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THE SPECIFIC CURE OF YAWS BY DIOXYDIAMIDO-
ARSENOBENZOL.*

BY

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A few months ago, through the kindness of Professor EHRLICH, I received a shipment of dioxidyamidoarsenobenzol for use for experimental purposes in syphilis. I take great pleasure in acknowledging here publicly my thanks to him for the opportunity to try the effect of this very valuable preparation. On account of the favourable results which were being obtained with it in the treatment of syphilis, the idea naturally suggested itself to try the remedy in yaws, on account of the morphological and biological relationship which exists between the spirochætæ giving rise to these two diseases.

Yaws is a disease which is not only highly disfiguring, but is very contagious, and usually runs a chronic course, frequently preventing the

* Preliminary remarks on this subject were made before the Manila Medical Society on September 5th, 1910, where photographs and one of the cured patients were presented.

patient from attending to his work, and sometimes eventually disabling him. The treatment has hitherto been most unsatisfactory, and usually a prolonged one is necessary before success is obtained. While, among the better classes afflicted, cures after long periods have frequently resulted, as a rule the disease is one of very long duration and yields but slowly to medication. Even the patients who can be seen in the dispensary and hospital usually become discouraged with the treatment long before a cure results, and often abandon it. In the cases among the lower classes of people, the successful treatment of this disease has hitherto been entirely impracticable, both for the reason that it has usually been impossible to persuade and to cause individuals to undertake a prolonged course of treatment, which, to be ultimately successful, frequently must be pursued for many months.

From the articles of MANSON, SCHEUBE, CASTELLANI, PLEHN, FIRTH, and JEANSELME, one is impressed with the very unsatisfactory status of the treatment of the disease at the present time. DANIELS, who has had a particularly wide personal experience in the treatment of yaws, writes:—

“Probably no drug influences the duration of the disease. Mercury and arsenic certainly do not. Potassium iodide is uncertain in its action. The eruption will sometimes disappear rapidly when iodides are given, but even in such cases when the use of the *drug is continued* fresh eruptions appear. The use of iodide is therefore limited. Local applications that merely serve to keep the granuloma clean are valuable, but escharotics and irritants, though they may destroy the yaws, are likely to cause the formation of scars. The painful granulomata on the feet are best destroyed by the action of nitric acid, acid nitrate of mercury or silver nitrate.”

It is not my intention here to enter into a prolonged discussion of the question of the specificity of yaws as a disease. Almost all observers agree that yaws is not identical with syphilis. SCHEUBE and FIRTH are inclined to support the original idea of HUTCHINSON that yaws was the original disease from which European syphilis has been evolved, or that the two diseases developed from a parent form, each having been modified by being propagated by different races in different climates. MANSON, CASTELLANI, JEANSELME and PLEHN regard the two diseases as specifically distinct.

The inoculation experiments in man and animals performed by CHARLOUIS, NEISSER, BAERMANN, HALBERSTADTER, CASTELLANI, ASHBURN and CRAIG, LEVADITI, and others, also confirm the idea that the two diseases are etiologically distinct.

Up to the present time I have treated thirty cases of yaws with dioxidyamidoarsenobenzol. A report of the cure of three of the most striking cases was made before the Manila Medical Society on September 5th, where photographs and one of the cured patients were exhibited. The report of all of the cases has been withheld until the present time, in order to ascertain if relapses would occur in any of them. So far there has been no evidence of a relapse, and the cases have all remained cured, although the majority of them were treated over six months ago.

The preparation was received in hermetically sealed capsules. The capsules were opened and the solution always prepared immediately before being inoculated. The preparation as EHRLICH has stated is not readily soluble, and in order to obtain a satisfactory solution his suggestions were followed. From 0.3 to 0.4 gram of the preparation was placed in a glass vessel, moistened with a few drops of methyl alcohol, and thoroughly rubbed up with a glass rod. From 20 to 30 cubic centimetres of distilled water were then added, the stirring with the glass rod being continued. When the solution was apparently completed, 5.5 cubic centimetres for 0.3 gram of the preparation of an N/10 sodium hydroxide solution was slowly added, stirring with the glass rod being continued and causing the precipitate, which forms on this addition, to slowly redissolve.

The injections were given deep into the gluteal muscle, from 15 to 20 cubic centimetres of fluid being usually injected in one place. On the following day after there was usually some reddening, swelling and induration of the skin and underlying tissues in the vicinity of the point of the inoculation. In no instance did suppuration result, and in no case did any unfavorable symptoms develop. Occasionally a transitory rise of temperature was noted a few days after the injection. In some of the instances, pain after the injection was complained of, sometimes lasting for from 10 to 24 hours, or sometimes even longer. However, usually following the inoculation no great complaint was made of pain. A number of the cases inoculated have been among young children who did not cry, neither during nor after the injection was given; usually they did not care to play for the first 24 hours following the injection. In one European suffering with tertiary lesions of syphilis, who was given a large injection into the buttock, severe pain lasting for nearly 24 hours was complained of. This case was given a second injection

intravenously twenty days later. No pain whatever followed this second injection.

