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## INFLUENCE OF DEHYDROCHOLIC ACID (DECHOLIN, N.N.R.) ON ORAL TOXICITY OF CHAULMOOGRA OIL

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Pharmacological studies of the acute toxicity of various chaulmoogrates administered parenterally have shown that water-soluble derivatives (2) are much more toxic than such insoluble chaulmoogrates as the ethyl esters (3). Thus a problem of some academic importance is the determination of the oral toxicity of chaulmoogra oil, which drug though taken as an insoluble oil is presumably absorbed chiefly as quite soluble soaps, phosphatides and choleic acids. Practically, the acute oral toxicity of chaulmoogra oil taken by mouth is of only theoretical interest in therapy, for the agent is emetic (4) in doses far below the toxic range. The emetic property of chaulmoogrates also forestalls the determination of oral toxicity in most laboratory animals, and it is not surprising that no accurate estimate of the oral toxicity of chaulmoogra oil occurs in the literature. Only animals unable to vomit, such as the rat or rabbit, are suitable for such studies.

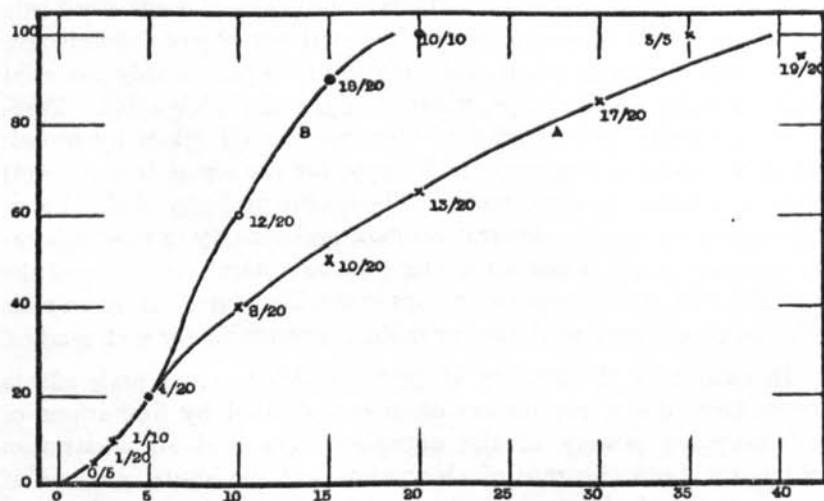
In examining the toxicity of agents which produce toxic effects only in large doses, results are often complicated by limitations of the absorptive powers of the organism. On oral administration particularly, both the rate of absorption and the actual amount of the agent absorbed may greatly modify the apparent toxic dose. Therefore in the following experiments a bile derivative was administered to promote absorption of the oil, to give a more exact picture of the true oral toxicity.

### EXPERIMENTAL

In the present work 240 rats<sup>1</sup> were used. All weighed between 175 and 300 gm. and were in good health, and before use they were maintained for at least two weeks on a standard diet. No pregnant females were included.

<sup>1</sup>Some of these 240 rats were supplied by the Department of Psychology of the University of California. Those rats had been blinded several months previously by extirpation of both eyes; none of the psychological tests used thereafter could conceivably injure the animals or alter their susceptibility to chaulmoogrates.

Chaulmoogra oil alone was given to 160 rats. They were lightly anesthetized with ether to permit passing a stomach tube, and were given doses of chaulmoogra oil U.S.P. intragastrically as noted in Text-fig. 1, curve A. The number of points chosen was unfortunately large, because of too great reliance on data in the literature pertaining to the toxicity of chaulmoogra oil and other chaulmoogra esters in different species (3, 5, 7, 8). Observations were continued for 14 days, although practically all deaths occurred in the first 3 days after treatment. The picture at necropsy was similar to that reported for ethyl chaulmoograte (3), with the difference that large residues of oil were present in the gut. The few immediate deaths which occurred with the higher doses were considered due to sudden dilation of the stomach, and the results are not included in the graph.



TEXT-FIG. 1. Oral toxicity of chaulmoogra oil. Curve A, chaulmoogra oil alone. Curve B, chaulmoogra oil after premedication with decholin.

Seventy rats were treated in the same way with intragastric doses of chaulmoogra oil as noted in Text-fig. 1, curve B. These rats had received intraperitoneally 100 mgm. kg. of dehydrocholic acid (decholin, N.N.R.) one hour before the oil was given. There were no deaths among ten control rats that were subjected to 100 mgm./kg. of decholin followed in one hour by light etherization without administration of chaulmoogra oil.

The chaulmoogra oil used agreed with U.S.P. standards for optical activity, free acidity, saponification value and iodine number. The iodine number indicated the presence of appreciable amounts

of hydnocarpic or other unsaturated fatty acids, so that the activity of this oil cannot be wholly ascribed to its chaulmoogric acid content. Dehydrocholic acid was administered intraperitoneally as the sodium salt, prepared by admixture of tablets of the acid with sufficient sodium bicarbonate to effect solution.

#### DISCUSSION

Examination of Text-fig. 1 reveals that while chaulmoogra oil is "toxic" in small doses, causing death in a dose of only 2.0 cc./kg., it is difficult to give sufficient oil to cause the death of all treated rats. Such results lead to a "skew" type of toxicity curve. Curve A is of this type.

On the other hand, if rats are premedicated with dehydrocholic acid, the toxicity of chaulmoogra oil is apparently increased at higher dosage levels, so that a dose of 20 cc. kg. results in the death of all rats. It may be noted that this effect applies only to the higher doses, and acts to correct the skewness of the normal curve. Curve B may be considered a corrected or true toxicity curve of chaulmoogra oil *per os*, with the factors of slow or incomplete absorption compensated for.

It may also be noted that curve B approximates an "ogive," or sigmoid curve, which is partly an expression of the normal distribution curve applied to toxicity studies. Such curves show the toxic range, the minimum lethal dose, and the certain fatal dose of agents, and are often referred to as the toxicity characteristic curve.

Skewness of curves representing graphed biological data relating dosage to effect is held to denote the presence of some interfering physiological or chemical factor which disturbs the normal sigmoid shape of such curves (1). The ease of fitting data to a sigmoid curve is not assurance of the simplicity of the effect measured, however. In the present work, therefore, it cannot be assumed that the success in obtaining a sigmoid curve upon correcting the only partially effective normal processes of absorption is any indication that chaulmoogra oil exerts its toxic effect by any simple mechanism. The pathology found at necropsy also indicates that the toxic effect is complicated.

It is also unsafe to apply the results to probable oral toxicities in other species, particularly those in which vomiting occurs. The cumulative dose of chaulmoogra oil in the customary oral doses in human lepers does not approach the single oral lethal dose in rats except when treatment is continued over extremely long periods. Other factors, such as hepatic or renal damage, presumably play a

greater part in cumulative toxicity. It may be concluded from the present work, however, that chaulmoogra oil by mouth is much less toxic than water-soluble chaulmoogrates administered parenterally (2).

#### SUMMARY

Comparison of toxicity curves indicates that chaulmoogra oil given orally is appreciably more toxic when preceded by parenteral injection of dehydrocholic acid, presumably through promotion of intestinal absorption.

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