2. An attempt to raise plants from rhizomes (Lot III) in the Pharmaceutical Garden gave unsatisfactory results. Transferred to the green house, three of the rhizomes developed plants of full size.

3. Fresh rhizomes contain about 80 per cent of moisture, whereas partially air dried rhizomes yield about 70 per cent. The high moisture content of the first two lots shipped from Manila is indicative of partial decomposition undergone by the rhizomes.

4. Ash determinations reveal an ash content within the standard requirements for ginger.

5. The presence of oxidase in the fresh rhizome is indicated.

6. The limit of pungency of 1, peridermal; 2, cortical; 3, parenchymal, and the 4, entire rhizome was determined. The cortical portion was found to be most pungent. The peridermal portion gave a limit of pungency greater than the parenchymal which indirectly shows that the periderm may affect the yield of the pungent and possibly other constituents.

7. A yield of 0.172 per cent of volatile oil was obtained. This oil has the following properties: $d_{25°}$, 0.8374; $n_{D25°}$ 1.4620; α_D −7.43 (50 mm.); A. V., 2.22; E. V., 32.80 (average); E. V. (after acetylation) 88.31 (average).

8. The presence of aldehyde having been indicated a small amount was isolated yielding a semicarbazone melting at 144–145°.

9. Oleic, linolic and stearic acids were isolated and identified.

10. The presence of melissyl alcohol and possibly other higher alcohols in the unsaponifiable matter was suggested.

11. An exceedingly small quantity of vanillyl alcohol was isolated.

12. A pungent material was isolated but the amount was too small to admit of the identification of a definite chemical compound.

13. About 0.137 per cent of *d*-glucose was isolated. The isolation of this sugar and that of vanillyl alcohol suggests the possible presence of vanillyl glucoside.

14. A hypothesis of the biogenesis of zingerone in ginger rhizome is recorded.

15. Philippine ginger does not differ materially from the other commercial varieties. Considering the current price in the Philippines, *viz.*, $0.05 to 0.20 per kilo of the partially air dried and $0.35, 0.50 and 0.60 per pound of the dried African and Jamaica varieties, respectively, the commercial possibilities are promising.

THE ACTION OF CAFFEINE ON THE POISONED HEART.*[1]

BY CHARLES C. HASKELL.

From a consideration of the action of caffeine on the normal animal, this drug would seem to be nearly an ideal circulatory stimulant. By an effect on the medullary center, caffeine tends to cause vasoconstriction; as a rule, however, the peripheral action, manifested on the vessel wall predominates, so that vascular relaxation of a moderate degree is produced. Along with this action on the vessels,

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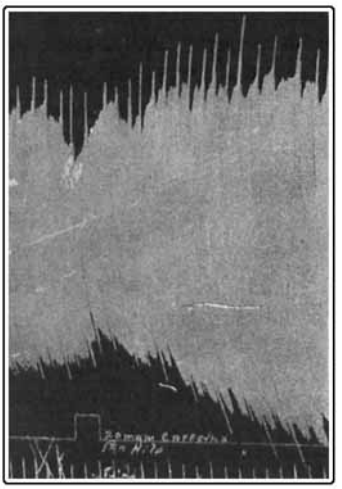
* Scientific Section, A. PH. A., Des Moines meeting, 1925.

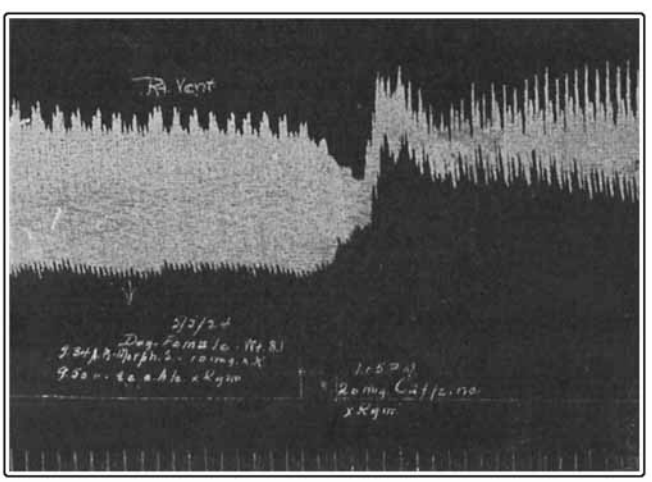
[1] The expense incident to this investigation was met by a grant from the Research Fund of the AMERICAN PHARMACEUTICAL ASSOCIATION.

