CHEMOTHERAPY: NEW REMEDIES IN THE TREATMENT OF SYPHILIS

Discussion

Dr. David Nabarro wished first to express to Dr. Findlay the hearty thanks of the members for his very interesting address. This was so full of information that it was difficult to know where to begin to discuss it.

The statement the lecturer made that one could not safely conclude from the action of a drug on rabbits what the effect would be on man was very important, and a truism that was not always borne in mind. The effects of the drugs on man himself must be studied. Dr. Findlay truly said it took a long time to be sure of a cure in a case of syphilis, and that made the subject all the more difficult. Syphilis was a life-long study, both for the patient and the doctor, and the best plan would be for the son and the grandson to see whether they had been cured. He had himself been at the work for twenty years, and as his son intended to enter the medical profession and carry on the speaker's work, his patients could perhaps be followed up and an answer to the question given. So that at the end of fifty years it might be possible to say what drug cured.

Dr. Findlay did not mention giving tryparsamide intramuscularly. He, Dr. Nabarro, used it intramuscularly in children, in $\frac{1}{4}$ up to $1\frac{1}{2}$ gm. doses, and latterly he had been mixing it with bismuth oxychloride in the same syringe, in cases of neuro-syphilis.

Stovarsol he had used in a number of cases in children who were much upset by injections. Some children did not mind injections, but others were distressed as soon as they came within sight of the hospital. For such, stovarsol by the mouth gave very good results: $\frac{1}{2}$ to 2 gr. twice a day for a week followed by a week's rest could be given month after month.

As Dr. Findlay said, the bismuth compounds were legion. The speaker had used a number of them but
recently he had come down to one which the lecturer did not mention, namely, the oxychloride of bismuth, which emanated from Denmark. He had had a number of cases in children in whom one series of 12 injections made the Wassermann negative, though that did not necessarily mean a cure. The preparation used was "Bisoxyl," made by the British Drug Houses.

Lastly, he had tried a bismuth and arsenic mixture, "Bistovol"; it was thick and liable to clog in the needle. He now gave bismuth oxychloride with tryparsamide, and it could be given with "914." Solganol, a gold preparation, was an expensive way of producing protein shock.

The foregoing were some points from his experience which might possibly be of use to members. The Society was greatly indebted to Dr. Findlay for bringing to notice the various drugs, and describing the results which have been achieved by other workers, which would probably coincide in many respects with members' own observations.

DR. MARGARET RORKE desired to express her intense gratitude to Dr. Findlay, and her admiration for the immensity of the work the paper represented. She knew that, theoretically, with the three metals being used syphilis should be cured, but she encountered so many cases of late "dug-in" cases of syphilis in women that she found herself longing for more drugs. Years ago there was on the market the compound Disodaluargol Arsenobenzol with antimony, which was excellent, but it had not now been obtainable for ten years. She was therefore interested to hear Dr. Findlay speak of it again to-night. She would also like to know from him whether two or three other preparations were still on the market; whether, for instance, an antimony preparation was obtainable; also calcium thiosulphite, and the gold preparation with a long formula, the name of which she had forgotten.

No reference had been made to silver, which she had been using in combination with salvarsan for some time. Had there been any fresh work done on silver in this relation?

She felt very grateful for the work which was being done in the laboratories to aid those engaged in this work of treating venereal disease.
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Dr. Anwyl Davies also thanked Dr. Findlay for his paper. Four or five years ago he, the speaker, watched ten cases on stovarsol alone, cases giving a positive Wassermann reaction, and in which spirochaetes were found. After being put on stovarsol regularly they were Wassermann-negative at the end of three months, and successively every three months over a period of two and a half years, which he regarded as fairly satisfactory. It showed stovarsol to be a potent drug.

