that the influence upon nucleic acids is the basic function of this vitamin. This may be the mechanism of its action as the maturation factor of erythrocytes.

Summary. Administration of 15 μg per 100 g body weight of vitamin B_{12} to rats preceding acute CCl_4 intoxication inhibits the development of histologic changes, especially fatty metamorphosis and depletion of ribonucleic acid. In addition, there is less deposition of lipids determined biochemically and less BSP retention than in the intoxicated controls. These results are tentatively related to an effect of vitamin B_{12} on cytoplasmatic ribonucleic acid, which has been shown to disappear early in hepatic injury.

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17301. Persistence of Desoxycorticosterone-Induced Hypertension in the Nephrectomized Rat.

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The administration of desoxycorticosterone acetate (DCA)* provokes hypertension characterized by persistent elevation of systolic and diastolic blood pressures. This has been observed in rats[1-4] and in dogs.[5] Elevation of blood pressure to hypertensive levels in patients with Addison's disease,[6,7] and also aggravation of essential hypertension[8,9] have been observed following DCA treatment.

Animals treated with this hormone develop nephrosclerosis[1,10] and periarteritis nodosa,[11] vascular lesions which are frequently observed in hypertension induced experimentally by various surgical interventions on the kidney.[12] This raises a question as to the mechanism whereby DCA exerts its effect. The most commonly encountered views are either that DCA causes the development of hypertension which then results in widespread vascular damage, or that the vascular tissue is affected first with hypertension developing as a sequel to interference with intrarenal haemodynamics.[5,13,14]

Whether or not the hypertensive effect of DCA is mediated via the kidneys is a question of fundamental importance in the interpretation of experimental results involving this hormone and is also intimately concerned with the nature of hypertension accompanying adrenal cortical hyperfunction.

Hypertension resulting from the application of a constricting ligature to one renal artery subsides completely and promptly to normotensive levels following total nephrec-

* The desoxycorticosterone acetate used in this experiment was generously provided by Dr. Erwin Schwenk of the Schering Corporation, Bloomfield, N. J.

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TABLE I.
Effect of Nephrectomy on the Blood Pressure of Hypertensive and Normotensive Rats.

		Blood pressure in mm Hg								
		Before uninephrectomy		Total nephrectomy						
Group	Rat No.	Initial	Final	Before	5 hr	21 hr	30 hr	45 hr	55 hr	72 hr
Control	1	98	112	106	129	119	139	—	—	—
	2	112	125	118	129	122	128	—	—	—
	3	100	123	116	138	124	118	123	148	—
	4	114	115	135	128	149	—	—	—	—
	5	112	139	127	131	150	127	—	—	—
	6	105	116	105	117	124	149	126	—	—
DCA	7	94	120	166	157	158	170	154	187	—
	8	86	115	178	205	183	200	201	191	—
	9	108	107	159	173	166	158	160	187	205
	10	117	124	157	166	156	182	193	187	—
	11	96	114	152	157	164	156	166	—	—
	12	95	106	143	168	149	158	186	151	—
	13	101	117	162	171	191	156	193	193	206

Blood pressures of controls and DCA treated rats at selected intervals during the course of the experiment. Controls animals Nos. 4 and 5 proved to have a mild interstitial nephritis.

tomy.[15] This led the authors to conclude that hypertension of renal origin cannot be maintained in the completely nephrectomized animal. If then, hypertension resulting from DCA treatment is in reality a renal hypertension provoked by a vasculo-toxic effect of DCA on the renal vessels, an immediate return of the blood pressure from hypertensive to normal levels would be expected to occur in the totally nephrectomized DCA treated animal. This hypothesis was tested in the following manner.

