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.

In most experiments there was an acute fall in arterial blood pressure. This started immediately after forcing in the material, returning to normal in less than 40 s. No consistent changes in central venous pressure, respiratory movements or e.c.g. occurred. However, in occasional experiments the hypotensive effect was more complex, accompanied by a rise in central venous pressure and changes in respiratory rate, and in two experiments the arterial pressure failed to return to its resting level.

Collection of the blood leaving the femoral vein when the material was forced into the medullary cavity did not prevent or reduce the hypotension. These animals were given 100 I.U. heparin/kg I.V. Fat and marrow cells were identified in the femoral venous blood samples. Reinfusion of this blood a few seconds later produced no acute effect, but in one animal there was a protracted fall in arterial pressure and a rise in central venous pressure. It is unlikely that the acute effect is a result of embolism, since it was not modified by delaying the femoral venous return and reinfusion of femoral blood known to contain emboli did not produce an acute response.

These preliminary experiments suggest that the response which normally occurs is produced by a nervous mechanism and that occasionally there is a response of longer duration which might be due to embolic effects.

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Studies on the mechanism of action of dihydroergotamine (DHE) on the vascular bed of cat skeletal muscle

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In the innervated skeletal muscle vascular bed, DHE elicits a slight dilator effect on the resistance vessels and a constrictor effect on the capacitance vessels (Mellander & Nordenfelt, 1970). The present experiments attempt to elucidate the mechanism by which DHE elicits these effects.

Male cats weighing 2·3–3·4 kg were anaesthetized with chloralose (46 mg/kg) and urethane (464 mg/kg) intramuscularly. The calf muscles (innervated and denervated) were prepared according to the method described by Mellander (1966). The doses of drugs were calculated as their bases.

The results are summarized in Table I. In denervated preparations, the intravenous injection of 15 μg/kg DHE resulted in constriction of both resistance and capacitance vessels, confirming the findings of Owen and Stuermer (1971). However, in innervated preparations, the dose-related constriction of capacitance vessels in response to DHE (15 μg/kg and 45 μg/kg I.V.) was accompanied by a dose-dependent dilatation of the resistance vessels. Phenoxybenzamine (2·5 mg/kg I.V.) abolished the DHE-induced constrictor effect on the capacitance vessels without affecting the dilator response on the resistance vessels. This latter effect was abolished by atropine (2 mg/kg I.V.), revealing a constrictor effect similar in magnitude to that observed in denervated preparations. The intraperitoneal administration of eserine (100 μg/kg) potentiated the dilator response. Intravenous pretreatment of cats with chlorpheniramine (100 μg/kg), propranolol (1 mg/kg) and acetylsalicylic acid (200 mg/kg) did not alter the DHE-induced dilatation of the resistance vessels.

It is concluded that the constriction of the capacitance vessels induced by intravenous administration of DHE is mediated peripherally by an action on α-adrenoceptors whereas the dilator effect on the resistance vessels appears to be mediated centrally through the release of acetylcholine.