CORRESPONDENCE

This department is provided for the publication of informal communications which are of interest because they are informative or stimulating, and for the discussion of controversial matters.

VITAMINS IN TREATMENT

To the Editor:

Some time ago I wrote to Professor Roger Adams, of Illinois, suggesting to him an idea regarding the treatment of leprosy. His reply indicated that he thought the idea worthy of some consideration.

The suggestion was that, in the use of chaulmoogric, hydnocarpic, or other natural or synthetic acids which may possess some therapeutic properties, to try, instead of the sodium salts, ethyl esters, or glycerides of these acids, the effects of the esters of complex natural alcohols such as vitamin A or any of the various xanthophylls. The esterification of these acids with such alcoholic carotinoids would probably result in heavy oils or waxes, but they should be relatively stable when pure and might perhaps lend themselves to use in local applications in a salve, or to injections in a thin, neutral oil. Esters of carotinoids are far more stable toward the effects of light, oxygen, etc., than are the free carotinoids. Possible advantages are:

1. Certain carotinoids are naturally-occurring constituents of many tissues, including the integument, playing in the latter a physiological role in the maintenance of the normal condition and function of the skin and the retina. Also, vitamin A or carotinoid precursors of it are probably effective in preventing and perhaps overcoming lesions of the mucous surfaces and skin initiated by microorganisms or dietary deficiencies.

2. An esterification product of vitamin A or one of the xanthophylls would probably be less irritating than the salts, ethyl or glyceryl esters, and should be relatively harmless.

3. Such esters should be more resistant to hydrolysis by the body lipases, should dissolve more slowly, and should exert their effects, if any, over a longer period and with the release

of smaller quantities of the hydrolytic products per unit of time than do the other esters.

Knowing something of the empirical physiological role of acids of the chaulmoogric series in the treatment of leprosy, also of the part played by certain of the carotinoids in normal metabolism, might we be justified in considering the idea as worthy of experiment?

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From Dr. R. G. Cochrane, Lady Willingdon Settlement, Chingleput, Madras:

With reference to the suggestion made by Dr. Fox, we have carried on a two-year experiment with concentrates of vitamins A and D, with completely inconclusive results. I do not think that such experiments will prove of value in the therapeusis of leprosy because it has been a general observation that, in areas where leprosy is most prevalent, the factors that are deficient in the dietary of the people are protein, vitamin B complex and possibly calcium. We have, therefore, been concentrating recently on these latter factors, and have just completed a preliminary experiment on the administration of skimmed milk to children. Our tentative conclusions are: (*a*) Skimmed milk in the amounts given, for the time of the experiment (9 to 18 months), seems to have no influence on the neural lesions of leprosy. (*b*) On the other hand there is evidence that this substance is of value in conjunction with the usual treatment in rendering cases of the lepromatous type negative in a shorter period of time than by the ordinary treatment alone. We have also carried out an experiment on wheat diet, and there seems to be definite evidence that it results, in the majority of cases, in complete relief of nerve pain.

From Dr. L. W. M. Lobel, Institute for Leprosy Research, Batavia, N. I.:

The communication of Dr. Fox has been submitted to a well known vitamin A man (Dr. van Veen), who believes that, even if the esterification of chaulmoogric and other acids with more complex alcohols than the usual ones might result in heavy oils or waxes which are more stable and more resistant to hydrolysis than the ethyl esters, it might have no advantage to use vitamin A or any of the various carotinoids for the esterification. (Xanthophyll, by the way, is not a provitamin A.) The possibility is great that vitamin A or the carotinoids would lose their useful properties in the new chemical structure. If a more stable and resistant product of chaulmoogric acids is wanted, it would be better to try esterification with one of the more complex alcohols, experimenting to determine which one gives the best results, without trying to combine the properties of a vitamin or carotinoid with it. If such a product could be made, it could be used apart from vitamins or carotinoids, administering the latter separately.

From Dr. H. E. Hasseltine, U. S. Federal Leprosarium, Carville, Louisiana:

The suggestions of Professor Fox are of course worthy of consideration. When I was in Honolulu, Drs. Dean and Wrenshall and I experimented with

different combinations of chaulmoogra esters, using some of the higher alcohols; and we also tried to combine them with other elements, particularly arsenic, hoping to get a more effective product. The esters of the higher alcohols seemed to give no better result than those made with ethyl alcohol. Some of our arsenic compounds were so lethal to experimental animals that they had to be abandoned. Any products which Professor Fox and his associates might work out should be tested thoroughly for harmful effects.

