Discussion. It is generally believed that Vit. D facilitates intestinal absorption of calcium(7,8). It has been suggested that Vit. D_2, similar to parathyroid hormone, causes mobilization of calcium from bones to the circulation(9,10). The importance of calcium in milk synthesis by the mammary glands is well recognized. A severe decrease in serum calcium may develop a condition of "milk fever" and it is believed that the cause of this condition is due to parathyroid hormone deficiency(11).

The present experiment showed that crystalline calciferol at the dose given was able to replace parathyroid gland function in TPEX lactating rats. In addition, these data confirmed the earlier report(12) in which it was suggested that the rise of serum calcium by calciferol was not mediated through stimuation of parathyroid glands. It is interesting that the milk secretion of the sham-operated group was higher than the milk secretion in normal non-sham-operated rats, indicating that the operation had no depressing effect upon subsequent lactation. It is apparent that the smaller sham-operated group included rats of somewhat greater normal lactation capacity than the larger control group.

Summary. Thyroparathyroidectomized lactating rats were administered calciferol (Vit. D_2) at a level of 0.2 mg/100 g BW in conjunction with 3 μg L-thyroxine/100 g BW from day 4 to 19. Milk yields determined on day 14, 16, 18, and 20 were not significantly different from the milk yield of a group of sham-operated rats but were higher than in a larger group of control animals. The litter weight of the experimental group was less than the sham-operated controls. Eight hours after operation serum Ca declined from 10.2 to 6.4 mg% but was restored to normal levels by calciferol on day 14 and 20. DNA content of the mammary glands of the two groups was similar. These data suggest that calciferol can take the place of the parathyroid hormone in mobilizing serum calcium adequate for the requirements of lactation in rats.

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Hemodynamic and Renal Effects of Octapressin.* (29032)

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Vasopressin possesses 3 main pharmacological properties: inhibition of diuresis, vasoconstriction, and contraction of intestinal smooth muscle. Recent studies(1,2) have indicated that a synthetic analogue octapressin† (2-phenylalanine-8-lysine-vasopressin) has marked vasoconstrictor but minimal antidiuretic activities.

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† Furnished as PLV-2 by Sandoz Pharmaceuticals, Hanover, U.S.A.

In the present studies, the effects of octapressin on systemic and regional circulation were investigated in dogs and man. Observations on changes in water and electrolyte excretion induced by infusion of this agent in human subjects are included.

Material and methods. I. *Animal Experiments.* Experiments were carried out on 13 pentobarbital anesthetized dogs (13-25 kg weight) ventilated mechanically with room air through an endotracheal tube by means of a Harvard respirator. Systemic arterial pressure was measured with a Statham transducer connected to a polyethylene catheter inserted into the aorta through the femoral artery. Cardiac output (ascending aortic flow), carotid, renal and femoral blood flows were measured with gated sine-wave electromagnetic flowmeters as previously described(3).‡ Flows, pressure and limb lead II electrocardiogram (EKG) were recorded simultaneously on an Offner dynograph equipped with electronic integrators.

Three types of animal preparations were used: (A) Normotensive dogs which were subjected only to the surgical procedures necessary to implant the electromagnetic flow probes and the pressure catheter; (B) Dogs in which endotoxin shock was induced with intravenous injections of 2 mg/kg of *E coli* lipopolysaccharide (Difco); (C) Dogs subjected to hypovolemic shock through intermittent bleeding until the mean arterial pressure was stabilized at 50-55 mmHg.

In the normotensive animals, after 30 to 60 minutes of control recordings of pressure and flows, octapressin was administered by constant infusion and the effects on pressure and flows were monitored continuously. In the animals subjected to endotoxin and hemorrhagic shock, the effects of these procedures on pressure and flows were recorded for 40 minutes. Thereafter, octapressin was given by constant infusion for a period of 30 to 60 minutes and the changes in flows and pressures were observed.

‡ All flow probes used in these experiments were made in our laboratories specifically for each vessel under study. A perfect fit without any undue constriction was obtained in each instance.