He would like to know what value Dr. Findlay attached to the chemo-therapeutic index. The speaker had read much of Ehrlich's work, and concluded that that worker, after he had the chemo-therapeutic index in his mind, may have made a number of mistakes by adhering to that index. The speaker regarded it as a very rough index or indication of the efficacy of the various drugs. Bismuth was a drug which concerned the syphilologist very much, and among so many preparations it was important to know which were the most effective. The literature at the moment, especially French literature, was full of lipo-soluble preparations. He had tried several of them, but without being able to get the results which the French claimed, i.e., killing the spirochaete within a certain number of days or hours. Perhaps this test was not satisfactory from all points of view, but it was the quickest we possessed; and life was short. The results of the Wassermann reaction must be watched, but this meant many years before the relative values of the drugs were accurately estimated.

His results, as in Dr. Nabarro's experience, had been most satisfactory with bismuth oxychloride. Workers on the Continent had said that an infinitesimal quantity of the metal sufficed, therefore the metal was probably as good as the lipo-soluble.

One's faith in much of this literature was shaken by the results claimed. Some time ago he, the speaker, was attacked by Levaditi, who said he had a new drug which was better than the others, for it killed the spirochaetes in forty-eight hours. It was named H-I3: it was bistovol. He, Dr. Davies, put a series of cases on this, but could not get the results which Levaditi claimed. He would like to know the result of the experience of others with bistovol; also, could Dr. Findlay tell him where he could obtain arsenobi? Dr. Mouneyrat, of
Paris, had written a book on this preparation, and in it she claimed magnificent results from this drug.

In September he visited some of the clinics in Holland and Germany, and was much struck by the results obtained there from skilfully applied mercurial inunction in association with organic arsenic; they were as good as the results in England with arsenic and bismuth; here not enough cases were treated with mercury.

Reference had been made to re-infection; he had seen a fair number of such cases; at the London there had been 3 or 4 such cases in the last two or three months, as far as could be judged, for it was difficult to obtain absolute proof of it.

The question of the spirochaete reaching the nervous tissues was an interesting one. Neisser said it reached the bone marrow in the first two or three weeks of the chancre, which made one reflect on the amount of treatment which would be required to kill the spirochaete in those inaccessible tissues.

Dr. Doble said he wrote to Dr. Hanyz, the inventor of disodaluargol, and he replied that as it was not stable he had to withdraw it. The French were very keen on treating syphilis with combined metals, and some practitioners in that country considered it was the best form of treatment. Dr. Schukoff Wyld said the English considered it damaged the kidneys, but he did not find that was so. He, the speaker, had tried various combinations of metals with arsenic in treatment. Gold and platinum he found too painful. Copper also was painful. Zinc he considered best of all. He gave only 0.15 to 0.3 gm. in the form of zinc-sulfarsenol.

With regard to stovarsol, he went to Paris one year and found it full not only of syphilis but of stovarsol. Levaditi was very keen on it, and it had been given for the serious treatment of syphilis in the French Army. Next year he found no one using it.

He had been using bis-cam, which was a combination of bismuth and camphor, and the result was good. It was being used successfully for the treatment of syphilis and yaws in Uganda; arsenic was too expensive to give on a large scale. With bis-cam there was not much pain, and not much chance of the drug being encysted.

Dr. Hanschell agreed with Dr. Anwyl Davies—in spite of Mr. Mills' cogent reminder of the very close
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similarity of results in treatment by arsenobenzene drugs of *Trypanosoma equiperdum* infection in the mouse and primary syphiloma in man—that the clinician must always prefer results as shown by a drug when tested in human syphilis. This was not easy to come by. For one required very extensive material to provide test cases and controls. All the preparations of arsenobenzene and bismuth gave clinical results which differed apparently too little to warrant confident conclusions from the small series of cases so far reported, and reported too often without any parallel controls.

