Cyproheptadine (5 and 10 mg/kg) significantly increased the body weight in a graded manner (Table 1). The effect of 15 mg/kg s.c., however, was almost the same as 10 mg/kg oral, but it failed to produce any increase in the body weight in weanling rats. There was increase in water but not food intake following the highest dose in the adult rats.

TABLE 1. *Effect of cyproheptadine on 4 h water and food intake and on body weight of fasted rats*

Treatment	Water intake 4 h† (ml./100 g)	Food intake 4 h† (g/100 g)	Body weight†† (% gain or loss)
Adult male rats			
Control (saline oral)	+1·6	+2·3	+0·7
Cyproheptadine (5 mg/kg oral)	+1·3	−0·5	+3·3**
Control (saline oral)	+1.3	+0.5	0
Cyproheptadine (10 mg/kg oral)	+0.7	−0·8	+6·4**
Control (saline s.c.)	0	+0.8	+0·6
Cyproheptadine (15 mg/kg s.c.)	+2·7*	−0·5	+6·8**
Weanling male rats			
Control (saline s.c.)	+3·8	+1·2	+21·4
Cyproheptadine (15 mg/kg s.c.)	+8·5	+1·4	+18·0

† Values indicate difference in the weekly average of pretreatment and treatment periods for 5 rats. †† Values indicate percentage gain or loss following 1 week treatment. * Significance of difference $P < 0{\cdot}01$. ** Significance of difference $P < 0{\cdot}001$.

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Pyridostigmine pharmacokinetics: evidence for an apparent capacity limited urinary elimination of the metabolites of pyridostigmine

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Deviations from apparent first order drug excretion kinetics may be detected by changes in the fractional composition of the excretion products with dose (Levy, 1968). The excretion of pyridostigmine and its metabolites were studied in the rat after portal administration of different doses, since no previous work has examined dose effects on pyridostigmine excretion.

^{14}C-pyridostigmine (dose: 1·25, 3 or 6 μmoles/kg) was administered by rapid intravenous injection via the portal vein to male Wistar rats (body weight 300–350 g) under urethane anaesthesia and mannitol diuresis (6% mannitol in 0·9% NaCl; infusion rate: 0·075 ml/min). Urine was collected from both ureters and assayed for total ^{14}C by liquid scintillation spectrometry, for pyridostigmine and its metabolites by electrophoresis (Somani, Roberts & Wilson, 1972).

When the rate of excretion of pyridostigmine was plotted semi-logarithmically with time at the midpoint of each urine collection period, the maximum rate was observed at about 30 min. It is considered that this indicates that the hepato-portal system behaves as a separate compartment in the distribution process.

Over the time period studied, the fraction of the dose excreted as pyridostigmine was the same at each dose but the fraction eliminated as metabolites was reduced at the two highest doses. The results shown in Table 1 indicate that a dose-dependent excretory process is involved. Since the excretion of pyridostigmine is apparently dose-independent, it is proposed that the reduced excretion of the metabolites of pyridostigmine is due to saturation of renal secretory processes.

TABLE 1. *Pyridostigmine pharmacokinetics: Fraction of pyridostigmine and its metabolites excreted after portal vein administration of different doses*

		a	b	c	
	Time (min)	1·25 μM/kg	3·00 μM/kg	6·00 μM/kg	p
Pyridostigmine	60	0·206±0·018	0·268±0·057	0·205±0·030	a to b > 0·30 a to c ≫ 0·90
	100	0·290±0·023	0·362±0·050	0·284±0·028	a to b > 0·20 a to c > 0·80
	140	0·328±0·053	0·414±0·042	0·340±0·023	a to b > 0·20* a to c > 0·80*
Metabolites	60	0·111±0·016	0·069±0·007	0·062±0·013	a to b 0·05 a to c 0·05
	100	0·225±0·020	0·148±0·008	0·139±0·027	a to b < 0·02 a to c < 0·05
	140	0·341±0·021	0·218±0·010	0·219±0·035	a to b < 0·01* a to c < 0·05*

Results are mean ±S.E. * Based on only 4 degrees of freedom. All other p values at 6 degrees of freedom.

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The effect of acrylic bone cement on the circulation in the rabbit

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In recent months concern has been expressed in the Medical Press over unwanted cardiovascular effects which follow the use of self-curing (polymethylmethacrylate) cement in the fixation of prostheses in major hip arthroplasty (Cadle, James, Ling, Piper, Pryer & Wilmshurst, 1972; Ellis & Mulvein, 1972). Hypotensive episodes are common and the occasional cardiac arrest has been reported (Thomas, Sutherland & Waterhouse, 1971). The present experiments were an attempt to establish an animal model of the human operative procedure, which might assist in the study of these effects.

New Zealand White rabbits, 2·3–4·4 kg body weight, of either sex, were anaesthetized with pentobarbitone sodium (30 mg/kg I.V.) and anaesthesia was maintained by additional doses of pentobarbitone sodium or ether. Recordings were made of the arterial blood pressure, the central venous pressure, respiratory movements, electrocardiogram and the rectal temperature.

The upper part of the femur was exposed by detaching the muscles from the greater trochanter. Then this was sawn off at approximately 45° to the long axis of the bone. The hip joint itself was left intact. The medullary cavity was reamed to approximately two-thirds of its length with a 4 mm diameter drill. Acrylic cement was inserted while still soft and forced into the cavity with a length of 4 mm diameter flat-ended steel rod. In some experiments plasticine was employed as a control material instead of cement. When either material was used, vasodepressor effects were seen.