ever, from this experiment that cold in the absence of the anterior lobe of the pituitary is not an adequate stimulus to release sufficient hormone from the thyroid gland to maintain a temperature characteristic of a normal rat in the cold.

The fall in temperature, asthenia and failure to grow indicates undoubtedly a multi-glandular disfunction due to hypophyseal insufficency.

*Summary.* 1. Normal young albino rats had a temperature of 36.4°-37.2°C. in the cold, in a warm room 37.7°-38.3°C. 2. Surviving hypophysectomized rats maintained their body temperature for 16 days in a cold room (2°-4.5°C.) at 35°-36.15°C. From the 20th to 34th days the temperature fell approximately 1.3°-2.7°C. 3. The thyroid glands of normal animals in the cold showed activity as previously described by other investigators. Those in the warm room had a lower epithelium and fewer absorption vacuoles. 4. The glands of hypophysectomized rats 38 days in the heat showed atrophy. Similar animals placed in the cold room 34 days showed signs of atrophy in the central part of the gland but absorption of colloid was indicated in the peripheral vesicles by the high epithelium, loss of colloid in the smaller vesicles, and many absorption vacuoles in the peripheral colloid of the larger vesicles. 5. The drop in body temperature of the hypophysectomized rats after 16 days in the cold as well as the histological picture of the thyroid gland indicates that cold in the absence of the anterior lobe of the pituitary is not an adequate stimulus to maintain either body temperature or a histological picture of the thyroid gland comparable to that of a normal rat.

9427

## Effect of Calcium on the Digitalized Heart.*

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The action of calcium upon the mammalian heart has certain similarities to that of digitalis. Slowing of the heart rate, A-V block of varying degree, and ectopic beats have been observed fol-

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lowing administration of either of these substances in adequate amounts, and have given rise to a generally accepted opinion that they both operate, at least in part, through a common mechanism. This has prompted attempts to detect additive or synergistic activities when both were given simultaneously. The studies of Billigheimer[1] and of Lieberman[2] support such a conclusion, and Bower and Mengle[3] explain the sudden death of patients given calcium chloride intravenously while under the influence of digitalis, on the basis of such additive effects.

The experiments upon which these conclusions have been based, however, involve doses of digitalis considerably greater than are usually employed in man, and in some experiments such large quantities were used that it may be questioned whether the entire phenomenon was not in fact due to the administration of lethal doses of digitalis. The death of patients reported by Bower and Mengle can further not be correctly assigned to an additive action of digitalis and calcium as long as the influence of calcium upon the damaged heart requiring digitalis is unknown. It seemed desirable, therefore, to determine the effect of carefully standardized doses of calcium chloride upon the heart of normal, unanesthetized animals, that had received digitalis in therapeutic and sub-lethal amounts.

Twenty-five unanesthetized rabbits weighing from 1.4 to 2.1 kg. were employed. In 12 the amount of calcium required to arrest the heart was first determined in the normal animal, and again several days later after they had received from ½ to ¾ of the calculated lethal dose of digitalis. Two of the remaining 13 animals served as controls of the effect of the calcium alone for 11 rabbits from the same group which were digitalized previous to calcium administration.

Digitalis was given in the form of digifoline, which contained one cat unit in 2.0 cc. Eighteen rabbits were given ½ to ¾ cat units per kg. subcutaneously 18 hours before calcium was administered. Five other rabbits received one-half cat unit per kg. in a similar manner, and were given an additional intravenous injection of ¼ cat unit per kg. one-half hour before the calcium was given.

A 10% solution of calcium chloride was injected intravenously at a rate of 2.0 cc. per minute.

Electrocardiograms were taken from Lead II after injection of

[1] Billigheimer, E., *Klin. Wchnschr.*, 1929, **8**, 724.

[2] Lieberman, A. L., *J. Pharm. and Exp. Therap.*, 1933, **47**, 183.

[3] Bower, J. O., and Mengle, H. A. R., *J. Am. Med. Assn.*, 1936, **106**, 1151.

each successive cubic centimeter of calcium chloride, and at brief intervals after cessation of injections.

