as with *dl*-methionine alone, arginine having an antagonistic effect to methionine.

Summary. When excess *l*-arginine is added to casein, the nitrogen balance index is reduced slightly. An excess of *dl*-methionine on the other hand reduces the nitrogen balance index markedly and the excretion of creatinine is increased. When both *l*-arginine and *dl*-methionine are added to casein the nitrogen balance index is not reduced as much as it is in the presence of casein plus methionine, but the creatinine excretion is increased. The animals receiving 12% casein and pair-fed with the group receiving 12% casein plus 4.8% *dl*-methionine lose weight slightly over a 20-day period. Those receiving 12% casein plus 4.8% methionine lose weight markedly, a loss which is overcome in part by adding 1.7% *l*-arginine to the methionine diet. The decrease in weight in the presence of a large excess of methionine is associated with a loss in body nitrogen and fat. The addition of *dl*-methionine increases the amount of nitrogen in the liver and reduces the amount of fat. Feeding *dl*-methionine plus casein increases the size of the kidney, an effect which is antagonized by *l*-arginine.

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Influence of Protein Reserves on Nephrectomized and Renal Artery Ligated Dogs.*

E. MYLON AND P. GOLDSTEIN.† (Introduced by M. C. Winternitz)

From the Laboratory of Pathology, Yale University School of Medicine, New Haven, Conn.

The contrasting symptomatology, speed of elevation of blood nonprotein nitrogen and survival period of animals, after bilateral ligation of the renal arteries and removal of the kidneys has been reported.[1]

Ligation of the arteries results in earlier and more severe evidence of toxicity, more rapid rise in blood nonprotein nitrogen and is more rapidly fatal. It is further of interest that the intravenous injection of renal extracts after bilateral nephrectomy tends to reproduce the effects of ligation of the arteries. In these circumstances toxicity and elevation of blood nonprotein nitrogen develop earlier and the duration of life is materially shortened. This evidence of association of accelerated nitrogen catabolism and toxicity is reinforced by the results of protein feeding to animals after removal of the kidneys[2] and also after substantial reduction of kidney function.[2,3] It points to a probable pathological nitrogen metabolism with production of toxic intermediates that represent some part of the augmented blood nonprotein nitrogen. Two factors seem to be concerned in the more rapid manifestations of toxicity and the rise in blood nonprotein nitrogen. They involve on the one hand some non-excretory renal function not yet known and on the other availability of tissue protein. The latter can be reasonably controlled by diet; this hypothesis is the basis of the experiments that follow.

Materials and Methods. Two groups of animals were given protein poor and protein rich diets respectively for protracted periods prior to the ligation of the renal arteries or the removal of the kidneys.

The daily ration of the protein poor diet per kilogram dog consisted of: Farina 15.0 g, Karo 2.5 g, Cod Liver Oil 0.4 g, Fresh yeast

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† James Hudson Brown Memorial Junior Fellow.

1 Winternitz, M. C., Mylon, E., Waters, L. L., and Katzenstein, R., *Yale J. Biol. and Med.*, 1940, **12**, 623.

2 Mylon, E., Smith, E. R., and Goldstein, P., *Am. J. Physiol.*, 1948, **153**, 55.

3 Addis, T., *Tr. Assn. Am. Phys.*, 1940, **55**, 223.

cake 0.2 g, Salt mixture 0.3 g. The diet corresponds to about 80 cal. per kilogram dog.

The composition of the salt mixture follows:

	g
Potassium chloride	30
Sodium chloride	40
Magnesium chloride	20
Di-sodium phosphate	100
Monocalcium phosphate	100
Calcium lactate	40
Ferric ammonium citrate	10

Nine animals included in this group were maintained on this diet for from 50-60 days. Then the kidneys were removed in 3 and the renal arteries ligated in the remaining 6.

Another group of 13 dogs were allowed 75 g each day of freshly ground horse meat per kilo—approximately the same caloric value as that of the protein poor diet. After 14 days of such feeding the renal arteries of seven of these animals were ligated and the kidneys removed in the other 6.

All operative procedures were facilitated with nembutal anesthesia, 30 mg per kilo. The exposures of the kidneys were by bilateral flank incisions and care was taken in ligation of the arteries to avoid inclusion of vein or ureter. The nonprotein nitrogen of the blood was determined with the half-micro Kjeldahl method.

