THE FATTY ACIDS OF CHAULMOOGRA OIL IN THE TREATMENT OF LEPROSY AND OTHER DISEASES

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Since my original publication,[1] much interest has arisen as to the value of these fatty acids in leprosy and other diseases, especially tuberculosis.

On reviewing the literature on the use of the oil by subcutaneous injections, I find that it was probably first used by Blanc of New Orleans as early as 1888, according to Dyer.[2]

Sandes [3] has also used it hypodermically at Robbins Island. Black [4] gave a mixture of olive oil and chaulmoogra oil.

Ohmann-Dumesnil [5] gives preference to the hypodermic administration of the oil.

Jeanselme,[6] in 1911, published the formula which was probably the basis of the Mercardo formula employed later in the Philippines. It was composed of chaulmoogra oil, guaiacol and camphor.

Tourtoulis [7] read a paper before the Academy of Medicine of Paris on several years' experience in the use of the oil subcutaneously.

Miguel [8] and Unna [9] both report good results from the use of the oil subcutaneously.

More recently Mercardo,[10] in the Philippines, obtained such excellent results that renewed attempts were made with the oil subcutaneously, and further experiments were encouraged, notably those of Sir Leonard Rogers in India and my own in Hawaii.

The chemical composition of chaulmoogra oil was first investigated by Powers and Gornall in 1904. They isolated a new series of fatty acids, among which were chaulmoogric acid ($C_{18}H_{32}O_2$) and hydnocarpic acid ($C_{16}H_{28}O_2$).

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1. Hollmann, Harry T.: Chaulmoogra Oil in Leprosy, J. Cutan. Dis. **37**: 367 (June) 1919.
2. Dyer: Am. J. Trop. Dis. **2**:295.
3. Sandes: J. Trop. Med. **15**:65.
4. Black: Lancet, April 28. 1906. p. 1167.
5. Ohmann-Dumesnil, A. H.: The Treatment of Leprosy, J. A. M. A. **40**: 1351 (May 16) 1903.
6. Jeanselme: Presse méd., 1911, No. 96, p. 989.
7. Tourtoulis: Lepra **2**:107.
8. Miguel: Lepra **2**:120.
9. Unna: Arch. f. Dermat. u. Syph. **105**:299.
10. Mercardo: Pub. Health Rep., Supp. 20 (Oct. 16) 1914.

In 1916, Dr. Sudhamony Ghosh [11] working in India on this problem, isolated seven fractions of fatty acids from chaulmoogra oil by a method of fractional crystallization. These were converted into sodium salts and used by Sir Leonard Rogers in the treatment of leprosy.

The results of Sir Leonard Rogers' work [12] is that in 40 per cent. of fifty-one patients treated the lesions completely disappeared.

About the time that Rogers and Ghosh were starting their investigations in India, in Hawaii I interested Miss Alice Ball, M.S., an instructress in chemistry at the College of Hawaii in the chemical problem of obtaining for me the active agents in the oil of chaulmoogra.

After a great amount of experimental work, Miss Ball solved the problem for me by making the ethyl esters of the fatty acids found in chaulmoogra oil, employing the technic herewith described:

BALL'S METHOD OF MAKING ETHYL ESTERS OF THE FATTY ACIDS OF CHAULMOOGRA OIL

The oil has been separated into four fractions by the following procedure, using 200 gm. of oil, or multiples thereof, at one time:

The 200 gm. of oil are saponified with alcoholic potash and the bulk of the alcohol subsequently distilled off. The potassium soap is poured into a considerable volume of water and acidified with hydrochloric acid. The fatty acids thus separated are washed with hot water, dried and dissolved in 450 c.c. of 92 per cent. alcohol. On standing overnight in the refrigerator, a large amount of fatty acid crystallizes out and is removed by filtration. From this first crop of crystals, by successive recrystallizations from alcohol, chaulmoogric acid is obtained. This is converted into the ethyl ester and forms Preparation A. The mother liquors from the successive recrystallizations of chaulmoogric acid, which contain all of the solid fatty acids which separated in the initial crystallization from alcohol, except the chaulmoogric acid recovered in A, are united and evaporated. The residue of solid acids is then esterified, forming Preparation B.

