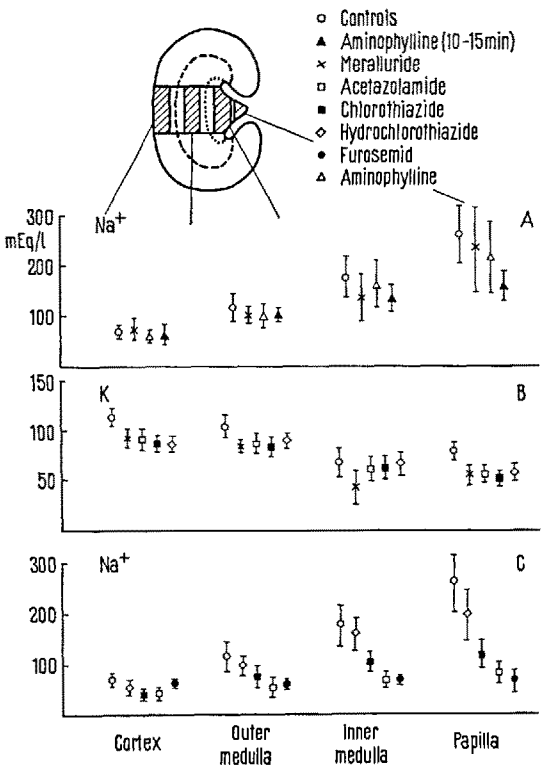
mechanism. The fact that there was no effect on concentration gradients after Aminophylline (1–2 h after administration) and after organic mercury injection need not be interpreted as a distal effect of these diuretic agents; it is more probable that the increase in flow through the loops of Henle was not sufficiently high to cause this 'washout effect', as the increase in urine flow in anaesthetized rats was only twice as high as in the control group. On the contrary, the decrease of sodium concentration gradient in rats sacrificed soon (10–15 min) after Aminophylline injection could be mediated via the increased blood flow through the vasa recta in the renal medulla, because purine diuretics shortly after injection cause a renal hyperaemia (SMITH[3]).



Sodium and potassium concentration gradients in rat kidneys. A, sodium gradients in control rats and 1–2 h or 10–15 min after administration of Aminophylline and Meralluride. B, potassium gradients in control rats and after Meralluride, acetazolamide, chlorothiazide and hydrochlorothiazide administration. C, sodium gradients in control rats and after acetazolamide, chlorothiazide, hydrochlorothiazide, and Furosemid (Lasix). The values are expressed in milliequivalents per 1 l of tissue water. Each point represents the mean value of 10 rats together with the standard deviation.

The efficacy of sulfonamides on the sodium concentration gradient decreases in the following order: acetazolamide, chlorothiazide, hydrochlorothiazide; nevertheless, their diuretic effect was in all experiments nearly the same and high diuretic potency of hydrochlorothiazide unaccompanied by any change in the sodium gradient is in good agreement with the results of BAER et al.[4]. These substances have the same order of efficacy on carboanhydrase inhibition in vitro; any correlation between this fact and our results could be difficult to evaluate. It is possible that each of these three substances influences different parts of the nephron: acetazolamide could work in proximal parts of the nephron while the thiazides could act in more distal parts. The complete disappearance of concentration gradients after Furosemid administration is not surprising, as its proximal effect is unquestioned (DEETJEN[5], VORBURGER[6]) and its explanation by the 'washout effect' seems therefore very probable.

In these experiments neither the osmolarity of tissue fluid nor of urine was directly measured. However, calculation of the 'osmolarity' according to the formula $C_{osm} = 2(C_{Na} + C_K) + C_{urea}$, where C denotes molarity, showed very good agreement between the urine 'osmolarity' and 'osmolarity' of tissue fluid on the tip of the papilla in all experiments.

Zusammenfassung. Die Konzentrationsgradienten von Na^+ und Harnstoff im Rattennierengewebe werden durch intravenöse Applikation von Merallurid, Salyrgan und Hydrochlorothiazid nicht beeinflusst. Die Änderung des Na-Gradienten nach Aminophyllin hängt von der Injektionszeit ab. Acetazolamid-, Chlorothiazid- und Furosemid-Injektion führt jedoch zur Senkung oder zum Verschwinden eines Na-Gradienten. Die Kaliumkonzentration in der Rinde und Papilla wird durch Hg- und Sulfonamid-Diuretica erniedrigt.