Materials and methods. Fourteen young male albino rats weighing between 88-138 g (avg 110 g) constituted the experimental series. For a period of 2 weeks prior to the initiation of DCA treatment several determinations of blood pressure were made in order to accustom the animals to the apparatus and to determine the basal pressure of the rats. During this period they received Purina dog chow and tap water *ad libitum*. On the 15th day all animals were subjected to left nephrectomy under ether anesthesia and divided into two groups. The 8 animals of Group I received subcutaneously two compressed pellets of DCA weighing 50 mg each, while the 6 rats of Group II served as controls. At this time the tap water was replaced by 0.85% NaCl solution which served as drinking fluid for both groups until the second nephrectomy was performed. The food was not altered. The sensitizing influence which uninephrectomy and sodium chloride exert on the hypertensive effect of DCA has been described previously.[11]

Throughout the course of the experiment blood pressure measurements were taken on the animals of both groups several times weekly until total nephrectomy, thereafter twice daily, using the method of Williams, Harrison, and Grollman[16] as modified by Sobin.[17] The measurements were made on unanesthetized animals after a preliminary warming for an adequate period in a specially constructed heating chamber, after which the tail was kept warm by the circulation of heated water through a jacket surrounding the membrane of the plethysmograph. At each determination the blood pressure was measured until two successive readings agreed to within 5 mm Hg then the 4 subsequent readings were taken and averaged. This method has proven to be simple and reliable under the conditions described.

[15] Rodbard, S., and Katz, L. N., *Am. J. M. Sc.*, 1939, **198**, 602.

[16] Williams, J. R., Harrison, T. R., and Grollman, A., *J. Clin. Invest.*, 1939, **18**, 373.

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Twenty-eight days after the initiation of DCA treatment the animals of Group I had developed definite hypertension. At this time the remaining kidney was excised from animals of both groups. Inasmuch as both food and water have been shown to exert a detrimental effect on survival after total nephrectomy[18] both were withheld from the animals for the remainder of the experiment. Blood pressure recordings were made on each animal in the early morning and late afternoon until death supervened. The kidney which was removed at the second operation was fixed in Bouin's solution for histologic examination. One of the rats in Group I died before the second operation and was thereby eliminated from the experiment.

Results. The basal blood pressure values prior to uninephrectomy and the institution of DCA treatment were essentially the same in the animals of both groups. Hypertension was observed in some animals of Group I as early as the 14th day after implantation of DCA and was manifest in all of the animals of the group by the 17th day. In accordance with previous experience the animals of Group I consumed a considerably greater quantity of fluid than the controls and developed a marked diuresis. During the period before total nephrectomy the blood pressure of the control animals (see Table I) exceeded 129 mm Hg on only one occasion whereas the animals of Group I on the contrary displayed a constantly rising blood pressure. At the time of total nephrectomy the average blood pressure of the control animals was 118 mm Hg (range 105-127) while that of the treated animals was 160 mm Hg (range 143-178).

Subsequent to total nephrectomy the blood pressure of the animals in Group II remained essentially unaltered at the preoperative normotensive level (Table I and Fig. 1). The only animal in this group which survived for 55 hours had a blood pressure of 148 mm Hg. This single value is probably without significance. Single hypertensive readings were occasionally encountered in other control animals, but no definite hypertensive trend was apparent, a hypertensive reading often being

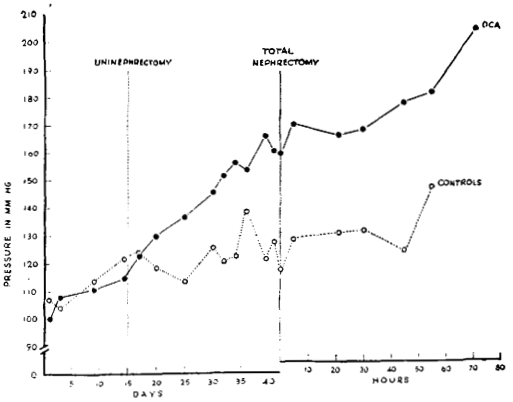

FIG. 1.
Blood pressure of DCA treated and control rats. A progressive rise in blood pressure to hypertensive levels followed the implantation of DCA on the 15th day. This was not abolished by total nephrectomy.

followed by one within the normal range. The reason for this is not clear. Further work is in progress to elucidate the reason for this behavior. Postoperatively the blood pressure of the animals of Group I rose from an average of 160 mm Hg to one of 178 mm Hg at 55 hours at which time the group was still intact, and to 206 mm Hg at 72 hours when 2 animals survived.