Results and Discussion. As can be seen from Table I and Fig. 1 and 2, the height of the nitrogen catabolism as well as the degree of toxic symptoms following either operative procedure, are greatly influenced by the diet fed prior to the operations. Table I demonstrates both elevated nitrogen catabolism and reduction of the survival period of meat fed animals (Group 1 and Group 3) as compared to the 2 groups of dogs conditioned by the protein poor diet (Group 2 and 4).

In addition, the figures obtained for the animals of Group 1 and 3 indicate anew the contrasting symptomatology between bilateral ligation of renal arteries and removal of the kidneys. It can be seen that the former procedure results in a more rapid rise in blood

TABLE I.

Average N.P.N.'s (in mg %) Following Bilateral Renal Artery Ligation.

Group	Diet	No. of dogs	Days 1	2	3	4	5	6	7	8	9
1	meat	7	45.5	115	211	293*					
2	carbohydrate	6	27	61.9	92.1	130.9	181.9	209.9†	283‡	363‡	395‡

* Avg of 3 survivors.
† " " 4 "
‡ Values of the 6th dog.

Average N.P.N.'s (in mg%) Following Bilateral Nephrectomy.

Group	Diet	No. of dogs	Days 1	2	3	4	5	6	7	8	9	10	11	12
3	meat	6	47.9	91.9	150.2	217.3	278	307*	310†					
4	carbohydrate	3	30	56.8	87.1	120.6	163	190.3	234.7	281.6‡	220§	208	252	327

* Avg of 3 survivors.
† " " 2 "
‡ Avg of 2 survivors.
§ Values of the third dog.

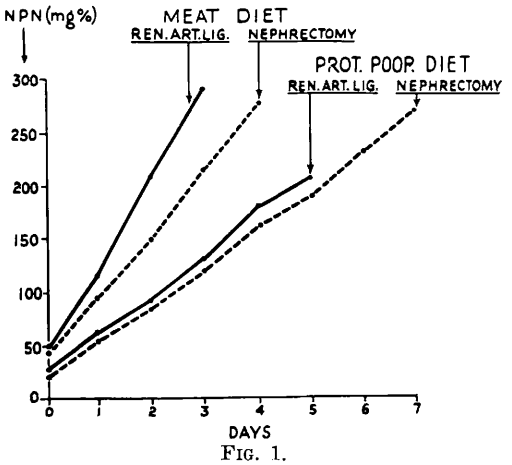

FIG. 1.

Nonprotein nitrogen of the blood of renal artery ligated and nephrectomized dogs pre-fed either a meat or a carbohydrate diet.

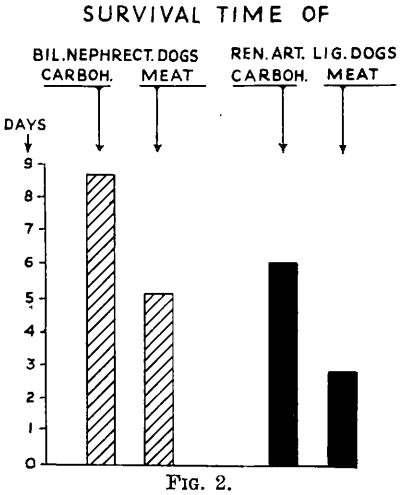

FIG. 2.

Survival time of renal artery ligated and nephrectomized dogs pre-fed either a meat or a carbohydrate diet.

nonprotein nitrogen‡ and in a significant reduction in the survival time. While obviously these effects are caused by substances liberated from the anoxemic kidney the mechanism of their action is not yet known. One lead may be available in the fact that these derivatives were only slightly active in animals of group 2, *i.e.* in those greatly deprived of their protein reserves. This observation suggests that renal substances, in themselves not very toxic, stimulate the intracellular nitrogen catabolism and that this stimulation is associated with the formation of toxic protein intermediates.

Summary and Conclusions. Renal artery ligation as well as nephrectomy was carried out in 2 groups of dogs, one maintained prior to the operation on a carbohydrate, the other on a protein diet. Following either operative procedure the nitrogen catabolism was more rapid, the toxic symptoms more severe, and the survival time shorter in protein pre-fed animals as compared with the carbohydrate group. In the former the contrasting results of renal artery ligation and nephrectomy are marked. It may be concluded both that substances derived from the ischemic kidney stimulate catabolism of protein reserves and that the toxic symptoms following renal artery ligation are associated with accelerated nitrogen catabolism.

‡ The differences in the nonprotein nitrogen between animals of Groups 1 and 3 for 48 hours and 72 hours after the operative procedures are highly significant. The p values for these two time periods are <0.01.