an air-hunger type of respiration and died on the fifth day.

3. The experiments indicate the ability of a dithiol when given to normal dogs in an appropriately large amount per kilo to induce an hepatic injury which is characterized by fatty degeneration of the hepatic epithelium and rarely by a necrosis of this tissue. Such observations do not necessarily imply that a similar order of cellular injury would be induced in the dog under the influence of an intoxication by salts of certain of the heavy metals. Such bodies offer a bond of union for the dithiols which in turn may prevent a toxic effect which they are capable of inducing in tissues of normal constitution.

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Influence of Diet upon the Hypertension and Nephrosclerosis Produced by Desoxycorticosterone Acetate Overdosage.*

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We have reported in a previous paper[1] that the hypertension and nephrosclerosis produced by administration of large amounts of anterior pituitary preparations may be prevented by decreasing the protein content of the diet from the normal of about 25% to 15%. In that publication attention was also called to the fact that adrenal enlargement was always marked in the hypertensive animals, which had been kept on a high protein diet, but was much less pronounced in the normotensive ones, which were given a low protein ration.

In order to clarify further the mechanism by which dietary protein affects the production of hormonal hypertension, we have now investigated its role in the production of the hypertension and nephrosclerosis induced by desoxycorticosterone acetate overdosage.

Material and Methods. Production of hypertension. Hooded castrated male rats, weighing 45 to 65 g, were unilaterally nephrectomized and implanted subcutaneously with two 40 mg pellets of desoxycorticosterone acetate (DCA). The animals were then divided into 2 groups: one received a 30% (Diet I), the other a 15% (Diet II) casein ration, both containing a large amount (4%) of NaCl, (for details see Table I). At the end of 40 days the surviving animals were killed and their kidneys and adrenals weighed and sectioned for histologic study, after fixation in "Susa" mixture. Eight animals in Group 1 and 5 rats in Group 2 were killed on the 20th day.

Blood pressure determinations. The blood pressure was determined by carotid cannulation (care being taken to avoid hemorrhages) on a representative number of rats on the 20th day of the experiment and in all surviving animals the day before autopsy, excepting 3 animals in which we missed the determinations. In order to spare the animals no control determinations were performed at the beginning of the experimental period; this appeared permissible as we had previously established[1] that the normal blood pressure of such rats, under our conditions, is 108 ± 14 (standard deviation) mm Hg. Statistical considerations revealed that 108 ± 28 mm Hg would include 95% of all normal rats, hence 135 mm Hg was taken as the highest normal blood pressure. The direct method

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1 Dontigny, P., Hay, E. C., Prado, J. L., and Selye, H., in press.

TABLE I.
Composition of Two Basic Synthetic Diets.
(Parts per cent.)

Diets	I	II
Casein	30	15
Corn starch	59	74
Fat	1	1
Cod liver oil	1	1
Bulk	1	1
Sodium chloride	4	4
Mineral mixture	4	4
Supplements:		
Thiamine chloride	0.8 mg/100 g diet	
Riboflavin	,,	,,
Pyridoxine	,,	,,
Ca pantothenate	4.0	,,
Nicotinic acid	1.0	,,
Choline chloride	100	,,
Tocopherol acetate	10 mg/rat/weekly	

of blood pressure determination gives the mean pressure only.

Kidney lesions. The incidence and severity of the kidney lesions were estimated by a procedure previously described.[3]

Diets. The complete composition of the diets employed is given in Table I.

Experiments. In a first series of experiments each group consisted of 15 rats. The experiment was then repeated with 10 animals in each group. The results were almost identical and will therefore be described conjointly.

Since under certain conditions[1] choline chloride appeared to counteract the hypertensive action of anterior pituitary preparation, an additional group of 10 rats was treated exactly as those on Diet I but they received 10 times the amount of choline chloride indicated in Table I.

Results. Table II summarizes our results. The average hypertension given in Table II refers to the average of the hypertensive animals only. It seemed appropriate to us not to include in the calculation the few normotensive rats, in order to obtain the true hypertensive average.

Confirming previous findings of this laboratory[2] it may be seen in Group 2 that the implantation of DCA produced a marked elevation of the blood pressure. This hypertension, which was present in almost all animals, was completely established on the 20th day of the experiment; it persisted for a period of at least 20 days which elapsed between the two blood pressure determinations. The kidney lesions in this group were also very prominent, as judged by the high incidence and severity of the pathologic changes.

