

that the appetite mechanism had been "reconditioned", *i. e.*, the dog, "satisfied" with the jejunal method of feeding, had lost the desire to eat by mouth, since the animal was doing well and a desire to take food by mouth could not be stimulated by administration of the various vitamins in large quantities. This explanation, however, was obviously unsatisfactory. Since we were primarily interested in the study of gastric secretion and motility of this animal, we desired to ascertain the effect of sectioning the vagi just above the diaphragm on these processes in this animal preparation. To our surprise, as soon as the animal recovered from the anesthetic, he bolted a pan of food belonging to another dog, and the following day manifested coprophagy. The excessive appetite of the dog has persisted unabated for the past 5 months and might be compared to that of a normal young dog starved for 48 hours. The only interpretation of this sudden return of appetite that has occurred to us is that section of the vagi severed the pathway of the impulses responsible for the production of anorexia. We believe the impulses responsible for the anorexia arose as the result of the disturbed gastro-intestinal state or irritation of the intestine and possibly the colon by the pabulum or method used in feeding. We hope to amplify and extend this observation by other experiments some time in the future.

This observation indicates that the anorexia associated with gastro-intestinal disturbances, and possibly vitamin B deficiency, is due chiefly to afferent sensations mediated by the vagi.

## 6129

### Effect of Reticulo-Endothelial Blockade on Uric Acid of Blood.

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Folin and his associates<sup>1</sup> demonstrated that uric acid injected intravenously into dogs in standard amounts disappears from the blood in a characteristic manner, *i. e.*, 70% is destroyed within the first 10 minutes and in 2 hours is down to 2 mg. per 100 cc. of blood. They obtained the same results in Eck fistula dogs and concluded that the process occurs within the blood stream, possibly through

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<sup>1</sup> Folin, Berglund and Derrick, *J. Biol. Chem.*, 1924, **40**, 361.

some "essential factor" elaborated in the liver. Bollman, Mann and Magath<sup>2</sup> have found that extirpation of the liver in dogs produces an increase in the uric acid of the blood, tissues and urine. When uric acid was injected intravenously into hepatectomized dogs, disappearance was considerably slowed and the uric acid could almost quantitatively be recovered from the urine. It was their opinion that destruction of uric acid in the dog is dependent on the liver.

During studies on the function of the reticulo-endothelial system we observed that when 8% india ink in normal saline was continuously injected intravenously into normal dogs, there was an appreciable increase in the uric acid of the blood. For example, after 6 hours, when 600 cc. of ink had been injected into a 14 kilo animal, the blood uric acid level was 3 mg. per 100 cc. This could be due to an increased production of uric acid or to a diminished destruction. Goldzieher and Sherman<sup>3</sup> observed an increase in urea following ink blockade in mice, rabbits and dogs. They interpreted this as due to an increased activity of the reticulo-endothelial system. We therefore studied the rate of disappearance of intravenously injected uric acid in animals which had been previously blocked.

The uric acid was injected as in the procedure of Folin, Berglund and Derrick, 100 mg. per kilo body weight, *viz.*, a 2% solution with 0.5% lithium carbonate. The blood uric acid was determined by Folin's indirect method.<sup>4</sup>

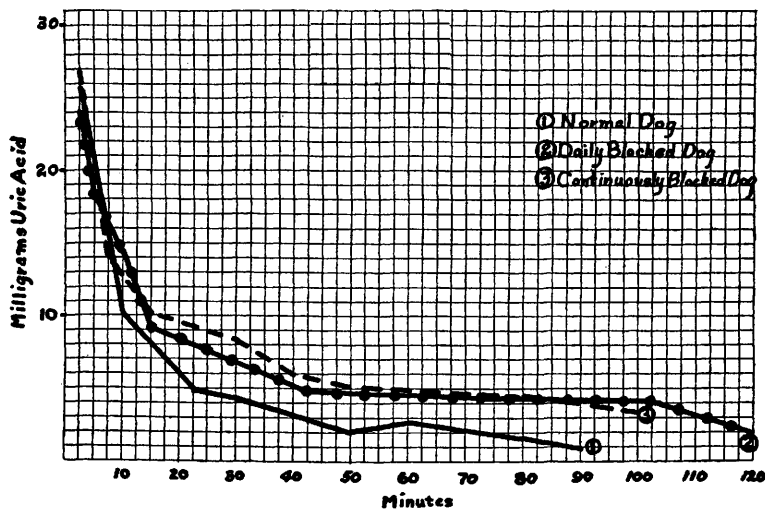


FIG. 1.

<sup>2</sup> Bollman, Mann and Magath, *Am. J. Phys.*, 1925, **72**, 629.

