(range 8–14 h). 3–15% of the dose was excreted unchanged in the urine in 72 h and excretion appeared to be pH dependent.

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## Evidence for a physiological role of prolactin in osmoregulation in the rat after its inhibition by 2-bromo-α-ergokryptine

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2-Bromo-α-ergokryptine was given, mixed in the feed, to 3 groups of 10 male and 10 female rats (OFA, IFFA-CREDO) at doses of 5 (mg/kg)/day, 20 (mg/kg)/day and 80 (mg/kg)/day in a 52-week toxicity experiment. Macroscopic and microscopic study of the kidneys revealed an improvement in the incidence and severity of spontaneous degenerative lesions in treated rats. This was particularly apparent in the males and resulted in the relative kidney weights of treated males being comparable with those of 6 month old control animals rather than the controls of this trial (control male relative kidney weight: 0·87% of body weight, low-dose group 0·65% ($P<0·001$), mid-dose group 0·68% ($P<0·001$), high-dose group 0·76% ($P<0·05$), but control male animals 6 months old 0·68%). In urine samples taken after 6, 13, 26 and 52 weeks, 24-h excretion values for calcium and urine specific gravity were consistently and significantly decreased. More importantly, values for sodium and potassium were significantly increased as were 24 h volume and pH. Furthermore, increased ovarian weights associated with high numbers of persisting corpora lutea occurred in mid- and high-dose groups.

An explanation of the mechanism by which 2-bromo-α-ergokryptine inhibited the development of spontaneous nephrosis was sought. The earliest observable lesion in spontaneous nephrosis is the accumulation of protein casts in the collecting tubuli, resulting in some degree of obstruction. The development of the more obvious macroscopic and microscopic lesions is considered to be secondary to this obstruction (Saxton & Kimball, 1941). It is possible that the higher urinary pH associated with medication inhibited the formation of such casts, protein being more soluble at high alkalinity. The additional flushing action of increased urine volume would act synergistically.

The only pronounced pharmacological action of 2-bromo-α-ergokryptine is its ability to inhibit prolactin secretion, as has been demonstrated through its inhibition of lactation in several species, its inhibition of implantation in the rat (but not the rabbit) and its inhibition of luteolysis in the rat. The build up of corpora lutea in this study provided morphological evidence that prolactin inhibition took place (Billeter & Flückiger, 1971).

It is known that prolactin is the most important hormone involved in osmoregulation in reptilia, amphibia, fish and birds (Meites & Nicoll, 1966; Ensor & Phillips, 1970). In addition, Lockett (1965) has shown that exogenous prolactin has a direct effect on the cat kidney, reducing the urinary excretion of sodium, potassium and water without effect on renal blood flow or glomerular filtration rate. Further work on man (Horrobin, Burstyn, Lloyd, Durkin, Lipton, & Muiruri, 1971) and rats (Lockett & Nail, 1965) supported these results.

The inhibition of prolactin produced in this study was associated with significant changes in urinary parameters which are in direct contrast to those obtained when pro-

lactin is injected exogenously. The urinary findings together with the observed improvement in renal lesions strongly implicate prolactin in the physiological control of water and electrolyte balance in rats.

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## Induction of liver microsomal drug metabolism in newly-hatched chicks

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The unexpectedly high drug metabolizing activity of liver microsomal preparations from 1-day-old chicks (Drummond, McCall & Jondorf, 1972) has been further investigated.

Microsomal subcellular fractions in 0·25 M sucrose were prepared using the technique of Jondorf, Simon & Avnimelech (1966) from pooled livers of embryos (1 day before hatching) and from groups of female chicks of the Hubbard Golden Comet strain ranging in age from 1 to 7 days. These preparations were assayed for their drug metabolizing capacity *in vitro*, by incubating them with substrates for N-demethylation (aminopyrine) and aromatic ring hydroxylation (aniline, naphthalene) in the presence of glucose-6-phosphate dehydrogenase and the supporting system of Jondorf *et al.* (1966). Washed microsomal preparations were also assayed for cytochromes $b_5$ and P-450, NADPH-cytochrome C reductase (Mazel, 1971) and NADPH-cytochrome P-450 reductase (Gigon, Gram & Gillette, 1969)

We were able to show that the 3–4 fold increase in the liver microsomal metabolism of all three substrates on the first day after hatching is maintained for a further two days. After this time the metabolic activity declines to about 50% of the neonatal peak value. The endogenous induction of drug metabolism in the newly hatched chick does not appear to be correlated with microsomal cytochrome $b_5$ or P-450 content or with NADPH-cytochrome C reductase activity. There is, however, a peak in NADPH-cytochrome P-450 reductase activity corresponding with the increased drug metabolizing activity in the first three days after hatching. This finding agrees with the suggestion by Davies, Gigon & Gillette (1969) that changes in this parameter most closely reflect changes in the rates of microsomal drug metabolism in different species.

The time-course of exogenous induction in 7-day-old chicks treated with sodium phenobarbital or 3-methylcholanthrene at the optimal dose levels (100 mg/kg I.P. in both cases) reveals that peak liver microsomal drug metabolizing activity which again is not substrate specific is attained after 12–18 h and then declines rapidly to control levels. The increased activity brought about by the exogenous inducers, as expected by analogy with other species (Sladek & Mannering, 1969) is related to cytochrome P-450 levels associated with the microsomal preparations.

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