**PRELIMINARY NOTE ON THE INTRAVENOUS
INJECTION OF GYNOCARDATE OF SODA
IN LEPROSY,****WITH FURTHER EXPERIENCE OF ITS
SUBCUTANEOUS USE.****By SIR LEONARD ROGERS, M.D., F.R.C.P.,
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In a recent paper¹ I recorded a long experience of gynocardates by the mouth, and six months' use of solutions injected subcutaneously in the treatment of leprosy, and stated that this line of treatment had given greater improvement in my hands than any other. I find from my correspondence that as early as July, 1912, I inquired from a leading firm of manufacturing chemists if they could supply me with a soluble form of gynocardic acid or magnesium gynocardate suitable for hypodermic injection, but received a reply in the negative. In my recent paper I regarded gynocardic acid and chaulmoogric acid as synonymous on the strength of the following statement in the last (1915) edition of Martindale and Westcott's *Extra Pharmacopoeia*:

Chaulmoogra oil contains a quantity of palmitic acid, with three other fatty acids; of these the so-called gynocardic acid (chaulmoogric acid) is supposed to be the active ingredient.

Dr. Pyman has kindly informed me that this view is erroneous, as the work of Moss, and subsequently of Power and Gornall, showed that, on fractionizing the total fatty acids of chaulmoogra oil, those with the higher melting points, including palmitic and chaulmoogric acids, the sodium salts of which are very sparingly soluble in water, first separate, while Moss gave the name of gynocardic acid to the residual acids with low melting point of about 29°C., the sodium salts of which are freely soluble in water. According to Power and Gornall, Moss's gynocardic acid is not an individual substance, but is comprised of a number of fatty acids with different melting points.

What I have used, then, for hypodermic injection in leprosy are the soluble soaps of lower melting point fatty acids of chaulmoogra oil, which, following Moss, are rightly designated gynocardic acid, and which give the characteristic reddish-brown colour, changing to olive green, with strong sulphuric acid. By further fractionization, several acids with different melting points can be separated, which may conveniently be called fractions B, C, etc. During the present year I have been isolating and investigating these with the help of Dr. Sudhamoy Ghose, D.Sc.Edin., working in the laboratory of Professor Rai Chuni Lal Bose Bahadur, and aided by a grant from the Indian Medical Research Fund, obtained through the kindness of Sir Pardey Lukis, Director-General Indian Medical Service, to each of whom I desire to express my thanks.

I have now discovered that the sodium salts of the lower melting point fatty acids can be safely given intravenously in animals in relatively very large doses, and I have already used them intravenously in some twenty well-marked leprosy cases during the last six weeks, with results which clearly show the intravenous route to present important advantages over the subcutaneous one. I therefore propose in the present paper to place on record briefly my methods so as to allow others to test them in this distressing and widely prevalent disease. I should mention that M. Vahram² has recently recorded cases of leprosy treated by subcutaneous and intravenous injections of a suspension of a dried and pulverized mixture of chaulmoogra oil and gum arabic, the dose of the oil having been only from $\frac{1}{100}$ to $\frac{1}{50}$ of a grain; yet two cases were reported as improved after some thirty injections. I find the sodium gynocardate I have been using is two hundred times less toxic for rabbits than his insoluble dried chaulmoogra oil, while my preparations have the immense advantages of being freely soluble in water, being, indeed, just the form of substance in which fats are normally absorbed from the digestive canal through the blood vessels, so the soluble gynocardates appear to possess manifest advantages over Vahram's insoluble suspension of dried chaulmoogra oil, which was fatal to rabbits in the small dose of 0.0004 gram per kilo.