In the primary chancre was a ready means of testing. The lesion could be seen, palpated, and measured, its age sufficiently determined, and its juices examined. The patient could be weighed, his occupation and age recorded, and his dosage measured; and changes in size, appearance, and spirochæte content of the lesion noted. After any given dosage the lesion could be excised and subjected to even closer microscopical scrutiny; accompanying all this the serum can be tested and retested, and all compared against parallel control chancres differently dosed. Moreover, if the later syphilomas in any part of the body were histologically chancres, what happened to the primary chancre was a good guide to what would happen to a tertiary syphiloma. But the clinician must have some indication for trying a new drug, and that indication and justification could be safely supplied him by the results of animal experiment.

He agreed with Mr. Mills that re-infection did occur: the later, sometimes years later, chancre appearing on a different penile site. Of non-penile cases he would like to report briefly a case he had observed from the start. A surgeon in 1916 circumcised, without gloves, a case of phimosis and chancre. A small septic sore developed later on his finger, its true nature not being recognised until, with sore still unhealed, secondary rash and periostitis of skin appeared. The sore was not examined for spirochætes, but healed very rapidly after the first arsenobenzene (Galyl) injection. The serum did not become Wassermann negative until after six months' almost continuous Galyl and mercury injections. Periodical blood and C.S.F. tests were negative and the patient in excellent health up to April, 1931—fifteen years later—when a septic sore developed from a scratched
papule on the wrist. High swinging fever, profuse night
sweats, and exhaustion followed seven months later.
The patient was put into nursing home with diagnosis of
septicaemia. Blood cultures were negative. The patient
then himself suggested syphilitic chancre. *Sp. pallidum*
was found in the sore secretion; blood Wassermann and
Kahn strongly positive. (C.S.F. examined later—normal.)
Rapid disappearance of fever and quick healing of sore
after first arsenobenzene and bismuth injections. The
patient had examined a supposed case of piles. He had
recognised these as condylomata, and during examination
had found the sleeve edge of his gown loose. He had
tucked it again under his rubber glove. On removing glove he
had noticed a small scratched papule just where the
glove wrist had ended. So the gown contaminated with
condyloma juice had rubbed, scratched, and infected the
papule in being tucked hurriedly and forcibly under the
tight wrist band of the rubber glove.

DR. VIOLET RUSSELL also wished to thank Dr. Findlay
for his most valuable paper. She had desired to put in
a word in favour of bistovol, which had been used at
Guy's, for more than five years, and all who employed it
there had been impressed with the good results in some
cases, especially in tertiary syphilis; gummata cleared
up under it very quickly. Wassermann-fast cases had
several times become negative after its use. Its dis-
advantages were that it was of thick consistency, required
a long course of injections, and sometimes there was
a mild toxic reaction. Clinically, however, as already
stated, they had been very favourably impressed by it,
and continued to use it in many cases.