II. *Human Experiments.* A. *Dose-response relationship:* The effective pressor dose of octapressin in human subjects was established in 4 normal women maintained in the supine position. Pulse rate and blood pressure (sphygmomanometer) were recorded every 5 minutes for one hour. Octapressin was then injected intravenously in doses varying from 0.001 to 0.08 pressor units (PU)/min. Pulse and pressure were recorded every minute for 20 to 30 minutes, and every 5 minutes for an additional 30 to 60 minutes. Subjective and objective manifestations which could be interpreted as side effects of the drug were noted.

B. *Effects on renal hemodynamics and water and electrolyte excretion:* Three normotensive women without any history of cardiovascular or renal diseases volunteered for these studies. Inulin and PAH clearances were performed by techniques previously described(4). Following 3 control clearances, octapressin was administered by continuous intravenous infusion in doses of 0.05 PU/min. Three clearances of 20-30 minutes duration each were collected during the drug infusion.

Results. I. *Animal Experiments.* A. *Response in normotensive dogs:* Fig. 1 illustrates a typical experiment. Fig. 2 presents the average changes in flows and pressure in 4 dogs given 0.01 PU/min. Table I lists data obtained from all animal experiments. Infusion of octapressin in doses ranging from .0005 to .01 PU/kg/min over 30 to 60 minutes produced a progressive rise in arterial pressure which lasted throughout the infusion. Bradycardia occurred without evidence of any EKG alterations. The hypertension was accompanied by a consistent fall in cardiac output, carotid and femoral blood flows. The fall in cardiac output persisted for some time after discontinuing the infusion of the drug. In 2 of the 8 normal dogs, *pulsus alternans* appeared shortly after discontinuing the infusion. Renal blood flow fell to a lesser extent than cardiac output suggesting an increase in renal fraction.

B. *Response in endotoxin shock:* Infusion of octapressin for 30 to 60 minutes in 2 dogs with endotoxin shock increased the arterial

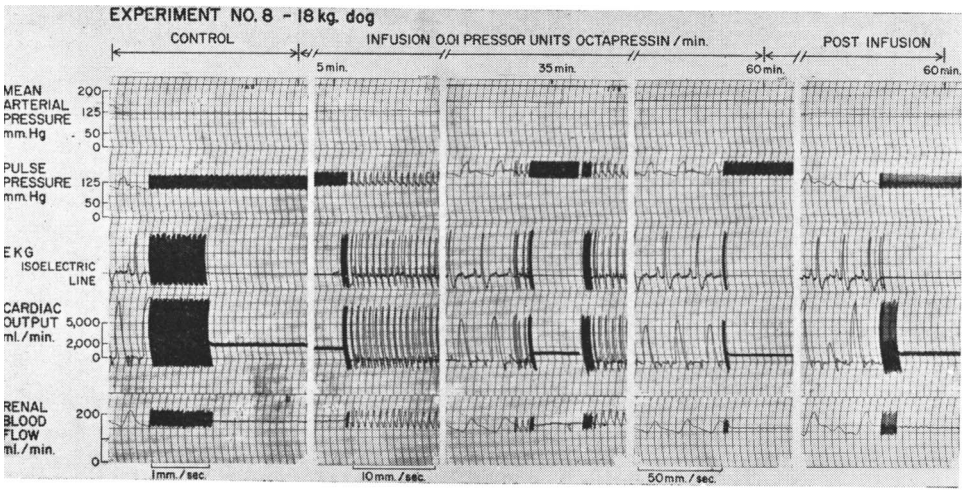

FIG. 1. Segments of record on effects of octapressin infusion in normotensive dog. Cardiac output fell consistently with the rise in pressure. Changes in renal flow were less marked.

TABLE I. Mean Changes (percent) in Flow and Pressure Induced by Octapressin in Normotensive Dogs and in Animals Subjected to Endotoxin and Hemorrhagic Shock. Figures represent maximum response observed.

