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

MAJOR ALDO CASTELLANI, M.D., M.R.C.P.,

MEDICAL SERVICE, ROYAL ITALIAN NAVY; CHIEF PHYSICIAN, ANGLO-SERB MILITARY HOSPITAL, SOTORIOTISSA.

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.,	...	...	...	2 fl. drms.
glycerine	...	...	...	
(3) As (No. 1), but, in place of the sod. tartarat.,	...	...	...	1 fl. drms.
syrup	...	...	...	

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

It is given in the same doses as the original formula, and, as is the case with the original mixture, only half doses should be given to European patients. It should always be given diluted with water. I wish to express my indebtedness to the Editor for the interest he has taken in the subject, and the successful modification of the mixture he has been instrumental in bringing about.

KALA-AZAR.

Tartar emetic was first used in the treatment of kala-azar in 1914 by myself in the tropics and Carona and Cristina in Europe. In Corfu, where I have been recently stationed for several months, infantile leishmaniasis is fairly common, as shown by Gabbi and others, and I have had the opportunity of treating four cases there; all were children between 2 and 4 years of age. Two were sent to me by Dr. Battinos, whom I desire to thank for his kindness. One of the children was in a dying condition when the treatment was started, and died five days after beginning it. The other three cases all recovered, and in them tartar emetic was given solely by intravenous injections in one; in another by intravenous injections, intramuscular injections, and by oral administration; in the third one the drug was given by intramuscular injections and by the mouth.

Intravenous Injections.

The usual 1 per cent. tartar emetic solution in sterilized normal saline answers well: 2 to 10 c.cm. of this solution are given daily for five to ten days, then every other day or twice a week. At times, especially in cases of relapsing fever, as I will mention later, I have used the following formula:

Tartar emetic	...	...	...	4 grams.
Sol. acid. carbolic	(2 per cent.)	...	...	100 c.cm.

Half to 2 c.cm. is diluted at the time of injection with sufficient sterile saline to bring it to 5 c.cm., and the whole injected into a vein, taking the usual precautions. It is, of course, necessary to make sure that the needle is actually in the vein, and that none of the fluid escapes in the surrounding tissues.

Intramuscular Injections.

These are extremely convenient, and especially useful in children in whom the superficial veins are often small. Unfortunately, as well known, the usual solutions of tartar emetic and other antimonial salts are very painful when given in this way, and may induce the formation of an abscess. The following formulae, however, will be found fairly satisfactory:

Formula No. 1.				
Tartar emetic	...	...	...	gr. viij
Ac. carb.	...	...	...	m x
Glycerin	...	...	...	5 ij
Aq. dest.	...	...	...	ad 5 j

Half to 1 c.cm. every other day in the gluteal regions by intramuscular injection.

At the time of the injection the patient as a rule feels absolutely no pain, but a few hours later in most cases there is a certain amount of inflammation accompanied by a modicum of pain, which is quite bearable, and followed by a slight amount of localized infiltration, comparable to what one sees after intramuscular injections of quinine hydrochloride or mercury perchloride salt solution (1 in 1,000), though generally very much less severe. If the pain and infiltration should be severe, hot fomentations will be found very useful. The presence of carbolic acid decreases the pain induced by tartar emetic and makes the solution sterile. The solution is prepared in bulk in a sterile bottle, and tested for sterility forty-eight hours after preparation; it may then be put up in small 1 c.cm. ampoules, which it is advisable to keep in a cool dark place.

Formula No. 2.				
Tartar emetic	...	...	...	gr. viij
Ac. carb.	...	...	...	m x
Glycerin	...	...	...	5 ij
Sod. bicarb.	...	...	...	gr. 4
Aq. dest.	...	...	...	ad 5 j

The only difference from No. 1 formula is the presence of sodium bicarbonate, which makes it slightly alkaline, while No. 1 is slightly acid. The results seem to be the

same, and the pain induced by it appears to be about the same as with formula No. 1.

Formula No. 3 (Martindale).