The filtrate from the initial separation from alcohol contains the acids which are more soluble in that solvent. These are converted into their lead soaps by first making the potassium soaps and then precipitating them with lead acetate. The lead soaps, dried either in vacuo or by repeatedly evaporating them down with alcohol on the water bath, are placed in 1,000 c. c. of ether. After thorough shaking, the mixture is allowed to stand overnight and the insoluble residue removed by filtration. These insoluble lead soaps, and the soluble

11. Ghosh: Indian J. M. Res. **4**:691 (April) 1917.

12. Rogers: Report of a Conference on the Leprosy Problem in India, 1920, Indian M. Gaz. **55**:125 (April) 1920.

portion recovered from the ether solution, are separately decomposed by treatment in hot water, with successive portions of acetic acid followed by hydrochloric acid. In this manner the lead is all removed and two portions of fatty acids recovered, differing from each other in the solubility of their lead salts in ether. These fractions are then esterified, yielding Preparation C from the fraction with soluble lead salts and Preparation D from that with insoluble lead soaps.

The four fractions are therefore:

(*a*) Ethyl ester of chaulmoogric acid.

(*b*) Ethyl esters of acids crystallizing from alcohol with chaulmoogric acid in the initial separation.

(*c*) Ethyl esters of acids soluble in 92 per cent. alcohol in first separation and which form ether soluble lead salts.

(*d*) Ethyl esters of acids forming lead salts insoluble in ether.

Sir Leonard Rogers [12] has followed out this line of work further and has used the sodium salts of the fatty acids of cod liver oil. In twenty cases, all patients improved, and in five all lesions disappeared.

Dr. E. Muir [13] reports that of 117 cases treated with sodium morrhuate, 71 per cent. manifested some measure of improvement, while 31 per cent. showed much improvement; and with the chaulmoogric sodium salt 132 cases, or 72 per cent., showed improvement and fifty-eight cases, or 32 per cent., showed marked improvement.

He says further that, from his experience, sodium morrhuate is as good as the sodium salt from chaulmoogra oil, and it has the advantage that it may be injected directly into the leprous nodules.

E. F. Neve [14] gives the results of treatment with both chaulmoogra and cod liver oil fatty acid sodium salts. He thus tabulates the results:

Gynocardate (chaulmoogra) treatment: much improved two, 10 per cent.; improved seven, 35 per cent.; not improved eleven, 55 per cent.

Morrhuate treatment: much improved two, 10 per cent.; improved six, 30 per cent.; not improved twelve, 60 per cent.

In his conclusions, he makes a pertinent remark: "Only about 10 per cent. show fresh manifestations of the disease while under treatment, some of which have been due to freeing of toxins by overaction of the drug."

The latter fact I also have observed in a number of cases under treatment with the ethyl esters of the fatty acids of chaulmoogra oil.

At times the ethyl esters will cause, in some of the cases, an apparent fresh manifestation of the disease; yet I am convinced, from the subsequent progress of these cases, that it is not a fresh manifestation of the disease, but an inflammatory reaction in previously unrecognized foci of the disease.

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13. Muir: Indian M. Gaz. **55**:139 (April) 1920.
14. Neve: Indian M. Gaz. **55**:128 (April) 1920.

McDonald and Dean [15] report that, in the use of the ethyl esters of the fatty acids of chaulmoogra oil in leprosy, they took the ethyl esters as isolated for me by Miss Ball and distilled them in vacuo at a pressure of from 30 to 34 mm. The distillate was cut into three fractions of different boiling ranges and was colorless. They say that the methods employed in their production did not result in the destruction of the therapeutic agent or agents.

I cannot see that there is any improvement whatsoever over the original technic as worked out by Miss Ball. The original method will allow any physician in any asylum for lepers in the world, with a little study, to isolate and use the ethyl esters of chaulmoogra fatty acids in treating his cases, while the complicated distillation in vacuo will require very delicate, and not always obtainable, apparatus.

McDonald and Dean report that of 186 patients under treatment during a period of fifteen months, 25 per cent. became bacteriologically negative. Unfortunately, they do not give any data as to the length of time these patients were under treatment. In their conclusions they say: "When combined with iodin, the fatty acids of chaulmoogra oil, and their esters, give good results; but there is no adequate proof that this addition of iodin causes any increase in the effectiveness of the material used."