	Dosage	Aortic pressure	Heart rate	Flow			
				Aorta	Renal	Femoral	Carotid
	(PU/kg/min.)						
Normal dogs (8)	.0005	+22	−17	−40	0	−32	−26
	.005	+28	−20	−69	−15	−35	−32
	.01	+37	−50	−71	−35	−50	−64
Endotoxin shock (2)	.05	+22	− 7	−34	+10		
Hemorrhagic shock	.005	+18	0	−12			−13

pressure significantly. The dose necessary to produce a given rise in pressure was, however, much larger than that used in normotensive dogs. Cardiac output, which had decreased considerably after injection of endotoxin, was depressed further by octapressin. Renal blood flow, which had been reduced by shock, increased slightly or remained unchanged during drug infusion.

C. *Response in hermorrhagic shock:* Infusion of .005 PU/kg/min of octapressin over 30 minutes to 5 dogs subjected to hemorrhagic shock elicited similar results to those observed in endotoxin shock. A rise in arterial pressure occurred which was, for that particular dose, significantly less than that oberved in normotensive dogs. A fall in aortic and carotid flows occurred with the rise in pressure.

II. *Human experiments.* A. *Dose-response relationship:* The effects of varying the dose of octapressin on pulse and blood pressure are presented in Table II. Increasing the dose elicited a progressively increasing pressor response and bradycardia.

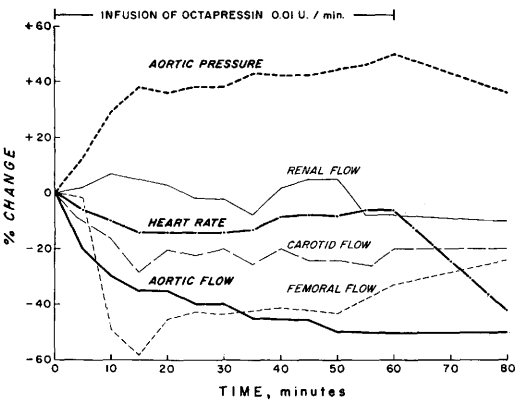

FIG. 2. Changes in aortic pressure, heart rate, aortic and regional blood flows induced by octapressin. All flows except renal decreased proportionally to the cardiac output.

TABLE II. Dose-response Relationship of Four Human Subjects to Octapressin. Figures on blood pressure and pulse rate represent average of 3 to 4 readings observed in the 4 subjects during peak action of the drug.

Dose (per min.)	Blood pressure	Pulse
Control	110/70	80
.001	110/70	80
.002	110/70	80
.003	120/70	72
.004	120/74	70
.005	126/76	68
.01	130/82	68
.02	132/84	72
.04	138/90	62
.05	142/96	60
.06	142/98	58
.08	146/94	56

B. *Effects on renal function:* Administration of 0.05 PU/min produced a significant rise in arterial pressure followed by a marked fall in urine flow, glomerular filtration rate, renal plasma flow and excretion of Na, K, Cl (Table III). Free water clearance (CH_2O) fell more than osmolal clearance (Cosm).

C. *Side effects:* During octapressin infusion, patients complained of generalized abdominal pain, headaches and fainting, and appeared critically ill. The severity of side effects prevented prolongation of the renal studies beyond 3 clearances.

Disscusion. The present data obtained from animals and man indicate that, in the normotensive state, octapressin has marked pressor activities which are, within certain ranges, linear with the dose. Such a pressor response is accompanied by a marked fall in cardiac output and a significant rise in total peripheral resistance. The exact mechanism of the decrease in cardiac output is not clear. The most likely explanation is that octapressin, while increasing peripheral resistance, produces a coronary vasoconstriction thereby depressing myocardial activities. This hypothesis is supported by the fact that other posterior pituitary hormones also have a constrictive action on the coronary vessels(7). The decrease in cardiac output which was observed in the post infusion period might also be attributed to the persistence of depressed myocardial activities consequent to octapressin infusion, although the presence of *pulsus alternans* might have been a contributing factor. The same mechanism might be operating in the dogs subjected to hemorrhagic and endotoxin shock. In these animals, the myocardium which is already depressed by the cardiovascular shock becomes further compromised by the coronary vasoconstriction produced by octapressin.

