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THE TOXIC EFFECTS OF ARSENOBENZOL TREATMENT AND THEIR PREVENTION

A discussion based upon the paper read before the Society by Mr. DAVID LEES on April 24th.

Dr. J. C. BUCKLEY said that his first acquaintance with the toxic crises to which the author had referred was when he was put in charge of the "606" department at Lichfield. There were some 800 patients, and after two injections at first it was customary to send them off to the Front. He divided these cases into pulmonary, cardiac, and a combination of pulmonary and cardiac. Sometimes patients got a very swollen tongue. Other cases were collapsed. After leaving Lichfield he came to the conclusion that the procedure of dissolving kharsivan in boiling water was not altogether effective. Since he had been at Nottingham he had seen two cases of what he used to call the "Lichfield disease." He thought that a good many of these crises were due to the fact that the water was too hot and that it decomposed the drug.

With regard to dermatitis, at first in his clinic dermatitis decreased and jaundice increased. For two years he gave novarsenobenzol in the old Rochester Row way, and never had a case of jaundice at all, but in the last five years he had had about 120, all mild except one, which proved fatal. The patient died four and a half months after the administration of the drug. Of his 120 cases of jaundice, twenty of them occurred in cases which were put down as provisionally cured. They had had a negative Wassermann for two years, and were coming up every six months or year to have a provocative dose or a test. The worst case of dermatitis he ever saw was long before "606" was introduced.

Dr. T. ANWYL-DAVIES said that the author's splendid paper stimulated deep thought. In his view the point of first importance in the paper was that the prophylactic against arsenical intoxication was intra-muscular administration. In addition to prophylaxis there were other advantages in such administration. One got a
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greater therapeutic value with half the dose so administered, and undoubtedly a negative Wassermann came about sooner by that method of administration than any other.

Dr. Fowler Ward said that formerly he had found a number of cases with acute stomatitis after treatment. He now made a practice, the first week, of giving arsenic, and, the second week, of giving mercury intramuscularly with the arsenic, and since then he had had very few cases of stomatitis at all. With regard to dermatitis, he had had one unfortunate case, that of a child with keratitis. Three doses of novarsenobenzol were given, and everything was right, but after two more the child had dermatitis, and it was found that the two last doses were from a batch that ought to have been withdrawn. The dermatitis, very definitely arsenical, was extremely severe, but the child eventually recovered, although for a long time there were secondary skin infections.

Dr. D. H. Nabarro spoke of his experience at Great Ormond Street Children’s Hospital. With regard to the immediate effects, he did not think the psychic effects could properly be attributed to the drug itself. He found that week after week it was the same children who were sick after injections. One patient—a nervous child whom he had some years ago—used regularly to vomit before the injection was started. Recently he had been treating an adult who had malaise and nausea after each intravenous injection of arsenic, and when he switched him off to intramuscular injections of bismuth the patient told him that he had the same symptoms. Vasomotor disturbances were very rare in children, he had only seen them occasionally, and then he thought they were due to rather too big a dose for the size of the child. One child, half an hour after injection, went very blue in the face, and the hands and feet were swollen. The effects passed off in a day or two. She had some albuminuria, but this cleared up entirely. As a rule, however, these vasomotor effects were not found in children. Indeed, toxic effects from arsenical medication at Great Ormond Street were very rare indeed.

Jaundice was extremely rare, in his experience, among children, and the only case which had occurred at Great Ormond Street within the last eight or nine years was a case in which the treatment of weekly injections of
novarsenobenzol was not for syphilis. In the treatment of syphilis in the children’s clinic he had not had one case of jaundice. Some years ago he had one case of dermatitis occurring after the fourth injection of novarsenobenzol. The rash occurred on the first or second day after the injection. Unfortunately the child was not brought directly back to the hospital, but was taken to a local doctor first. When the child was brought to the hospital the condition was doubtful. It looked exactly like measles. The child was taken into the special observation ward and, unhappily, died.

With regard to the preparation of the drug, he had given probably between 10,000 and 15,000 doses of arsenic preparations to children, and he never filtered the drug. He took it out of the ampoule and left any residue that there might appear to be at the bottom. Apart from the few accidents he had mentioned, he had never seen any untoward happening.

