Beneficial Effect of Propranolol in a Histologically Appropriate Model of Postischemic Acute Renal Failure

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Acute renal failure caused in the rabbit by clamping one renal pedicle for 1 hour and removing the opposite kidney produced a histologic picture very similar to that observed in "hypotensive" acute renal failure in man. Intravenous infusion of propranolol, a drug which prevents renin release, at 1 mg/kg for 70 minutes beginning at time of pedicle clamping resulted in significantly lower serum creatinine in this model (2.8 ± 0.2 mg% at 48 hours with propranolol versus 5.2 ± 0.8 mg% without). Renin stimulation by dehydration or feeding a low-salt diet enhanced the difference between treated and untreated groups (2.6 ± 0.4 mg% with propranolol versus 6.2 ± 1.8 mg% without, after dehydration; 3.5 ± 1.0 mg% with propranolol versus 7.6 ± 1.4 mg% without, after low-salt diet). Suppression of renin production by saline feeding eliminated propranolol's beneficial effect (5.6 ± 0.9 mg% with propranolol versus 4.0 ± 0.6 mg% without). In rabbits with a normal food and water intake, renal denervation using phenol also eliminated propranolol's effect (creatinine 8.6 ± 1.4 mg% with propranolol versus 8.6 ± 1.8 mg% without). In rabbits with intact kidneys, flow probe recording of renal blood flow showed a significantly higher blood flow immediately after unclamping in the propranolol-treated animals, and renal angiograms showed less vasoconstriction in this group after unclamping. In this model of acute renal failure, renal vasoconstriction plays an important role following the initial ischemic insult. Propranolol lessens the severity of this vasoconstriction and the resulting acute renal failure. Its probable action is interference with neurogenically stimulated renin release. (Am J Pathol 88:163–192, 1977)

RESEARCH IN THE FIELD of acute renal failure (ARF) has long been hindered by the lack of appropriate animal models. Both the initiating events and the resulting histologic changes in the glycerol, mercuric chloride, uranyl nitrate, and norepinephrine infusion models of ARF are quite different from those encountered in the common type of ARF in man, which occurs following shock, sepsis, burn injury, or transfusion reaction [1–4] and is sometimes referred to as acute tubular necrosis but should probably be called *hypotensive ARF*. While the mechanisms of ARF in these various animal models remain unclear,[5–8] they may be entirely different from the mechanism of ARF in man.

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There is one animal model which appears to mimic closely a clinically important type of ARF. We have confirmed the original observation of Badenoch and Darmady [9] that ARF in the rabbit caused by occlusion of one renal artery for 1 hour coupled with removal of the opposite kidney resembles hypotensive ARF in man. It also resembles ARF in human cadaver renal transplants which have suffered ischemic damage during the interval between removal from the donor and placement in the recipient. In this experimental model the initiating event—an interference with blood flow—and the resulting histologic changes of tubular dilatation, cast formation, interstitial edema, and mild degenerative changes in the tubular epithelium are quite similar to those in human ARF of the hypotensive type.[1,9]

Iaina *et al.*[10] have recently demonstrated that infusion of the beta-blocking agent propranolol at 15 minutes before, during, and 15 minutes after a 70-minute occlusion of one renal pedicle in rats with the opposite kidney removed greatly diminishes the severity of renal function failure 24 hours later compared with rats with 70-minute occlusion and contralateral nephrectomy alone. One explanation for the beneficial effect of propranolol may be its ability to inhibit renin release.[11-13] If it can be assumed that the functional renal failure is caused in part by continuing vasoconstriction following release of renal artery obstruction, and if this vasoconstriction is due to activation of the renin–angiotensin system, propranolol could act by interfering with the initial release of renin by the kidney.

Because it is difficult to study the renal hemodynamics and to do renal angiography in the rat, we set out to determine whether propranolol has a similar beneficial effect in the rabbit with ARF produced by pedicle occlusion. We have studied the role of vasoconstriction, the renin–angiotensin system, and the renal nerves in this model by measuring renal blood flow, vasoconstriction as judged by angiography, and peripheral plasma renin activity. In addition, the histologic changes observed in this model have been compared with those encountered in the common "hypotensive" type of ARF in man.

Materials and Methods

Experiments were carried out on 3 to 4 kg female New Zealand white rabbits (Bunnyville Farms) which were allowed free access to tap water and Purina Chow.

Induction of Acute Renal Failure in Rabbits

Rabbits were anesthetized with intravenous sodium pentobarbital (50 mg/kg). Under sterile conditions, the abdomen was opened through a midline incision. In the standard operation, which was modified in some animals as described under Experimental Groups,

the right kidney was removed. The left kidney was then separated from the perirenal fat and a small rubber-covered bulldog clamp placed on the left renal artery and vein. In this paper we have referred to this maneuver as *pedicle clamping*. The ureter was not clamped. The clamps were removed from the artery and vein of the left kidney after 1 hour, and the surgical incision was closed using sutures. In initial studies, the rabbits were killed with an overdose of sodium pentobarbital 1 hour or 1, 2, 4, or 7 days after the initial surgery. In later experiments, all animals were killed at 2 days.

Renin, Urea Nitrogen, and Creatinine Determinations

Blood was taken from the marginal ear vein or distal inferior vena cava for plasma renin activity, serum urea nitrogen, and serum creatinine determinations before surgery and at the time of sacrifice. Plasma renin activity was measured using the antibody micromethod of Poulsen and Jørgensen [14] with a 16-hour incubation step and substitution of a 3.0 molar Tris buffer for the 6.0 molar buffer described in the original procedure. A 10-μl and a 50-μl aliquot of each sample were run concurrently. Serum urea nitrogen and creatinine were determined using automated methods.[15,16] Using these techniques, the following values for normal rabbits under pentobarbital anesthesia were found: renin, 0.32 ± .04 ng/ml/hr (N = 30); urea nitrogen, 18 ± 0.5 mg% (N = 74); and creatinine 1.3 ± 0.03 mg% (N = 74). It is appreciated that anesthesia may influence renin levels; for this reason the pentobarbital was given in a uniform fashion in all animals and care was taken to avoid excitement during induction.

Experimental Groups

The 23 groups from which renal functional and histologic data were obtained are described below. The procedures in these groups are also briefly outlined in Tables 1–5.

Groups A through D consisted of rabbits that underwent the standard operation outlined above and then were killed at 1 day (Group A), 2 days (Group B), 4 days (Group C), or 7 days (Group D).

Groups E, F, and G consisted of rabbits that underwent the same procedure as Group B except that propranolol (1 mg/kg) was administered as a constant infusion of a 1 mg/ml solution into the marginal ear vein over a 70-minute period beginning at the time of pedicle clamping (Group E), at the time of pedicle unclamping (Group F), or 10 minutes before pedicle clamping (Group G). Previous studies in this laboratory have shown that this dose of propranolol has no detectable effect on blood pressure.

In Group I, propranolol (0.005 mg/kg in 2 ml of heparinized saline [50 units heparin/ml]) was injected directly into the left renal artery distal to the occluding clamp immediately after placement of the arterial clamp and immediately before placement of a second clamp on the renal vein. Since this small dose of propranolol was given in a volume of fluid approximately equal to the volume of the vasculature in one rabbit kidney,[17] it is unlikely that it had a systemic effect. Rabbits given an injection of heparinized saline alone were used as controls (Group H).

Groups J–S were designed to study the influence of hydration, the renin–angiotensin system, and the renal nerves on propranolol's effect in this model of acute renal failure. Animals in Groups J and K were given 1% NaCl rather than tap water to drink for 3 weeks before surgery to suppress the renin–angiotensin system. Group J was otherwise similar to Group B (untreated) and Group K similar to Group E (propranolol treated). Groups L and M were similar to Groups B and E, respectively, except that water was withheld for 24 hours before surgery. Groups N and O were fed a sodium-deficient diet (< 40 mEq Na/kg diet; Nutritional Biochemicals Corp., Cleveland, Ohio) for 10 days prior to surgery and given furosemide 1 mg/kg daily in their drinking water on Days 2 to 9 of the diet to stimulate the renin–angiotensin system. They were otherwise treated similarly to Groups B and E, respectively, as were Groups P and Q, in which a bolus of intravenous furosemide (1

mg/kg) was given 30 minutes before pedicle clamping, and 10 minutes before the preoperative blood sample was taken. Groups R and S were treated similarly to Groups B and E except that the left renal artery was denervated by applying 10% phenol in ethyl alcohol to the renal artery and carefully stripping the adventitia. This denervation procedure was carried out after the placement of the clamp on the renal pedicle and was designed to assess the possible usefulness of propranolol in preventing ischemic damage in transplanted kidneys, which are of necessity denervated.

