Five other volunteers exercised on a cycle ergometer (150 watts for 3 min) before and 1, 2, 4, 6 and 8 h after the oral application of pindolol (5 mg), LF 17-895 (2·5 mg) and propranolol (100 mg) administered in random order. These doses of the three drugs reduced exercise tachycardia to about the same extent with a maximum after two hours. The reductions after 4, 6 and 8 h were expressed as % of the effect at 2 h (Table 1). The duration of action of pindolol (5 mg) and LF 17-895 (2·5 mg) is significantly longer in this test than that of propranolol (100 mg).

TABLE 1

A. Isoprenaline antagonism
Dose of isoprenaline (μg/min) required to increase heart rate to 120 beats/min. (2 h after oral application of the drug) (n=3).

Placebo	Pindolol			LF 17895			Propranolol	
	1·0 mg	2·5 mg	5·0 mg	0·5 mg	1·25 mg	2·5 mg	40 mg	80 mg
3·9±0·8	66±11	169±48	279±50	80±13	220±61	486±103	83±21	126±24

B. Duration of action (exercise induced tachycardia) (n=5)

		Reduction of 'end of exercise heart rate' (beats/min) 2 h	(% of reduction at 2 h) 4 h	6 h	8 h
Pindolol	5 mg	41·7±1·9	89·8±2·6	87·0±4.8	84·3±4·8*
LF 17895	2·5 mg	37·3±3·7	90·3±0·9	86·4±2·0*	80·8±2·9*
Propranolol	100 mg	40·8±2·3	89·8±1·9	74·6±4·2	66·9±4·4

* Significant difference to propranolol ($P<0·05$, paired t-test)

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Clinical pharmacological studies of Kö 1173—a new antiarrhythmic agent

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Kö 1173 1-(2, 6-dimethylphenoxy)-2-amino-propane has anticonvulsant properties and can suppress ventricular arrhythmias in experimental animals by reducing the maximal rate of ventricular depolarization (Allene, Kofi Ekue, Shanks & Zaidi, 1970; Singh & Vaughan Williams, 1972).

Kö 1173, given intravenously or orally, successfully controlled ventricular arrhythmias in 35 of 47 patients. Plasma concentrations of the drug were measured by gas-liquid chromatography in 38 patients.

In acute ventricular arrhythmias the mean minimum effective plasma concentration of Kö 1173 was 1·6 μg/ml (range 0·8 to 2·9 μg/ml) whereas the corresponding value in stable ventricular arrhythmias was 0·7 μg/ml (range 0·5 to 1·3 μg/ml). Central nervous and cardiovascular toxicity was often observed with concentrations above 3·0 μg/ml.

Following intravenous injection the drug disappeared quickly from the plasma and high rates of infusion were required initially to maintain adequate plasma concentrations. An initial intravenous bolus of 150–200 mg is followed by an infusion at the rate of 250 mg in 30 min, 250 mg in the next 2·5 h and 500 mg in the subsequent 8 h. For maintenance therapy 500 mg is infused every 12 h.

After intravenous infusions lasting 24–72 h were discontinued, the mean plasma half-life in 11 patients with myocardial infarction was 18·6 h (range 10–26 h). The long half-life may result in cumulation and late toxicity. The apparent volume of distribution was in the range 200–400 l.

Kö 1173 was well absorbed when given orally to 11 patients. A loading dose of 600 mg produced peak plasma concentrations of 1·6 to 2·8 μg/ml in 3 h and effective concentrations were maintained with 450 to 1,050 mg daily.

In 6 healthy volunteers peak plasma concentrations of 0·3 to 0·5 μg/ml occurred 1–4 h after ingestion of 3 mg/kg of Kö 1173 in solution. The mean plasma half-life was 11·5 h

(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-