We wish to emphasize particularly that a 15% casein diet does not prevent the production of hypertension and nephrosclerosis under these conditions. In fact our results show that at the end of 40 days 100% of the animals in Group 1 were hypertensive, with an average blood pressure of 161 mm Hg and had as marked kidney lesions as in the 30% casein group.

Ten times the usual amount of choline chloride (Group 3) effected no detectable improvement.

Discussion. Our earlier experiments[1] showed that the hypertension produced by anterior pituitary overdosage is prevented by a 15% casein diet; the present observations indicate that DCA-hypertension, on the other hand, cannot be prevented in this manner. According to the working hypothesis prevalent in this laboratory, the anterior pituitary increases the blood pressure by stimulating the adrenal cortex.[4,5] Since it now appears that the DCA-hypertension is obtained even on low protein diets, it is probable that the site of action of dietary proteins is between the pituitary and adrenal cortex; either proteins increase the efficacy of the corticotrophic hormone or they stimulate corticotrophin production. Experiments on hypophysectomized rats are now under way in this Institute to elucidate this last-mentioned point.

Choline chloride had no influence upon the establishment of hypertension by DCA overdosage.

Summary. While the hypertension and nephrosclerosis produced in the rat by anterior pituitary preparations are prevented by low-

2 Selye, H., and Pentz, E. I., *Canad. M. A. J.*, 1943, **49**, 264.

3 Hay, E. C., and Seguin, P., *Am. J. Physiol.*, 1946, **147**, 299.

4 Selye, H., and Stone, H., *J. Urology*, 1946, **56**, 399.

5 Hall, C. E., Dontigny, P., Beland, E., and Selye, H., *Endocrinology*, 1946, **38**, 296.

TABLE II.
Effect of Dietary Protein Concentration upon Hypertension and Nephrosclerosis Produced by Desoxycorticosterone Acetate Overdosage.
(Averages and standard errors.)

Groups	No. rats at end of exper.	Diets*	Final body wt	Nephrosclerosis		Hypertensive mean pressure		
				Incid. %	Severity %	Avg hypert.† 20 days	Avg hypert.† 40 days	% hypert. rats. 40 days %
1	16	15% casein	130 ± 5.2	100	79	154 ± 2.7 (19)	161 ± 3.8 (15)	100
2	13	30% "	135 ± 7.0	100	79	160 ± 3.0 (25)	157 ± 5.9 (11)	82
3	8	30% " + 10 X choline chl.	144 ± 7.3	100	79	—	163 ± 9.9 (8)	87

* Diets I and II.
† Figures in parentheses refer to number of determinations.

protein diets, the otherwise similar lesions induced by desoxycorticosterone overdosage are largely independent of the dietary protein intake.

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Effects of Dithiobiuret on the Central Nervous System.*†

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Astwood *et al.*[1] reported that 0.002% solution of dithiobiuret, substituted for drinking water, paralyzed and killed rats in 7 days although each took less than .5 mg per diem. Peripheral nerve, myoneural junction and muscle were normal in function. Muscle, peripheral nerve, brain, spinal cord, root and ganglion were microscopically normal. On return to drinking water, the animals promptly recovered, but while paralyzed, strychnine failed to induce convulsions. Effects of dithiobiuret on cortex and convulsant threshold is reported here.

Method. Dithiobiuret, prepared by the American Cyanamid Co., is sparingly soluble in water and as it goes into solution smells of hydrogen sulfide. Saturated solutions in saline or distilled water were used for local applications, intramuscular and intravenous injection, and 0.001 and 0.002% in tap water orally and intraperitoneally.

Two dogs, 3 cats and a fourth that had received 5 cc saturated solution intramuscularly for 8 days were used to determine effects of dithiobiuret when applied to cortex and injected intramuscularly or intravenously in animals under Dial.‡ Electroencephalograms of the fourth cat and one rat that had received 0.002% dithiobiuret for 9 days were

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1 Astwood, E. B., Hughes, A. M., Lubin, M., Vanderlaa, W. P., and Adams, R. D., *Science*, 1945, **102**, 196.

‡ The author wishes to thank Ciba Pharmaceutical Products who kindly supplied this drug.