Method of Preparation of Sodium Gynocardates.*

These substances may be prepared either from the cold-drawn chaulmoogra oil, or, as I pointed out in my former paper, from the buttery substance obtained by further compression of the seed of *Taraktogenos kurzii* (products of which alone are dealt with in this paper, although hydnocarpus oils are also being investigated, but the soluble sodium soaps of which have been found to be more irritating when injected subcutaneously than those of *Taraktogenos kurzii*) with the aid of heat obtained by steam circulating around the compression chamber. Hitherto this product has been regarded as a waste product, although I have found it to contain a large proportion of the active substances of the oil. Briefly, the method of preparation is to saponify the oil or butter with caustic potash and absolute alcohol, the soaps thus obtained being converted into fatty acids by means of sulphuric acid. These fatty acids are dissolved in hot alcohol and separated into fractions with varying melting points by gradual cooling and removal of the acids, which solidify at differing degrees. The fractions thus obtained may be further purified by dissolving in ether and recovering again by evaporating off the solvent, by which means they are rendered somewhat less irritating when the sodium salts are injected subcutaneously, for which purpose they must be neutralized accurately with the aid of phenolphthalein. When about two-thirds of the fatty acids have thus been separated the residual third, which is liquid at room temperature in Calcutta (about 28°C.), is obtained by distilling off the alcohol, and may be provisionally termed gynocardic acid C. Of the first separated two-thirds those with the higher melting points of from 43° to 40.8° C. form sodium soaps which are insoluble, or only slightly soluble, in water, and may be termed fraction A. They include palmitic and chaulmoogric acids, and are unsuited for either hypodermic or intravenous use, while it is very doubtful if they are of any value internally. They constitute about half of the total fatty acids. The remaining acids of this two-thirds have melting points from 37° to 40° C. and form sodium soaps which are freely soluble in water and may be termed gynocardic acid B. A still larger number of fractions may be separated out if desired, as we have recently done. The best product for clinical use which we have yet obtained was got by extracting finely divided and dried *Taraktogenos* seeds with ether and subsequent fractionization as above. The sodium soaps of fractions B and C mixed together caused very little local irritation when injected subcutaneously, while the observations on intravenous injections recorded later in this paper are mainly based on the use of this product, which clearly contains all the lower melting point acids of both the cold compressed oil and the butter obtained by further compression of the seeds with heat. It will be referred to as fractions B and C of the whole seed.

**Further Results of Subcutaneous Injections of
Gynocardate of Soda.**

First, with regard to the further progress of the three cases described in my first paper. Case I has not been seen again, but I have received reports that the satisfactory condition recorded previously is maintained. Case II wrote to me several months after his return to Europe that a leading British authority had declared him to be free from all active signs of the disease, so he may be regarded as apparently cured, although a longer period must elapse before it will be evident if the recovery will be permanent. Case III is still under observation, although she has only been able to attend very irregularly for the injections. After a month's absence she returned with slight recrudescence of the macular patches, but improved again with further treatment, but is still not clear of the disease, having given the method no fair trial.

I have now just completed a year's experience of the subcutaneous method, but, owing to my cases having been, with one exception, entirely out-patients or very advanced cases in a leper asylum, and to the earlier preparations in particular having given rise to considerable local pain and induration, only one patient has been under observation

* Messrs. Smith, Stanistreet and Co. of Calcutta (London agents, Messrs. Evans, Sons, Lescher, and Webb, Ltd., 60, St. Bartholomew's Close) can supply gynocardate of soda made in accordance with my directions either in powder form or in solution in sterile capsules ready for intravenous injection.

for the full period of a year, and eight more have been under regular treatment for six months and over. Five of the cases were of the anaesthetic type and four tubercular. The former includes the patient who has been under observation for a full year, and at the end of eight months all the light patches had disappeared and sensation had returned in them, which was complete except in the largest patch, where there is still slight loss of response to a light touch. An ulcer early healed, and he has regained power in one foot which previously showed foot-drop. During the last four months he has only received occasional injections, so as to keep him under observation, and he continues free from symptoms and appears to be practically cured. Two other cases in which the hands were affected have nearly regained the lost anaesthesia and some power, and continue to improve steadily. The fourth case showed typical claw hands, with great loss of sensation and power, and also foot-drop, as well as anaesthetic patches on the face and neck. After six months' treatment he has regained nearly all the lost sensation, except in one hand, where it is partially restored, and much of the power, being able to shave himself with a razor, and his case is most promising. The fifth anaesthetic patient improved so much that after eight months he considered himself cured and went to his country against advice. He returned after four months with some return of anaesthesia and is improving again under the intravenous treatment. The results, then, in the anaesthetic cases may be regarded as very promising.