In order to produce a model of ARF more similar to "hypotensive" acute renal failure in man (in which both kidneys are involved), experiments were carried out in which both renal pedicles of rabbits were occluded for 70 minutes. In Group T, no propranolol was given. In Group U, propranolol (1 mg/kg) was infused intravenously during pedicle clamping. In Group V a similar infusion (70 minutes) was given beginning at the time of unclamping. In addition, a group of animals (Group W) was prepared which was identical to Group B except that the left renal pedicle was clamped for 70 minutes rather than 60. Animals in Group E–W were all killed at 2 days after operation. In addition to these groups there were two groups of animals similar to Groups B and E that were killed 1 hour after unclamping and used for histologic studies. All groups were allowed free access to tap water and Purina Chow for the 2 days after operation, except Groups N and O which were maintained on a low-sodium diet and tap water.

Histologic Methods

Sections of the kidney taken through the midportion of the kidney parallel to its short axis were fixed in buffered 10% formalin for light microscopic examination immediately after the rabbits were killed. The number of hyaline casts observed in five random cortical, outer medullary, and inner medullary fields at a magnification of 100 times was determined for each rabbit, and the accumulation of leukocytes in the vasa recta was graded on a scale of 0 to 3+. These determinations were made without knowledge of the rabbit's treatment or renal function.

Angiographic Studies

Aortograms were performed in a separate set of experiments. Transfemoral artery catheterization was carried out using a 4 French end-hole polyethylene catheter under pentobarbital anesthesia. The tip was placed in the aorta approximately 2 cm below the origin of the left renal artery to minimize the chance of catheter-induced vascular spasm or renal embolization. The animals were heparinized with 10 units heparin/kg at the time of initial insertion of the catheter, and this dose was repeated 1 hour later. The right kidney was removed, and the left renal pedicle was clamped for 60 minutes. One group received propranolol (1 mg/kg), administered with a constant infusion pump for 70 minutes beginning at the time of pedicle clamping. The control group received no propranolol. Aortograms were obtained preceding surgery and at 8-, 20-, and 45-minute intervals after the release of the clamp on the renal pedicle. For each arteriogram, Renografin-60 (combined meglumine and sodium ditrizoate salt) was injected using an Amplatz injector at 100 lbs/sq inch in a dose of 2.2 cu cm/kg. The filming sequence was 2 films/sec for 3 seconds and then 1 film/sec for 6 seconds. Five minutes following the 20-minute arteriogram, a 4× magnification intravenous urogram was obtained using a 0.3 mm bias grid Machett tube. The bladder was emptied by manual pressure at the time the renal pedicle was clamped. Samples of blood for renin determination were obtained from the aortic catheter immediately before each arteriogram was performed. Following completion of arteriographic studies, each rabbit was killed by pentobarbital overdose and sections of the kidneys were fixed in buffered 10% formalin for light microscopic examination as described earlier. The arteriograms were analyzed for several different features: a) Function of the kidney was evaluated by observing the presence or absence of contrast material within the

collecting system. b) The lack of homogeneity of the nephrogram was evaluated against a group of standards. c) The degree of narrowing and irregularity of the main renal artery and the intrarenal branches was evaluated on a scale of 0 to 4+. Zero was considered normal. The case with the greatest degree of renal artery irregularity was considered 4+ abnormal.

Determination of Renal Blood Flow

Blood flow in the left renal artery was determined using a Narco Biosystems RT-400 electromagnetic flowmeter with a flow probe having a luminal diameter of 1.5 mm. The rabbits were anesthesized with sodium pentobarbital (50 mg/kg), and the abdomen was opened through a midline incision. The right kidney was removed as described earlier. The mobile loops of bowel in the vicinity of the left kidney were placed in a plastic bag and moved to the right to allow for easy visualization of the left renal pedicle. The left kidney was freed from the perirenal fat, and the flow probe then placed on the left renal artery. Dissection around the renal artery was kept to a minimum to avoid denervating the kidney. After a 30-minute period of equilibration, a small bulldog clamp was placed on the renal artery distal to the probe. After 1 hour, the clamp was removed, taking care not to alter the physical relationship of the flow probe to the renal artery, and blood flow was measured for an additional 60 minutes. Propranolol (1 mg/kg) was infused intravenously during the hour of clamping in 8 animals; another 8 received no propranolol. A control group of 8 animals was also studied in which the right kidney was removed, but no clamp was placed on the left renal artery.

Statistical Treatment

Student's t test [18] (two-tailed) was used to evaluate the significance of differences between means in the experimental groups. Linear correlation coefficients were determined as described by Dixon and Massey.[18]

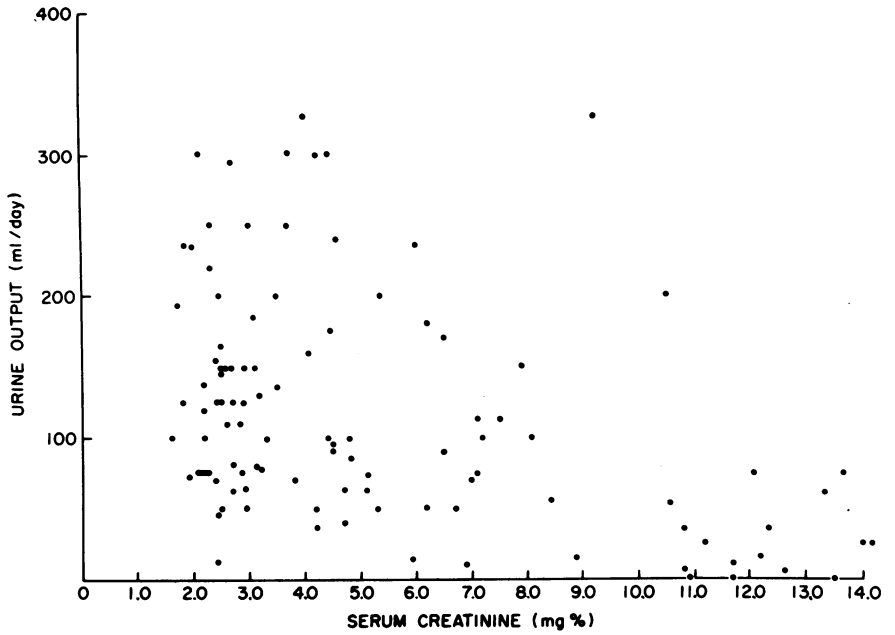
Results

Characteristics of the Renal Failure

As is seen in Table 1, removing the right kidney and clamping the pedicle of the left kidney for 1 hour resulted in moderately severe renal failure which was uniform in its severity through the second day but was more variable at 4 and 7 days. Although there were no meaningful differences in urine output among any of the experimental groups, animals with severe renal failure did tend to be oliguric during the first 2 days after surgery (Text-figure 1) and there was a significant inverse correlation between serum creatinine and urine output ($r = 0.41$, $P < 0.001$). Urine output in 6 normal control rabbits given the standard dose of pentobarbital was 159 ± 28 (SE) ml/day. Urine output in 9 control rabbits during the last 24 hours of 36-hour period of dehydration was 54 ± 5 (SE) ml. Using the 95% confidence limits for these two groups to generate a conservative definition of oliguria, 10 of the 37 rabbits with creatinine values greater than 5 mg% were oliguric (urine output, <20 ml/day). Thirteen of these 37 rabbits (35%) had urine outputs below the published normal range for rabbits (34 to 935 ml/day).[19]

Table 1—Changes in Serum Urea Nitrogen and Creatinine Levels and Renal Histology Over Time in Pedicle Clamping Model

Group	Procedure	SUN (mg/dl ± SEM)	Creatinine (mg/dl ± SEM)	Casts (No. in five random 100 × fields)			Vasa recta lesion (0–3+)
				Cortex	Outer medulla	Inner medulla	
A	Right nephrectomy; left renal pedicle clamped for 1 hr; sacrificed 1 day later (N = 6)	56 ± 6	3.8 ± 0.5	24 ± 4	102 ± 20	134 ± 36	1.0 ± 0.1
B	As in A, but sacrificed 2 days after operation (N = 11)	84 ± 11	5.2 ± 0.8	46 ± 11	78 ± 21	111 ± 39	1.3 ± 0.3
C	As in A, but sacrificed 4 days after operation (N = 6)	84 ± 22	6.2 ± 2.0	47 ± 10	65 ± 29	79 ± 47	1.1 ± 0.3
D	As in A, but sacrificed 7 days after operation (N = 6)	115 ± 55	7.8 ± 3.4	7 ± 3	35 ± 23	71 ± 33	.9 ± 0.3



TEXT-FIGURE 1—Plot of average daily urine volume for the 2 days following temporary pedicle clamping versus creatinine at 2 days in the animals in Groups B, E–G, and J–Q.