THE PRESIDENT associated himself with the other
members in congratulating Dr. Findlay on having given
the Society a remarkable survey of the progress of chem-
therapy as applied to syphilis. A survey such as this was
invaluable in refreshing our minds of the multitude of
remedies and the main facts concerning them as used in
the treatment of syphilis. The clinical syphilologist was
at times apt to get into a groove and to keep on using
what he regarded as a standard treatment. In his view,
standardisation of the treatment of syphilis was undesir-
able until we could standardise the human being. A
great many of the preparations which Dr. Findlay had
discussed had given good results in animal experimenta-
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tion. He did not quite agree with Mr. Mills on the value he placed on this. He was of the same opinion as Dr. Hanschell in regarding the experimental results with caution until the substances could be tried out in the human being. Not infrequently it was found that the effects obtained in the test tube and in the experimental animal were not confirmed by the results obtained in the infected patient. When Dr. Fraser worked with him in the Edinburgh University Laboratory he tried the effect of various chemotherapeutic remedies on animals infected with syphilis and with rat bite fever; it was interesting to note that the effect of tryparsamide administered intravenously in clearing up the lesions and the Wassermann test was less marked than when parosan, a sodium salt of the same substance, was given by mouth. This was the reverse of what happened in the disease in man. One very great value which experimental research on animals did have was in the assessment of the toxicity of the various drugs. He had used many of the prepa-
rations which Dr. Findlay had discussed, and was very interested in his observations upon tryparsamide, which he had used in the past eight years on close on 500 patients, chiefly cases of neuro-syphilis. Considering the high arsenic content which it contained and the large dose which was given, it was very well tolerated by most patients. In cases of visceral and cardio-vascular syphilis, where the patient was debilitated and difficult to handle, it often appeared to act as a valuable tonic in addition to its specific action. In the majority of cases of neuro-syphilis, and especially in the earlier cases, it appeared to be the drug of choice. The risk of ambylopia following its use was not so serious as at first thought, and in his experience it did not affect more than 1 per cent. The earlier the cases were seen, the better the results. It was important to remember, however, that unless it was used carefully at first, it might cause a Herxheimer reaction, which was seen sometimes in the aggravation of the pains of tabes and in the increased excitement that follows its administration in a case of G.P.I. The only cases in which he hesitated to use it without a preliminary course of iodides were cases of meningo-encephalitis and spinal meningitis. In such cases iodide and mercury inunction initially, followed later by tryparsamide intravenously, was a safer course.
to pursue. In cases which had any disturbances of vision, it was desirable to warn the patient that this might be aggravated by the drug, and to have the optic discs kept under observation by an ophthalmologist. If no disturbance of vision occurred after the first 4 or 5 injections, they were not likely to occur at all. Dr. Findlay had mentioned that the largest amount of the drug used was from 50 to 150 gm. spread over one to two years. He himself was accustomed to give much larger amounts, and this probably accounted for the larger percentage of cases in which he was able to obtain sterilisation of the blood and cerebro-spinal fluid. The largest amount which he had given to any patient was 480 gm., and, in his experience, even in large amounts the drug did not appear to damage the liver. If given in therapeutic doses it had a good tonic effect on the patient’s tissues, and the weight was maintained and even increased during its administration. This was also the opinion and experience of Dr. Louise Pearce. He had recently come across a case in which twelve weekly doses of 5 gm. each had been administered; undoubtedly, excessive dosage such as this was responsible for some of the cases of optic atrophy. The average dose of 3 gm. per week should not be exceeded in the adult male, and it was advisable to give an interval of rest after eight to ten weeks of treatment, to allow for elimination of the drug. He was interested in the remarks which were made regarding halarsol. In his experience it was not any more effective than “914” preparations in clearing up lesions or in altering the positivity of the Wassermann test. Acetylarasan was a very useful preparation which contained a high arsenic content. He had been using it in children for eight or nine months with quite good results. It was very convenient to use and its intramuscular administration was painless. The use of stovarsol in the prevention of syphilis was of very limited value, and he felt that its administration should always be under close medical observation. It was unfortunate that in India it could be purchased by patients, and its promiscuous use was apt to lead to intolerance and complications. With regard to bismuth preparations, he was in complete agreement with Dr. Findlay’s advocacy that they should be standardised. Many of the preparations produced by commercial firms
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were not as efficient as they were made out to be in the recommendations, which, there was reason to suspect, were at times obtained from subsidised clinics. As the greater number of clinicians were using bismuth preparations in conjunction with the arsenobenzols it was next to impossible to assess the merits of the respective drugs. This could only be done by a series of parallel cases in which bismuth alone was used and observation of these cases for years afterwards. In view of the excellent results obtained by using arsenobenzols it was difficult to justify this procedure. The experimental work which had been done on animals with bismuth did not encourage one to follow this line of treatment. More recently, combinations of arsenic and bismuth had been prepared and the preparation known as bistovol had been tried. In his experience it caused pain and discomfort after intramuscular injection and had nothing to recommend it over the administration of the drugs separately. Dr. Findlay had referred to Fraser's work with tellurium administered intramuscularly which had been carried out in his own clinic. This preparation cleared up syphilitic lesions very effectively, and often influenced the Wassermann test in intractable cases. The odour of the breath which followed its use was very obnoxious and made its use impracticable. Apart from sanocrysin he had had little experience with gold preparations. Even when administered with sodium thiosulphate, sanocrysin was very toxic. He intended to put the less toxic preparation, solganol B, on trial in a series of resistant cases. He would like to ask Dr. Findlay if the preparation which he had mentioned, calcium thiosulphate, could be obtained, as, in his experience, sodium thiosulphate was not always effective in preventing or in treating the various types of intolerance to the arsenobenzols. Of the more recent preparations which had been introduced to produce pyrexia, he had been disappointed with sulphosin. Its administration was often painful, and the resulting pyrexia rarely exceeded 102° to 103° F. The combination of milk and sulphur was often more effective. The question had been raised in the discussion as to whether rapid healing of primary and secondary lesions implied a complete destruction of the spirochaetes in the central nervous system and whether a continuously negative Wassermann test in such cases was evidence of cure.
This could only be answered by observation of the case over a long enough period. If any case was well treated and the blood Wassermann test and the various tests of the cerebro-spinal fluid were negative continuously until the end of the third year after infection, there was reason to think that such a patient would not subsequently develop nerve syphilis. He would like to ask Dr. Findlay whether he advised the giving of arsenobenzols as early as possible in the course of syphilis, or whether he preferred to wait until the infection was generalised throughout the body. In his own opinion he had no doubt that the former was the correct method. Many cases of syphilis were cured, and in an appreciable number there was definite evidence that re-infection had occurred. This has been proved by Major White, while working in France, and by many other workers. He could not agree with the statement of Warthin that he had never seen a case of cured syphilis. He wished to assure Dr. Findlay of his own personal appreciation and of the thanks of the members of the Society for a most interesting and instructive paper.