caffeine distinctly affects the heart; the force and the frequency of the contractions being increased. This cardiac action of caffeine is illustrated in *Tracing No. 1;* which is a record of contractions of the right ventricle of a decerebrate dog. After exposing the heart in the usual manner, the wall of the right ventricle is attached to a Cushny myocardiograph, so arranged that the contractions of the heart cause the recording lever to descend; the down-stroke in the record, therefore, represents cardiac systole. At the signal, represented by the break in the line immediately beneath the cardiac record, 20 mgm. of caffeine per kilogram were injected intravenously. There occurs an immediate increase, both in the extent of relaxation and of contraction; which would lead to an increase in the amount of blood discharged at each systole. The drug produces an increase in cardiac rate also; this not being apparent in the tracing. The cardiac effects, associated with vascular relaxation, would lead to a marked acceleration of the blood flow.



Tracing 1.

From such experiments on normal dogs, it has been assumed that caffeine is a valuable circulatory stimulant. Not only does the drug seem to have a favorable action on the circulation but it is also one of the most potent of the respiratory stimulants. This effect may be elicited either in the normal animal or in one where the respiration is depressed by the administration of some narcotic drug, such as alcohol, morphine, or hydrated chloral.



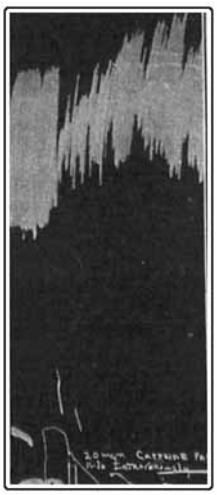
Tracing 2.

Because of the actions of caffeine on both the circulation and the respiration, the drug has been recommended as a physiological antidote for a number of narcotic poisons. Experimental evidence, in the case of alcohol and morphine indicates, however, that caffeine, instead of being of value actually lessens the chances of recovery. This surprising result raises the question as to how caffeine acts in order to increase the toxicity of the poisons that it was supposed to antagonize.

In the case of poisoning by morphine, it has been the common belief that the toxic action is manifested chiefly or entirely on the respiratory center; death being

due to failure of the respiration at a time when the circulation is little affected. The recent experiments of Schmidt, however, along with clinical observations that this author has been able to make, throw much doubt on this supposition and indicate that after large doses of morphine the circulation is comparatively early depressed; the progress of this depression playing a prominent part in bringing about death. Hale has shown that doses of caffeine which normally stimulate the heart of a dog will depress this organ, if given after a toxic dose of acetanilid; Pilcher suggests that caffeine and alcohol act synergistically to depress the heart when large doses are employed. Because of these suggestions and experiments, the attempt has been made to ascertain what the effect of caffeine will be in a variety of conditions where cardiac depression is present.

The simplest method of producing cardiac depression is by the use of some drug of constant composition and known action. In large enough doses, ethyl alcohol, morphine, or hydrated chloral will depress the heart; consequently, in the present investigation, these drugs were first utilized to "poison" the heart, if such a term is permissible in describing their cardiac action. Dogs were used exclusively. After the large doses of alcohol or chloral, no other anesthetic was necessary; where morphine was employed, anesthesia for operation was obtained by the perorbital injection of 10% magnesium chloride.



Tracing 3.

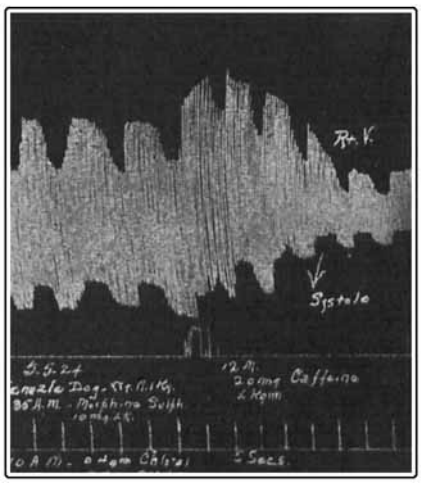
Tracing No. 2 illustrates the cardiac effects of 20 mgm. of caffeine in a dog that had previously been poisoned with ethyl alcohol. At 9:34 A.M., this dog received a subcutaneous injection of 10 mgm. of morphine sulphate per kilogram; 16 minutes later, she was given 8 cc. of ethyl alcohol per kilogram orally; this being about the fatal dose of alcohol. Three hours and a quarter after administration of the alcohol, the dog had been arranged for recording contractions of the right ventricle in the manner previously described; at this time she received an intravenous injection of 20 mgm. of caffeine per kilogram. Instead of the normal stimulant effect of this dose, it is seen that there occurred a very pronounced depression, which persisted for some little time; the heart never regaining the strength manifested before the caffeine injection.

