2 hours. Cycloheximide, an inhibitor of protein synthesis did not produce paling of skin in amphiuma. Melatonin which has been known as a potent lightening agent in frog did not produce such an effect in amphiuma. The possibility that actinomycin D produced paling of the skin by blocking the secretion of MSH by the pituitary and that *in vivo* the mechanism of synthesis of this hormone may be different from other polypeptides has been discussed.

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Limitations of Antiadrenergic Therapy for Refractory Traumatic Shock.* (31808)

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The generally accepted principle that prolonged and excessive vasoconstriction is a self-defeating defense mechanism led to the use of antiadrenergic therapy in experimental traumatic shock. There was no appropriate pharmacologic agent of sufficient potency until phenoxybenzamine became available. The effectiveness of these and other related substances as prophylactic agents has been repeatedly affirmed(1-3), but their effectiveness when applied during shock remains in doubt(4-6) because none of them can consistently achieve a significant salvage rate in the experimental animal or in man. On this account we made a study of coeliac blockade as a method for maximum exploitation of the therapeutic principle involved, for it achieves immediate and total release of sympathetic activity in the splanchnic viscera, and so facilitates preferential diversion of flow to the region most in need of it(7).

In this communication we report a comparison of the effects of this therapy with that of phenoxybenzamine in endotoxic and hemorrhagic shock.

Procedure and results. 1. *Endotoxic shock in rabbits (Table I).* Adult white rabbits received an MLD/100 *E. coli* 0111:B4 endotoxin intravenously. Three types of antiadrenergic therapy were studied, in each instance in a group of 12 rabbits and at different times, as follows:

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TABLE I. Antiadrenergic Therapy of Endotoxic Shock in Rabbits.

Therapy	No. of exp	Time of administration after endotoxin in min: 5	15	30	72-hr survival rate* in %
None	12	—	—	—	8.
Coeliac blockade	12	—	+	—	58.
" "	12	—	—	+	25.
Phenoxybenzamine (intraaortic)	12	—	+	—	66.
" "	12	—	—	+	17.
" (intravenous)	12	+	—	—	0.

* Survival rate by *pretreatment* with coeliac blockade was 91%; by intraaortic phenoxybenzamine 83%; and by intravenous phenoxybenzamine 58%.
+ = time of institution of therapy.

TABLE II. Antiadrenergic Therapy of Endotoxic Shock in Dogs.

Type of therapy	No. of dogs	Early* therapy	Late* therapy	72-hr survival rate in %
None	11	—	—	0
Coeliac blockade	20	+	—	65
" " (+ Metaraminol)	5	+	—	0
" "	5	—	+	0
Phenoxybenzamine (intravenously)	11	+	—	27

* "Early" refers to the period after injecting endotoxin before full blown hemodynamic collapse is present, *i.e.* before sustained hypotension. "Late" refers to the period of sustained hypotension.
+ = application of therapy.

(1) Coeliac blockade (1.5 ml of 0.5% xylocaine in 50% ethyl alcohol) was produced immediately before injecting the endotoxin in one group, 15 minutes afterward in a second group, and 30 minutes afterward in a third group.

(2) Phenoxybenzamine (1 mg/kg) was administered intravenously to a fourth group 15 minutes before, and to a fifth group 5 minutes after injecting the endotoxin.

(3) Phenoxybenzamine in *half the intravenous dose* (0.5 mg/kg) was injected into the upper abdominal aorta to a sixth group 15 minutes before, to a seventh group 15 mintes afterward, and to an eighth group 30 minutes afterward.

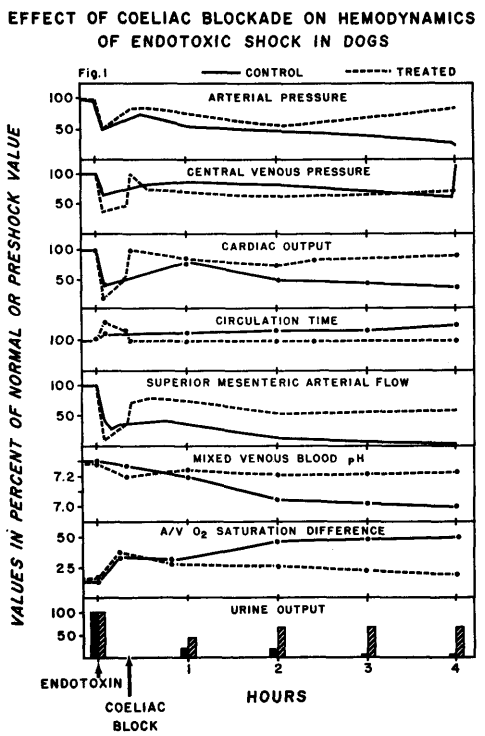
The survival data, listed in Table I, show that the results of treatment by coeliac blockade are matched by those of intraaortic phenoxybenzamine. But the good survival rate from both types of therapy given at 15 minutes was not obtained at 30 minutes. Since intravenous phenoxybenzamine in twice the intraaortic dose is useless even 5 minutes after injecting endotoxin, it is plain that the amount of drug needed to achieve sufficient antiadrenergic activity where it is most needed, *i.e.*, in the splanchnic area, is not delivered by the intravenous route.