Dr. Findlay, in reply, said he had very much enjoyed listening to the discussion, as it was extremely good for the laboratory worker to come among physicians and hear their views, both on the work in the laboratory and the clinical results. It would be excellent if such a Society as this could lay down some standard treatment for syphilis. One of the difficulties, both for the laboratory worker and the clinician, was the question of adequate controls. A new drug was tried out in a dozen cases and the result was found to be favourable, or the reverse, but there were no careful controls, a matter which the laboratory worker knew to be essential. One found that a difference in the weight of the experimental animals, food and other things, influenced the result. He did not think it was recognised in clinical work as much as it might be that there might be more than one race of spirochætes. In working at bacteria and other organisms he was often convinced that there were several different strains of the organisms.

Recently some French workers in Lyons had reported encountering strains of spirochætes which were arsenic-resistant at the start.

He was interested in the question of re-infection.
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During the war he saw a curious case of what he thought was re-infection. He was a man aged sixty who served in the Navy, on a trawler, and came with a typical secondary rash. He reported that he had had a primary chancre thirty years before, with adenitis and secondary symptoms. But the speaker could not find any primary chancre. The man who shared the trawler cabin with him was also a syphilitic. The patient had been walking about the boat without socks on, and a chancre was found on the foot, so evidently he got his re-infection from the deck floor.

He favoured treating experimentally infected animals at the earliest moment. When the spirochæte got into the central nervous system it could not be eradicated from there. In relapsing fever it was well to wait for a time, then the infection could be cured by smaller amounts of arsenic.

With regard to the use of antimony, Lumier had found that a trivalent antimony compound rapidly cured the symptoms of rabbit syphilis, but the animals quickly relapsed. It was curious why antimony did not have more action on the spirochæte, as it was one of the earliest drugs tried for the disease, and was largely used in the treatment of trypanosomiasis in domesticated animals. Silver seemed to have no spirochæticidal action; it merely acted as a heavy metal in causing protein shock.

He was interested in the President's reference to milk. Milk had been considerably used in the treatment of leprosy; injections of condensed milk in leprosy caused excellent protein shock, and the patients showed marked improvement.

He did not think calcium thiosulphate had been produced in this country, but he did not know why it should not be.