Effects of Propranolol Treatment on Severity of Renal Failure

As shown in Table 2, intravenous infusion of propranolol (1 mg/kg) during the hour of pedicle clamping and for 10 minutes after release of the clamp (Group E) resulted in significantly lower serum urea nitrogen and creatinine levels at the time of sacrifice 48 hours later compared with animals subjected to 1 hour of pedicle clamping and no propranolol

Table 2—Effects of Propranolol Given Systemically Measured at 48 Hours After Administration

Group	Procedure	SUN (mg/dl ± SEM)	Creatinine (mg/dl ± SEM)
B	Right nephrectomy clamp left pedicle for 1 hr (N = 11)	84 ± 11	5.2 ± 0.8
E	As in B, but IV propranolol infusion given for 70 minutes beginning at time of clamping (N = 6)	50 ± 8*	2.8 ± 0.2*
F	As in B, but IV propranolol infusion given for 70 minutes after unclamping (N = 6)	63 ± 17	3.9 ± 1.4
G	As in B, but IV propranolol infusion given for 70 minutes starting 10 minutes before clamping (N = 7)	100 ± 18	5.7 ± 1.5

* Values significantly different from those in Group B ($P < 0.05$).

Table 3—Effects of Propranolol Given Directly Into Renal Artery on Serum Urea Nitrogen and Creatinine Levels, Plasma Renin Activity, and Renal Histology at 48 Hours

Group	Procedure	SUN (mg/dl ± SEM)	Creatinine (mg/dl ± SEM)	Renin (ng/ml/hr)	Casts (No. in five 100 × fields)			Vasa recta lesion (0–3+)
					Cortex	Outer medulla	Inner medulla	
H	Right nephrectomy; left clamp for 1 hr and saline into renal artery distal to clamp (N = 9)	138 ± 12	9.9 ± 1.3	0.69 ± 0.17	132 ± 62	116 ± 23	127 ± 37	1.4 ± .3
I	Right nephrectomy; left clamp for 1 hr; propranolol into renal artery distal to clamp (N = 8)	92 ± 15*	5.9 ± 1.2*	0.55 ± 0.09	105 ± 61	107 ± 26	89 ± 34	1.0 ± .3

* Values significantly different from those in Group H ($P < 0.05$).

Table 4—Effects of Hydration, Sodium Balance, and Renal Denervation on Action of Propranolol

Group	Procedure	At 48 hours (mg/dl ± SEM) SUN	Creatinine	Plasma renin activity (ng/ml/hr ± SEM) Preoperatively	48 hr postoperatively
B	Right nephrectomy; clamp left pedicle for 1 hr (N = 11)	84 ± 11	5.2 ± 0.8	0.32 ± .07	0.97 ± .32
J	Saline for 3 weeks; right nephrectomy; clamp left pedicle for 1 hr (N = 10)	63 ± 10	4.0 ± 0.6	0.13 ± .02	0.21 ± .03
K	As in J, but IV propranolol infusion given for 70 minutes from beginning of clamping (N = 12)	90 ± 12	5.6 ± 0.9	0.16 ± .02	0.40 ± .07
L	No water for 24 hrs; right nephrectomy; clamp left pedicle for 1 hr (N = 6)	98 ± 20	6.2 ± 1.8	0.71 ± .12	0.71 ± .19
M	As in L, but IV propranolol infusion given for 70 minutes from beginning of clamping (N = 6)	47 ± 7*	2.6 ± 0.4†	0.74 ± .05	0.39 ± .05
N	Low-sodium diet for 10 days; furosemide (1 mg/kg) on Days 2-9 of the diet; right nephrectomy; clamp left pedicle for 1 hr (N = 7)	99 ± 16	7.6 ± 1.4	1.31 ± .27	1.05 ± .12
O	As in N, but IV propranolol infusion given for 70 minutes starting at time of clamping (N = 6)	58 ± 10	3.5 ± 1.0‡	1.30 ± .17	1.16 ± .20
P	Furosemide (1 mg/kg) given IV 30 minutes before clamping; right nephrectomy; clamp left pedicle for 1 hr (N = 8)	122 ± 17	6.8 ± 1.0	0.80 ± .10	0.65 ± .15
Q	As in P, but IV propranolol infusion given for 70 minutes starting at time of clamping (N = 9)	111 ± 16	6.9 ± 1.2	0.72 ± .10	0.71 ± .13
R	Renal denervation with phenol; right nephrectomy; left renal artery clamping for 1 hr, (N = 7)	120 ± 18	8.6 ± 1.4	0.33 ± .06	0.52 ± .08
S	As in R, but IV propranolol infusion for 70 minutes starting at time of clamping (N = 6)	113 ± 21	8.6 ± 1.8	0.30 ± .02	0.60 ± .08

* Value significantly different from that in Groups L and B ($P < 0.05$).
† Value significantly different from that in Group B ($P < 0.05$).
‡ Value significantly different from that in Group N ($P < 0.05$).

(Group B). When propranolol was infused for 70 minutes beginning at the time of unclamping (Group F) or 10 minutes before clamping (Group G), it had no significant effect. We have attributed the absence of a beneficial effect of propranolol in Group F to an inadequate blood level of the drug immediately after unclamping and in Group G to the vasoconstrictor effect of propranolol in the preclamping period (see Discussion).

Table 3 shows that when propranolol (0.005 mg/kg in 2 ml of heparinized saline) was injected directly into the distal renal artery immediately after pedicle clamping (Group I), the resulting serum urea nitrogen and creatinine levels were significantly lower than those of rabbits in which heparinized saline alone was injected into the distal renal artery after pedicle clamping (Group H). Values in both groups were higher than in corresponding Groups B and E, possibly as a result of trauma to the renal artery. Plasma renin levels were elevated at the time of sacrifice in both Groups H and I.

Giving 1% NaCl as drinking water resulted in significant suppression of plasma renin activity but had no significant effect on the severity of renal failure (Group J compared with Group B, Table 4). No beneficial effect of propranolol could be demonstrated in these saline-treated animals (Group K compared with Group J). Dehydration for 24 hours (Groups L and M), did result in elevation of renin activity but did not produce more severe renal failure. In animals so treated, propranolol retained its beneficial effect, Group M being significantly different from L and B. In Groups N and O, furosemide treatment and a low-salt diet resulted in marked elevation of renin activity but no significant increase in the severity of renal failure (Group N compared with Group B). In this setting, propranolol had a beneficial effect. Propranolol was ineffective in lessening the severity of renal failure in rabbits in which renin release was acutely stimulated by an intravenous bolus of furosemide 30 minutes before clamping the renal pedicle (Groups P and Q), perhaps because renin release in this setting is not dependent on the renal sympathetic nerves (see Discussion). Acute renal denervation (Group R) resulted in significantly more severe renal failure. Propranolol was ineffective in reducing the severity of renal failure in the denervated rabbit kidney (Group S).

When both renal pedicles of rabbits were clamped for 70 minutes, propranolol had a salutary effect when infused during or after clamping (Groups U and V compared to T in Table 5). When one kidney was removed and the other clamped for 70 minutes (Group W), the resulting renal failure was significantly more severe than in Group B (60-minute clamp).

Plasma renin values were significantly elevated in Groups B, L, N, O, S,

Table 5—Effects of Propranolol on Bilateral Clamping Model 48 Hours Postoperatively

Group	Procedure	SUN (mg/dl ± SEM)	Creatinine (mg/dl ± SEM)	Plasma renin activity (ng/ml/hr ± SEM)
T	Both renal pedicles clamped 70 minutes (N = 6)	125 ± 10	8.7 ± 1.5	0.77 ± 0.17
U	As in T, but IV propranolol infusion during clamping (N = 6)	43 ± 3*	2.2 ± 0.5*	0.39 ± 0.05
V	As in T, but propranolol infused for 70 minutes beginning at time of unclamping (N = 5)	54 ± 11*	2.7 ± 0.9*	0.52 ± 0.08
W	Right nephrectomy; left renal pedicle clamped for 70 minutes (N = 6)	130 ± 18	9.2 ± 1.6	0.55 ± 0.22

* Values significantly different from those in Group T ($P < 0.01$).

T, and V at the time of sacrifice, but no correlation was observed between renin levels and plasma creatinine ($r = 0.08$). Renin levels in propranolol-treated groups were not significantly different from those in corresponding control groups.