The effect of calcium upon the 14 normal unanesthetized rabbits were in every respect identical with those previously reported from these laboratories.[4] In brief, they consisted of (1) typical changes in the ventricular complex of the electrocardiogram; (2) slowing in rate of the heart and delay in A-V conduction, becoming more pronounced with increasing quantities of calcium, (3) auricular fibrillation and ectopic ventricular beats, and finally, with continued injection of calcium, cardiac arrest. The quantities of calcium required to arrest the heart varied from 1 to 5 cc., and did not seem to depend upon variations in size of the animal, within the limits shown in Table I.

TABLE I.

| Exp. No. | Wt., kg. | Amount of 10% calcium chloride in cc. required to arrest heart | | Cat units of digifoline given | Cat units per kg. |
|---|---|---|---|---|---|
| | | A. Normal | B. Digitalized | | |
| 82 | 1.8 | 3.0 | 3.0 | 1.0 | 1/2+ |
| 83 | 2.1 | 3.0 | 3.0 | 1.0 | 1/2— |
| 84 | 1.5 | 3.0 | 3.0 | 1.0 | 2/3 |
| 85 | 1.4 | 2.0 | 2.0 | 0.75 | 1/2 |
| 86 | 1.8 | 3.0 | 3.0 | 1.0 | 1/2+ |
| 87 | 1.8 | 4.0 | 3.0 | 1.0 | 1/2+ |
| 88 | 1.6 | 4.0 | 4.0 | 1.2 | 3/4 |
| 89 | 1.2 | 1.0 | 2.0 | 0.9 | 3/4 |
| 90 | 1.5 | 4.0 | 4.0 | 1.15 | 3/4 |
| 91 | 1.6 | 5.0 | 4.0 | 1.2 | 3/4 |
| 92 | 1.8 | 2.0 | 3.0 | 1.35 | 3/4 |
| 93 | 1.7 | 1.5 | 3.0 | 1.3 | 3/4 |

The effects of injections of calcium upon digitalized hearts were not to be distinguished from those occurring in the normal heart. Similar arrhythmias were produced by the same amounts of calcium in both normal and digitalized hearts, and it required the same total quantity of calcium to arrest the digitalized heart as the normal heart. The total duration of the calcium effect varied in both from 3 to 10 minutes (Fig. 1 Table I.)

Three of the 5 animals which received an additional intravenous injection of digitalis a half hour before the calcium died about 4 hours later.

These experiments indicate that in unanesthetized rabbits, the amount of calcium required to arrest the thoroughly digitalized heart is no less than that necessary in a non-digitalized heart. Further, the arrhythmias produced by calcium in the digitalized

[4] Hoff, H. E., and Nahum, L. H., *J. Pharm. and Exp. Therap.*, 1937, in press.

