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## OIL OF STROPHANTHUS AND THE EMETIC ACTION OF STROPHANTHUS.

BY ROBERT A. HATCHER, M.D.

The chemistry and pharmacology of strophanthus and other members of the digitalis group have long presented many difficulties to the investigator, and the confusion resulting from unavoidable errors has been augmented by the publication of papers by careless observers and by those whose purpose was to mislead physicians in the interests of proprietary substitutes for the official drugs and preparations of this group.

The emetic action of strophanthus and other digitalis bodies is so annoying that many efforts have been made to discover its cause, and many suggestions have been offered concerning means of avoiding it.

So long as it was not known how these drugs induced emesis it was only natural that the various means suggested for avoiding it should usually prove futile when employed by the general practitioner.

Strophanthus contains a fixed oil, and it has been suggested that this oil is responsible, in part at least, for the nausea and vomiting occasionally seen after the therapeutic use of the tincture, which contains small amounts of the oil. The disagreeable odor of the isolated oil has given the suggestion a certain degree of plausibility.

It has been shown conclusively by Hatcher and Eggleston [1] that all of the digitalis bodies investigated by them induce nausea and vomiting through their action on the vomiting centre in the medulla, and that therapeutic doses of these drugs are without important direct action on the gastric mucous membrane.

It follows, from the foregoing statement, that the nausea and vomiting can be avoided only by the proper regulation of the dose, and any attempt to suggest ways of avoiding these disagreeable side actions without taking the cause into consideration merely serves to mislead in so far as the proffered suggestion is accepted.

The possibility that the oil or fat in digitalis and that in strophanthus might exert some nauseant action led me to undertake an investigation of the question some years ago, but the investigation was abandoned after I had become convinced that the nauseant action of therapeutic doses of these drugs was invariably of central origin, and that very large doses of the fixed oil or fat from these drugs could be administered to cats by the mouth without inducing symptoms of any kind.

The absence of any nauseant or emetic action of the oil or fat in therapeutic doses of digitalis and strophanthus was mentioned by Eggleston and Hatcher [2] in a paper dealing with the relative emetic activities of various digitalis bodies.

[1] Journal of Pharmacology and Experimental Therapeutics, 1912, iv, 113.

[2] Journal of the American Medical Association, 1913, lx, 499.

It has been said that when once an error finds a place in a text-book it becomes immortal, and so long as errors find champions they will demand refutation, and I have therefore extended the work done some years ago in order to obtain more exact information on the subject.

A discussion of the literature of the subject would be profitless, and I will say at once that I do not know of any investigator who has obtained evidence that the oil or fat present in therapeutic doses of tincture of strophanthus (or that of digitalis) has any action on the gastric mucous membrane that can be detected.

The present paper is intended to enable those readers who are not trained in the methods of pharmacologic research and in the interpretation of the results thus obtained with reference to their therapeutic significance to estimate correctly the work of those who attempt to show by the results of experiments that the oil of strophanthus contributes to the nausea and vomiting that are sometimes seen after the use of therapeutic doses of the tincture of strophanthus.

## OIL OF STROPHANTHUS.

The official strophanthus (*S. Kombé*) contains about 30 to 34 percent of a greenish-yellow, non-drying oil, that is only slightly soluble in 95 percent alcohol, and soluble only in minute amounts in a mixture of alcohol and water in the proportion directed by the Pharmacopœia for making tincture of strophanthus. The isolated oil has a slightly disagreeable odor, somewhat resembling that of linseed oil, but the odor of the seed and that of the tincture are pleasant to many, and rather suggestive of the odor of certain edible nuts.

The several specimens of the oil of strophanthus that were used in the present series of experiments were obtained as follows:

1. A bright green oil, or fat,[8] solid at room temperature, readily soluble in 95 percent alcohol, obtained from a specimen of ground *Strophanthus Kombé* in an original package bearing the label of Gilpin, Langdon & Co.

This oil was obtained by shaking the ground seed with successive portions of petroleum benzin, filtering and evaporating off the benzin over a water-bath.

2. Green oil, similar to No. 1, extracted from the residue of an evaporated tincture of the ground seed just described.

3. A green oil closely resembling No. 1, extracted from the marc left after making the tincture from another portion of the seed that yielded No. 1.