While the decreases in carotid and femoral flows are proportional to the decrease in cardiac output, the fall in renal flow is less marked. Octapressin seems to decrease renal vascular resistance thereby maintaining the renal fraction of the cardiac output at a higher level than the femoral and carotid fractions. This particular pharmacologic action of octapressin on the kidney is different from that of angiotensin and of catecholamines(5) and deserves further investigation.

In normotensive human subjects, octapressin depressed renal hemodynamics as well as water and electrolyte excretion. The magnitude of antidiuresis was closely similar to that induced by pitressin and oxytocin in a similar group of subjects(6). It is probable that the antidiuresis is not only related to the effects of this agent on water reabsorption, but also to its action on renal hemodynamics, since marked depression of glomerular filtration rate also depresses water excretion. It is not possible to assess the contribution of these 2 factors to the octapressin antidiuresis from these data.

TABLE III. Changes in Blood Pressure, Renal Hemodynamics and Electrolyte Excretion During Intravenous Infusion of Octapressin in Humans. Control figures represent average of 3 clearances.

Clearance	PB, mmHg	Pulse	U.F., ml/min.	GFR, ml/min.	RPF, ml/min.	Na, μEq/min.	K, μEq/min.	Cl, μEq/min.	Cosm	CH_2O
Control	110/70	81	4.56	129	815	120	75.5	87.5	2.64	1.76
1	140/88	79	1.31	99	728	118	102.9	74.4	1.79	.3
2	151/95	66	.85	83	368	96	60.9	76.8	1.54	.69
3	143/93	65	.75	71	313	88	48.0	69.2	1.32	.56

The present studies also show that while octapressin increases arterial pressure in the dog subjected to shock, it does not reverse the fall in cardiac outut brought about by endotoxin or hemorrhagic shock. In fact, cardiac output was further depressed by octapressin suggesting that the rise in the systemic pressure was accomplished at the expense of further increase in peripheral resistance. Moreover, the animals with shock seem to require larger doses to obtain a comparable rise in systemic pressure. This suggests a diminished responsiveness of the shocked animal to octapressin. These hemodynamic changes together with the severe side effects observed during administration of this agent to humans suggest that octapressin may have little use in the clinical management of shock.

Summary. 1. Circulatory effects of octapressin were investigated in normal human subjects, in normotensive dogs and in dogs subjected to endotoxin or hemorrhagic shock. 2. In normotensive dogs, octapressin produced a rise in arterial pressure and a fall in cardiac output, carotid and femoral flows, with a lesser fall in renal flow. 3. In dogs subjected to endotoxin or hemorrhagic shock, octapressin produced a rise in arterial pressure but did not reverse the fall in cardiac output. A larger dose was required to produce a given pressure rise in these animals. 4. In human subjects, octapressin decreased glomerular filtration rate, renal plasma flow, and the excretion of water and electrolytes.

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A Modification of the Traditional Thiry-Vella Loop for Precise Quantitative Absorption Studies. (29033)

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In 1864 Thiry(1) described his isolation of a segment of small intestine with its mesentery attached and reestablishment of bowel continuity by an end-to-end anastomosis. One terminal of the isolated loop was closed off, and the other led out and fastened to the skin. Later, Vella successfully performed a modification of the Thiry procedure by bringing both ends of the isolated loop of bowel out of the abdominal cavity onto the skin surface(2). This double orifice preparation has come to be known as the Thiry-Vella loop.

Leakage from the skin orifices of the standard loop proved incompatible with precise quantitative recovery, and in 1886 Gumilewski(3) proposed the modification of an internally placed balloon wrapped around the test catheter and inflated when the tube had been placed inside the Thiry-Vella loop. In 1902 Nagano described the use of a Thiry fistula with an internal water-filled balloon (4). Cobet, 1921, held his catheter in the fistula opening by individually custom-fitted internal and external balloons, thereby attempting to prevent catheter displacement and leakage due to inward migration by peristalsis(5) (Fig. 1).

Johnston(6) later published an operative modification of the Thiry fistula. He inverted