2. *Endotoxic shock in dogs (Table II).* A group of 11 dogs received a lethal dose of *E. coli* 0111:B4 endotoxin (1 mg/kg), but no therapy, and all died within 36 hours.

Another group of 20 dogs were given the same dose of this endotoxin and received coeliac blockade (20 ml of 0.25% xylocaine) 30 to 40 minutes later, *i.e.*, prior to the onset of sustained hypotension. Of these, 13 (65%) were alive 72 hours later. It is noteworthy that in 5 additional dogs an attempt to counter the hypotensive effect of blockade by a pressor agent (Metaraminol) failed and all 5 died within 24 hours.

A group of 5 dogs in endotoxic shock was treated by blockade instituted late in shock, *i.e.*, from 2 to 7 hours after injecting the endotoxin. All 5 died within 12 hours.

In a further series of 11 dogs an intravenous drip of phenoxybenzamine (1 mg/kg) in 250 ml saline was started 15 minutes after injecting the endotoxin and completed within 90 minutes. In 8 dogs there was no re-



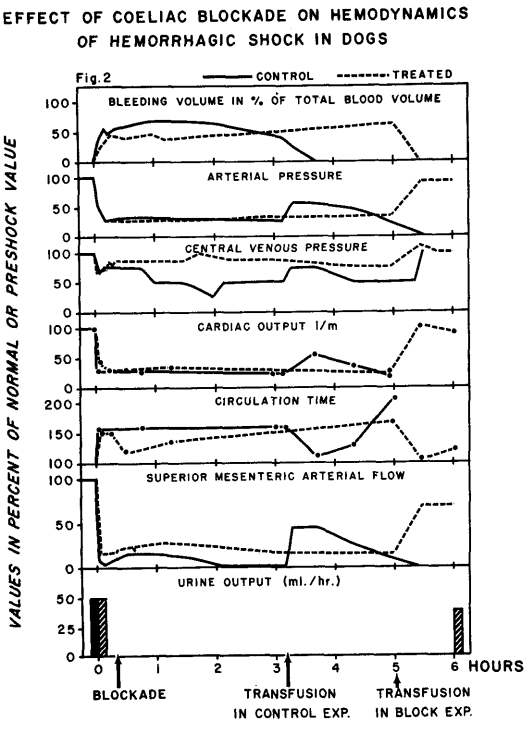


FIG. 1. Representative hemodynamics from control animals (untreated) and from animals receiving early treatment (coeliac blockade alone, Table II). For urine output, solid bars refer to control animals; hatched bars refer to treated animals.

FIG. 2. Representative hemodynamics from control animals (untreated) and from animals receiving early treatment (Group I, Table III). For urine output, solid bars refer to control animals; hatched bars refer to treated animals.

covery from the hypotensive effect of the drug and all died within 36 hours. In the remaining 3 the blood pressure did return to its previous level, and these survived.

The hemodynamic effects of successful coeliac blockade were studied in detail in 10 dogs. These are depicted in Fig. 1, and may be briefly summarized as follows: Almost immediately after blockade there is an abrupt rise in central venous pressure, in cardiac output and in flow through the superior mesenteric artery as measured directly with a Gregg electromagnetic flow meter. Concurrently the circulation time and the AV oxygen difference decrease, the blood pH rises slowly, and the flow of urine resumes. These changes are of varying magnitude from one animal to the next, but the general pattern is uniform.

Comment. These data indicate that antiadrenergic therapy given by a systemic vein is inferior to that applied selectively to the splanchnic viscera, and that selective therapy can prevent death only if it is applied soon after shock is induced, *i.e.*, in less than 30 minutes in the rabbit, and in less than an hour in the dog.

Antiadrenergic therapy for hemorrhagic shock. 1. Hemorrhagic shock in dogs (Table III). Morphinized dogs were put into hemorrhagic shock as follows: A femoral artery, exposed under local anesthesia was connected to an elevated reservoir and bleeding into it allowed so as to maintain the mean systemic blood pressure at 30 to 35 mmHg for 6 hours, or until 40% of the maximum blood loss had spontaneously returned to the dog from the reservoir. All the blood left in the reservoir was then returned rapidly *via* a femoral vein. The dogs were considered normovolemic at this time because significant intestinal bleeding usually does not begin until after all the blood has been returned.

TABLE III. Antiadrenergic Therapy of Hemorrhagic Shock in Dogs.

Therapy	No. of exp	MBV, ml/kg	Early* therapy	Late* therapy	72-hr survival rate in %
None	8	50	—	—	0.
Coeliac blockade (Group I)	16	51	+	—	62.
" " (Group II)	4	51	—	+	0.
" " (Group III)	4	52	—	+	0.

* "Early" refers to the period of bleed out, *i.e.* before the maximum bleed out volume is reached—as in Group I. "Late" refers to the period of uptake, as in Group II, or after normovolemia was restored, as in Group III.
+ = application of therapy.