4. A greenish-yellow oil, liquid at all temperatures above 0° C., only slightly soluble in 95 percent alcohol, and even less soluble in a mixture of alcohol and water in the proportion directed for making tincture of strophanthus. The seed

[8] Catillon (Bul. et Mem. de la Soc. thérap., Paris, 1887, p. 217) examined a specimen of *Strophanthus hispidus* that had been obtained from Africa and which he claimed to be of undoubted authenticity. He reported that the seed yielded 32 percent of a beautiful green oil, that was soluble in alcohol and which was probably inert. His description agrees exactly with the oil obtained by me from a specimen of ground *Strophanthus Kombé* bearing the label of Messrs. Gilpin, Langdon & Co., who have assured me they identify all lots of strophanthus ground by them.

from which this oil was extracted were supplied to me by Professor H. H. Rusby several years ago, and by him identified as *Strophanthus Kombé.* The seed were beaten in a mortar with sand and extracted in the manner described for No. 1. The yield of fixed oil was 34 percent of the weight of the seed.

5. An oil closely resembling No. 4 in appearance and solubility in 95 percent alcohol, extracted in the manner just mentioned from brown seed supplied by Professor Rusby and by him marked "Spurious" strophanthus (*Strophanthus hispidus?*).

No attempt was made to estimate the amount of oil in this seed, but about 25 percent was obtained by imperfect exhaustion.

PHARMACOLOGIC EXPERIMENTS WITH OIL OF STROPHANTHUS.

Two experiments were conducted by simply smearing the oil on meat and feeding it to cats. These ate the meat readily, while a third refused the meat so treated. In the remainder of the experiments the oil was weighed or measured and made into an emulsion with acacia and water, ten parts of the emulsion containing one part of the oil. The emulsion was administered to the cats through a stomach-tube, a little water being used to wash the vessel and the tube, the washings then being passed into the stomach.

The animals were observed until emesis occurred or for periods of one to three hours, and usually on the following morning, to see whether vomiting had occurred during the night.

It will suffice in most cases to report the results of the experiments, but a few of the protocols will be given in detail.

A cat of medium size received a dose of 100 mg. of the green (No. 3) oil per kilogramme of weight and another received a dose of 275 mg. of the same specimen of oil per kilogramme. Neither animal showed any symptoms.

One cat vomited and defecated after receiving a dose of 450 mg. of the green oil (No. 2) per kilogramme of weight, the effects being strongly suggestive of strophanthin poisoning.

I had gained the impression, from the results of experiments conducted some years previously, that the oil of strophanthus contained traces of strophanthin, and the impression was strengthened by the observations of the effects just mentioned. The following test was performed in order to determine whether traces of strophanthin were actually present in the oil:

A specimen of the green oil (No. 1) was dissolved in 95 percent alcohol and precipitated by the addition of water. The mixture was filtered through a previously-wetted filter, evaporated on a water-bath to a small volume, traces of oil being removed from the residue, and the latter injected intramuscularly into a cat. The animal died in thirty-eight minutes after having exhibited the typical symptoms of strophanthin poisoning, including nausea, respiratory disturbance, a peculiar cry that is typical of the sudden stoppage of the heart-beat, and convulsions. Another test gave nearly similar results, hence there can be no doubt that the specimen of green oil used in the experiment already recorded contained

traces of strophanthin, and steps were taken to purify the oils used in the subsequent experiments, by shaking them with alcohol and adding an excess of water to precipitate the oil. In one case (that of No. 5) a mixture of alcohol and ether was used in order to effect the solution of the oil. The oils were then collected on paper previously moistened with diluted alcohol.

The presence of the contaminating strophanthin is probably explained by the following observation: When the benzin with which the ground strophanthus had been shaken was decanted onto the filter-paper it was observed that a trace of impalpable powder passed through the filter; the filtrate was then passed through a second paper, an apparently clear filtrate being obtained, but when this was allowed to stand a trace of precipitate formed. The solution was filtered again and apparently all of the powder was removed, but doubtless traces of the powder continued to pass through the paper, though the filtrate was of a beautiful clear green color.

Doses of 250 mg. and 500 mg. of the purified green oil (No. 1) per kilogramme of weight respectively were administered to two cats through the stomach-tube without inducing perceptible effects. The following experiment may be described in some detail:

December 24, 1915, cat in poor condition, weight 1.4 Kg.

11:32 A.M., administered 850 mg. of purified green oil (No. 1) per kilogramme through a stomach-tube.