Histologic Changes

One hour after removal of the pedicle clamp, dilatation of all segments of the nephron (especially distal tubules and collecting ducts) was observed (Figure 1A). This was more striking in animals which had received radiographic contrast medium. Loosely-formed eosinophilic hyaline masses (Figure 1B) were present in tubular lumina. As shown in Table 6, in

Table 6—Histologic Changes 1 Hour After Unclamping

Procedure	Casts (No. in five 100 × fields)			Vasa recta lesions (0–3)
	Cortex	Outer medulla	Inner medulla	
Like B (right nephrectomy; clamp left pedicle for 1 hr) (N = 8)	26 ± 5	22 ± 3	45 ± 9	1.7 ± .2
Like B, but IV propranolol infusion given for 70 minutes from beginning of clamping (N = 8)	25 ± 6	26 ± 4	25 ± 7*	1.5 ± .2
Like B, but contrast material given before clamping and 8, 20, and 45 minutes after unclamping (N = 6)	8 ± 2*	6 ± 2*	1 ± 1*	0.3 ± .1*
Like B, but both propranolol and contrast material given in the manner detailed above (N = 6)	5 ± 1*	5 ± 2*	1 ± 1*	0.3 ± .1*

* Significantly different from corresponding value in first group in this table ($P < 0.05$).

animals which did not receive contrast material, propranolol infusion for 70 minutes beginning at the time of clamping resulted in fewer inner medullary hyaline casts ($P < 0.05$). There was no difference in the number of cortical casts or outer medullary casts. Polymorphonuclear leukocytes were present in the vasa recta and peritubular capillaries of the renal medulla (Figure 1C). Average scoring of the vasa recta lesion was no different in propranolol treated and untreated rabbits. In the animals which had received radiographic contrast material, the situation was quite different. In these groups, there were no differences between control animals and those which received propranolol, but the numbers of casts observed in all areas of the kidney and the severity of changes in the vasa recta were less than those observed in animals which did not receive contrast material.

One day after pedicle clamping, dilatation of tubules was less prominent than at 1 hour but was still obvious, especially in the outer medulla. The tubular epithelium in the cortex appeared intact. In the outer medulla, however, isolated necroses were seen in segments of the thick ascending limbs. Marginating polymorphonuclear leukocytes were present in nearby vasa recta and peritubular capillaries (Figure 2).

Two days after pedicle clamping, the most striking morphologic abnormality was the presence of hyaline and granular casts in tubules lined by intact tubular epithelium (Figures 3 and 4). Obvious necroses were rare and, when they did occur, they affected isolated tubular cells rather than whole tubular cross sections (Figure 5). The extensive and obvious tubular necrosis found in most other animal models of ARF, with replacement of entire tubular cross sections by granular debris, was not observed. Tubules and collecting ducts were moderately dilated, and the epithelium was frequently flattened, especially in tubules containing casts. Some tubular cells had large nuclei and basophilic cytoplasm, features suggesting regeneration. These morphologic alterations made it difficult to differentiate proximal and distal tubules. Occasional mitoses were seen in tubular epithelial cells. There was mild-to-moderate interstitial edema. In the medulla, accumulations of mononuclear cells as well as polymorphonuclear leukocytes were observed in the vasa recta (Figure 6). Chronic inflammatory infiltrates were sometimes seen at the corticomedullary junction (Figure 7). Electron microscopy performed on 4 animals showed no foot process fusion in glomeruli, which otherwise appeared normal. Histologic findings at 4 days were similar to those at 2 days, except that there was less evidence of necrosis and more regeneration (Figure 8). In animals sacrificed at 7 days after pedicle clamping, the number of casts had greatly diminished, even in those animals with severe renal failure. In those

animals in which renal function had largely recovered by this time, the kidney showed only mild interstitial edema. In those animals with severe renal impairment at 7 days, there was marked interstitial edema, striking dilatation of distal and sometimes proximal tubules, a moderate interstitial chronic inflammatory infiltrate at the corticomedullary junction (Figure 9), and prominent accumulations of leukocytes in the vasa recta.

Overall, the changes observed in this animal model of ARF were similar to those previously described in ARF in man.[1,3,9,20]

In general, histologic changes at 2 days after operation appeared to be less severe in the propranolol-treated groups than in the untreated groups (Table 7). Statistically significant differences in number of cortical casts were observed between Groups B and E, L and M, and N and O. Considering the combined data from all the groups, there was a signifi-

Table 7—Histologic Findings at 48 Hours

Group	Procedure	Casts (No. in five 100 × fields)			Vasa recta lesion (0–3+)
		Cortex	Outer medulla	Inner medulla	
B	Right nephrectomy clamp left pedicle for 1 hr (N = 11)	46 ± 11	78 ± 21	111 ± 39	1.3 ± 0.3
E	As in B, but IV propranolol infusion given for 70 minutes from beginning of clamping (N = 6)	19 ± 3	29 ± 6	16 ± 4	0.9 ± 0.2
J	Saline for 3 weeks; right nephrectomy; clamp left pedicle for 1 hr (N = 10)	27 ± 8	81 ± 27	72 ± 12	0.3 ± 0.1
K	As in J, but IV propranolol infusion given for 70 minutes from beginning of clamping (N = 12)	34 ± 9	127 ± 24	139 ± 20	0.8 ± 0.1
L	No water for 24 hrs; right nephrectomy; clamp left pedicle for 1 hr (N = 6)	39 ± 7	72 ± 20	147 ± 55	1.8 ± 0.6
M	As in L, but IV propranolol infusion given for 70 minutes from beginning of clamping (N = 6)	11 ± 3	53 ± 8	80 ± 11	0.8 ± 0.3
N	Low-sodium diet for 10 days; furosemide (1 mg/kg) on Days 2–9 of the diet; right nephrectomy; clamp left pedicle for 1 hr (N = 7)	42 ± 8	37 ± 14	15 ± 8	1.6 ± 0.2
O	As in N, but IV propranolol infusion given for 70 minutes starting at time of clamping (N = 6)	17 ± 10	26 ± 22	23 ± 17	1.5 ± 0.1

* Significantly different ($P < 0.05$) values are marked with braces.

cantly linear correlation between the severity of the vasa recta lesion and serum creatinine ($r = 0.51$, $P < 0.001$) and between the number of cortical casts and serum creatinine ($r = 0.49$, $P < 0.001$). There was no significant correlation between outer or inner medullary casts and serum creatinine ($r = 0.09$ and 0.14, respectively). Massive cortical necrosis was observed in 2 animals in Group H, 2 in Group I, 1 in Group R, 2 in Group S, and 1 in Group T. It is likely that thrombosis of the renal artery occurred in these 8 rabbits, but this was not documented histologically. There were no qualitative differences between the histologic changes in the three groups (T, U, V) in which the pedicles of both kidneys were clamped and the changes in other groups.

Angiographic Studies

Angiographic changes previously reported in "acute tubular necrosis" (hypotensive ARF) include a gentle attenuation of the distal interlobar and arcuate arteries with failure of visualization of the more peripheral vessels, abnormalities of the cortical portion of the nephrogram reflecting these vascular changes, and a slow transit time of contrast media through the renal vessels.[21] With our technique and equipment, it was not possible to see the smaller intrarenal vessels with any precision.

The most striking radiographic difference between the propranolol-treated and untreated rabbits was seen on the intravenous pyelogram films obtained 25 minutes after unclamping of the renal pedicle. At that time, 5 of the 6 propranolol-treated rabbits showed evidence of good renal function with contrast material seen in the renal pelvis and ureter, while equivalent evidence of function was seen in only 2 of the 6 untreated rabbits.

Mean levels of renal vasoconstriction of the main renal artery and its major branches were lower in the propranolol-treated group 8 minutes after unclamping (Table 8), but little difference was seen between the two groups at later time periods. Renin levels were significantly elevated at 8 minutes in the untreated group but not in the treated group. In the untreated group the severity of vasoconstriction tended to decrease during the 45 minutes after unclamping. This trend was less apparent in the treated group (Table 8 and Figure 10A and B).

An evaluation of the cortical nephrogram, a reflection of the perfusion of small vessels of renal cortex, revealed a lack of homogeneity in 5 of the 6 control animals and in 4 of the 5 propranolol-treated animals (in 1 it could not be assessed) (Figure 10A and C). While the groups are small, the degree of homogeneity in the control animals was slightly less than in the propranolol-treated animals.

