In previous studies angiotensin has been infused in acute experiments without prior sodium loading into either untrained[2,4] or anaesthetized rats[1,3], conditions under which we have also failed to elicit an antinatriuretic effect. In habituated chronically sodium-loaded rats, on the other hand, a consistent antinatriuretic effect is readily demonstrated, but only with small doses (0.005 µg/kg/min and below). Large doses (0.05 µg/kg/min and above) increase sodium excretion. Thus, in the rat angiotensin has the dose-dependent opposite effects on sodium excretion observed in dog[5], rabbit[6], and man[7]. The physiological role of angiotensin in the rat, as in these other species, is more likely to resemble the effect of small rather than large doses and to be that of a sodium-retaining hormone.

The influence of the experimental conditions on the renal response to infused angiotensin may be mediated by their effect on local renal angiotensin concentration. Thus, with sodium depletion, endogenous angiotensin production is increased and may lead to a local renal concentration of the hormone which exerts its maximal antinatriuretic effect. Infusion of additional hormone will then either have no effect or, by summating with endogenous hormone, lead to excessively high levels which increase sodium excretion. Similarly, in acute experiments involving traumatic procedures on untrained animals, greater activity of the sympathetic nervous system may increase endogenous angiotensin production[8], so that infusion of exogenous hormone can only elicit a natriuretic response.

The opposite effect that angiotensin has on sodium excretion from the 2 kidneys in rats with unilateral renal ischaemia, further suggests that the concentration of endogenous angiotensin in the kidney may be crucial in determining the renal response to infused hormone. Thus, angiotensin reduces sodium excretion from the unclamped kidney, which has a subnormal renin content, but increases it from the clamped kidney, with a raised renin content[3,9].

These results indicate the importance of the experimental conditions in assessing the effect of angiotensin on renal function and have other important implications. Thus, micropuncture studies of sodium transport and glomerulo-tubular balance should be interpreted in the understanding that in such acute experiments on anaesthetized animals the renin-angiotensin system may well be operating at maximal activity, since, at least in the rat under these conditions, infused angiotensin is incapable of exerting any further antinatriuretic effect. This point is especially important in view of the likelihood that angiotensin plays a crucial role in the control of glomerular and tubular function.

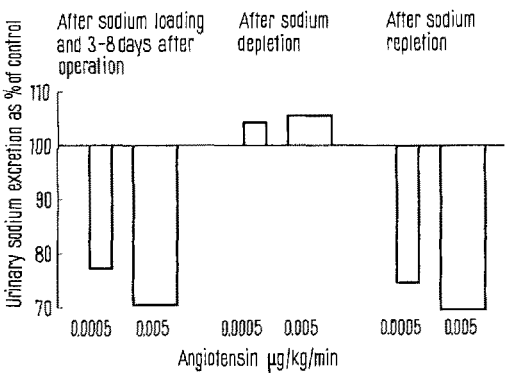

Fig. 2. The effect (A) of sodium loading; (B) sodium depletion; and (C) sodium repletion on the response of urinary sodium excretion to the same doses of angiotensin.

Mean urinary sodium excretion during angiotensin infusion is expressed as a % of the mean of the control periods immediately before and after its infusion. The average of all experiments is shown.

Résumé. Les conditions expérimentales déterminent la réponse rénale à l'angiotensine chez le rat. Antérieurement, on a seulement demontré une réponse natriurétique à cette hormone. Cependant, chez les rats chargés chroniquement de sodium, on a demontré que l'angiotensine en doses de 0,00005–0,005 µg/kg/min est toujours antinatriurétique. Après une opération récente, ou sous anesthésie ou en présence d'une déplétion de sodium, l'angiotensine à ces doses, chez les mêmes animaux, est soit sans effet ou même natriurétique.

M. A. BARRACLOUGH, V. A. PERRIELLO[10], C. D. MARSDEN, and N. F. JONES

Department of Medicine, St. Thomas's Hospital Medical School, London S.E.1 (England),
September 13, 1966.

[5] J. K. HEALY, C. BARCENA, J. M. O'CONNELL, and G. E. SCHREINER, Am. J. Physiol. *208*, 1093 (1965).
[6] M. A. BARRACLOUGH, Lancet *2*, 987 (1965).
[7] W. J. LOUIS and A. E. DOYLE, Clin. Sci. *29*, 489 (1965).
[8] R. L. HODGE, R. D. LOWE, and J. R. VANE, J. Physiol. *185* 613 (1966).
[9] G. PETERS, Nephron *2*, 95 (1965).
[10] Present address: Department of Pediatrics, Duke University Hospital, Durham (North Carolina, USA).

The Protective Effect of Small Amounts of Selenite in Sublimate Intoxication

The necrotizing effect of parenteral injection of small doses of cadmium cations on the testis[1,2] can be prevented by simultaneous injection of a small dose of selenium salts[3,4]; in our laboratory we were able to show a similar protective effect of salts of selenium[5,6] against the toxic effects of cadmium in other reproductive organs, i.e. in the non-ovulating ovaries of rats in permanent oestrus[5,7] and in the placentae[8,9]. In order to understand the mechanism of this protective effect of selenite and the nature of interaction between cadmium and selenium compounds, it was necessary to show how far the protective effect of selenite is specific for the effect of cadmium and its effect in reproductive organs only, or how far selenium compounds can act as a highly efficient protective agent in intoxication by toxic metals in general.

