TINCTURE OF CANTHARIDES—CONTINUED.

WILBUR L. SCOVILLE.

In 1910 I called the attention of this Association to the fact that the official Tincture of Cantharides is unwittingly misbranded, in that it does not and cannot properly represent the drug. Operating on four different samples of cantharides, by the official process, I found that 30%, 44%, 54% and 63% of the activity of the respective drugs used was represented in the tinctures. By using a menstruum of 10% Glacial Acetic Acid and 90% of alcohol, by volume, tinctures were prepared from three of these drugs which represented 81%, 87% and 91%, respectively of their activities.

This acid menstruum has been declared objectionable by some, though for what reasons I have thus far been unable to discover, since acetic acid is an excellent adjuvant to the action of cantharides.

Last year I presented a second paper on the subject in which the results of fifteen further attempts at making a representative tincture were shown. These experiments were made with menstrua composed of alcohol-acetone, alcohol-chloroform and alcohol-acetic ether, each being supplemented by the addition of 0.5 parts of acetic acid per 100 volumes, to free the cantharidin. The results showed an exhaustion of 26% to 46% by the usual percolation method, and 66% to 74% when the percolation was preceded by digestion at 40° to 50° C. The only conclusion from these experiments was that digestion is a very material aid to extraction, but even then the results were far from satisfactory. Furthermore the results were very puzzling, inasmuch as solvents had been used which were certainly capable of dissolving the cantharidin present, yet some had failed to extract any more than the best samples of a straight alcohol-menstruum. Also these results were less satisfactory than those obtained by direct percolation with a cold menstruum of alcohol-acetic acid.

In the present series, eighteen experiments have been made.

Since the beetles have shown a considerable indifference to alcoholic solvents under varying conditions, and even to mixtures of alcohol and chloroform, or alcohol-acetone and acetone-acetic ether, another line of attack was sought.

Reasoning humanly, a creature which could resist unlimited quantities of alcoholic liquids might succumb to hot water—a reasoning which had some support in the known effectiveness of boiling water in assaying the drug and its tincture, the following experiments were tried:

A—50 Gm. of drug, assaying 0.75% of cantharidin were digested with 25 cc. of diluted hydrochloric acid and 25 cc. of water for fifteen hours at a temperature of about 50° C., a reflux condenser being used. Then there were added 175 cc. of acetic ether and 275 cc. of alcohol; and the mixture macerated, with occasional shaking for two days, then filtered.

B—50 Gm. of the same drug were digested for fifteen hours with 25 cc. of diluted acid and 100 cc. of water, then 175 cc. of acetic ether and 200 cc. of alcohol were added and the mixture macerated two days before filtering.

C—50 Gm. of the same drug were digested with 25 cc. of diluted acid and

150 cc. of water for fifteen hours, then 175 cc. of acetic ether and 150 cc. of alcohol added, the mixture macerated during two days, then filtered.

Results—"A" Tincture (10% water) assayed 0.059 gm. per 100 cc.
"B" Tincture (20% water) assayed 0.066 gm. per 100 cc.
"C" Tincture (30% water) assayed 0.057 gm. per 100 cc.

These show an exhaustion of 78.6%, 88.8% and 76.0%, respectively, and indicate that the beetles yield in some degree to the hot water treatment, but that there are limits to which the menstruum can be diluted with water and still retain the cantharidin in solution.

The rest of the experiments were therefore conducted on this line, striving for conditions that would give a tincture which would fully represent the drug.

Experiment D tried 25% of acid-water and yielded 0.060 gm. cantharidin per 100 cc. or 80% exhaustion.

Experiments E, F and G were made to determine whether chloroform or acetic ether would give the best results in the menstruum.

These were made on a drug assaying 0.70% of cantharidin. E was made with 25% of acid-water and 35% of acetic ether (by volume) in the menstruum, and F with 25% of acid-water and 20% of chloroform. G was made with 25% acid-water and 20% acetic ether.

"E" Tincture assayed 0.054 gm. per 100 cc.=77.1% exhaustion.
"F" Tincture assayed 0.053 gm. per 100 cc.=76.0% exhaustion.
"G" Tincture assayed 0.057 gm. per 100 cc.=80.0% exhaustion.

This shows the perversity of the insects and leads to no conclusions.

Experiment H, made on the drug assaying 0.75% of cantharidin, used 35% of acid-water and 35% of acetic ether in the menstruum. Results=0.057 gm. per 100 cc. or 76% exhaustion—the same as C.

Experiment I, used the same drug and menstruum as C, but added the acetic ether to the hot aqueous mixture, shook until cold then added the alcohol and macerated the whole four days. Results=0.060 gm. per 100 cc. or 80% exhaustion—a trifle better than C.

Experiment J, used 25% water (including 50 cc. of acetic acid per 1000) and 20% of chloroform, and the same method as I—that is, the hot aqueous mixture was shaken with chloroform until the mixture became cold (about fifteen minutes) then the alcohol was added and the mixture macerated four days. Results=0.074 and 0.077 gm. per 100 cc., or 100%!

Victory at last! Here was a tincture which fully represented the drug used, and a drug of good grade, too. It had a brownish-green color, was a little darker than the present U. S. P. tincture and had a noticeable odor of acetic acid and of chloroform—though the latter was not as prominent as I had expected. It was brilliantly clear, and did not precipitate on standing several months—as ascertained afterward.

This was the first tincture in my experience which was known to fully represent the drug, and it only remained now to prove that the process would apply to various grades of drugs.

