Increasing the injected dose does not result in a significant rise in the maximal steroid levels, but prolongs the duration of adrenocortical stimulation. A dose of 5 U appears to stimulate the adrenals for only 1 h. Doubling the dose results in 2 h stimulation, while with 125 U, or 200 μg of peptide, the effect lasts about 4 h.

In equivalent dosage, DW 75 causes more prolonged adrenal stimulation than a polypeptide containing only 24 amino acids of the natural ACTH sequence[21]. This more prolonged duration of action seems to result from the delayed enzymatic breakdown of the synthetic polypeptide suggested by in vitro studies[17]. DW 75 is the first synthetic polypeptide with an adrenocorticotropic action which has, due to its slower enzymatic breakdown, an effect apparently more prolonged than naturally occurring ACTH[22].

Résumé. L'action adrénocorticotrope d'un polypeptide à 25 acides aminés, comprenant 3 modifications de structure par rapport à la séquence 1–25 de l'ACTH naturelle est étudiée et démontrée. La destruction enzymatique de ce pentacosapeptide paraît être plus lente dans le sang que dans les tissus musculaire et sous-cutané. L'augmentation de la dose injectée produit un allongement de la durée de stimulation de la cortico-surrénale.

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Department of Medicine of the University of Geneva, Hôpital cantonal, Geneva (Switzerland), May 13, 1966.

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[22] The technical assistance of Miss S. WÖRNER and Miss M. NAGTEGAAL is gratefully acknowledged.

Tetracycline Toxicity

We have shown previously that tetracycline induces tubular necrosis in the kidneys of rats if hemoglobinuria is present and have suggested that this might be due to either a short period of ischaemia produced by the tetracycline or to a direct nephrotoxic effect of tetracycline[1]. In either case the effect of tetracycline would be potentiated by the presence of hemoglobin[2,3]. In the present paper the toxicity of tetracycline is examined further and in particular experiments are described which were carried out in order to examine the possibility that tetracycline might induce a transient ischaemia in the kidney.

A total of 90 female albino rats of the Wistar strain were used. Tetracycline was given by intravenous injection into the tail vein in a dose of 15 mg/100 g body weight.

In the first series of experiments 3 different methods were used in an attempt to demonstrate ischaemia in the kidney.

In some rats the abdomen was opened and the appearance of the kidney following the injection of tetracycline observed directly in normal light. This has been found to be a satisfactory method of detecting transient periods of ischaemia in the kidney[2]. There was no change in the appearance of the kidney during the 15 min following the injection.

In other rats 2 ml of Indian ink was injected rapidly into the abdominal aorta at various times up to 15 min after the injection of tetracycline. The kidneys filled normally with Indian ink on all occasions and there was no evidence of patchy ischaemia.

In a further group of rats the rate of exogenous creatinine clearance was measured during the period immediately following the injection of tetracycline and in control animals which received a similar volume of isotonic saline. The method used was that described by MUNTWYLER and GRIFFIN[4], and the tetracycline was given immediately before the collection period. The results of this experiment are given in the Table. They do not show any evidence of a reduction in glomerular filtration rate during the 30 min following the injection of tetracycline.

The above experiments failed to demonstrate any significant ischaemia in the kidneys following the administration of tetracycline. This finding has some importance experimentally as well as clinically in view of the fact that tetracycline has been used to assess renal blood flow[5,6].

In the next series of experiments an attempt was made to see if any toxic effect of tetracycline would be manifested in the presence of other nephrotoxic agents.

Rats were given tetracycline as before and then immediately after the injection either the renal pedicle was clamped for periods varying between 15 and 60 min or one of the following nephrotoxins was given by subcutaneous injection in the amounts indicated per 100 g body weight; potassium dichromate 6 mg, D-L serine 75 mg, uranium nitrate 30 mg. Control animals were treated in exactly the same way except that they were not given tetracycline. All the animals were killed 24 h later and histological sections prepared from the kidneys. The extent of the tubular necrosis following each procedure was

Substance injected before collection period	No. of animals	Body weight (g)	Creatinine clearance (ml/min/100 g body weight)
Tetracycline	10	214	0.65 ± 0.15[a]
Isotonic saline	10	215	0.70 ± 0.19[a]

[a] Standard deviation.

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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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