Antimonii oxidi	...	...	...	gr. 50
Glycerin	...	...	...	aa m xv
Aq. dest.	...	...	...	

(One ampoule.)

This preparation is good and its use practically painless, but I have the impression that the curative action of antimonium oxide is inferior to tartar emetic.

Oral Administration.

The oral administration of the drug is often useful in conjunction with the intravenous or intramuscular injections. The following is the formula of the mixture I use at the present time:

Tartar emetic	...	...	...	gr. v
Sod. bicarb.	...	...	...	gr. xxx
Glycerin	...	...	...	5 j
Aq. chlorof.	...	...	...	5 j
Aquae	...	...	...	ad 5 ij

(5j to 5ij in water t.d.)

In adults the dose can be doubled. It may be noted that in the very first case of kala-azar treated with tartar emetic, besides giving it intravenously I gave it also by the mouth in the form of my yaws mixture.

ORIENTAL SORE.

The curative effect of tartar emetic in dermal leishmaniasis has been noted by many observers. I have treated recently a case in Corfu, a boy, aged 16 years, with a typical oriental sore on the left cheek; microscopical examination was positive. He received twelve intramuscular injections (formula No. 1) and took 2 teaspoonfuls of the tartar emetic mixture three times a day. A complete cure was obtained very rapidly. In this case the signs of improvement appeared so quickly that I did not use any local treatment, though the local application of antimonial ointment, as advised by G. C. Low, is often successful, even when it is the only treatment carried out.

RELAPSING FEVER.

I used tartar emetic in 14 cases of relapsing fever in Macedonia last year and 3 cases in Corfu this year. As I propose to give my observations on the treatment of the disease as well as the results of the clinical and etiological investigation of the malady, the etiological spirochaete of which I am inclined to believe to be a slightly different variety from *S. recurrentis*, in a separate paper, I will limit myself here to the statement that tartar emetic appears to be beneficial in relapsing fever, but far less so than salvarsan, neo-salvarsan, and similar preparations. It seldom cuts short the first attack of fever, but in a large percentage of cases it has apparently prevented the relapses. I have generally given it once or twice daily by intravenous injections, using the usual 1 per cent. tartar emetic saline solution (2 to 10 c.cm. at a time), or oftener, and I think with better results, the tartar emetic carbolic solution the formula of which I have already given.

In a few cases I have given also intramuscular injections (formulas Nos. 1 and 2) and by the mouth. For oral administration I have generally used the tartar emetic, glycerine, bicarbonate mixture I have already mentioned. At times I have used the yaws mixture (one-third doses), in which I have incorporated liquor arsenicalis 3 to 5 minims in each dose. The intravenous injections give the best results.

CONCLUSION.

Tartar emetic is of great efficacy in various protozoal diseases. Its powerful action in trypanosomiasis has been well proved, and it can be considered a specific in espundia, granuloma inguinale, kala-azar, and oriental sore. It is efficacious in yaws, especially if combined with other drugs, and seems to have a beneficial action also in relapsing fever.

REFERENCES.

- Aragao: Quoted in *Bull. Trop. Diseases*, 1915.
 Carona and Cristina: Various papers in *Riv. Pediatria, Riforma Medica*, etc., 1915-1916.
 Castellani: Several papers in Reports Trop. Dis. Ad. Comm. (second half-year, 1914); *Journal Ceylon Branch, British Medical Association*; *Riv. Pediatria*; *BRITISH MEDICAL JOURNAL*, etc., 1914-1915.
 Daniels: Several papers in *Journal of Tropical Medicine*, 1911-1912.
 Low: *Journal of Tropical Medicine*, November 15th, 1915.
 Mackie: *BRITISH MEDICAL JOURNAL*, 1915, vol. ii, p. 745.
 Manson: *Journal of Tropical Medicine*, 1911.
 Rogers: *BRITISH MEDICAL JOURNAL*, 1915, vol. ii, p. 197.
 Spaar: *Journal of Tropical Medicine*, 1915.