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Effect of Changes of Blood pH on Reaction of Heart to Cocaine.

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Changes in the concentration of hydrogen ions of the blood previously reported[1] produced well-marked effects in the reaction of the heart to caffeine. Other drugs under these conditions have since been studied, among them cocaine. Observations were made on the heart *in situ*, after removal of the anterior portion of the chest wall. The experiments were done on cats anesthetized with urethane, under artificial respiration. The contractions were recorded on smoked paper by means of levers attached with fine threads to the right auricle and right ventricle.[1]

The results obtained were in several respects much more striking than in the experiments with caffeine or the other drugs. The resistance of the heart to cocaine was greatly increased by the intravenous injection of alkali, and very much diminished by acid. Small doses of the alkaloid administered after the intravenous injection of weak acid caused pronounced depression of the heart. While alkali did not necessarily nor always prevent the action of cocaine, its injurious effect was greatly decreased and often entirely suppressed.

Experiment No. 1. Sodium carbonate in a concentration of 2.5 per cent was injected intravenously in divided doses, into a cat weighing 2.5 kilos, until a total of 0.9 gm. was given. The subsequent injection of 1 cc. of 1 per cent cocaine hydrochloride, or 4 mg. per kilo, failed to produce any noticeable change in the action of the heart. The same amount of the alkaloid, administered 33 minutes after 0.75 gm. sodium acid phosphate, given in a dilution of 2.5 per cent, decreased the frequency of the heart about 60 per cent, and greatly weakened the force of the contractions.

Experiment No. 2. A dose of 3 mg. cocaine hydrochloride, injected one minute after administration of 3 cc. of 1 per cent HCl acid, reduced the strength of the contractions 60 to 70 per cent and considerably decreased their frequency. The same amount of cocaine, given after the administration of 1 gm. Na_2CO_3, in a 2.5 per cent dilution, failed to produce the effect which was previously observed after acid. Four more doses of cocaine, in the same amount as before, produced no noticeable change in heart action.

The comparative toxicity of cocaine when the C_H of the blood is normal, and when the pH is increased by alkali, was shown in several instances, the following being a typical case.

The first dose of cocaine hydrochloride, 4 mg. per kilo, decreased the strength of the contractions in both auricles and ventricles, the effect being greater in the former than in the latter. Each pair of contractions of the auricles was also unequal. While the frequency was considerably reduced in both, the slowing was much greater in the ventricles than in the auricles. The rhythm was 5:2. A complete recovery of the ventricles occurred within two minutes but only partial improvement was observed at the end of this time in the auricles. Blood pressure in this, as in other experiments under similar conditions, was greatly decreased and followed the auricles. The same amount of cocaine, after the injection of 20 cc. 2.5 per cent Na_2CO_3 or 0.5 gm. per kilo, caused only a slight decrease of

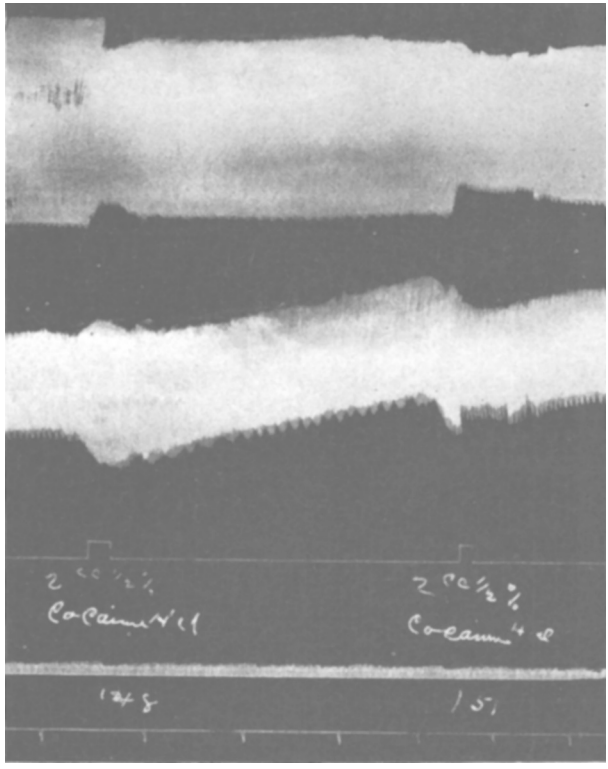

FIG. 1.