Table 8—Changes in Renin Activity and Vascular Caliber in Angiographic Studies

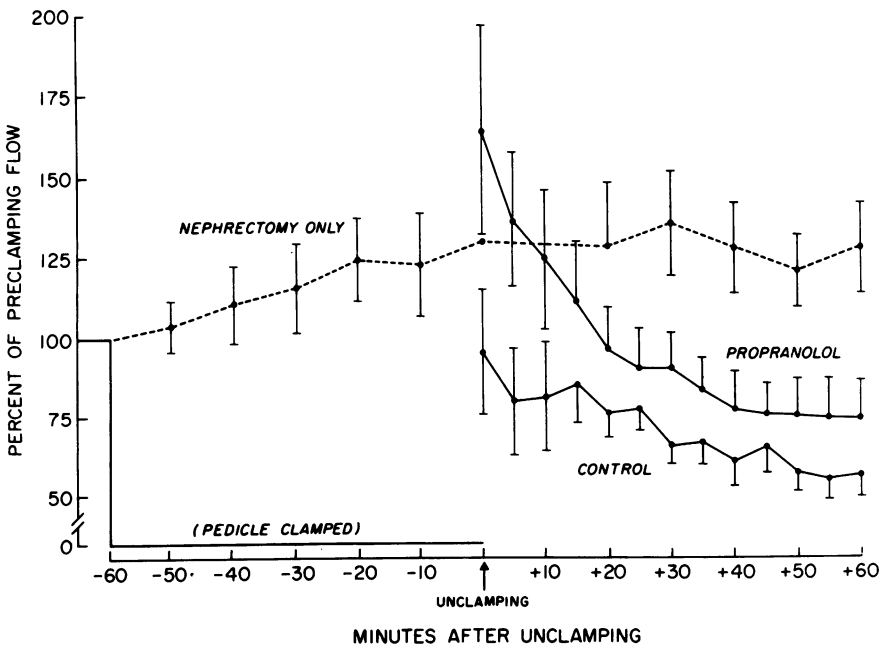
	Control period (before clamping)		8 minutes after unclamping		20 minutes after unclamping		45 minutes after unclamping	
	Renin (ng/ml/hr)	Vaso-constriction	Renin (ng/ml/hr)	Vaso-constriction	Renin (ng/ml/hr)	Vaso-constriction	Renin (ng/ml/hr)	Vaso-constriction
Untreated (like B) (N = 6)	0.54 ± 0.11	0.5 ± 0.1	0.84 ± 0.20*	2.3 ± 0.4	0.95 ± 0.19*	1.2 ± 0.3	0.96 ± 0.13*	1.1 ± 0.3
Propranolol-treated (like E) (N = 6)	0.37 ± 0.10	0.5 ± 0.1	0.69 ± 0.17	1.2 ± 0.5	0.70 ± 0.13*	0.8 ± 0.1	0.99 ± 0.28*	1.1 ± 0.3

* Renin values significantly elevated compared with preclamping levels in same animals ($P < 0.05$).

In summary: The findings of the radiographic studies give further graphic evidence that a process radiologically resembling "acute tubular necrosis" in man was produced in most of the experimental animals and also confirmed the finding of a lesser degree of impairment of renal function in the propranolol-treated animals.

Renal Blood Flow

Baseline blood flow before clamping was similar in the three groups studied (44.5 ± 5.0 ml/min in the control group, 44.3 ± 3.8 ml/min in the group later given propranolol, and 43.0 ± 5.1 ml/min in the group in which right nephrectomy only was performed [no clamping]). Blood flow after unclamping was expressed as a percentage of preclamping flow for each rabbit. As can be seen from Text-figure 2, mean blood flow was consistently higher in the propranolol-treated group after unclamping compared with the control group, and these differences were statistically significant immediately after unclamping and 5 and 10 minutes after unclamping. In both of these groups, blood flow steadily decreased in the period after unclamping (from 164 ± 33.5% to 74.1 ± 12.7% in the propranolol-treated group, and from 95.5 ± 20.1% to 55.8 ± 7.2% in the



TEXT-FIGURE 2—Renal blood flow over time in control group, propranolol-treated group, and nephrectomy-only group.

untreated group). In the group in which only the right nephrectomy was carried out there was a slight rise in blood flow over the 2-hour period of observation.

Discussion

Three aspects of the present study warrant discussion: a) the histologic similarity of the pedicle clamping model of ARF in the rabbit to "hypotensive" ARF in man, b) the apparent involvement of the renin–angiotensin system in both the renal failure itself and in propranolol's beneficial effect on it, and c) the dependence of propranolol's effect on the intactness of the renal nerves.

"Hypotensive" ARF in man is characterized histologically by interstitial edema, tubular dilatation, accumulations of white cells in the vasa recta, and relatively inapparent tubular necrosis.[1] The model in ARF described in this paper appears to differ histologically from "hypotensive" ARF in man only to the extent that the normal rabbit differs from the normal human kidney (different size and configuration of glomeruli and tubules, relatively narrow medullary outer stripe,[22] etc.). The absence of extensive tubular necrosis makes this model strikingly different from other animal models of ARF,[3,23,24] The tubular dilatation observed at 1 hour after unclamping is similar to that commonly seen in wedge biopsies of ischemically damaged human renal allografts taken 1 hour after vascular anastomoses are completed. This tubular dilatation lends support to the idea that increased intratubular pressure, perhaps caused by obstruction of the tubule by debris, plays a role in the initiation of acute renal failure.[5] Tubular dilatation is present to a variable degree at later time periods, being especially prominent in animals with more severe renal failure. It is possible that the marginating polymorphonuclear leukocytes in medullary vessels observed at 1 hour and 1 day after unclamping also occur in postischemic or "hypotensive" ARF in man but have not been observed because the customary wedge biopsies of renal transplants do not contain medullary tissue, and percutaneous needle biopsies are not performed so early in the course of human ARF. This polymorphonuclear leukocyte response in the vasa recta and peritubular capillaries may be a reaction to focal necrosis of medullary thick ascending limbs and appears to be the forerunner of the accumulations of polymorphonuclear leukocytes, lymphocytes, and monocytes in the vasa recta that are a characteristic feature of established ARF in both man and experimental animals.[3] These accumulations persist even though the necrotic lesions in the medulla heal quite rapidly, presumably because of their very focal nature. At no time is there necrosis of more than a few isolated tubular epithelial cells in the

renal cortex in the rabbit model used in this study. Thus the model is morphologically quite different not only from the "nephrotoxic" animal models but also from "circulatory" models such as the glycerol[23] and norepinephrine infusion models.[24]

It seems likely that the basic pathophysiology of the rabbit model described in this paper resembles that in human hypotensive ARF and differs from that in other animal models.[3,23,24] Significant oliguria is observed in this type of experimental ARF, a feature not observed in most other types. The elevation of plasma renin activity observed during the established phase of ARF is evidence in favor of a significant role for the renin–angiotensin system in this model. This contrasts with the normal levels of plasma renin observed in many other animal models.[6] The higher blood flow immediately after unclamping in propranolol–treated animals is probably due to inhibition of renin release in this group and probably accounts for propranolol's beneficial effect. Blood flows were significantly different in the propranolol–treated and untreated groups for 10 minutes (Text-figure 2). To demonstrate that these 10 minutes could be of crucial importance, we prepared a group of animals identical to Group B except that the left renal pedicle was clamped for 70 minutes rather than 60 minutes (Group W). Renal failure was significantly more severe ($P < 0.05$) in this 70-minute group (Tables 2 and 5). Thus, it would appear that propranolol's effect could be explained by the blood flow alterations observed. Propranolol had no beneficial effect in renin-depleted animals and had its greatest effect in sodium-depleted animals in which the renin system was highly active. However, several observations indicate that the renin–angiotensin system is not the only important factor. In contrast to other models,[25,26] renin depletion caused by saline loading did not significantly decrease the severity of ARF (although histologic changes were significantly less severe, see Table 7, and levels of SUN and creatinine were lower, although not significantly, Table 4), nor did stimulation of the renin–angiotensin system by sodium depletion or dehydration significantly increase the severity of ARF (although SUN and creatinine levels were higher, Table 4). In the angiographic studies, plasma renin activity measurements did not correlate with the degree of renal vasoconstriction. Angiotensin II is apparently incapable of producing large vessel vasoconstriction of the sort observed angiographically in this model of ARF and in ARF in man [7] and it is possible that these changes are brought about through neural stimulation or the action of circulating catecholamines.[27] Although serum urea nitrogen and creatinine levels in Groups J, L, and N are not significantly different from those in Group B, it is interesting to note that the rankings of mean serum urea nitrogen,

creatinine, and plasma renin activity are identical in the four groups (J lowest, then B, L, and N), and creatinine levels in Group J are significantly lower than those in Group N. These facts suggest that the renin–angiotensin system plays an important role in this model of acute renal failure.

Propranolol is known to inhibit basal plasma renin activity in the rabbit when given in the dose employed in this study.[28] Unlike the situation in many other animals, the rabbit's cardiovascular response to propranolol is very similar to that observed in man.[29] The relatively unimpressive differences between plasma renin activity 8 minutes after unclamping in the propranolol-treated and untreated rabbits (Table 7) may be misleading. If the renin–angiotensin system is reducing renal blood flow after unclamping through renin and/or angiotensin gaining access to arterioles from the adventitial side, the peripheral plasma renin activity measurements may be a poor index of such intrarenal renin release. Thurau and Mason [30] have estimated that renin activity in the lymph surrounding the juxtaglomerular apparatus is 10^9 times higher than that in peripheral plasma. These investigators have accumulated evidence that renin released into the renal interstitium could bring about the production of angiotensin II without first gaining access to the blood stream. In well-established mercuric chloride–induced acute renal failure, it has been found that plasma renin activity is low whereas renal renin content is nearly twice normal.[31]

While it is likely that the hemodynamic effects of propranolol are renin-mediated, this is not absolutely certain. Recent studies have shown that propranolol has many effects that cannot be attributed to either β-adrenergic blockade or the prevention of renin release.[32,33] Propranolol has been alleged to alter the oxygen affinity of hemoglobin,[34] an effect which could have an influence on the kidney.

