later, the rats on the lysine-deficient ration had shown a slight weight loss, while those receiving l-lysine were gaining weight. The largest weight losses were recorded by the rats receiving the synthetic racemic compound (Table 1). One of the rats in this group died on the 11th day, and the experiment was discontinued. The animals were sacrificed and the kidneys were dissected and weighed. Kidneys of rats receiving the α-amino-ε-hydroxy caproic acid were slightly heavier, but histological examination[1] failed to reveal any differences between groups.

TABLE 1

WEIGHT CHANGES (GRAMS) IN RATS RECEIVING α-AMINO-ε-HYDROXY CAPROIC ACID AND IN CONTROL GROUPS

	Zt	Ztl	Ztl-OH
No. of rats per group	4	6	6
Wt. changes during last 10 days of preliminary period (24 days)	−4	−3	−2
Range	−3, −6	−1, −4	−2, −3
Wt. changes during experimental period (11 days)	−2	+5	−8
Range	−1, −3	+2, +9	−6, −10

It is concluded that α-amino-ε-hydroxy caproic acid cannot replace lysine in the diet and that it may have some toxic effect.

[1] Kindly done by C. Auger, of the Pathology Department.

Mechanism of Renin Tachyphylaxis—Restoration of Responsiveness by Tetraethyl Ammonium Ion

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The pressor responses to repeated intravenous injections of renin in intact animals diminish progressively. This phenomenon is known as tachyphylaxis. The action of renin is dependent on the presence of plasma renin-substrate, the exhaustion of which might account for tachyphylaxis. But administration of large amounts of α_2 globulin, the fraction of plasma protein containing substrate, does restore the response in tachyphylactic animals (*6*).

Renin through its effector agent, angiotonin, acts directly on peripheral blood vessels. Nevertheless, sectioning of the brain at certain levels causes the pressor response to be reversed to depressor (*3*), a phenomenon which has been further localized by Euler and Sjöstrand (*2*). Widespread direct injury to the central nervous system also temporarily abolishes the pressor response to angiotonin (*4*), as does severe shock produced by a variety of means (*5*). Thus, the nervous system influences vascular responsiveness to angiotonin.

One of the difficulties of accepting the renal-vasopressor system as a cause of renal hypertension has been the phenomenon of renin tachyphylaxis.

Acheson and Pereira have shown that injection of tetraethyl ammonium chloride (*1*) blocks sympathetic ganglia. We have found that repeated (1–4 times) intravenous injections of 100 mg. into normal dogs anesthetized with pentobarbital completely overcame tachyphylaxis induced by repeated injection of renin. The response to angiotonin itself was also augmented. Even more striking was the manyfold increase in the response to adrenalin at a time when the response to nicotine was wholly abolished. The responses to histamine, mecholyl, and barium chloride were usually also augmented. Without anesthesia the same phenomena occur, but to a lesser degree. Adrenalectomy or nephrectomy in brief experiments did not alter these responses.

If the caudal spinal cord was destroyed after section at C_8 and the animal tested the next day after complete recovery from anesthesia, the responses to renin were augmented. Further, 8 injections of renin did not lead to appreciable tachyphylaxis. Administration of tetraethyl ammonium ion now did not further augment the already large response.

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Absence of a Macrocytic Anemia in Dogs Fed Choline or Choline Plus Fat

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Several groups of investigators in this university have been interested in choline since this substance was established as a dietary factor by the work of Best and Huntsman (*1*). While no detailed study of the effect of choline on the blood picture had been made here, a number of hemoglobin and red cell estimations in dogs fed large amounts of choline had failed to reveal any signs of anemia. A series of papers by Davis (*2*), in which it was reported that the administration of choline or choline plus fat produced in dogs a macrocytic anemia, came, therefore, as a surprise. An additional stimulus to the investigation of Davis' claims was provided by the fact that choline or its precursor, methionine, is now being used in many clinics in an effort to determine its role in the prevention of fat deposition or cirrhotic changes in the liver of patients.

