to depend on salvarsan alone as to be almost unjustifiable. In tertiary lesions salvarsan should be used only in the expectation of clearing symptoms.

Two courses, therefore, are open to us. One is to give a set of three or more injections of salvarsan, neo-salvarsan, or galy, in the first month or six weeks after the disease has come under observation, following it up by a full course of mercury, continuous or intermittent, with an occasional injection of salvarsan, if one thinks it worth while, spread over the next two years. After this, treatment may reasonably stop, with the proviso that the blood should be tested every six months for the next eighteen months to make certain that all is right.

This is the obviously safe treatment. It may, possibly, be unnecessarily safe; but it is the treatment one would recommend to one's best friend—the treatment one would adopt oneself if one were so unfortunate as to acquire the disease—and that is, after all, the ultimate criterion.

But it is a tedious method, and possibly unnecessary. The experience of the officers of the Royal Army Medical Corps at the Rochester Row Hospital suggests that it may be considerably shortened. The results there, following a course of intermittent salvarsan and mercury, appear to be excellent. They commence with one full dose of salvarsan, follow it with nine weekly injections of mercury, and wind up with a second injection of salvarsan. This makes about a three months' course; and in many of the patients it is stated the reaction has remained negative for a year afterwards. For greater safety it has been suggested that another dose of salvarsan should be sandwiched in the middle of this course, making, now, one salvarsan, five mercury injections; one salvarsan, five mercury injections; and a final salvarsan injection.

These two courses, known respectively as the "191" and the "15151" methods, have been tried, and are still being tried, at the Harrow Road Lock Hospital. The results of the first series have been collected by Lieutenant Corbett, R.A.M.C., late house-surgeon at Harrow Road, but are not yet published. Without anticipating his paper it is permissible to say that our results are not anything like as good as those obtained at Rochester Row—a large percentage of our cases giving a positive Wassermann reaction at the end of this course, before and after a final provocative salvarsan injection. This may possibly be due to the known greater intractability of women to treatment in this disease, or to another factor—the use of neo-salvarsan in a large proportion of the cases—for there seems to be little doubt that, judging from the Wassermann results, neo-salvarsan is not nearly as powerful a drug as salvarsan. The only advantages it possesses, indeed, seem to be its solubility and its neutral character. Even these advantages, however, are very slight, as we find that, with well drilled assistants and all the conditions favourable, it is possible to give twelve intravenous injections of salvarsan in an hour as against sixteen of neo-salvarsan.

SUMMARY.

Collecting all the evidence together, then, we may say that any of these substances—salvarsan, neo-salvarsan, or galy—can be used with apparent safety. Whether galy possesses the extra advantages claimed for it we have not yet had enough experience to decide. That salvarsan has advantages over neo-salvarsan would seem to be indicated by the Wassermann results. How galy compares with either of them in this respect we do not as yet know. Finally, it would appear that mercury is regaining once more its old position as the main stand-by in the treatment of syphilis; and that the real progress of arsenotherapy lies not in the direction of complete cure, but rather in its rapid healing effects on the early, highly contagious stages of the disease—truly an almost inestimable boon from the standpoint of the public health and the well-being of the nation.

REFERENCES.

- ¹ *Paris Clinique et Thérapeutique*, February 5th, 1913. ² *Journ. de Méd. Interne*, February 10th, 1912.