It is clear that the effect of propranolol is dependent on the intactness of the renal nerves. It is not apparent from our data whether denervation *per se* makes the renal failure more severe in this model. The results from Group H in which heparinized saline was injected into the renal artery suggest that mechanical trauma to the renal artery increases the severity of the renal failure (perhaps because thrombosis sometimes results).

The results of the denervation experiment are consistent with the idea that renin release brought about by stimulation of the renal β-adrenergic nerves [35] plays an important role in this rabbit model of ARF. Propranolol prevents this type of renin release. Denervation presumably prevents neurogenic renin release but also prevents α-adrenergic stimulation of the kidney, which may tonically inhibit renin release,[36,37] and traumatizes the renal artery. These last two effects presumably outweigh the first, result-

ing in significantly more severe renal failure in the denervated kidney (Group R in Table 4 versus Group B).

We have noted that, in the normal rabbit, propranolol causes a decrease in renal blood flow. This may explain the failure of propranolol to lessen the severity of renal failure when it is given 10 minutes before clamping of the renal pedicle and during clamping (Group G in Table 2).

Bailey *et al.*[38] have reported that a single subcutaneous injection of furosemide (50 mg/kg) protected against acute renal failure caused by a combination of cephaloridine, glycerol, and furosemide given 12 hours later. We observed no such protective effect in the pedicle clamping model when furosemide (1 mg/kg) was given intravenously 30 minutes before clamping (Group P). When administered in this way, furosemide resulted in a significant elevation of preoperative plasma renin activity, but unlike the situation in the other high renin groups (L-O), propranolol had no beneficial effect on the severity of the resulting renal failure. The explanation may be that propranolol only inhibits renin release mediated through the sympathetic nervous system, and furosemide's renin-stimulation effect is independent of the renal nerves.[39-41] Administration of radiographic contrast medium was shown in this study to result in less severe histologic changes 1 hour after unclamping, and it is possible that this is due to the osmotic diuretic and volume expansion effects of the contrast material.

The occurrence of "hypotensive" acute renal failure in human renal allografts has been cited as evidence against any participation of the renal nerves in the pathogenesis of this condition.[6] On the other hand, Fekete *et al.*[42] have shown that splanchnicotomy affords protection against acute renal failure in dogs. The present study suggests that in the innervated kidney with acute renal failure, neurogenically stimulated renin release plays an important role and that it is this sort of renin release which propranolol prevents. Studies from this laboratory on postischemic acute renal failure in the autotransplanted rat kidney have confirmed the fact that propranolol has no beneficial effect on acute renal failure occurring in the transplanted (denervated) kidney.[43]

"Hypotensive" acute renal failure occurs very frequently in patients who receive renal transplants,[44] while it is a rare occurrence in other patient groups at risk. [45] Despite the demonstration of a beneficial effect of propranolol in a histologically-appropriate model of acute renal failure in the innervated kidney, the search should continue for an agent which has a similar beneficial effect in a denervated kidney.

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[*Illustrations follow*]

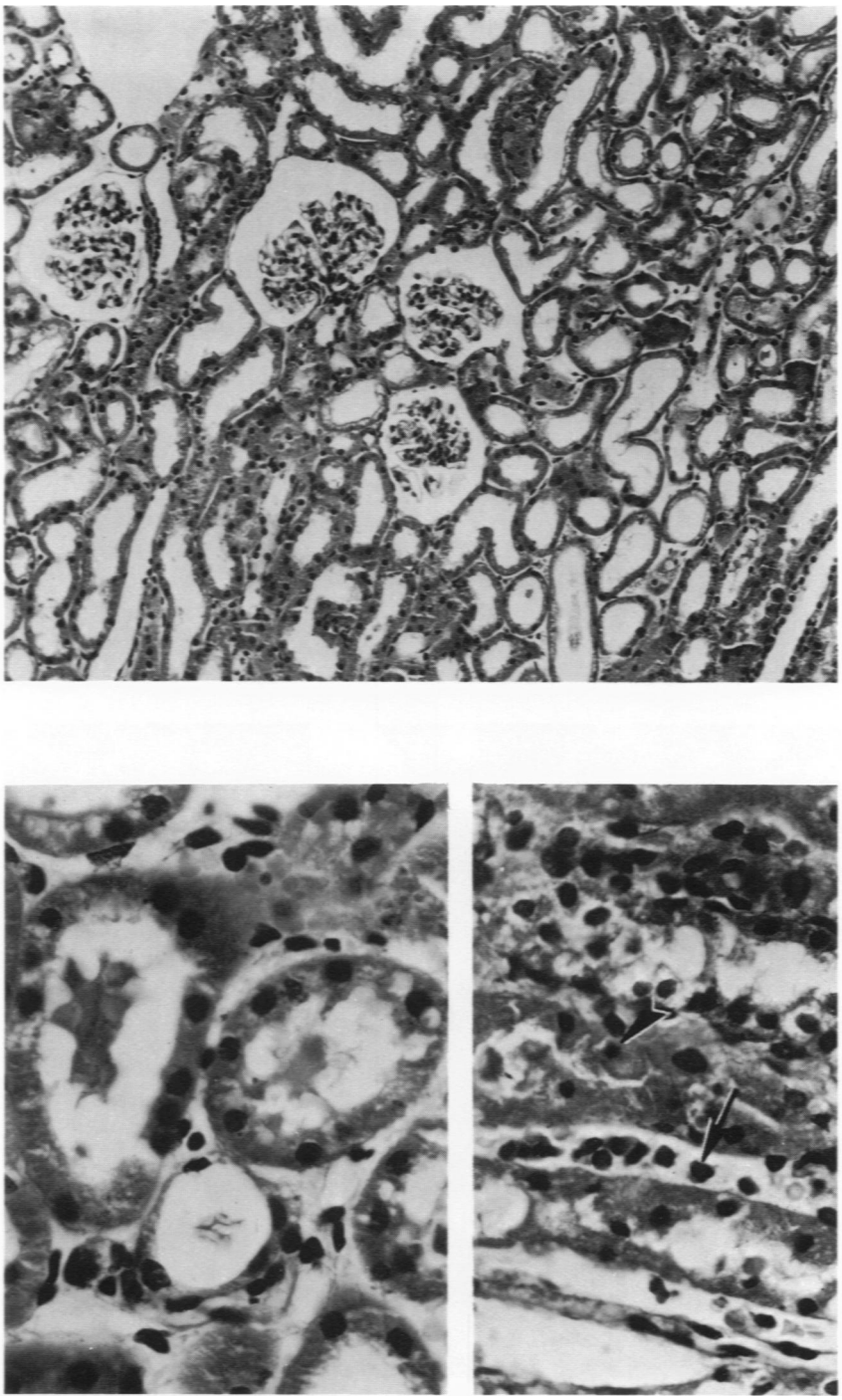
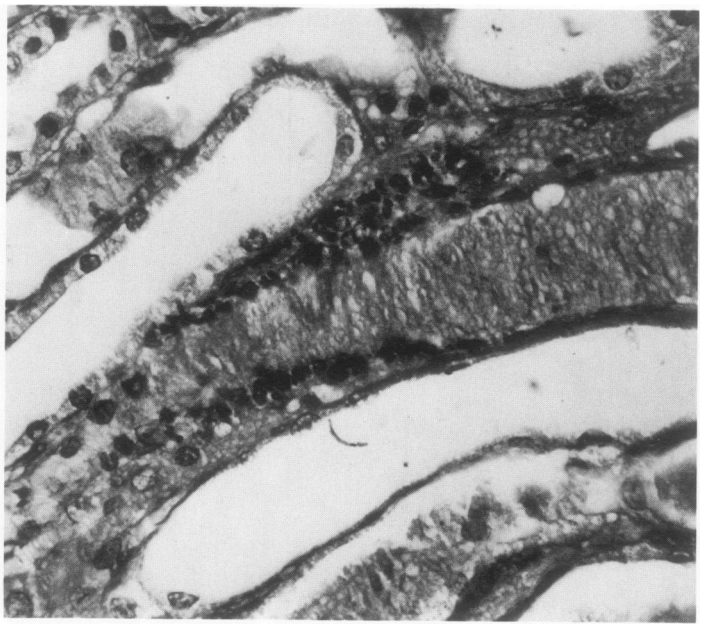


Figure 1A—Marked tubular dilatation 1 hour after release of pedicle clamp (H&E, × 150). **B**—Hyaline debris in tubular lumina 1 hour after release of pedicle clamp (H&E, × 625). **C**—Accumulation of polymorphonuclear leukocytes in outer medullary vasa recta 1 hour after release of pedicle clamp (*arrow*). Note the pyknosis of some nearby tubular epithelial cell nuclei (*arrowhead*). No pyknosis was noted in cortical tubules at this time. (H&E, × 400)