Vagi cut. First and second injection cocaine HCl. Dose 5 mg. per kilo. Thirty cc. 2½ per cent Na_2CO_3 administered before cocaine. Upper tracing auricle, lower ventricle.

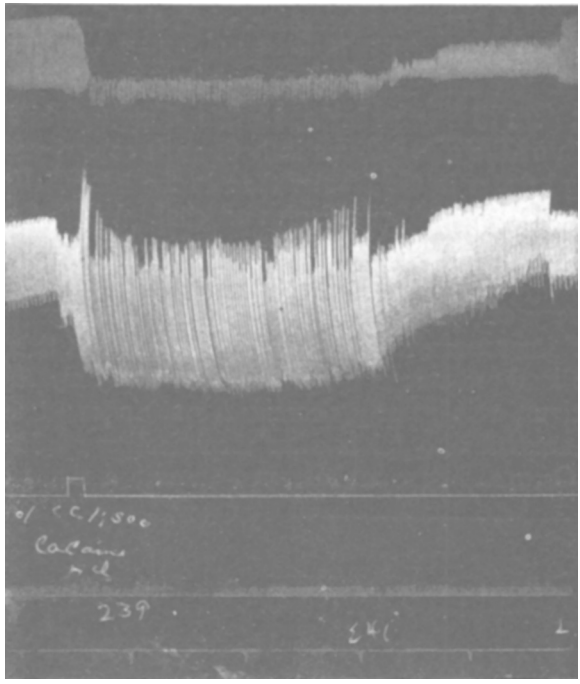

FIG. 2.

Vagi cut. Third injection of cocaine HCl. Dose 1 mg. per kilo. Total cocaine previously injected 3 mg. per kilo in 2 injections. Twenty-four cc. 1 per cent HCl administered before cocaine. Upper tracing auricle, lower ventricle.

the force of the auricular beats, while that of the ventricles was somewhat increased. The rate was not affected in either case. The fall of blood pressure amounted to a few mg. only. In this connection attention may be called to another experiment, in which the same amount of cocaine per kilo, administered after 8 cc. sodium acid phosphate, stopped the heart in about 50 seconds. The effect of changes in the C_H of the blood on the action of cocaine was demonstrated even more satisfactorily when larger amounts of acid and alkali were given at frequent intervals. After increased amounts of acid, the minimum toxic dose of cocaine was reduced to about half. One mg. per kilo was sufficient to cause depression of the heart, a single dose of 4.7 mg. per kilo caused paralysis. When the amount of acid was increased, cardiac paralysis was produced by a dose of 3.5 mg. cocaine per kilo.

The protection against cocaine, conferred by alkali received further corroboration in two experiments in which the pH of the blood was maintained at a high level by the frequent injections of Na_2CO_3.

The surely toxic or even fatal dose of cocaine could thus be given repeatedly without causing any significant effects on the heart. In one experiment doses of 5 mg. per kilo were injected until 85 mg. per kilo were administered. The effect of the drug became pronounced only after the fourth injection. Furthermore, when the last dose was given, the auricles, though depressed, were still contracting, while the ventricular beats were quite vigorous. The resistance to cocaine was still greater in another cat. The total amount of the drug tolerated was 105 mg. per kilo, which was administered in divided doses in one hour and 41 minutes. Heart action was fairly good even after the last dose, while distinct evidence of toxicity was first obtained only after eight doses were given, or a total of 40 mg. per kilo.

[1] Salant, William, and Nadler, J. Ernest, *Am. J. Physiol.*, 1926, lxxviii 308.

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Feeding Experiments With Plants at Different Stages of Development. III: Synthesis of Vitamin in Plants.

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In a previous publication[1] we have pointed out that in order to determine whether there is a synthesis of vitamin during the germination and greening of corn, it is not enough to compare *equal weights of the dried material* (ungerminated, germinated and green), as other workers have done before us, but to compare *an equal number of seeds.* This we have now done, in a continuation of our experiments. Fifteen rats were kept on a synthetic diet, deficient in vitamin A, until they became stationary in weight. To the diet of the first five (group A) was now added the equivalent of six seeds of ungerminated corn per rat per day; to the diet of the second group of five (group B) was added the equivalent of six seeds of germinated corn per rat per day; to the diet of the third five (group C) was added the equivalent of six seeds of green seedlings per rat per day. Within 81 days after the corn feeding had begun, all the rats in groups A and B had contracted xerophthalmia, and 8 had died while all the rats in group C were in excellent condition and were continuing to gain in weight.