Of the four tubercular cases one advanced case in a boy has been under treatment for ten months, during which greatly thickened and nodular ears have become smooth, and his face is now normal. Very few broken down bacilli could be found at the last microscopical examination, and he appears to be nearly free from the disease, the improvement having been most remarkable. The second case showed a number of tubercles on the chin and nose, up to half an inch in diameter, being the most advanced case I have ever seen. Here again the improvement after eight months has been great, although numerous bacilli can still be found, and progress is slow. It has been more rapid since intravenous injections have been given. Two other cases with well marked facial affection have also greatly improved after seven and eight months' treatment respectively, but are still not well. In addition, an earlier case with affection of the face, and hard nodes on the arms containing numerous bacilli at first, after treatment for four months has lost nearly all his lesions, and no leprosy bacilli could be found in the remains of a node recently examined, so in this case the outlook is very hopeful. On the whole the tubercular cases have responded rather more slowly to the treatment than the anaesthetic ones, while I have noticed that there is greater local pain and induration at the sites of the injections in the former class. It is not improbable that intramuscular injections of sodium gynocardate would be more rapidly absorbed and more effective than subcutaneous ones, but I have not yet tested this point. Dr. Victor G. Heiser,* obtained his very favourable results in leprosy by intramuscular injections of chaulmoogra oil combined with camphorated oil and resorcin.

The Toxicity for Animals of Gynocardates of Soda given Intravenously.

In the case of pigeons the minimal lethal dose of a 2 or 3 per cent. solution of fractions B and C was 0.045 gram per kilo. Of fraction B it was 0.04 and of fraction C 0.06 per kilo, so the sodium soaps of the lower melting point acids are less toxic for pigeons than the higher melting point ones; 4 and 5 per cent. solutions are more toxic for pigeons than 2 and 3 per cent. ones containing the same amount of the drug. In the case of rabbits, 0.1 gram per kilo in a 3 per cent. solution proved fatal, but 0.075 produced no effect, although it is equivalent to 78 grains in a man of 70 kilos, showing the very slight toxicity of the drug even intravenously. Lieutenant-Colonel W. D. Sutherland, I.M.S., Imperial Serologist, has very kindly tested the haemolytic action of sodium gynocardate, and he informs me that it produces a slight and interesting type of haemolysis, but one which is negligible from the practical point of view. When death takes place in pigeons it occurs within one to four minutes with convulsions. If this period is survived vomiting often occurs,

but is followed by recovery. When over 1 grain had been given without any harm in rabbits of 1,500 grams, equivalent to over 50 grains in a man of 70 kilos, I felt justified in trying the drug intravenously in leprosy cases, beginning with one-tenth of a grain, and increasing by one-tenth at each successive dose, using a 2 per cent. solution, and have already given up to four-fifths of a grain with no immediate effect, or any sign of toxic influence, apart from the local reactions and fever to be described later, and rarely some headache.

Technique and Advantages of Intravenous Injections of Sodium Gynocardates.

A 2 or 3 per cent. solution may be made in distilled water (or normal saline), and after sterilization in an autoclave $\frac{1}{2}$ per cent. carbolic acid is added. For intravenous use the solution should be quite clear, and if any precipitate forms it should be filtered and re-sterilized. The veins in the forearm are distended by stretching a stout piece of rubber tubing around the upper arm, one end being put through in a loop under the other, so that it can be rapidly loosened by pulling out the loop. If the veins are very small the air bag of a sphygmomanometer may be used and pumped as tight as necessary to fully distend the veins. The selected vein is punctured through the skin of the forearm or hand with a fine sharp needle, and, if there is any doubt about the vessel having been entered, a drop of blood may be drawn up into the syringe, and the whole quickly injected before clotting can take place. The pressure band may now be released, the needle withdrawn, and collodion applied on cotton-wool. Little or no irritation results if some of a 2 per cent. solution escapes into the tissues around the vein, so the same vessel may be used repeatedly.

The two great advantages of the intravenous over the subcutaneous method are its painlessness and greater efficiency. As nearly all my cases are Indian out-patients, over whom there is no control, some of them ceased to attend long before any material result could be expected from the subcutaneous injection on account of the pain and induration at the seat of injection. Since the intravenous route has been used no such disappointments have been experienced. Of much greater importance is the more rapid improvement which has been observed to follow the intravenous injections, which is already clearly evident. Several months are required to produce any decided improvement by the subcutaneous method, while, especially in tubercular cases, the progress is apt to be disappointingly slow even after it has started. It is far too early to say what will be the ultimate results of the intravenous medication, but my present experience is decidedly encouraging.