11:56, nausea.

11:57, emesis. (Note promptness with which emesis follows nausea.)

In order to determine so far as possible whether emesis had been due to contaminating strophanthin, which would have had to be absorbed to produce that effect, a test was made according to a method that I have described elsewhere,[4] which consists in determining the fatal dose of strophanthin by intravenous injection. Had strophanthin been absorbed from the gastro-intestinal tract less than the normally fatal dose would have been required by intravenous injection to kill the animal, but since it required the full normally fatal dose it is fair to conclude that emesis had not been due to strophanthin, but to the oil alone. This is the first instance in which it has been shown (so far as I am aware) that oil of strophanthus devoid of traces of strophanthin caused emesis in such small amounts, and it is the only instance in my series of experiments even where larger doses were given.

A cat received 0.25 Cc. (225 mg.) of purified yellowish oil (No. 4) per kilogramme of weight through a stomach-tube, and a second cat received twice as much relative to its weight. There was no perceptible effect in either case. Both cats ate small pieces of meat greedily at intervals of an hour for three hours. Two experiments deserve detailed consideration.

January 5, 1916, cat, weight 2.3 Kg.

2:38 P.M., 1250 mg. purified yellow oil (No. 4) per kilogramme through stomach-tube.

3:38 P.M., animal perfectly normal; excited when shown food.

4:38 P.M., observation exactly as preceding.

January 8, 1916, cat, weight 1.52 Kg.

1:23 P.M., 1250 mg. purified yellow oil (No. 5) per Kg. through stomach-tube.

2:23 P.M., cat arches back and shows satisfaction when stroked; does not eat.

3:33 P.M., observations exactly as preceding.

4:33 P.M., observations exactly as preceding. At this time an associate was requested to examine the cat to see if any abnormal behavior could be detected. The cat appeared absolutely normal.

[4] Journal American Medical Association, 1910, lv, 746.

Table I gives the results of the later experiments, except one in which a precipitate from tincture of strophanthus, obtained by chilling, was used. This precipitate was so obviously impure that the experiment was discarded, the cat having vomited from a large dose.

TABLE I.

| Date | Dose in mg. of oil per Kg. weight. | Specimen No. | Result |
|---|---|---|---|
| 12/ 6/'15. | 450 | 2. | Emesis in 23 minutes. |
| 12/ 8/'15. | 100 | 3. | None; ate when fed after 3 hours. |
| 12/ 8/'15. | 275 | 3. | None; ate when fed after 3 hours. |
| 12/24/'15. | 250 | pure 1. | None; ate when fed hourly, for 3 hours. |
| 12/24/'15. | 500 | pure 1. | None; ate when fed hourly, for 3 hours. |
| 12/26/'15. | 850 | pure 1. | Emesis in 25 minutes. |
| 1/ 4/'16. | 225 | pure 4. | None in 3 hours. |
| 1/ 4/'16. | 450 | pure 4. | None in 3 hours. |
| 1/ 5/'16. | 1250 | pure 4. | None in 2 hours. |
| 1/ 6/'16. | 1250 | pure 5. | None in 3 hours. |

## DISCUSSION.

The results of the foregoing experiments seem to show that the purified green oil of strophanthus (*Kombé?*) may sometimes cause emesis when administered to cats in doses of 850 mg. per kilogramme of weight, and that doses of 500 mg. per kilogramme may fail to induce any perceptible effect. The results of the experiments would also suggest that when emesis occurs with smaller doses of strophanthus oil it is probably to be attributed to traces of strophanthin, of which as little as 0.2 mg. per kilogramme of weight will cause vomiting after its absorption.

The experiments also show that the pure greenish-yellow oil obtained from *Strophanthus Kombé* of unquestioned authenticity, and an oil of similar appearance and solubility in alcohol, obtained from brown strophanthus seed (*hispidus?*) may be administered to cats by the mouth in doses of 1250 mg. per killogramme of weight without causing the slightest evidence of nausea, or any other perceptible effect.

The seed from which the green oil was obtained may be considered as fairly representative of the strophanthus used by the pharmacists of the United States, and I concede willingly that doses of 500 mg. of the oil per kilogramme of weight may cause nausea and vomiting in man, for it is well known that the sensitiveness of the gastric mucous membrane of the cat and that of man are of the same general order. It becomes necessary, therefore, to determine the amount of the fixed oil that may be taken by man during the therapeutic administration of the tincture of strophanthus, and to compare this with the amount probably required to induce nausea and vomiting.