The results, summarized in Fig. 1, indicate that rather than declining after total nephrectomy the blood pressure of the animals of the DCA treated group continued to rise, while that of the control animals remained unaltered.

In accordance with previous findings[19] DCA prolonged the survival time of the completely nephrectomized animal (Table I). No attempt was made to accurately determine the time of death in these animals.

Histologic examination of the kidney which had remained *in situ* throughout the period of DCA treatment failed to reveal the presence of vascular lesions. In some of them a few convoluted tubules were dilated and an occasional cast was observed. Two of the control animals (Table I) exhibited interstitial nephritis of a mild degree.

Discussion. Hypertension is one of the most commonly encountered symptoms in

[18] Bergman, H. C., and Drury, D. R., *J. Clin. Invest.*, 1939, **18**, 777.

[19] Selye, H., *Canad. Med. Assn. J.*, 1940, **43**, 333.

clinical cases of adrenal cortical hyperfunction, especially of the Cushing's disease type. In such cases, just as in chronic essential hypertension, renal arteriosclerosis (nephrosclerosis) is usually an associated manifestation. In renal hypertension produced by the application of a partially constricting ligature to one renal artery, again hypertension and nephrosclerosis are present.[20] Therefore there is a school of thought which holds the hypertension of adrenal cortical hyperfunction and of essential hypertension to be due to renal mechanisms. The belief that essential hypertension is a renal disease has led to numerous attempts to relieve or cure the disease by uninephrectomy. The successes following such operations[21-23] have been paralleled by the failures,[24-26] the latter occurring even when tests revealed the remaining kidney to be normal. Thus the role of the kidney in the genesis and maintenance of essential hypertension is uncertain. However, since in animals with experimental renal hypertension removal of the ligated kidney will result, at least in the acute phase, in abolition of the hypertension, it is reasonable to assume that if DCA induces hypertension by a renal mechanism this should be "cured" by nephrectomy.

The role of the adrenal cortex, from which desoxycorticosterone may be extracted,[27] in essential hypertension is similarly unsettled. A high degree of correlation between the occurrence of adrenal cortical adenomas and essential hypertension has been reported by some observers, but others have not noted the association.[13] Similar disagreement exists as to the status of urinary cortin in essential hypertension. The methods at present in use permit separation of the true corticoids, which may be mineral-active or carbohydrate-active, from testoid cortical hormones, but they do not sharply separate the individual hormones from one another. It may be that the cortical hormone or hormones involved in essential hypertension escape detection by current methods.

The present data indicate that the kidneys are not necessary participants in the maintenance of DCA hypertension.

This experiment does not explain the mechanism whereby DCA exerts a hypertensive effect, but it does indicate that the hormone does not induce hypertension by evoking the renin-angiotonin system. On similar grounds the hypertension of early adrenal cortical hyperactivity is probably of non-renal origin. It is possible, however, that when the nephrosclerosis develops, whether in the DCA treated animal or in the clinical conditions of essential or adrenal cortical hypertension, a renal hypertension may become superimposed upon a non-renal form.

Absence of vascular lesions in the acutely hypertensive DCA treated rat and their invariable presence in the chronically treated rat suggests that hypertension precedes nephrosclerosis in development. Therefore either hypertension causes the renal vascular lesions or the two are independent manifestations of DCA overdosage. The former hypothesis would seem to be the more tenable.

Summary. The blood pressure of rats rendered hypertensive by treatment with desoxycorticosterone acetate continues to rise following total nephrectomy. Hypertension of this type is not dependent upon a renal mechanism for its maintenance and it is not a consequence of renal vascular damage which is a later development. The relationship of the adrenal cortex to certain forms of clinical hypertension is discussed.

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