compared in animals which had received tetracycline and in the control animals. It was found to be present to a similar degree following a period of ischaemia or a particular nephrotoxin irrespective of whether or not tetracycline had been given.

There was no evidence in these experiments that tetracycline is capable of potentiating other procedures which cause tubular necrosis. It would appear therefore that the tubular necrosis produced by tetracycline in rats with hemoglobinuria is related to some peculiarity of hemoglobin and may not occur under other circumstances.

Résumé. On a étudié la toxicité de tétracycline injectée par voie intraveneuse chez le rat. On a montré qu'il n'y a pas d'ischémie significative du rein après l'administration de tétracycline. On a demontré aussi que la nécrose expérimentale des tubules rénales du rat provoquée par diverses substances chimiques n'est pas augmentée par la tétracycline.

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Course of Hypertension During Prolonged Treatment with Heterologous Renin[1]

A type of hypertension similar to experimental renal hypertension has been produced by administration of renin to uninephrectomized rats[2]. Hog renin being readily available has been mostly used. Knowing that its heterogenicity in rats would lead to formation of antirenin[3], such studies have been arbitrarily limited to periods of about 10 days. The present experiments were undertaken to see whether and when complete remission of hypertension occurs under prolonged treatment and if so, its relationship to antirenin formation. Also included are observations on cardiovascular reactivity to renin and angiotensin.

Methods. Female Sprague-Dawley rats weighing around 150 g were uninephrectomized and divided into 4 groups of 12 animals each: 2 experimental (groups 1 and 2) and 2 control (groups 3 and 4). Animals of groups 1 and 2 received hog renin dissolved in physiologic saline containing 7% gelatin; a daily dose of 40 Goldblatt U was administered in 2 s.c. injections. Animals were kept in metabolism cages. Blood pressure was measured regularly by tail sphygmography about 7 h after the morning injection. The diet consisted of a commercial chow and tap water. Renin treatment lasted 8 days in group 1 and 20 days in group 2. On the 9th day, animals of groups 1 and 3, and on the 21st day, animals of groups 2 and 4 were tested for cardiovascular responsiveness to angiotensin II and hog renin. Under ether anesthesia, a plastic catheter was inserted into the aorta through the femoral artery. Following recovery, animals were placed in a harness which permitted free movement; arterial pressure was then registered on a Sanborn recorder through a Statham P23db pressure transducer. Angiotensin II and hog renin were administered subcutaneously at the standard doses of 10 μg and 25 U respectively. At the end of each experiment blood was collected for determination of antirenin titer, by adding known amounts of plasma to 1 U of hog or rat renin and determining the pressor activity of the mixture by bioassay in rats. Tissues were removed for weighing and histologic examination. A piece from each kidney was kept frozen for determination of renin content.

Results. Initially renin treatment caused growth inhibition; in animals of group 1 killed on the 9th day body weight averaged 164 g as compared with 204 g in the control group 3. However, on continued treatment growth was gradually resumed and accelerated (group 2) so that final values were similar to those of control group 4. Renin caused an early and intense diuresis, which was maintained during about the first 7 days then decreased to near normal values around the 14th day (Figure 1). Arterial pressure remained within the normal range during the first 2 days then increased sharply to hypertensive levels; a maximum was reached around the 8th day followed by a gradual decline to normal. Blood pressure curves paralleled quite closely those of urine flow. Heart weights reflected final blood pressure values, being significantly elevated in group 1 and near normal in group 2 (Table). Pressor responses to a standard dose of angiotensin were increased in group 1 and normal in group 2, while responses to renin were increased in group 1 and almost abolished in group 2 (Figure 2). It should be noted that since these tests were performed about 16 h after the last renin injection arterial pressure in animals of group 1 was back to normal. All deviations from normal were statistically significant ($P < 0.01$). No antirenin to hog or rat renin was demonstrable in the plasma of control rats (groups 3 and 4) as well as in that of animals which were hypertensive (group 1). Rats of group 2, on the other hand, were found to have an average antirenin level of 9.5 U/ml against hog renin. This antirenin cross-reacted with rat renin with approximately 20% efficiency (titer 2.0 U/ml). Renin concentration in kidneys was decreased in group 1 ($P < 0.01$) and increased in group 2 ($P < 0.05$). The width of the zona glomerulosa was significantly increased in group 1 ($P < 0.01$) but not significantly different from normal in group 2. Vascular disease was present in animals of groups 1 and 2. However, lesions in animals of group 1 were in the active stage with prominent inflammatory cells and exudate particularly in the small hepatic arteries while those in animals of group 2 were healing. A similar reversal has been noted after removal of a clipped kidney or cessation of renin treatment[4]. It is of interest to note that 2 out of 12 animals of group 2 behaved in most respects like animals of group 1. Rat No. 1 maintained a pressure around 200 mm Hg from the 7th day until the 20th day. Rat No. 2 had a

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final pressure of 160 mm Hg, which had gradually fallen from a high of 200 mm Hg. On the 20th day rat No. 1 showed the following changes: diuresis, 30 ml/24 h; heart weight, 430 mg; response to angiotensin and renin, 30 and 43 mm Hg respectively; antirenin titer, not measurable; renal renin, 3.9 U/g; and width of the zona glomerulosa, 73 μ. Although the zona glomerulosa was not larger than in animals of group 1, it showed numerous vacuoles similar to the watery vacuoles described in animals on low sodium diet[5].