Dr. H. C. G. Semon said that he had had one case of dermatitis, but never one of jaundice. He wondered whether Mr. Lees had ever tried, for the prevention of the crises to which he had referred, a solution of calcium chloride in a German preparation called "athenal." It had some effect, probably a central one, and was well worth trying where these crises continued. He was surprised that Mr. Lees did not suggest thiosulphate of soda in the treatment of jaundice. His own experience with that drug had been confined almost exclusively to the treatment of jaundice, and he had certainly found it extremely valuable. In the British Medical Journal about a month ago there was recorded a case treated at St. Pancras Infirmary of a woman deeply jaundiced and comatose, and they had no thiosulphate of soda, sterile at any rate, to give as an injection, so they administered it by the mouth in large doses. It was returned immediately, and no effect was produced. Some thirty-six hours later supplies of the drug were obtained, and it was given intravenously, with very strikingly good results.

With regard to the preparation of novarsenobenzol, the speaker was tending more and more to use the substances already put up in solution in ampoules. Not only was it unnecessary to filter under these circumstances, but the substances were put up in glucose, thus providing in itself the glucose which otherwise would be administered by the
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mouth, and one was less likely to run any risk of sepsis in giving a drug prepared away from the clinic than in using the ordinary material that, in his case, was put up for him by a nurse.

With regard to the substance sulph-oxy-salvarsan, the latest German preparation seemed to be extremely good. The substance was given once a fortnight, and four doses were given in a course. It was very slowly excreted, and was said to be exceedingly valuable in cases of inveterate Wassermann reaction. He thought it would come to be a line of practice they would institute in prolonged Wassermann reactions. Its safety and also its cheapness seemed to him to commend it.

Dr. C. H. MILLS referred to the actual advances which have been made since 1910 in eliminating the side effects in arsenobenzol therapy. He considered that the direction in which most had been done was from the clinical aspect. Undoubtedly it was being accepted that only by careful routine examination of the patient under treatment for the very earliest signs and symptoms of intolerance could the more serious toxic effects be aborted.

Another important advance was in the preparation of the patient. Whereas formerly we were wont to put the patient on a starvation diet as for a major operation, we now know, thanks to the physiologist, that the liver is less vulnerable to toxic damage from the arsenobenzols when rich in its store of glycogen. We now, therefore, enforce a diet rich in carbohydrates and, in addition, administer a large dose of glucose by the mouth prior to each injection. The patient is warned to avoid excess, especially alcohol, to correct constipation, and should refrain from exacting physical exertion.

With regard to the latter, he recalled a case of a jockey, who, in order to make a certain weight, underwent a most vigorous course of sweating and starvation. He developed toxic jaundice after the second intravenous injection of 0·3 grammes silbersalvarsan.

We had acquired valuable clinical experience also in respect to dosage, and the spacing of the intervals and rest periods.

From the biologists (here he referred to Dr. Dale and his colleagues) we had gained most valuable information from investigations, at the request of the Medical Research Committee, upon the relative toxicity and
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therapeutic efficacy of the various preparations of arszenobenzol in common use.

The speaker described the case of a patient invalided home from India owing to an extensive extravasation resulting from a faulty intravenous injection of a massive dose of arszenobenzol.

There was considerable "brawny" oedema, the limb being fixed to a right angle. On resuming cautious treatment with an initial small intravenous injection into the opposite arm a giant urticarial eruption immediately developed over the original extravasation, and the limb could be straightened. This phenomenon made him wonder if there is not more in the theory of anaphylaxis as an explanation of some of the side effects than is generally accepted. It also suggested to him the possibility of some such simple method as an intradermal test for tolerance to arszenobenzol. He therefore tried the effects of an intradermal injection of arszenobenzol solution, using five minims of the same concentration as the intravenous solution. Patients at different stages in their courses of treatment were investigated, but the degree of local reaction did not afford any reliable definite indications as to tolerance. One of the greatest difficulties he had to contend with was that certain of the toxic effects—unhappily the most dangerous—jaundice and exfoliative dermatitis, frequently do not develop until two to three months after administration of the drug.

It has been proved by the physiologist that it is at this stage that the liver generally shows most signs of intolerance.