A tincture of strophanthus was prepared from the commercial ground seed (that which yielded the green oil used in my experiments) according to the pharmacopœial directions. It was of a milky appearance and when chilled to a temperature of about 0° C. it deposited a copious whitish precipitate containing a little of the green fixed oil.

Ten Cc. of the filtered, chilled tincture were evaporated on a water-bath, and from the residue thus obtained there was extracted green fixed oil that weighed 0.046 Gm. When to this was added an aliquot part of the fixed oil obtained from the precipitate formed during chilling, the total amount of fixed oil in the recently-prepared tincture was found to be 0.62 w/v percent. That in the filtered, chilled tincture was 0.46 w/v percent.

The amount of fixed oil that might be present in an official tincture prepared from the official strophanthus supplied by Professor Rusby was calculated as follows: Five Cc. of the oil were shaken with 65 Cc. of 95 percent alcohol, which dissolved about 1 percent of its volume of the oil, and 35 Cc. of water were added. The mixture became creamy in appearance, owing to the precipitation of the oil, leaving a supersaturated solution of the oil in a

menstruum similar to that used in making the official tincture of strophanthus. The solution, or mixture, was then filtered through paper previously moistened with alcohol and water in the proportion used for making the solution. The filtrate was quite milky in appearance, owing to the formation of extremely small globules of the oil that passed through a hard filter-paper.

On evaporation the solution yielded 0.38 percent of oil. A little of the oil was precipitated in larger globules when the mixture was chilled to about 0° C., and when filtered it contained 0.24 percent of the fixed oil.

The lower content of oil in this case than in that of the tincture is due to the fact that the yellow oil is far less soluble in 95 percent alcohol and in alcohol of lower percentages than is the green oil present in the seed used for making the tincture.

Accepting the higher percentage of fixed oil as fairly representative of that present in ordinary tincture of strophanthus, we may calculate the amount present in the average therapeutic dose of the tincture, which is 0.5 Cc., or about 0.0075 Cc. per kilogramme of body weight for a man of average size. Sixty-two hundredths of 1 percent of this dose is equal to 0.0000465 Cc., or, roughly, one-twentieth of a milligramme, which is, therefore, the amount of the fixed oil present in an ordinary therapeutic dose of the tincture per kilogramme of body weight, or one ten-thousandth of the amount required to cause nausea and vomiting in the cat, relative to the size.

As a matter of fact, we have seen that each of two animals received much larger doses of oil obtained from *Strophanthus Kombé* and from a specimen of brown seed (*hispidus?*), and not less than 60,000 therapeutic doses of a tincture of the latter would be required to furnish the amount of oil that was administered to a cat without inducing any symptoms whatever. The presence of the fixed oil does appear to render the tincture of strophanthus opalescent, and for the sake of pharmaceutical elegance the removal of the oil from the seed before making the tincture may be desirable, but there is no justification for the claim that this removal of the oil is necessary from a therapeutic standpoint.

## SUMMARY.

1. The pure green oil of strophanthus (*Kombé?*) is apparently capable of causing nausea and vomiting when administered to cats in doses of 850 mg. per kilogramme. The greenish-yellow oil obtained from an authentic specimen of *Strophanthus Kombé* failed to induce any symptoms when administered to a cat through a stomach-tube in a dose of 1250 mg. per kilogramme.

2. The tincture of strophanthus contains only traces of fixed oil (0.24 to 0.62 percent), and the average therapeutic dose of the tincture contains an amount of the oil corresponding to less than one ten-thousandth of that required to cause nausea and vomiting in the cat, relative to the weight.

3. No evidence that is worthy of mention has ever been obtained (so far as the writer is aware) in support of the claim that the oil present in tincture of strophanthus contributes to the nauseant and emetic actions sometimes seen after the *therapeutic* use of the tincture.

4. Oil of strophanthus, obtained by shaking the powdered seed with petroleum benzin, filtering and evaporating, is likely to contain traces of strophanthin, which is an exceedingly active emetic.

5. The oil present in tincture of strophanthus renders the latter opalescent, and its removal from the seed previous to the preparation of the tincture results in a more sightly preparation, but this is of pharmaceutical—and not of therapeutic—importance.

LABORATORY OF PHARMACOLOGY OF CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY.