antibodies in amounts far in excess of that produced by intact animals. This is evident not only by definite reactions in higher dilution but by the more massive precipitate in low dilutions. The prevention of the lymphoid hypertrophy by administration of adrenal cortical hormones does not reduce the amount of antibodies in the sera. This is probably due to the disruptive action of the hormone on the lymphocyte with a more rapid release of the immune globulin than would normally take place.

16073

Prevention of Experimental Arteritis in Dogs by Vitamin E.*

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In a recent publication[1] data were presented to show that the combination of a specified high fat diet and experimentally induced renal insufficiency in dogs is regularly followed by predictable lesions in the arterial system. The lesions have been found in elastic arteries, in muscular arteries, and in arterioles in practically every organ and tissue of the body with the exception of the kidney and liver. Essentially the lesion is an acute necrotizing arteritis whose closest human counterparts are periarteritis nodosa and rheumatic arteritis.

When it was found that the dietary factor was lipid in nature, the question naturally arose as to the effect of vitamin E—the so-called "fat anti-oxidant" vitamin—on these experimental arterial lesions.

Methods. The methods have been detailed in previous publications.[1] Briefly these consist of feeding selected table scrap to which is added each day 3.0 cc/kg of a commercial grade of cod liver oil. After this diet has been consumed for 8 weeks or longer, the kidneys are severely damaged by any one of several methods (heavy metal injury, bilateral nephrectomy, *Leptospira Canicola* — usually uranium nitrate, 10.0 mg/kg injected subcutaneously) and the arterial system is examined both grossly and histologically when the dogs die or are sacrificed days to weeks later.

In the first series of 4 dogs vitamin E—one capsule containing 20 mg of mixed natural tocopherols—was given by mouth between 8 and 10 o'clock in the morning and the dogs were fed the diet of table scrap and cod liver oil around 4 o'clock in the afternoon. Following kidney damage the dogs usually quit eating on the fourth to seventh day. Administration of vitamin E capsules was continued until the dog died.

In the second series of 4 dogs vitamin E (in the same form as above) was not started until *after* the kidneys were damaged. The dogs were fed table scrap and cod liver oil for 8 weeks or longer, then a lethal dose of uranium nitrate was injected and a single capsule of 20 mg mixed natural tocopherols per day by mouth was started 0, 24, 48, and 72 hours after the heavy metal injury. Vitamin E therapy was continued until the dogs died in uremia.

In these 8 dogs the single capsule of 20 mg of mixed natural tocopherols amounted to 2.5 to 4.0 mg/kg/day.

Experimental Observations. The significant data on the 4 dogs fed vitamin E concomitantly with the specified high fat diet for 8 weeks or longer before kidney damage was

* This work was aided by a grant from The John and Mary R. Markle Foundation. The mixed natural tocopherols and helpful suggestions were furnished by Distillation Products, Inc.

1 Holman, R. L., and Swanton, M. C., PROC. SOC. EXP. BIOL. AND MED., 1946, **63**, 87.

TABLE I.
Effect of Vitamin E on Incidence of "Experimental" Arterial Lesions.

Group	Dog No.	Body wt at time of renal injury, kg	Period on high fat diet before renal injury, weeks	Day following renal injury on which Vit. E was started	Survival interval following renal injury, days	Arterial* lesions
A Vit. E—fed concomitantly with high fat diet	45-84	5.8	8	—56	10	—
	45-85	5.9	9	—63	11	—
	45-86	7.5	10	—70	12	—
	45-87	9.4	12	—84	13	—
B Vit. E—Started *after* renal injury.	46-8	19.0	14	0	10	—
	46-9	13.7	14	1	8	—
	46-13	13.0	14	2	30	—
	46-12	13.7	14	3	20	+

* The grading of the lesions here is the same as that employed in previous publications, namely,
+++ = gross lesion greater than 1 cm in maximum dimension;
++ = gross lesion less than 1 cm in maximum dimension;
+ = lesion discovered in routine histological section;
— = negative.

induced are given in Table I, section A; and section B of this table gives the same data for the 4 dogs in which vitamin E was started 0, 1, 2, and 3 days *after* renal insufficiency was produced. There is a striking difference in the incidence of arterial lesions in these two groups as compared with similar experiments in which vitamin E was not administered (Table II).