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Institute of Industrial Hygiene and Occupational Diseases, Prague (Czechoslovakia), March 9, 1965.

[3] H. W. SMITH, *The Kidney* (Oxford University Press, New York 1951).
[4] J. E. BAER, A. V. BROOKS, R. M. NOLL, and K. H. BEYER, J. Pharm. exp. Therap. *137*, 319 (1962).
[5] P. DEETJEN, LASIX, Erg. internat. Furosemid-Symposium, Bad Homburg v.d.H., Farbwerke Hoechst, Frankfurt (M) (1963), p. 52.
[6] CHR. VORBURGER, LASIX, Erg. internat. Furosemid-Symposion, Bad Homburg v.d.H., Farbwerke Hoechst, Frankfurt (M) (1963), p. 54.

Renal Lesions Induced by the Simultaneous Administration of Angiotensin and Hexadimethrine Bromide

During studies on the pathogenesis of the lesions caused by the antiheparin agent hexadimethrine bromide[1,2], we observed renal infarction in some rats which had been given angiotensin followed by hexadimethrine bromide. Further investigations of this subject are described in the present paper.

Methods. A total of 76 female rats of the Wistar strain were used. Fourteen of the animals were given an intraperitoneal injection of 0.5 mg angiotensin (Hypertensin

[1] K. KOVÁCS, R. CARROLL, and E. TAPP, Lancet *1964 ii*, 919.
[2] R. CARROLL, K. KOVÁCS, and E. TAPP, Lancet *1964 ii*, 921.

II amide, val 5 Octapeptide, Ciba), followed a few minutes later by an intravenous injection of 5 mg of hexadimethrine bromide (Polybrene, Abbott). For control purposes twelve animals were given angiotensin alone, and fifty were given hexadimethrine bromide alone by the same routes.

All the animals were killed at 2 days. The kidneys were fixed in formol saline, and paraffin sections at 5 μ were stained with hematoxylin and eosin.

Results. No histological changes were seen in the kidneys of animals which had received angiotensin alone.

All the animals which had been given hexadimethrine bromide had necrosis with calcification of the broad ascending limbs of the loops of Henle in the intermediate zone of the kidney, similar to that described previously by SELYE et al.[3] and TAPP et al.[4]. In a small number there was also necrosis of occasional isolated proximal convoluted tubules in the cortex. There were no glomerular lesions, and the renal vessels were quite normal.

All fourteen rats which had been given the combination of the two drugs had the typical hexadimethrine bromide lesions in the intermediate zone of the kidney but in addition twelve of them had gross lesions in the cortex. The six most severely affected kidneys had wedge-shaped areas of infarction (Figure 1), and in two of them these were confluent so that the lesions corresponded to those of renal cortical necrosis. In four of the less severely affected animals patches of the cortex showed necrosis and thrombosis of the glomerular tufts and also necrosis of proximal tubules (Figures 2 and 3). The remaining two animals had only patchy necrosis of tubules without any glomerular changes.

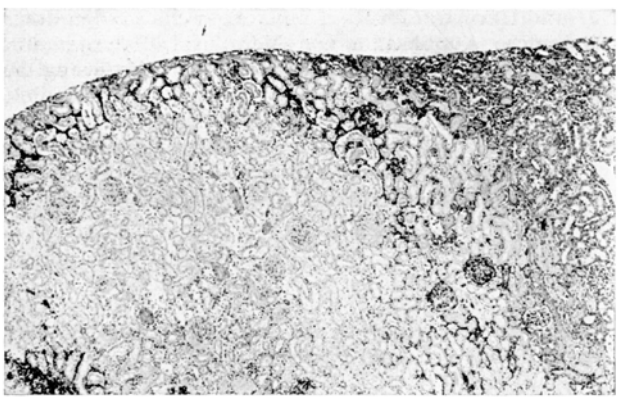

Fig. 1. A wedge-shaped area of infarction in the renal cortex of a rat 48 h after the administration of angiotensin and hexadimethrine bromide. Hematoxylin and eosin × 60.