A series of four normal male dogs was carefully observed by one of us (M. F. C.), and after the somewhat extended period necessary to obtain satisfactorily constant basal values for the red cell counts and the hemoglobin levels, choline or choline plus fat was added to the stock diet of the animals, which consisted of Canada Packers Frozen Dog Chum, sucrose, and bone meal. Dried yeast and cod-liver oil were provided twice each week and tomato juice once a week. All four dogs were on this diet for at least three months before the feeding of choline or choline plus fat. During this period they all gained weight, and their coats improved in texture.

For two of the dogs 10 mg. of choline/kg. of body weight and 60 grams of lard were added to the stock diet. The daily ration was fed at one meal, and the choline was incorporated in the center of a small portion of meat and offered to the dogs before the balance of the meal was given. In this way it was made certain that the dogs ingested all of the choline offered. Both animals ate their fatty meals well for the first week and then refused to eat all of the food. The fat and choline were discontinued after the eighth day. Davis reports an anemia on the second and third day under these dietary conditions.

For the second pair of dogs the daily ration of the stock diet was divided into three equal feedings, and with each feeding 10 mg. of choline/kg. of body weight was administered in the same manner as previously described.

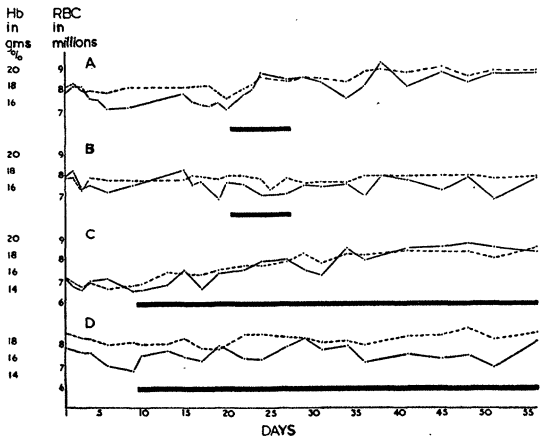

FIG. 1. Red cell counts and hemoglobin levels as influenced by choline or choline plus fat feedings. Solid lines represent red cell counts; broken lines, hemoglobin level; and solid black bars, the periods of choline or choline plus fat feeding. A and B were fed choline plus fat; C and D were fed choline three times a day.

The findings are illustrated in Fig. 1. It will be observed that we failed completely to confirm Davis' finding that a macrocytic anemia is produced in dogs when choline or choline plus fat is administered. In two dogs, A and C, there was an increase in the hemoglobin level and in the erythrocyte number. We do not ascribe this increase to the choline or choline plus fat, but strongly suspect that the rise is produced by a continued administration to the animals of a diet more adequate in the various hemopoietic factors than that which they had previously received. If Davis' results are confirmed under dietary conditions differing from those followed in our laboratory, the nature of the stock diet should be closely examined to determine the part it plays in the production of the findings. As estimated in this laboratory, Purina Dog Chow Checkers, of which Davis' stock diet is composed, contains 1.5 mg. choline/gram, and the Canada Packers Frozen Dog Chum contains 1.04 mg./gram. Our dogs received in the stock diet approximately 429 mg. of choline daily. We have found that they will not eat more than 180 grams of the Purina Chow daily. Consequently, they may have received about 160 mg. more choline/day in their stock diets than Davis' dogs.

In another group of four normal male dogs 10 mg. of choline/kg. of body weight was fed in dilute solution by stomach tube once a day, before the stock diet supplemented with 60 grams of lard was offered. During the eight days of the experiment there was no evidence of a macrocytic anemia.

An analysis of nurses' diets used in one of the large hospitals in Toronto showed that up to 500 mg. of choline may be available in a normal diet each day. This amount is presumably supplemented by choline arising from its precursor, methionine, which is supplied by the protein of the diet. There is, of course, no indication that normal diets, most of which provide appreciable amounts of choline, play any role in the production of an anemia.

Our results permit us to state quite definitely that, under the conditions of our experiment, the addition to stock diets of the amounts of choline or choline plus fat recommended by Davis does not produce in dogs any trace of a macrocytic anemia. It is apparent, therefore, that the acceptance of Davis' general conclusions cannot be justified and that further work is necessary to determine the explanation of his findings.

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