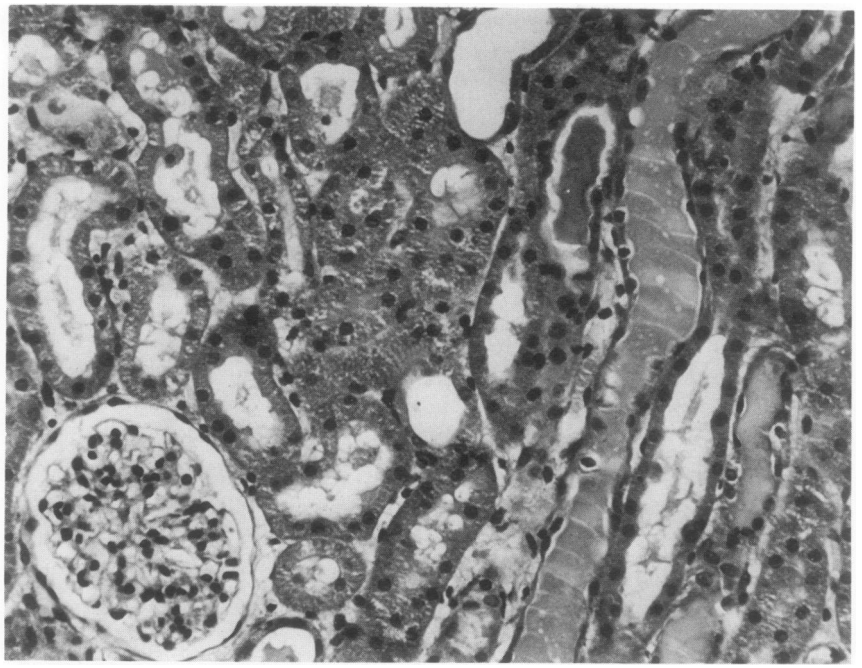
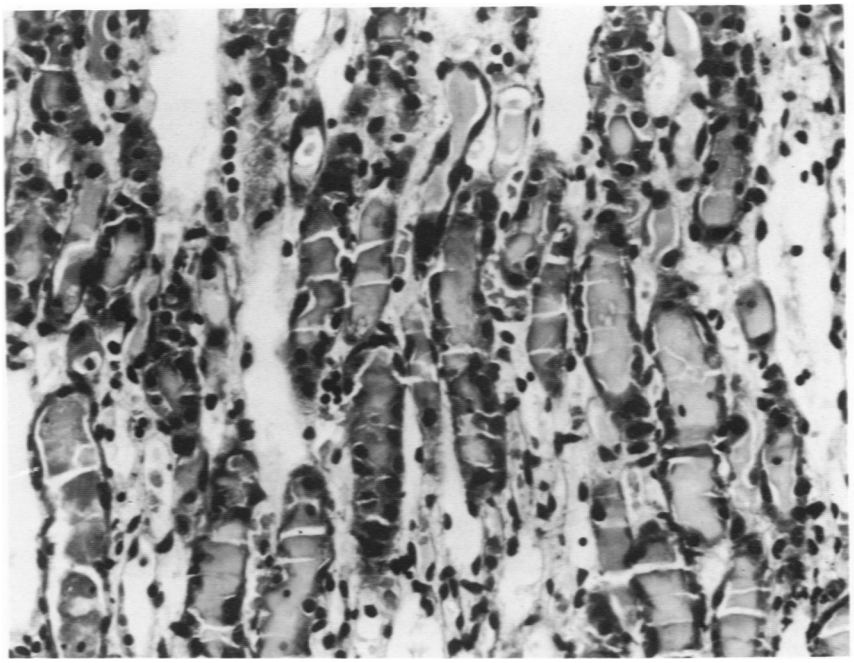


Figure 2—Polymorphonuclear leukocytes in peritubular capillaries surrounding necrotic tubule in outer medulla 1 day after pedicle unclamping; note dilatation of other (intact) tubules (H&E, × 450). **Figure 3**—Representative area from a rabbit with severe renal failure 48 hours after 1 hour of pedicle clamping. Tubules are dilated and contain hyaline casts. No necrosis of tubular epithelium is evident. (H&E, × 240).



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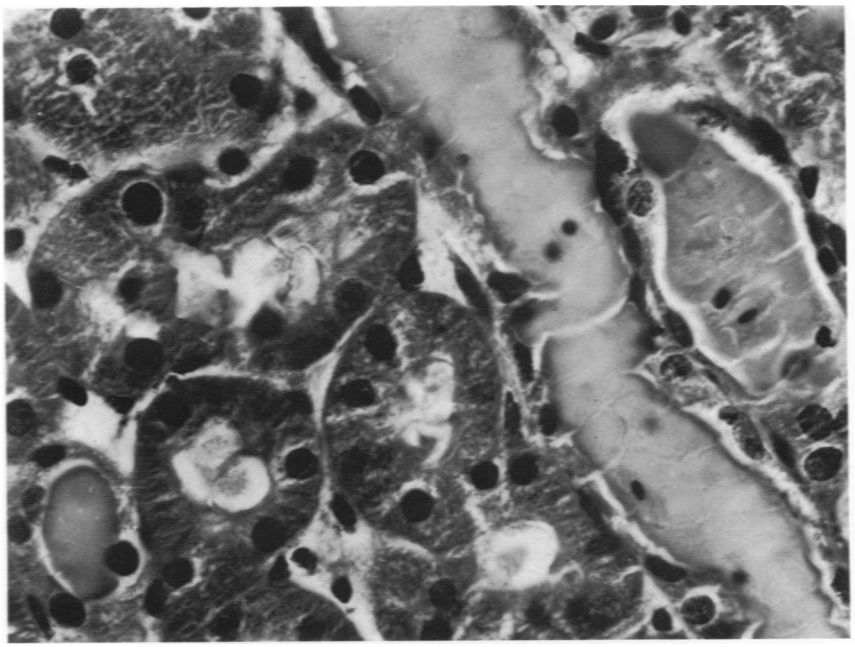

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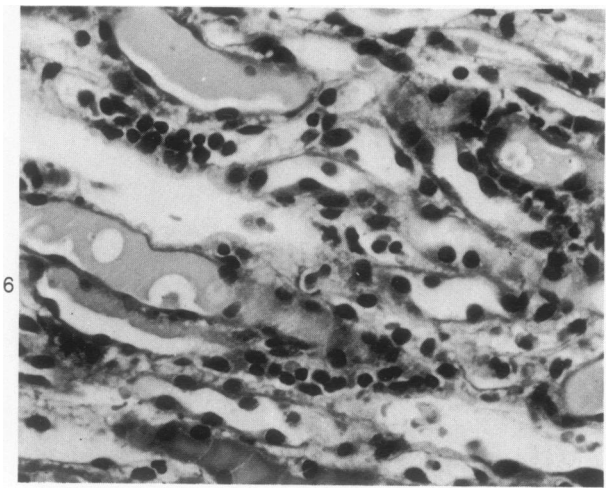
Figure 4—Large numbers of casts in outer medulla in same animal as in Figure 3 (H&E, × 265). **Figure 5**—High-power view of renal cortex from same animal as Figure 3. The two larger tubules containing casts show focal loss of tubular epithelial cells, but elsewhere the epithelium is intact. (H&E, × 600)