Local Reactions in the Affected Parts.

The most striking result is the occurrence of definite local reactions in the diseased tissues, sometimes accompanied by fever, which has been seen in several cases after from two-fifths to three-fifths of a grain of sodium gynocardate intravenously, of a degree that I have not seen occur after subcutaneous injections, although Dr. Heiser* has recorded some local reaction after intramuscular injections of chaulmoogra oil, and I have seen more rapid improvement of lesions in whose neighbourhood the subcutaneous injections of gynocardates have been made. The most decided reaction was in the greatly thickened ears of a tubercular case, in whom fever occurred for three days with redness and swelling of the helix, accompanied by some serous discharge containing broken down leprosy bacilli. After the subsidence of the reaction at the end of ten days the diseased tissues were decidedly softer and less indurated than before, while nodules on the face, not showing the local reaction, were also diminished in size. In another case with very large tubercles on the face, a similar but less acute reaction was also followed by distinct improvement. In two anaesthetic cases, with greatly thickened ulnar nerves, tenderness and slight swelling appeared in the affected portions after intravenous injections, which has been followed by some return of sensation in previously anaesthetic areas of the hand. One of these patients also had fever, but had been previously subject to it. It is thus clear that intravenous injections of the drug have produced selective local reactions in the diseased tissues, which have been most evident in those patients

with the greatest amount of infiltration of the tissues with leprosy bacilli, so they are most interesting and suggestive. It is too early to say whether the drug should be pushed to the extent of producing such reactions, but I am inclined at present to think they are decidedly beneficial when moderate in degree, while I have as yet seen no ill effect to follow them, although the possibility of dissemination of the bacilli in the body must not be lost sight of.

Conclusions.

I have now given about two hundred intravenous injections of gynocardate, and my experience has led me to substitute it almost entirely for the subcutaneous method. Further experience is required to ascertain how far it is advisable to push the doses, but there can be little room for doubt that even half a grain intravenously is likely to have a greater effect than four grains slowly absorbed from a subcutaneous injection. My present impression is that the intravenous method is likely to prove as great an advance on the subcutaneous one as the latter has in my hands on the oral administration of gynocardates or chaulmoogra oil. I desire, however, once more to clearly state that I make no claim to be able to cure leprosy, although I now have hopes that in time even this may eventually result from continued researches on the lines indicated in this and my previous paper on gynocardates, which are largely an extension of Dr. Heiser's important work on the treatment of leprosy by injections of chaulmoogra oil.

In conclusion, I may point out that the reactions produced by gynocardates in leprosy tissues, and the apparent destruction of Hansen's bacillus, raises the very important question as to whether some such similar reaction may not be obtained in the case of another human acid-fast bacillus—namely, that of tuberculous disease. Fortunately, this hypothesis can be tested by animal experiment, and I have already commenced a research on the subject.

REFERENCES.

- ¹ *Lancet*, February 5th, 1916. ² *Progrès médical*, February 5th, 1916.
³ *Amer. Journ. Trop. Dis.*, 1914, 300, and *New York Med. Journ.*, February 12th, 1916, 289.

THE TREATMENT OF CERTAIN DISEASES OF PROTOZOAL ORIGIN BY TARTAR EMETIC, ALONE AND IN COMBINATION.

BY

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THE great efficacy of tartar emetic in some diseases of protozoal origin has generally been recognized since Plimmer and Thompson introduced it in trypanosomiasis, and since Vianna some years later used it in espundia and ulcerating granuloma, while I myself in the tropics, and Carona and Cristina in Europe, first used it in kala-azar. The credit of having first suggested antimonial salts as likely to be of use in certain diseases of protozoal origin (trypanosomiasis) belongs, however, to Mesnil.

I propose in this paper to give briefly my further results in the use of tartar emetic alone or in combination with the other drugs in yaws (framboesia), kala-azar, Oriental sore, and relapsing fever.

YAWS.