In sodium thiosulphate we certainly had a very valuable corrective in cases exhibiting toxic effects.

Stomatitis, resulting either from mercury or bismuth, cleared up almost miraculously under its influence. This drug should be given at the very earliest signs of dermatitis, and vigorously—with, of course, cessation of the arszenobenzol. He could not express an opinion yet as to whether it tended to lessen the therapeutic value of the arszenobenzols when given concurrently with these as a routine prophylactic.

With regard to cerebral oedema following arszenobenzol therapy, he stressed the tremendous importance of doing a lumbar puncture immediately. He thought it would be interesting to know the incidence of jaundice occurring
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normally as compared with its occurrence in arsenobenzol therapy. He thought that jaundice due to syphilis itself must be rare. He had treated a considerable number of severe cases of dermatitis, and after treatment he had started again very cautiously with minute doses intramuscularly, without any untoward results. It had been his experience that the Wassermann in the majority of these cases had turned negative, but they could relapse. He recalled a case in private practice which bore out what had been said about the need for preventing patients doing intense physical exertion. With regard to the safety of the intramuscular route, his experience, in general, had been that it was very well tolerated.

The President, after congratulating Mr. Lees on his paper, said that it had occurred to him that one’s private cases did not get jaundice because they were better fed. With regard to the prevention of encephalitis, he was quite convinced that there was a very definite relation between the size of the dose and the interval between the doses. In the early days of salvarsan therapy he had noticed that the great majority of such cases came within the groups which had been injected with full doses of "606" at intervals of something less than a month, and the shorter the interval the greater the incidence of encephalitis. It was at one time the fashion in London to give two full doses of "606" within forty-eight hours and encephalitis was then rather common. He himself believed that it was by giving small doses that they were able to give them more frequently. If 2-4 grammes of "606" had been given in doses of 0.6 within a month there would have been far more cases of encephalitis than had occurred during the war. He agreed with Dr. Mills that lumbar puncture was very valuable in these cases.

Mr. Lees had mentioned that he did not agree with him (the speaker) as to the action of cold in increasing the predisposition to dermatitis. But he remembered very well in France, in the large hospital with which he was connected, that there was a greater incidence during the cold weather than during the hot. That was a true test, because the men, being in tents, were really exposed to weather conditions.

With regard to the question of thiosulphate as a prophylactic, a doubt had been expressed as to whether it would not interfere with the therapeutic action of the
remedy. This gave him an opportunity of recanting an opinion to that effect which he had expressed in the *Medical Annual*. After a conversation with Dr. Dale, who had carried out some animal experiments to test the effect on its therapeutic power of dissolving arsenobenzol in a solution of sodium thiosulphate, he had tested the effect of solution in thiosulphate on the power of arsenobenzol to cause disappearance of *Sp. pallida* from early syphilitic lesions, and he must take back the view he had expressed that the therapeutic value of the remedy might be interfered with by thiosulphate.

He thought it was necessary to be very cautious in recommencing the treatment of patients who had suffered from dermatitis, but now that thiosulphate was available one might possibly be able to go ahead a little more boldly.

Mr. Lees, in view of the extreme lateness of the hour, condensed his reply. He thanked the Society for the kind way in which his remarks had been received. With regard to mercury and arsenic causing stomatitis, he thought the cause of stomatitis was dental sepsis. He had not meant to suggest that the psychic symptoms were necessarily due to the salvarsan. He thought in intramuscular therapy it was very sound practice to filter. There was less discomfort and less pain by so doing. He reiterated his opinion that in intramuscular therapy one had the method of choice as a prophylatic against toxic effects and as a means of efficient therapeutic administration. He did not agree with Dr. Semon in using prepared solutions in ampoules, but he could not pursue the matter at the length it deserved at that hour of the evening. Several interesting points had been raised by Dr. Mills, and he would like to say that if there was anything of interest in his own paper it was largely due to the tuition he had had at his hands, and at those of the President some years ago. There was one test in dermatitis which he had found in three cases to be very helpful, namely, the painting of iodine on the surface. With regard to encephalitis, he did not doubt that nearly all the people who developed that after arsenobenzol treatment were alcoholics. He urged that clinicians should think as much of bringing the patient's general health up to the highest level as of filling him up with salvarsan or its substitutes.