For the cases of yaws treated it was found that in almost every instance a single injection of the drug was sufficient to produce a cure,* even though a number of the cases showed tertiary lesions with ulcerations. In none of the cases was any local treatment employed, or was any other treatment internal or otherwise administered after the injection. In the few cases that had been treated with iodides previously, these were discontinued a few days before the injection of dioxydiamidoarsenobenzol was given.

CONCLUSIONS.

Dioxydiamidoarsenobenzol appears to be an ideal specific for yaws. Three or four days after the injection of the drug, the granulomatous lesions begin to disappear, and in the course of from ten to twenty days they have usually entirely disappeared, leaving a perfectly smooth pigmented skin where the lesions previously existed. The absorption of tumor masses measuring several centimetres in diameter and about a centimetre in thickness in so short a time, and under the influence of no local treatment whatever, has been very striking and surprising. Indeed, in the severe cases, the disappearance of the lesions and the cures produced could be most aptly spoken of as marvellous. Even in cases where large granulomatous masses or deep ulcerations existed, these were healed within from two to four weeks. I do not know of any more striking example in medicine of a specific action than of that produced by dioxydiamidoarsenobenzol on the lesions of yaws.

A slight reddening appears about the margins of the lesions in from twenty-four to forty-eight hours after the injection of the preparation. The centre of the lesion then usually assumes a purplish or bluish congested appearance. Phagocytes are attracted to this area, which now assumes a greyish or brownish hue. The spirochætæ quickly disappear and the granulomatous tissue becomes absorbed, leaving dark pigmented areas of skin, which later resume their normal colour. In the cases where crusts have existed, these frequently are not absorbed, but drop off.

* Only two of the cases required a second injection.

As stated above, none of the cases have shown any signs of relapse, although all with the exception of two received but a single injection, and over six months have elapsed since most of the cases were inoculated.

Nevertheless, I believe that in a few of the most severe cases of the disease, where the ulcerations are extensive and of long-standing, a second inoculation, about three weeks after the first one, may be advisable. Only in No. IV. of the first series of yaws cases which I treated with this preparation was there any question as to whether a second dose should have been given, and as to whether a second one might not have hastened the cure. However, the lesions eventually entirely healed as a result of the primary dose.

The dose of the preparation for the treatment of yaws should be from 0.25 to 0.3 gram for children, and from 0.5 to 0.7 gram for adults. Small doses may not give such favourable results.

Some observers have claimed that it is not advisable to attempt to repress the eruption of yaws, as this may be accompanied by considerable constitutional disturbance. The employment of dioxydiamidoarsenobenzol simply caused the eruption to fade away. There were no unfavourable constitutional symptoms other than an occasional transitory rise of temperature produced thereby, and the patients seemed improved in health following the disappearance of the eruption. A number of authors have also laid great distress upon the local treatment of the disease. If dioxydiamidoarsenobenzol is employed, the local treatment, except in cases of severe ulcerations, and where other organisms than *Treponema pertenuis* have invaded the lesions, is entirely unnecessary. Case IV. would undoubtedly have been cured more quickly if the ulcerating granulomatous masses had been curetted and disinfected and dressed daily with sublimate solution, since other spirochæta than *spirochæta pertenuis*, and bacilli, and cocci were present in the lesions. However, even in this case the lesions eventually entirely healed without local treatment.

The cure of yaws by this preparation, and the successful results which have been obtained with it in the treatment of certain cases of syphilis may suggest again the identity of yaws and syphilis. It does not appear strange that this preparation should have such a destructive action against both *Treponema pertenuis* and

Treponema pallidum, since both from a morphological and biological standpoint these two organisms appear closely related. Indeed, potassium iodide, which is so valuable in the treatment of syphilis, has hitherto been the most successful remedy employed in the treatment of yaws. As has been pointed out by other observers, the therapeutic argument for the identity of yaws and syphilis, and hence for the identity of their specific organisms, is very fallacious. Many instances in medicine might be quoted in support of this statement. Quinine which destroys certain forms of *Plasmodium malariae*, *Plasmodium vivax*, and *Laverania malariae*, also destroys *Amœba dysenteriae*.

In conclusion, it would appear that dioxydiamidoarsenobenzol is as important a specific for yaws as quinine is for malaria, and hence a fourth medicinal specific in medicine has been discovered.