Walker and Sweeney [16] summarize the results of their experiments in the bactericidal action of the fatty acids of chaulmoogra oil thus: "Chaulmoogra oil contains bactericidal substances that are about 100 times more active than phenol. The bactericidally active substances of chaulmoogra oil are the fatty acids of the chaulmoogric series, chaulmoogric and hydnocarpic acids, and possibly lower isomers of this series. The bactericidal activity of the chaulmoogric acid series is specific for the acid-fast group of bacteria and inactive against all other bacteria tested."

RESULTS OF TREATMENT

Since the establishment of the treatment of leprosy by the ethyl esters of chaulmoogra oil by me at the leprosy hospital (Kalihi Hospital), United States Public Health Service, Honolulu, eighty-four patients who have been on the treatment for periods ranging from four years to three months, have become bacteriologically negative and free from all lesions of the disease and have been discharged from segregation (paroled). These patients, before being paroled, were examined by a board of three medical men, whose duty it was to recommend whether or not the patients should be paroled from segregation.

15. McDonald and Dean: Pub. Health Rep. **35**:1959 (Aug. 20) 1920.
16. Walker and Sweeney: J. Infect. Dis. **26**:238 (March) 1920.

Of the eighty-four patients, thirteen were under treatment less than six months; twenty-eight from six months to one year; thirty-six from one year to two years; five from two years to three years, and two from three years to four years. It will be seen that 76 per cent. of the patients were under treatment for a period ranging from six months to two years.

Of the eighty-four patients thirty-six were male, twenty-five having nodular leprosy, and eleven anesthetic leprosy. Forty-eight were female, thirty-five having nodular leprosy, and thirteen anesthetic leprosy.

It will, therefore, be evident to any one that of these eighty-four patients that have been paroled, at least sixty (having nodular leprosy) gave a bacteriologically positive reaction at the time of beginning treatment, and if reaction became negative under treatment and the patients were free from lesions, it is positive and undisputable evidence that the ethyl esters of chaulmoogric fatty acids, as isolated by Miss Ball for my use in treating leprosy, are capable when administered to patients with leprosy, of causing the disappearance of the lesions and the leper bacilli.

STAGE OF THE DISEASE AT THE BEGINNING OF TREATMENT

From the history obtainable from these patients, it was learned that twenty-one had shown evidence of the disease for only six months; thirteen from six months to one year; sixteen from one year to two years; eleven from two to three years; six from three to four years; five from four to five years, and twelve for more than five years. Of the eighty-four patients treated, and becoming free from all evidence of the disease, twenty-one had incipient cases (under six months); forty moderately advanced (from six months to three years); twenty-three advanced cases of leprosy (existence for more than three years).

From a careful study of the relation of the stage of the disease and the length of the time of treatment, it became evident that there was no relation between the stage of the disease and the length of treatment as many of the patients suffering from advanced cases gave a bacteriologically negative reaction as soon as some of the patients in the incipient stages. This is explainable, on the grounds that many of the patients having advanced cases have already produced within themselves certain protective or curative agents which need only assistance from without to eradicate the disease from the body.

ETHYL ESTERS OF THE FATTY ACIDS OF CHAULMOOGRA OIL IN TUBERCULOSIS

I have treated only two patients with tuberculosis with the ethyl esters as isolated according to Miss Ball's technic. For use in these cases I prepare the esters thus:

1. One hundred and twelve gm. of caustic potash is placed in a flask and 1 liter of 95 per cent. alcohol is added. The mixture is shaken frequently until the potash is dissolved.

2. The alcoholic potash is poured into a second flask containing 400 gm. of chaulmoogra oil. The second flask and contents are placed in a hot water bath and a reflux condenser is connected with the mouth of the flask. The water in the bath is allowed to boil about one hour, being watched closely so that it (the waterbath) does not boil dry and that the alcoholic potash oil mixture does not boil up into the condenser. It is well to wrap a wet towel around the upper part of the flask in order to keep it as hot as possible. Should the mixture become too hot and start to accumulate in the condenser, the light should be lowered or turned out, and a cold wet towel should be wrapped around the flask in place of a dry one.

The water running through the condenser condenses the alcohol as it enters the middle tube of the condenser and it drops back into the flask.

The cold running water should enter the condenser through the lower end and leave through the upper one.

3. The light is turned out under the water bath and the reflux condenser is removed from the top of the flask. A bent glass tube is inserted in a rubber cork into the mouth of the flask. The other end of the bent tube is connected with the larger end of the reflux condenser by means of a rubber cork. The reflux condenser is slanted so that the smaller end is lower than the larger end and a second flask is placed under the smaller end of the reflux condenser.