To test this possibility, we decided first to study the effect of simultaneous injection of selenite on the development of renal necrosis produced by sublimate intoxication. Male (50 rats) and female (24 rats) adult white rats (Wistar substrain Konárovice), kept on a standard laboratory diet and in standard laboratory conditions,

were injected with 0.02*M* solution of mercuric chloride (sublimate) in a dose of 0.02 mmole/kg body weight. Half of these (37 rats) received in addition to sublimate an injection of 0.02*M* solution of sodium selenite in a dose of 0.03 mmole/kg body weight; the second half served as a control group receiving mercuric chloride without any additional treatment (20 rats) or together with sodium sulphite (homologous to selenite: 0.02*M* solution in a dose of 0.03 mmole/kg body weight; 17 rats). The solutions used were isotonized with sodium chloride and injected s.c. In all experiments, the solutions used were injected into different regions simultaneously so that direct contact of solutions injected was avoided. The rats were killed 24 h and 5 days after injection and the renal changes were studied morphologically. In all control rats mercuric chloride produced typical macroscopically easily detectable changes; histological examination (formol, haematoxyline eosine staining) revealed renal necrosis typical for intoxication with sublimate in all cases. In all rats receiving mercuric chloride with sodium selenite, no macroscopic changes were present in the kidneys; histologically no necrotic changes on the renal tubules were detectable. In contrast to selenite, sodium sulphite had no protective effect. In addition to renal necrosis in all rats receiving sublimate, typical intestinal necrosis was detected. In contrast to this, no macroscopically detectable changes were observed in rats treated with sublimate together with selenite.

In the second series of experiments, the effect of selenite injection on the mortality of rats intoxicated with sublimate was tested. In this second series of experiments 90 adult male rats were used. 30 of them served as controls receiving 0.02 mmole mercuric chloride/kg body weight without any additional treatment. Another 20 rats served as controls intoxicated with the same dose of mercuric chloride which was followed, after an interval of 1 h, by an injection of sodium sulphite (0.03 mmole/kg body weight). 40 rats received, 1 h after the injection of the same dose of sublimate, sodium selenite (0.03 mmole/kg body weight). All injections of sublimate were given s.c. into the interscapular region, all injections of selenite and sulphite were given s.c. above the tail. As seen from the Table, injection of selenite proved to be a highly protective agent in sublimate intoxication, even when the injection of selenite was given 1 h after injection of sublimate. All rats intoxicated with sublimate had typical macroscopical lesions on kidneys and intestines. The only rat which did not survive after sublimate and selenite injections had no morphologically detectable renal or intestinal changes typical for sublimate.

Thus sodium selenite is a highly effective agent preventing selective toxic effects of another bivalent cation-mercury in addition to those of cadmium. The experiments in progress are intended to show how far the protective effect of selenium could be a result of some change in the distribution of mercury in organs, or in the chemical form in which mercury is present here, or if selenium compounds affect the sensitivity of organs to the toxic effects of bivalent cations (mercury and cadmium) by some other means. From this standpoint, it seems to be of interest that the excretion of volatile selenium compounds by expired air is affected not only by cadmium[10], but by mercuric chloride application as well[11].

It would be highly desirable to learn, of course, whether the protective effect of selenite described could be of some use in human intoxication too. From this point of view, research concerned with the questions of delayed injection of selenite (or other selenium compounds) on the development of toxic symptoms, and the effect of different levels of intake of selenium in food on the toxicity of sublimate, could be of some interest. Further research has to show how far the toxic effect of other metals could be prevented by selenium compounds (selenite) in a similar way. These results might also throw some light on the role of selenium as an essential nutrient.

The effect of successive injections of sodium selenite on the survival of rats injected with sublimate

Group of rats	No. of rats	Surviving rats 2nd day		7th day	
		No. of rats	%	No. of rats	%
Hg	30	30	100	1	3.3
Hg-S	20	20	100	1	5.0
Hg-Se	40	39	97.5	39	97.5

Hg = group of rats injected with 0.02 mmole mercuric chloride/kg body weight only; Hg-S = group of rats injected with the same dose of mercuric chloride but followed within 1 h by an injection of sodium sulphite in a dose of 0.03 mmole/kg body weight; Hg-Se = group of rats injected with the same dose of mercuric chloride followed within 1 h by an injection of sodium selenite in a dose of 0.03 mmole/kg body weight. In each group, adult male rats were used and injected s.c. Number of rats in each group and number of rats surviving on the second and seventh day are given.

Résumé. L'injection de très petites quantités de sélénite de sodium, administrées simultanément ou 1 h après l'intoxication par le sublimé corrosif, en abaisse considérablement la toxicité: les rats blancs intoxiqués par une dose létale de sublime corrosif survivent sous l'effet du sélénite dans un % important et les lésions typiques des reins et d'autres organes n'apparaissent pas.

J. Paříček and Ivana Ošťádalová

Czechoslovak Academy of Sciences, Institute of Physiology, Prague-Krč (Czechoslovakia),
August 29, 1966.

[1] J. Paříček and Z. Záhoř, Nature, Lond. *177*, 1036 (1956).
[2] J. Paříček, J. Endocr. *15*, 56 (1957).
[3] A. B. Kar, R. T. Das, and B. Mukerji, Proc. natn. Inst. Sci. India *26 B*, 40 (1960).
[4] K. E. Mason, J. O. Young, and S. E. Brown, Anat. Rec. *148*, 309 (1964).
[5] J. Paříček, *Cadmium and Reproduction.* WHO, Scientific Group on the biochemistry and microbiology of the female and male genital tracts (Geneva 1965).
[6] J. Paříček, I. Ošťádalová, I. Beneš, and A. Babický (1966), to be published.
[7] J. Paříček, Čslká Fysiol. *11*, 466 (1963).
[8] J. Paříček, J. Reprod. Fert. *7*, 263 (1964).
[9] J. Paříček, J. Reprod. Fert. *9*, 111 (1965).
[10] H. E. Ganther and C. A. Baumann, J. Nutr. *77*, 210 (1962).
[11] J. Paříček, I. Beneš, A. Babický, and J. Benes (1966), to be published.