Of the 32 dogs in this study 8 received no other therapy. The remainder received coeliac blockade (25 ml of 0.25% xylocaine) at different times after the onset of bleeding—in Group I (16 dogs) within 30 minutes after bleeding was started, *i.e.*, about half-way through the bleedout period; in Group II (4 dogs) 60 minutes after blood had started to return from the reservoir to the circulation, and in Group III (4 dogs) immediately after normovolemia was restored.

The only survivors were 10 of the 16 dogs (Group I) blocked very early in shock, *i.e.*, before blood begins to return spontaneously from the reservoir to the animal (Table III).

Fig. 2 depicts the effect of early blockade on the hemodynamics of the hypovolemic phase, and on the response to transfusion. The release of vasoconstriction by blockade is signaled by a rapid return of blood from the reservoir, which, in the survivors, stops after some 200 ml of blood has returned. Thereafter, the animal bleeds back into the reservoir to a varying degree, so that by the sixth hour very little of the maximal volume of blood lost has returned to the circulation. Restoration of normovolemia at that time is curative. In the non-survivors the increase in rate of uptake from the reservoir produced by blockade does not abate, and after all the shed blood has been returned there is progressive collapse until death.

Another feature of a favorable response to blockade is a substantial increase in mesenteric flow in spite of a continuing loss of blood into the reservoir up to the time of transfusion. This is in contrast to the continuing decline in mesenteric flow in the control animal even while the deficit in blood volume is being reduced by progressive uptake from the reservoir.

Comment. The reservoir technic for producing and maintaining hemorrhagic shock is peculiarly appropriate for visualizing the functional status of the peripheral vessels. The increasingly rapid return flow of blood from the reservoir back to the circulation in the control animal signifies progressive loss of tone in the peripheral vessels. Preservation of the integrity of the circulation by regional antiadrenergic therapy is protrayed by the opposite phenomenon, *i.e.*, by further bleeding into the reservior that occurs soon after the production of successful coeliac blockade.

The therapeutic failure of antiadrenergic blockade, when induced after more than a brief period of severe hemorrhagic or endotoxic shock, also applies in shock that follows release of the superior mesenteric artery (8). A measure of the speed with which severe ischemia inflicts damage on the vascular system(9) is the fact that the most effective type of antiadrenergic blockade is futile within 45 minutes of onset of shock. Hence the need for a more promising type of therapy for severe or advanced shock.

Some advocates of antiadrenergic therapy account for its failure on the ground that the increased volume of the peripheral vessels makes the existing blood volume inadequate. They suggest that to be effective this therapy must be supplemented by the infusion of blood sufficient to fill the expanded vascular space. The experiments herein reported and others already reported(10), as well as clinical experience, demonstrate that blood infused in sufficient volume to pro-

duce a plethora is not helpful when vascular muscle has lost tone.

Conclusion. Antiadrenergic therapy by coeliac blockade or phenoxybenzamine injected *via* the upper abdominal aorta prevents death from otherwise lethal endotoxic or hemorrhagic shock if administered within 30 minutes after onset of the shock state. Phenoxybenzamine intravenously is not effective in twice the dose that is effective when it is administered *via* the upper abdominal aorta. The failure of antiadrenergic therapy can be accounted for by the speed with which severe ischemia inflicts irreversible injury to vascular muscle and to the endotoxin-detoxifying mechanisms in the splanchnic tissues.

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Effect of Thyrocalcitonin, Administered During Peritoneal Lavage, on Removal of Bone Salts and Their Radioisotopes.*‡ (31809)

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The existence of thyrocalcitonin, a hypocalcemic agent produced in the thyroid of all mammals studied, has been thoroughly confirmed(1-3). This hormone has been extracted in relatively pure form and is known to be a peptide of low molecular weight, similar in some respects to parathyroid hormone(1,4-7). While several investigators have explored the possibility of an extraosseous site of action of this principle(1,8), it is generally assumed that bone is its primary target(9). Experiments have demonstrated that increased secretion of thyrocalcitonin occurs during conditions of hypercalcemia(10). Whether or not it is also secreted at lower rates in normal or hypocalcemic conditions has not yet been established. Such information will be of importance in determinining the physiological significance of this newly identified hormone, since in the normal mammal the problem of hypocalcemia tends to be more acute than that of hypercalcemia.

A major question concerning the action of thyrocalcitonin is whether its hypocalcemic effect is accomplished through increasing bone accretion, or by decreasing the processes removing calcium from bone, or both. It has been pointed out by Gaillard that the hormone "can nearly abolish the effect" of parathyroid extract on his organ culture of mouse radii(11). The hormone's effect on inhibiting bone resorptive processes has also been demonstrated by Friedman and Raisz(12) and by Aliapoulios *et al*(9), using *in vitro* systems. Recent *in vivo* studies by Johnston and Deiss(13) have also led to the suggestion that thyrocalcitonin inhibits metabolic bone resorption. Since the peritoneal lavage technique employed in our laboratories exaggerates bone resorptive processes by removing an average

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