<sup>3</sup> Goldzieher and Sherman, *Arch. Path.* 1931, **12**, 180.

<sup>4</sup> Folin, D., *J. Biol. Chem.*, 1922, **54**, 153.

The chart illustrates the results obtained in typical normal and blocked animals. Curve 1 is that of a normal 9 kilo dog. Two and one-half minutes after the uric acid injection the blood uric acid level was 24 mg. per 100 cc. Within the first 10 minutes it had fallen to 10 mg. and in 90 minutes to 1 mg. This illustrates the normal curve of destruction mentioned previously.<sup>1</sup> Curve 2 is that of an 8 kilo dog that received 4 daily injections of 50 cc. of india ink into a vein of the foreleg. The last ink injection was given the day before the uric acid injection. The uric acid level here parallels that of the normal dog. Curve 3 represents the result obtained in a 14 kilo dog that had just before received a continuous intravenous injection of 400 cc. of ink over a period of 2 hours. This curve also is parallel with that of the normal animals. The slightly higher values at the end of the experiment in the blocked animals is due to the block itself. The control uric acid values after blockade were 0.8 mg. in the daily injected animal and 1.1 mg. in the other.

Saxl and Donath<sup>5</sup> studied the effect of the intravenous administration of electrocollargol on the subsequent injection of water, dyes (phenoltetrachlorophthalein), drugs (adrenalin), and antiseptics (argochrome). Each of these substances was found to remain longer in the circulation than in the control cases without electrocollargol. These findings they attribute to functional paralysis of the reticulo-endothelial system, which normally appears to remove these substances with great rapidity. Whether the reticulo-endothelial cells are stimulated to activity or depressed is, however, not a simple matter, depending on many factors, Jaffe<sup>6</sup> believes.

We believe that by injecting large amounts of material over short lengths of time we obtained good blockade. At autopsy, on gross examination, the liver, spleen, lymph nodes, omentum, peritoneum, adrenals and lungs were all black. The bone marrow seemed resistant. Microscopically the hepatic and splenic endothelial cells were well blocked.

We conclude that blockade of the liver as performed by us does not affect the destruction of uric acid as does extirpation of the liver. The increase of the uric acid in the blood during and immediately after blockade is not apparently due to a defect in uricolysis since intravenously injected uric acid disappears from the blood at a normal rate. The blockade of the reticulo-endothelial system may stimulate the liver cells themselves to an increased production of

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<sup>5</sup> Saxl, P., and Donath, F., *Wien. Klin. Wochen.*, 1925, **38**, 66.

<sup>6</sup> Jaffe, R. H., *Physiol. Rev.*, 1931, **11**, 277.

uric acid. It seems, therefore, that the reticulo-endothelial system is not the seat of uric acid destruction in the dog.

## 6130

### Histamine and Acetyl Choline Contraction-Ratio in the Surviving Intestinal Strip.

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Knowledge of the significance of histamine in biological processes would be materially increased if assays of higher specificity and sensitivity were available. In the absence of such tests it is necessary to look for an increased number of reactions both chemical as well as biological, indicative of histamine. Such reactions might aid by their variety rather than by their specificity.

Experiments with various smooth muscle contractants, forms of shock, etc., now in progress in this laboratory made it advisable to compare the reactivity of chicken and mouse intestine to histamine and acetyl choline. This ratio is well known to be 2:1 in the guinea pig.<sup>1</sup> This figure agrees on the average with our own observations. However, we have not infrequently dealt with individual variations such as guinea pig intestinal strips with a histamine-acetyl choline ratio of 5:1 or 1:1. It should be remembered that the iliac end of the guinea pig intestine is generally conceded to be more reactive than the duodenal.

The action of histamine and acetyl choline upon the mouse and chicken intestine does not appear to have been studied previously. The reactivity of the mouse uterus to histamine has been shown to vary with the concentration.<sup>2, 3, 4</sup> Low concentrations (1:1,170,000) stimulate contraction, while high ones (1:1,250) inhibit. Generally speaking, the use of intestinal strips in preference to other smooth muscle seems advantageous in some instances, because a number of strips of the same intestine can be used and checks can be run conveniently.

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<sup>1</sup> Guggenheim, M., *Die Biogenen Amine*, Springer, Berlin, 1924, 103, 219.

<sup>2</sup> Cow, D., *J. Pharm. Exp. Therap.*, 1920, **14**, 275.

<sup>3</sup> Abel, J. J., and Macht, D. I., *J. Pharm. Exp. Therap.*, 1920, **14**, 279.

<sup>4</sup> Adler, L., *Arch. f. Exp. Path. u. Pharm.*, 1918, **83**, 248.