From Dr. G. A. Ryrie, Sungei Buloh Settlement, Selangor, F. M. S.:

The suggestion that the esters of vitamin A alcohols or alcoholic carotinoids be used in leprosy I find both interesting and attractive. In this hospital there are between two and three thousand lepers—Malays, Chinese and Indians. The disease runs a comparatively benign course in the Indian, showing as a rule an abundant defence mechanism. In Chinese and Malays it is much more virulent. Indians (Hindus) take an oil bath once a week; i.e., they massage themselves all over with an oil extracted from seeds, called "gingelley oil." Mohammedan and Christian Indians tend to give up the oil bath. I have only a few of these last but, curiously enough, they are practically all of the malignant type of leprosy. Leprosy is practically unknown among Sikhs whose staple diet is wheat, eggs and butter.

In recent work with leprotic ulcers, which are one of the bugbears of the care of patients, fairly definite indications have been seen that local applications of vitamin A have an almost specific effect on such ulcers. Any dressing with a substance rich in that vitamin will do—cod liver oil, red palm oil, mashed goat's liver, etc.—made up as an ointment. At present I am using shark liver oil, which is cheap and has an enormous vitamin A content. It is possible, however, to get too much of the vitamin, with resulting hyperstimulation and irritation of the tissues. It is really amazing —and very pleasant—to see large, intractable ulcers healing up. In any place where sharks are to be had it is a simple matter to obtain a vitamin-rich oil. [See the Brief Report in this issue.]

From Dr. B. Moiser, Ngomahuru Leprosy Hospital, Southern Rhodesia:

During the year 1938 Messrs Bayer Ltd. donated for trial a generous supply of their synthetic preparation of vitamin B_1 called "betaxan." Five cases of the neural type were under prolonged treatment with this preparation, and although 4 of them showed improvement I reported adversely on the experiment, for these cases would surely have shown similar or even better improvement had they been treated with chaulmoogra ethyl esters. I do not consider leprosy to be a "deficiency disease," and did not expect any dramatic results from betaxan. The drug which during the past few years has been found to produce the best results is moogrol and now it is practically the only one used in Southern Rhodesia. Of 376 patients who received regular treatment during 1938, 69 were much improved (50 of them arrested and discharged), 252 were improved and only 10 became worse.

[A news items from the *National Zeitung* (Basel) states that Prof. Fonesca de Ribeiro, of Brazil, has experimented with a new treatment material consisting of a mixture of a "tissue substance from leprosy patients with a certain carotinoid solution." A patient treated by injections

and internally with this material was cured in three months, the report states.—EDITOR.]

Certain of the foregoing comments were forwarded directly to Dr. Fox for his information and comment.

Rejoinder by Dr. Fox.—This correspondence reveals an interesting difference of opinion between Dr. Ryrie and Dr. Cochrane, but apparently their experiences have been very dissimilar. I gather that Drs. Hasseltine, Dean and Wrenshall did not include vitamin A among the higher alcohols which they esterified with chaulmoogric acid.

Regarding Dr. Lobel's letter, I am unable to recognize any underlying known facts which might lead to his conclusions as to the inefficacy of vitamin A chaulmoogrates. The body does take in esterified vitamin A, and the body lipases hydrolyze such compounds. Very probably the blood and tissue lipases would effect the hydrolysis readily enough to set free the two resulting therapeutic compounds, but not so rapidly, perhaps, as to produce the irritating effect of larger concentrations of the acid. That xanthophylls are not ordinarily recognized as provitamin A is well known. But xanthophylls are higher alcohols capable of esterification. Furthermore, they are found naturally in many tissues, and so could do no harm. Again, the esters of such alcohols and chaulmoogric acid would probably be hydrolyzed fairly slowly, and that may be a desirable feature. Dr. Lobel did not apparently state his reasons for supposing that vitamin A, etc., would lose their useful properties in the new chemical structure. I think that they would not, for reasons given above. I may say that Dr. L. J. Harris and Dr. Thomas Moore, both well known vitamin A men at the University of Cambridge (England), in conversations which I had with them regarded the possibility of using such esters quite favorably.

I hope that someone in one of the various hospital-laboratories or elsewhere may attempt a careful synthesis and isolation. I should add that my own research program is not associated with therapeutic work or synthesis of drugs, and that I do not expect to prepare any materials. I shall be only too happy if my suggestions may be used by other biochemists or organic chemists who may care to undertake the synthesis suggested. The job will not be very easy but it is quite possible, and it might bring some reward even if only to suggest a new line of attack. It is indeed quite possible that the new compounds might be disappointingly inconclusive, but I cannot help feeling that it would be worth while giving them a trial, as I find no evidence or hypotheses in the correspondence which contraindicates clinical experimentation.