Discussion. Since the pathogenesis of the arterial lesions related to high fat diet and renal insufficiency is not understood, there is no ready explanation for the protective action of vitamin E. The problem might be approached indirectly. If we assume that vitamin E exerts its usual "anti-oxidant" action, we can postulate pathogenesis as follows: During the 8 weeks or more of dietary feeding, one or more of the "toxic" substances (fatty acids are under suspicion) contained in the diet saturates the tissues with the excess spilling over in the urine. When this safety valve is destroyed, the excess piles up to "explosive" levels and the arterial lesions ensue.

If our present theory that the toxic substance is fatty acid proves correct, a corollary of it would be that the fatty acid damages collagen, for the first detectable anatomical change is edema, swelling, fragmentation and necrosis of collagen. The subsequent fibrin, "fibrinoid" and intense leukocytic reactions that are seen in the typical arterial lesion presumably represent the response of the body to the necrotic collagen. Why the assumed fatty acid selects collagen in certain sites of the body for this activity—also whether it acts directly on the collagen in these sites or does so by inactivating vitamin C (which it has been shown to do in aqueous solutions *in vitro*[2]) are not known. Attempts thus far to demonstrate any variations in ketone bodies in the urine or any consistent variations in the blood plasma lipids at different stages in the experimental procedures have not yielded definite confirmatory evidence for the above hypothesis.

2 Strohecker, R., and Buchholz, E., *Chem. Abstr.*, 1943, **37**, 5763.

TABLE II.
Effect of Vitamin E on Incidence of "Experimental" Arterial Lesions.

Diet	Weeks*	No. with lesions	
		No. in group	% positive
Table scrap + C.L.O.†	8-15	22/25	88.0
Table scrap + C.L.O. + Vitamin E	8-14	1/8	12.5

* Weeks of dietary feeding before production of renal insufficiency.
† C.L.O. = Cod Liver Oil.

Summary. 1. Twenty-two of 25 dogs fed a kennel diet of selected table scraps to which was added each day for 8 weeks or longer 3.0 cc/kg of cod liver oil developed typical arterial lesions when they died in uremia 7 to 35 days after the experimental production of renal insufficiency.

2. When vitamin E (mixed natural tocopherols, 2.5 to 4.0 mg/kg/day by mouth) was administered along with the diet, none of 4 dogs subjected to the same experimental procedures developed any arterial lesions.

3. Vitamin E was equally effective in preventing or retarding the arterial lesions when its administration by mouth was started 0, 1, and 2 days after renal insufficiency was induced.

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Cataract Development in Animals with Delayed Supplementation of Tryptophane.

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In several recent papers[1-4] demonstrating the production of lesions in the eyes of experimental animals on inadequate diets, corneal vascularization was encountered more frequently and as a more general response to deficiencies than cataract formation. The latter lesion was observed only rarely, chiefly in rats fed on tryptophane or histidine deficient diets. The development of cataract might be a result of disturbed protein synthesis due to the absence of the essential amino acids; however, since cataract did not develop in animals on diets deficient in other essential amino acids such as lysine, leucine, threonine, valine, isoleucine, arginine, etc., the possibility of a specific role of tryptophane and histidine in the metabolism of the lens must be considered. It was the intention of the present study to investigate this possibility by the method of delayed supplementation of tryptophane. One of the authors[5] has shown that infantile rats, on a diet of incomplete amino acid mixtures, did not grow if the missing amino acid was fed separate from the rest of the diet several hours later. These experiments indicated that amino acids are not stored in the body, and that protein synthesis can proceed only when all essential amino acids are simultaneously present in the tissues.

If the delayed supplementation of tryptophane would prevent cataract formation with-

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1 Chan, T. T., Chang, C. Y., and Luo, T. H., *Chinese J. Physiol.*, 1941, **16**, 241.

2 Totter, R. J., and Day, P. L., *J. Nutrition*, 1942, **24**, 159.

3 Albanese, A. A., and Buschke, W., *Science*, 1942, **95**, 584.

4 Sydenstricker, V. P., Schmidt, H. L., Jr., and Hall, W. K., PROC. SOC. EXP. BIOL. AND MED., 1947, **64**, 59.

5 Geiger, E., *J. Nutrition*, 1947, **34**, 97.