For the next experiment (K) an exceptionally rich drug was employed—one assaying 0.92% of cantharidin. The menstruum consisted of 25% water and

20% chloroform with acetic acid as the freeing agent and the chloroform added directly to the hot aqueous mixture and shaken until cold, as in experiment I. Result 0.064 gm. per 100 cc. or 70% exhaustion! This is tobogganing with a sharp start!

Experiment L.—Again 25% acid-water and 15% chloroform, and the mixture was digested three days after the chloroform had been well shaken as before. Result, 0.0745 gm. per 100 cc., or 81% exhaustion. This is better, but still considerably below 100%.

Experiment M.—Twenty-five percent acid-water and 20% chloroform treated as L. Result 0.075 gm. per 100 cc. or 81% exhaustion.

Experiment N.—Same as L but macerated in the cold instead of digesting the final mixture. Result 0.072 gm. per 100 cc. or 78% exhaustion.

Experiment O.—Twenty-five percent acid-water, 15% chloroform and macerate six days after the chloroform and alcohol were added. Result 0.068 gm. per 100 cc. or 74% exhaustion.

Experiment P.—The drug used on Experiments K to O, inclusive, was in a moderately coarse powder—about No. 40. Now some of this was ground to pass through a No. 80 sieve, then treated with 25% acid-water and 20% chloroform menstruum, the water digestion being continued for two days, then the mixture macerated one day with heat and two days without. Result 0.064 gm. per 100 cc. or 70% exhaustion.

Experiment Q.—Same as P but with shorter digestion and maceration—three days total. Result 0.057 gm. per 100 cc.=62% exhaustion.

Experiment R.—Twenty-five percent acid-water—which was digested at about 50° C. over night (15 hours) then on a steam-bath at 95° to 100° C. under a reflux condenser for six hours, then cooled to about 70° C., the chloroform 15% added and the mixture shaken until cold. Then alcohol (55%) added and the mixture macerated three days. Result: 0.056 gm. per 100 cc.=60% exhaustion.

Experiment S.—Twenty percent water, 35% acetic ether and 45% alcohol, digestion with water at 50° C. carried on 24 hours, then maceration with the rest two days longer. Result: .065 gm. per 100 cc.=70% exhaustion.

Conclusions: I have none. This is still a continued quest,—the conclusion to follow.

The cantharides fly seems to be like the proverbial flea—"when you put your finger on him he isn't there."

There is some encouragement in getting one tincture that fully represents the drug, but that is of little value unless the formula can be depended upon. In this case it worked on one drug, and not on another. And lest somebody questions whether the assay on this sample was reliable, let me say that three assays on this particular lot checked to 0.3% and in all the experiments at least two assays were made, the results checking closely. Probably long practice has enabled me to make assays of this drug and tincture with reasonable accuracy, though I do not expect very close results among different operators by the present known methods.

The present situation on the extraction of cantharides is as follows:

1. Alcohol alone fails to extract more than half to two-thirds of the cantharidin present.

2. Heat favors extraction, but has less effect in anhydrous than in hydrated menstrua.

3. The best menstruum thus far found is a mixture of one volume of glacial acetic acid with nine volumes of alcohol.

4. Mixtures of water, alcohol and chloroform, acidulated with acetic or hydrochloric acid have given good results in some cases, but the proportions and method which will give uniformly satisfactory results have not yet been discovered.

PARKE, DAVIS & Co., Detroit, Mich.

DISCUSSION.

Otto Raubenheimer, of Brooklyn, said Mr. Scoville's work was certainly a valuable one, and proved without doubt that the Brussels International Conference had made a mistake when they made the international agreement that tincture of cantharides should be made 10 percent strength. Instead of using a menstruum of 70 percent alcohol by percolation, Mr. Scoville recommended making a glacial acetic acid menstruum, which seemed to extract the cantharidin and made a 100 percent tincture, by mixing one part of glacial acetic acid with nine parts alcohol. He thought this was a good means of extracting the cantharides. But at the same time it was doubtful whether it could be used, because frequently tincture of cantharides was administered internally, and especially as a veterinary remedy, for horses and cattle. He thought this formula was objectionable because of its high percentage of glacial acetic acid.

Mr. Scoville responded to this that in the official dose of tincture of cantharides the equivalent would be given. For instance, 5 minims tincture cantharides made with acetic menstruum equals 8 drops of ordinary vinegar; so even with a horse or other animal, where a relative amount was given, he did not see how it could be objectionable.

F. T. Gordon, of Philadelphia, wanted to know the effect of cantharides used as a hair tonic, and Mr. Scoville responded humorously that it was "a psychological effect only," inasmuch as there was no cantharidin really in these remedies.

L. F. Kebler, of Washington, D. C., wanted to know of Mr. Scoville on what basis he made the statement that the present pharmacopœial tincture of cantharides was misbranded, in view of the fact that this was recognized as standard in the Federal Food and Drugs Act.? The law declared that if it was prepared in accordance with the pharmacopœial method, it was a proper standard. He remarked that the results here stated brought to mind the possible reason why so many hair-tonics, said to be made with cantharides, had failed. He thought it was worth while to investigate this subject, for the benefit of mankind in general.

DETERMINATION OF SANTONIN IN SANTONICA.

CHARLES E. CASPARI, ST. LOUIS.

During the past winter, the fact was brought to my attention that Santonica was being bought and sold on its santonin assay, in fact, a certain manufacturer of stock remedies was in the market for Santonica with a guaranteed santonin content, claiming that he had always been able to procure such. At that time I knew of no published method for the determination of santonin and after correspondence and conversation with a number of my pharmaceutical-chemical friends, I learned that they knew no more than I did about the determination of santonin. I discovered that a firm of crude drug dealers in Chicago was assaying Santonica, but when I applied to that firm and requested it to give me