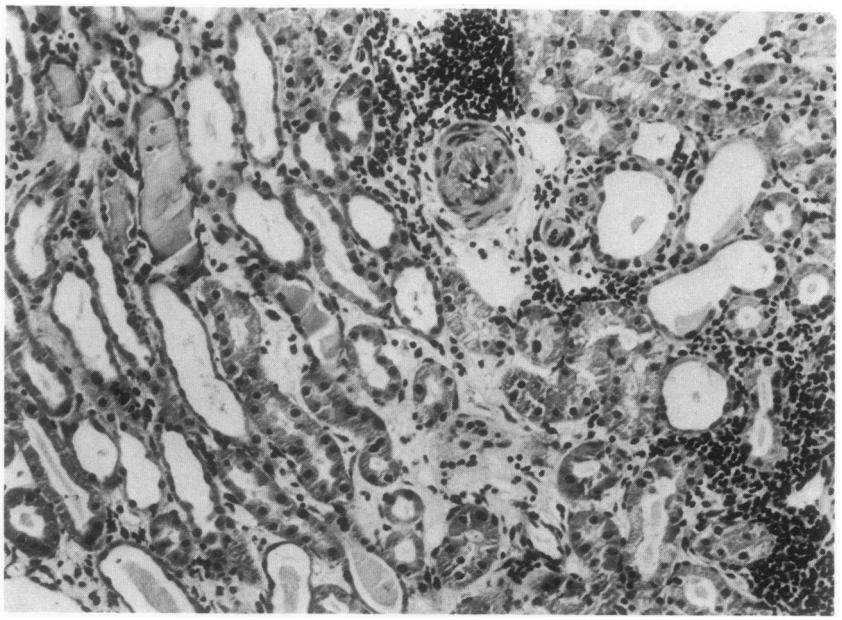
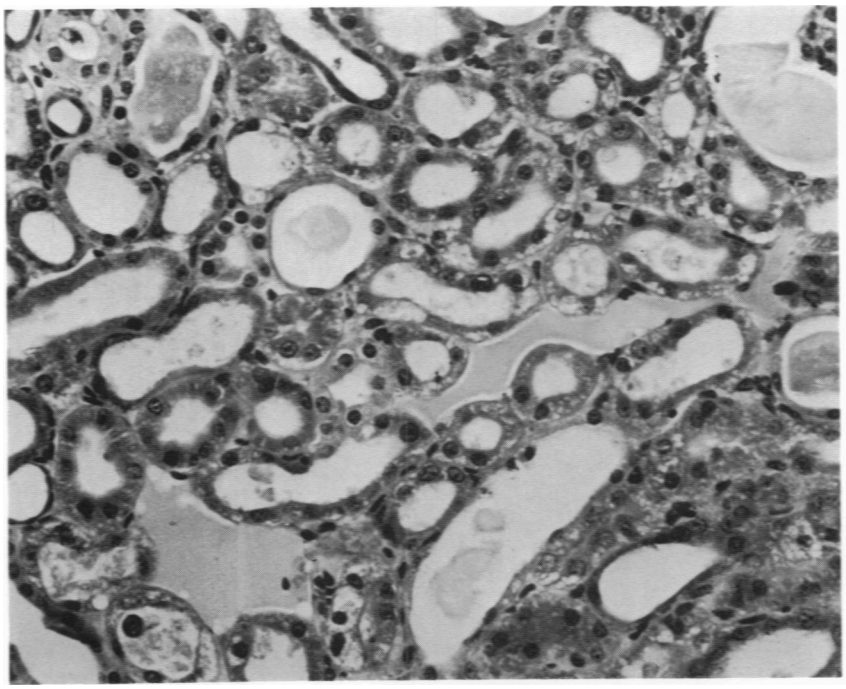


Figure 6—Accumulations of leukocytes in the vasa recta of the inner medulla. The extent of this lesion correlated well with serum creatinine concentrations. (H&E, × 370) **Figure 7**—Tubular dilatation and interstitial lymphocytic infiltration at corticomedullary junction 2 days after 1 hour of pedicle clamping (H&E, × 170).



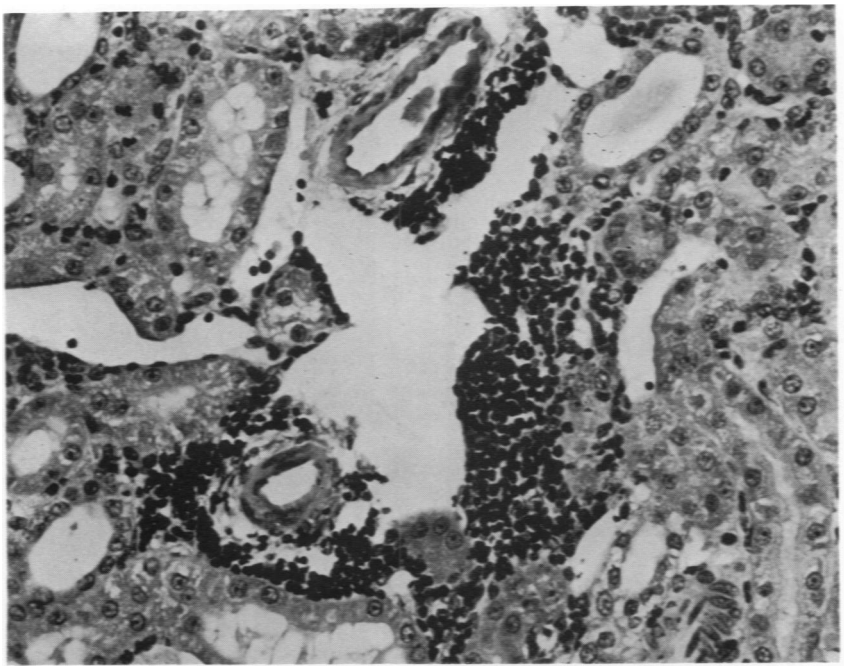
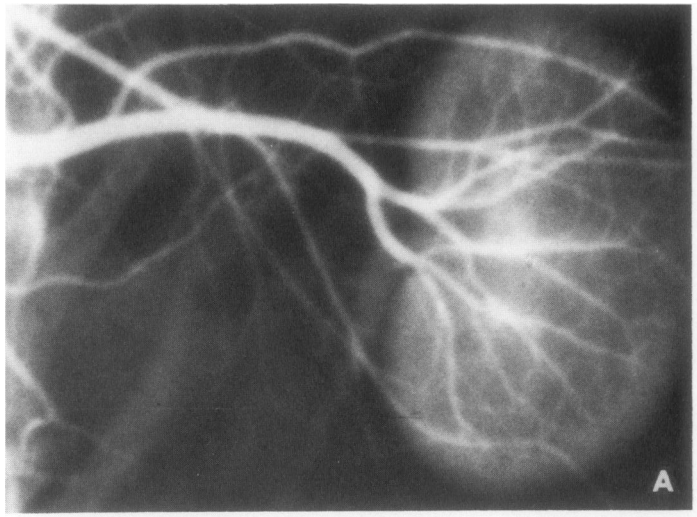
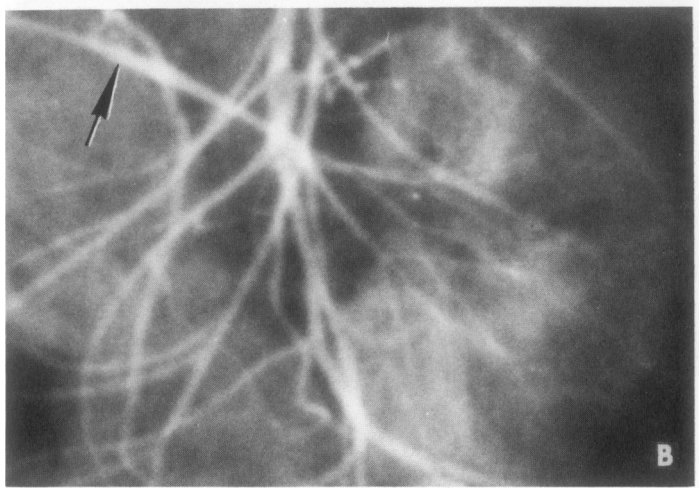


Figure 8—Tubular dilatation, casts, and regenerative changes at 4 days (H&E, × 265). **Figure 9**—Perivascular infiltrate of lymphocytes at the corticomedullary junction in a rabbit with severe renal failure 7 days after 1 hour of pedicle clamping (H&E, × 265).





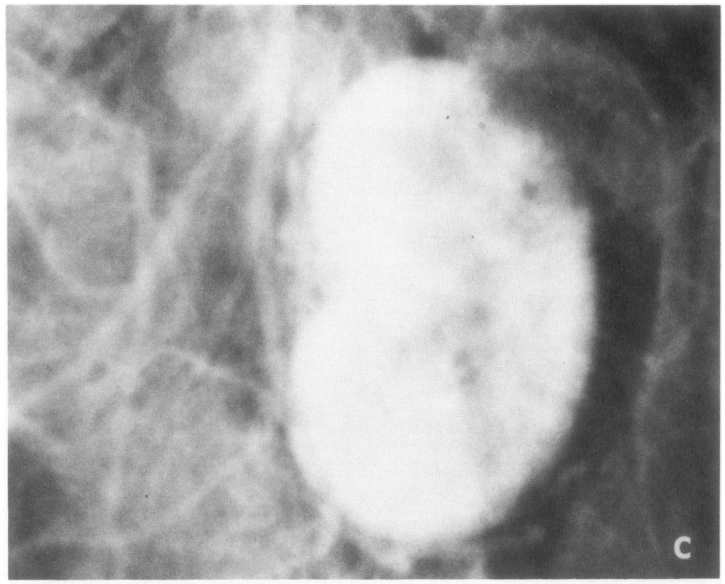


Figure 10—Selected views from the arteriograms of a rabbit not treated with propranolol. **A**—Arteriogram obtained prior to the clamping of the renal artery demonstrates the normal caliber of the renal artery and intrarenal branches and the homogeneous appearance of the cortical nephrogram. **B**—Arteriogram obtained 8 minutes following unclamping of the renal pedicle. The main renal artery (*arrow*) and its major branches are moderately narrowed. **C**—Nephrogram phase of arteriogram obtained 8 minutes after unclamping renal pedicle. The cortical nephrogram is not homogeneous.