Discussion. Remission of hypertension, healing of vascular lesions and normal heart weight in rats chronically treated with renin are all consistent with neutralization of exogenous renin by circulating antirenin. First, high antirenin titers were found only in animals which became normotensive. Secondly, other effects specifically attributed to renin, such as diuresis and stimulation of the zona glomerulosa, gradually vanished; there is an inverse relationship between diuresis, proteinuria and antirenin titers[3]. Finally, pressor responses to a standard dose of renin were either abolished or markedly decreased, while responses to angiotensin remained unaffected. The high antirenin titer also explains the high renin content found in the kidneys of these animals. Although the neutralizing capacity of hog antirenin against rat renin is only 20% of that against hog renin, the total amount present in plasma may be sufficient to inactivate endogenous rat renin.

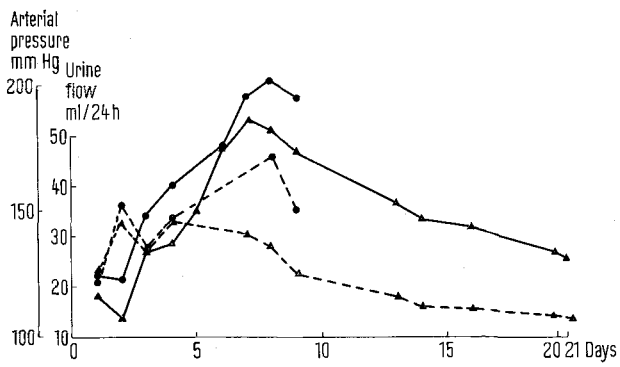

Fig. 1. Changes in blood pressure (solid lines) and urine flow (broken lines) during chronic treatment with hog renin. Curves with black circles are from group 1 and those with black arrows from group 2.

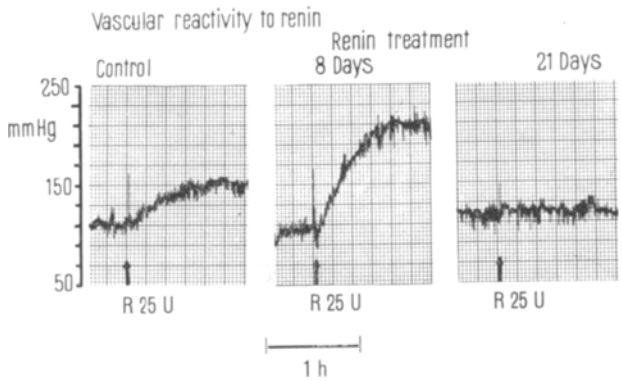

Fig. 2. Pressor responses to administration of a test dose of 25 U of hog renin to control, 'hypertensive' and normotensive rats.

Thus the high renin content would represent a compensatory reaction to an absence of feedback mechanisms resulting from lack of circulating renin, exogenous as well as endogenous. A similar increase has been reported in dogs chronically treated with hog renin[6]. The large responses to standard doses of renin and angiotensin found during renin-induced hypertension cannot be clearly interpreted. Previous experiments in which animals were made hypertensive by renin or angiotensin[7] administration, indicated that such hypertension could not be explained exclusively on the basis of the acute pressor effect of angiotensin. The intervention of other mechanisms presumably of adrenal[8] or nervous origin[2] has been suggested. The potentiation to renin and to angiotensin seen in rats which were hypertensive and its absence in those which reverted to normotension is not incompatible with such an interpretation.

Effects of chronic treatment with hog renin

	Group 1	Group 2	Groups 3 and 4
	Renin 8 days	Renin 20 days	None
Heart weight mg/100 g body weight	439 ± 41	350 ± 24	316 ± 12
Pressor response mm Hg			
to angiotensin	63.2 ± 10.6	23.9 ± 10	25.8 ± 13.2
to renin	90.5 ± 39.7	12.7 ± 11.7	46.7 ± 9.3
Zona glomerulosa width in μ	74.5 ± 10.7	51.0 ± 5.7	44.1 ± 1.9
Renin content U/g	1.9 ± 1	25.4 ± 16.8	12.4 ± 3.8

Résumé. L'hypertension artérielle causée par des injections sous-cutanées de rénine de porc disparaît graduellement au cours d'un traitement prolongé. L'élévation du taux d'anti-rénine plasmatique est vraisemblablement responsable de ce retour à la tension normale. Pendant la phase d'hypertension, on a noté une potentiation des effets cardiovasculaires de la rénine et de l'angiotensine, potentiation dont le rôle dans la pathogénèse de l'hypertension reste à déterminer.

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