The efficacy of tartar emetic and other antimonial preparations in yaws has been proved by the researches of Brault, Ranken, and myself. Brault and Ranken used always intravenous injections. I have given tartar emetic intravenously, by intramuscular injections, by the mouth, by rectum, by inunction, and I have compared the results obtained by giving tartar emetic alone with those obtained by giving it combined with various other drugs. In practice one must keep in mind the following two points: (1) The mode of administration of the drug must be easy, as in certain yaws districts there are thousands of patients to be treated, and very often the only medically trained persons available are Singhalese or Tamil apothecaries who could not be entrusted to perform intravenous injections. The oral administration is of course the simplest of all, but the emetic effects of tartar emetic given in that way are well known. (2) Tartar emetic, in my

experience, though efficacious in yaws, is far from being speedily curative, and gives much better results when combined with other drugs of which potassium iodide is most beneficial; mercury has practically no action.

Bearing in mind the above two points I devised, after a certain number of experiments, as a routine treatment the mixture which is generally known after my name in the tropics. The original formula is as follows:

Tartar emetic	...	...	...	gr. j
Sod. salicyl.	...	...	...	gr. x
Potass. iodid.	...	...	...	3j
Sod. bicarb.	...	...	...	gr. xv
Aquae	...	...	ad	3j

This dose is given diluted in three or four ounces of water three times daily to adults and young persons above 16 years; half doses are given to children from 8 to 14 years of age, and one-third or less to younger children. To European patients I generally give half the doses I have mentioned, as they seem to be more affected by the various drugs contained in the mixture. The results of the treatment are generally speedy and very satisfactory; in fact, in many recent cases strikingly so, as confirmed by Spaar and others. The active drugs in the mixture are the tartar emetic and the potassium iodide, while the sodium salicylate, though not having any specific effect on the malady, seems to hasten the disappearance of the thick yellow crusts capping the framboeeting nodules. The presence of a large amount of sodium bicarbonate, though making the mixture very inelegant, decreases its emetic properties and prevents to a certain extent symptoms of iodism, thereby rendering possible the administration of very large doses of both drugs.

Recent Modifications in the Preparation of the Mixture.

In one of my papers on the subject (*Journal Ceylon Branch British Medical Association*, 1914) I stated that the mixture is pharmacologically a very inelegant one, owing to the incompatibility of potassium iodide and tartar emetic with alkalis. It is cloudy and has a sediment. At the time of administering it, however, a dose is diluted with three or four times the same amount of water, and then becomes fairly clear. Several observers, though generally confirming the efficacy of the mixture, have noted its pharmacologically erroneous composition. Some communications on the subject were received by the Editor of the *BRITISH MEDICAL JOURNAL*, who, thinking that the matter of getting a permanent "tartar emetic potassium iodide mixture for yaws" was important, had various experiments made on the best way to prepare it. The following is the report received by the Editor, a copy of which he has kindly forwarded to me for remarks.

The precipitation of the antimony, which occurs on keeping the mixture, can quite easily be prevented by the addition of small quantities of tartarated soda, glycerine, or syrup, the quantities tried being as follows:

(1) Tartar emetic	...	...	...	gr. j
Sod. salicyl.	...	...	...	gr. x
Potass. iodid.	...	...	...	3j
Sod. bicarb.	...	...	...	gr. xv
Sod. tartarat.	...	...	...	gr. x
Aquae	...	...	...	1 fl. oz.
(2) As (No. 1), but, in place of the sod. tartarat.,	...	...	...	...
glycerine	...	...	...	2 fl. drms.
(3) As (No. 1), but, in place of the sod. tartarat.,	...	...	...	...
syrup	...	...	...	1 fl. drms.

All the above mixtures showed no appreciable insoluble antimony after standing twelve days, No. 1 being perhaps slightly the best, although for practical purposes the differences were of no account. A control experiment, in which the liquid was made up according to the original formula, resulted in a large proportion of the antimony being precipitated.

With the kind assistance of Dr. Baines, chemist to the Sotoriotissa Military Hospital, I have made up the various formulae, and have come to the same conclusion. The addition of glycerine, however, seemed to give the clearest mixture.

The modified formula of the mixture is therefore as follows:

Tartar emetic	...	...	...	gr. j
Sod. bicarb.	...	...	...	gr. xv
Sod. salicyl.	...	...	...	gr. x
Potass. iodid.	...	...	...	3j
Glycerine	...	...	...	3ij
Or syrup	...	...	...	3j
Or sod. tartarat.	...	...	...	gr. x
Aquae	...	...	ad	3j