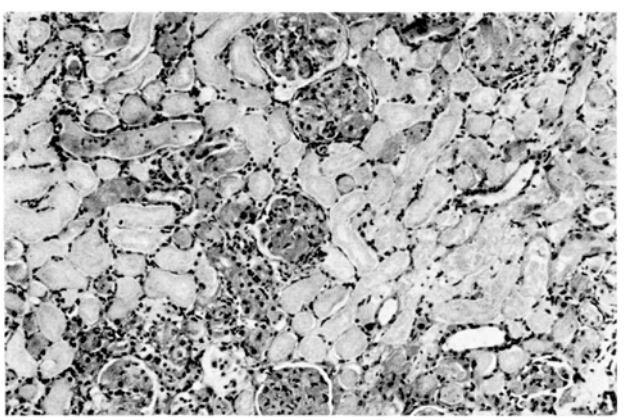

Fig. 2. Necrosis of proximal convoluted tubules in the renal cortex of a rat 48 h after the administration of angiotensin and hexadimethrine bromide. Hematoxylin and eosin × 150.

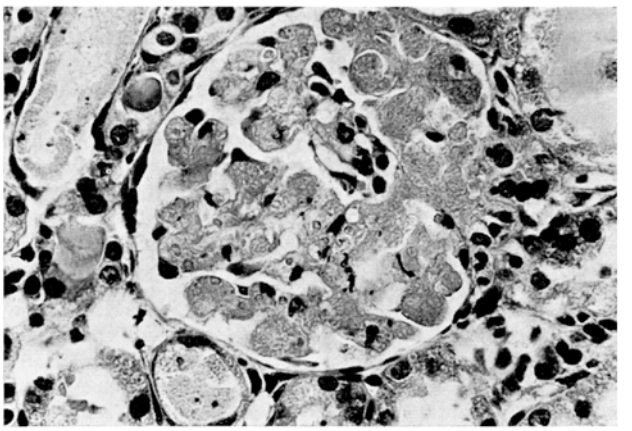

Fig. 3. Necrosis with thrombosis of the glomerular tufts in the renal cortex of a rat 48 h after the administration of angiotensin and hexadimethrine bromide. Hematoxylin and eosin × 600.

Discussion. The lesions produced by the combination of angiotensin and hexadimethrine bromide are clearly ischaemic in origin. The evidence is insufficient to determine whether the glomerular lesions are the primary cause of the ischaemia or are secondary to a prolonged spasm of pre-glomerular vessels[5].

On the other hand, the two drugs separately produce only minor lesions in the cortex. BYROM[6] reported kidney damage consisting of aneurysms and focal necroses of glomeruli and lesions in renal arteries after the intravenous injection of up to 0.1 mg angiotensin alone. We could not find any lesions of this type in our animals treated only with angiotensin in an intraperitoneal dose of 0.5 mg. In an attempt to reproduce Byrom's findings we have given 0.5 mg of angiotensin intravenously to ten further rats, but this did not produce any lesions in the kidney or the renal arteries. The reason for the discrepancy is not clear.

Zusammenfassung. Einmalige Verabreichung von Angiotensin oder Hexadimethrin-bromid verursacht bei der Ratte keine signifikante Schädigung der Nierenrinde. Wird zuerst Angiotensin und wenige Minuten später Hexadimethrin-bromid injiziert, so kommt es zu Nierenrindeninfarkten, fokalen glomerulären und tubulären Nekrosen.

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Department of Pathology, University of Liverpool (England), March 17, 1965.

[3] H. SELYE, G. GABBIANI, and B. TUCHWEBER, Med. exp. *8*, 74 (1963).
[4] E. TAPP, R. CARROLL, and K. KOVÁCS, Arch. Path., in press.
[5] H. L. SHEEHAN and J. C. DAVIS, J. Path. Bact. *78*, 105 (1959).
[6] F. B. BYROM, Brit. J. exp. Path. *45*, 7 (1965).