The hot water bath is heated, and the alcohol that is condensed in the reflux condenser will now pass through into the second flask instead of dropping back into the first flask as previously.

Heating the water bath and distilling off the alcohol is continued until the alcohol drops very slowly into the second flask. All the alcohol cannot be distilled off, but it can be distilled off until the soapy substance in the first flask is quite thick.

While this fluid soapy mixture in the flask is still hot, it is poured into a large volume of water and shaken well several times. It is then acidified with chemically pure hydrochloric acid until it is acid to litmus. This makes a fatty acid of the soapy mixture. It will now begin to separate, fatty globules of a dark brown color rising to the top of the mixture.

To aid the separation, three or four tablespoonfuls of common salt is added and the mixture shaken well. After there is a clear separation of the acid to the top, as much as possible of the liquid below is drawn off.

The fatty acid mixture is washed with plain boiling water at least three times. The last time the mixture will have to be put in a separatory funnel to remove all the water.

4. The fatty acid mixture is dissolved in absolute alcohol in an amount sufficient for the purpose. The alcohol fatty acid mixture is boiled on the hot plate with hydrochloric acid gas passing through (an operation consuming from forty minutes to one hour) until there is a separation in the flask. The ester is a muggy brown on top, and the lower layer is the alcohol.[17]

5. The whole content of the flask (ester and alcohol) is added to a large volume of water in a separatory funnel, while it is still hot, to remove the

17. For details of esterification, consult any analytic chemistry.

alcohol and hydrochloric acid. Some common salt is added to further the separation. It is allowed to stand over night, in order to obtain a clear separation.

The lower layer is poured off leaving the layer of ethyl ester in the separatory funnel. The ethyl ester is dissolved in the separatory funnel with ether. About a handful of calcium chlorid is added to the ethyl ester, and it is corked and shaken well. It is then allowed to stand twenty-four hours. This removes all the water. It is then drawn off from the separatory funnel into a clean separatory funnel, leaving the calcium chlorid in the first funnel.

A flask is placed on an electric hot plate and the ethyl ester is allowed to drop into it, drop by drop through filter paper. This evaporates the ether.

The product is now ready for use. It does not need to be sterilized.

CASES TREATED

In an advanced case of pulmonary and intestinal tuberculosis, the patient received ten weekly injections of 2 c. c. each without improvement.

In a case of incipient tuberculosis, with bacilli in the sputum, the roentgen ray showing involvement of the apex, the patient has so far received twelve injections of the ethyl ester, totaling 14 c. c. There has been a cessation of all cough, an increase of 15 pounds in weight and disappearance of night sweats. As there has been no expectoration it has been impossible to examine for bacilli.

I have treated two patients with lupus vulgaris of the face with small doses of the ethyl esters injected directly into the lesions, with complete disappearance of the lesions in one case and great improvement in the other. One drop was the amount injected into each lesion. The injections caused a marked erythema of the lesion, which lasted about ten days, and was followed by retrogression of the lesion. The injection was repeated as soon as the reaction had passed.

In one case of psoriasis I have given the patient fifteen injections, totaling 40 c. c., with no results.

SUMMARY

The fatty acids of chaulmoogra oil are bactericidal for the acid-fast group of bacteria [16] and cause the lesions and bacilli to disappear when administered to lepers, either in the form of the sodium salt [12] or the ethyl ester.[1]

It is too early to say that in the fatty acids of chaulmoogra oil we have a cure for leprosy. The patients who have become free from all lesions and give a bacteriologically negative reaction should be under observation for a much longer period before making such a statement, although a number of the patients have been under observation for three years or longer (those recorded in my preliminary report) after parolment, with, so far as I know, no return of the symptoms of the disease.

CONCLUSIONS

1. We have in the fatty acids of chaulmoogra oil, either in the form of the sodium salt [12] or in the ethyl ester,[1] a remedial agent that will cause a disappearance of the leper bacilli and the lesions of the disease, if administered over a sufficiently long period.

2. All patients who give a bacteriologically negative reaction should continue under observation and treatment for at least two years more.

3. From the results obtained in two cases of lupus, the ethyl esters of chaulmoogra oil fatty acids should be given a trial in cases of this disease, as well as in other forms of tuberculosis.