According to Sollmann, Lentharz places the M. F. D. of morphine sulphate for the dog at 400 mgm. per kilogram. *Tracing No. 3* was a record of the injection of 20 mgm. of caffeine per kilogram after the subcutaneous injection of 200 mgm. of morphine sulphate per kilogram; the animal being anesthetized by the intracerabral injection of magnesium chloride and the contractions of the right ventricle recorded as in the other experiments. There occurs the initial stimulation of caffeine; this is soon followed by definite permanent depression.

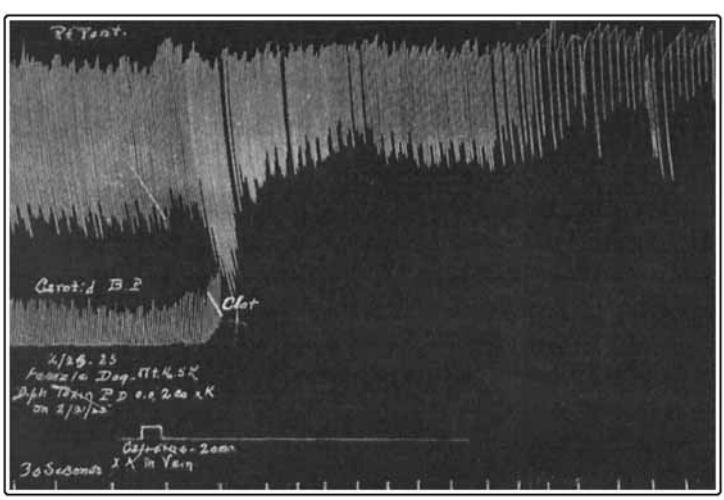
With large doses of hydrated chloral, also, the subsequent injection of caffeine will still further depress the heart. This is illustrated by *Tracing No. 4*. The dog from which this record was obtained received a subcutaneous injection of 10 mgm. of morphine sulphate per kilogram at 9:35 A.M.; at 10:00 A.M., she was given 0.4 gram of hydrated chloral per kilogram orally; 2 hours later, the intravenous in-

jection of a dose of 20 mgm. of caffeine per kilogram lead to a pronounced and permanent depression of the heart.

If caffeine acts deleteriously upon a heart affected by these depressant poisons, it is, at least, possible that an unfavorable action may result from the use of the drug in some forms of bacterial infection. To test this out on animals is somewhat difficult; in doses which are quite comparable to those used clinically, it may be shown that caffeine shortens the life of guinea-pigs that have received a fatal dose of diphtheria toxin. If dogs are injected with fatal doses of diphtheria toxin, and are arranged for recording cardiac contractions as in the previous experiments, injection of caffeine may be followed by depression of the heart. It cannot be stated positively that this depression is due to the caffeine; the animals are usually in such poor shape as a result of the action of the toxin and the trauma of the operation that the heart soon ceases, even in the absence of caffeine medication. In some instances, the cardiac depression and administration of the caffeine are so closely associated as to lend strong support to the assumption that they are related as effect and cause. *Tracing No. 5* is illustrative example of this. It must be stated, however, that if the tracing is obtained at a time when the animal is in fairly good condition, caffeine administration is followed by a definite increase in the extent of the cardiac contractions; in other words, the action of the drug appears to be fully as favorable as in the unpoisoned animals. The question of the effects of caffeine upon animals poisoned by diphtheria toxin and by other bacterial products is now under investigation; at present, positive statements as to the results of caffeine medication in such cases cannot be made.



Tracing 4.



Tracing 5.