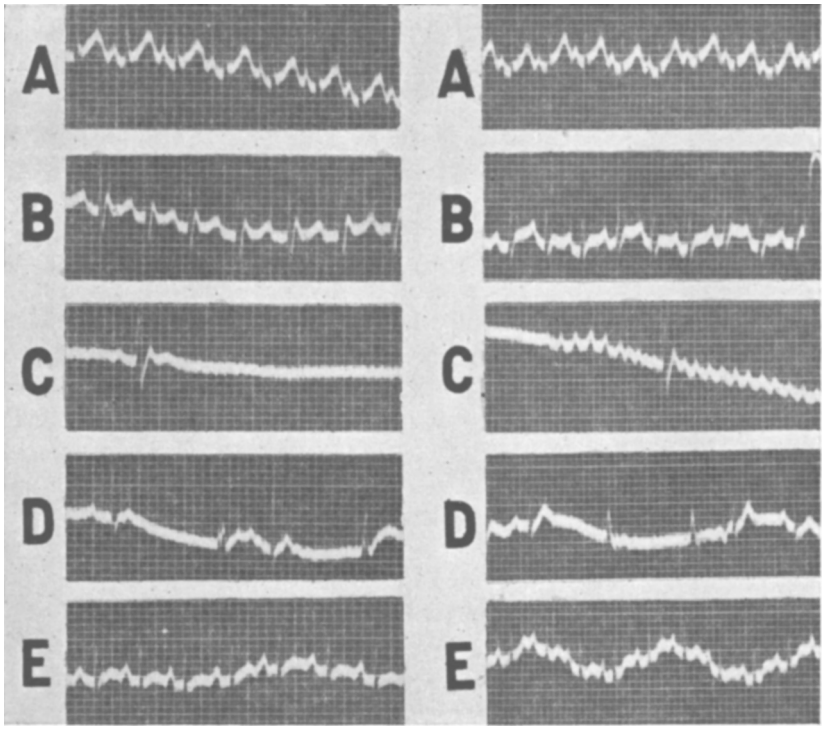


FIG. 1. FIG. 2.

FIG. 1.

Rabbit 82. Before digitalization. 3 cc. 10% $CaCl_2$ intravenously. 2 cc. per min. Lead II. A Control. B. After injection of 2 cc $CaCl_2$. C. Immediately after injection of 3 cc. D and E. Records at 30-second intervals, showing recovery.

FIG. 2.

Rabbit 82, 7 days after Fig. 1. Given ½ cat units digifoline per kg. subcutaneously 18 hours previously. A. Control. B. After 2 cc. $CaCl_2$. C. After 3 cc. $CaCl_2$, showing ventricular arrest with auricular flutter. D and E. Records at 30-second intervals showing recovery.

heart are the same as are produced in the normal heart by the same amount of calcium. Finally the digitalized heart does not exhibit any evidence of an increased tendency to develop ventricular rhythms.

The amounts of digitalis administered in these experiments were greater than the usual doses employed in clinical medicine, and 3 animals receiving the greatest amounts died several hours later. Failure to obtain so-called additive effects in these animals cannot, therefore, be attributed to inadequate amounts of digitalis. Similarly calcium was administered in amounts which actually produced arrest in control experiments on the same animals several days before they were digitalized, so that obviously adequate quantities of calcium were given.

The absence of additive phenomena in these experiments does not permit the assumption that these substances may be administered with impunity. The toxic effects of digitalis are well known, and those of calcium are also being recognized. In digitalis administration the presence of a damaged heart in which sudden circulatory accidents may occur, is usually a complicating factor. Likewise, calcium alone produces a wide range of cardiac arrhythmias, some of which might well prove fatal in the presence of preëxisting cardiac damage. It has been observed that atropinized hearts occasionally develop ventricular fibrillation with calcium, and it is possible that hearts which because of disease show a tendency to ectopic ventricular rhythms might be set into ventricular fibrillation by amounts of calcium which produce only transient disturbances in a normal heart. This may be the mechanism of sudden death reported by Wolffe and Bellet which occurred during administration of calcium to a patient suffering from paroxysmal tachycardia.[5]

*Conclusion.* In the normal unanesthetized rabbit heart the effects of calcium and digitalis are not additive.

## 9428 P

## Total Coproporphyrin I Excretion in Pernicious Anemia.

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The mechanism of the disturbed metabolism of the respiratory pigments in pernicious anemia has been a matter of controversy.[1-4] Theoretically, qualitative and quantitative disturbance may occur at any stage in the construction and destruction of the hemoglobin molecule, but it is not clear whether the increased bile-pigment production and excretion is consequent to a quantitatively increased destruction of hemoglobin similar to that of hemolytic jaundice, or whether it is due to a partial or total pathologic metabolism of the precursors of hemoglobin.

[5] Wolffe, J. B., and Bellet, S., *Ann. Int. Med.*, 1930-31, **4**, 794.

[1] Addis, T., *Arch. Int. Med.*, 1915, **15**, 413.

[2] Eppinger, H., *Die hepatolienalen Erkrankungen*, Berlin, 1920.

[3] Whipple, G. H., *Arch. Int. Med.*, 1922, **29**, 711.

[4] Rous, P., *Phys. Rev.*, 1923, **3**, 75.