While these experiments in treatment were in progress, the articles of NICHOLS were published on the successful transmission of the spirochætæ of yaws to the rabbit's testicle ("Journ. Exp. Med.", Sept., 1910), and on the cure by injections with dioxydiamidoarsenobenzol of these experimentally produced lesions in four of these animals and in three monkeys moderately infected with yaws ("Journ. Am. Med. Assn." July 16, 1910).

DISCUSSION.

Dr. CARNEGIE BROWN: I should like to mention that with reference to the very remarkable advance in the treatment of yaws recorded in Dr. STRONG'S paper, an article on the same subject has recently been published in the "Archiv. für Schiffs und Tropen-Hygien" by Dr. CASTELLANI, which supplies very strong corroboration of the efficacy of dioxydiamidoarsenobenzol. No doubt most of you have seen that paper, but for the benefit of those whose attention it has escaped, I may say that a series of cases of yaws were treated in Ceylon, much in the same way as those in Manila by Dr. STRONG, by injections of "606," which had been sent to Dr. CASTELLANI by Professor EHRLICH—and that in almost every instance, the effect of a single injection was to induce a very remarkable amelioration in the condition of the patient. The improvement was specially marked in recent cases, but apparently the beneficial effects of the drug are by no means limited to the earlier stages of the disorder.

Dr. C. W. DANIELS: Judging from the photographs the treatment with "606" would appear to be very successful. Occasionally under potassium iodide in the past as rapid improvement takes place, but these cases have been rare and the recurrence of the disease has been almost invariable. The new treatment certainly looks most promising and I only hope that it will be possible to reduce the cost of the drug. It is also to be hoped that the drug will not have the effect some people say it has in syphilis, viz., that it so effectually eradicates the disease that there is no subsequent immunity; because if it destroys immunity I am not at all sure that the last state would not be worse than the first; for when adults contract the disease at a more advanced age it occurs in rather a serious form and is the cause of a good deal of inconvenience. Dr. CORNEY, who is present, is the authority on the subject of yaws and will no doubt give his opinions.

Dr. B. G. CORNEY: I am afraid, Mr. Chairman, I have very little to say about the matter as it is now some few years since I left the colony where yaws was prevalent; I quite agree, however, with my friend and former colleague, Dr. DANIELS, that the treatment we have heard described to-night does appear undoubtedly very promising. I do not wish to be pessimistic, but I think perhaps the claims made for the new treatment are a little premature as regards the tertiary conditions of yaws. Judging from my own knowledge of the course of the disease in South Sea Islanders, I think that in 15 years' time we may be able to say definitely whether this is a cure or not, but not at present. I have no doubt the treatment has relieved the cases just described in the paper, and to that extent it is likely to prove of great use, qualified by the very pertinent remarks and suggestions of Dr. DANIELS; but I certainly think a much longer period than a few months ought to elapse before we draw positive conclusions as to the efficiency of this drug as an eradicator of yaws from the system. It is a known fact for the disease to spontaneously disappear in many South Sea Islanders who have had yaws in childhood, and then, after an interval of from 15 to 18 years, for the tertiary conditions to arise. We shall therefore have to wait some time before we can say definitely that the administration of this drug is going to prevent the tertiary conditions altogether.

Mr. T. PUGH BEDDOES: These results are extremely favourable but with different technique similar results (possibly even more favourable) with distinctly less pain would be obtained if, instead of a solution of methyl alcohol and sodium hydroxide, an emulsion made in sterile olive oil is used, and if in place of injecting 30 to 35 c.c. only 6 c.c. were injected, that is, 3 c.c. into each buttock. This quantity could be injected into the patient in one operation and after one or two hours rest there is absolutely no pain. There is practically no pain at the time of the injection if a slightly soluble cocaine substance is used, such as orthoform, anæthesin or betaucain, $\frac{1}{2}$ grain to 6 c.c. of sterile oil. The only case treated in this way in which there was any pain, was that of a patient who, 48 hours after injection, took a fairly long walk and then had pain in the back. One patient who had been treated with calomel injections said that calomel was much more painful.

Fleet-Surgeon BASSETT-SMITH: There is just one point not touched upon in Dr. STRONG'S paper to which I should like to draw attention. Yaws is one of those diseases in which the Wassermann's Serum reaction test should be used before one can say whether the patient is cured or not. In syphilis, after the patient has been treated with "606" and has apparently been miraculously cured, the reaction yet remains positive for a long time, and until that reaction is proved negative, and continues negative, it is impossible to say that the patient is permanently cured. The same reasoning, therefore, should I think apply in regard to the treatment of yaws.