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Renal function and cortical blood flow during the recovery phase of acute renal failure

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Renal function and cortical blood flow during the recovery phase of acute renal failure. The characteristics of the recovery process in dichromate-induced acute renal failure were determined. Rats were studied 1, 4, 7, and 14 days after the s.c. injection of either saline or potassium dichromate. In the sham-injected control animals, all values at each interval were similar. The typical pattern of acute renal failure was seen one day after dichromate injection: glomerular filtration rate (GFR) fell 80%, total renal blood flow (TRBF) was reduced 35%, the proportional flow to the outer cortex was diminished, and the urinary to plasma (U/P) inulin clearance was reduced. The early recovery phase, days 4 and 7, was characterized by: *1)* a mild but significant diuresis, *2)* progressive improvement in GFR and an increase in the proportional flow to the outer cortex, which actually exceeded control values, *3)* a dissociation between improvement in renal function and changes in TRBF, since GFR increased progressively while TRBF remained relatively fixed, and *4)* improvement in GFR that was associated with a progressive and parallel increase in absolute perfusion of the outer cortex. The present data suggest that the recovery process occurs in two stages. In the first stage, the restoration of outer cortical perfusion and renal function precedes the recovery of TRBF and tubular function, which occur during the second stage of the recovery process.

Fonction rénale et débit sanguin rénal cortical au cours de la période de récupération de l'insuffisance rénale aiguë. Les caractéristiques du processus de récupération après une insuffisance rénale aiguë induite par le dichromate, ont été déterminées. Des rats ont été étudiés 1, 4, 7, et 14 jours après l'injection s.c. de dichromate de potassium ou de soluté salé. Chez les animaux contrôles, toutes les valeurs obtenues sont semblables. L'aspect typique de l'insuffisance rénale aiguë est observée un jour après l'injection de dichromate: GFR diminue de 80%, le débit sanquin rénal (TRBF) est réduit de 35%, la fraction de ce débit délivrée au cortex superficiel diminue et le U/P de l'inuline est abaissé. La phase de récupération précoce, aux jours 4 et 7, est caractérisée par: *1)* une diurèse peu importante mais significativement plus grande, *2)* une amélioration progressive de GFR et une augmentation de la fraction du débit délivrée au cortex superficiel, qui devient supérieure aux valeurs contrôles, *3)* une dissociation entre l'amélioration de la fonction rénale indiquée par l'augmentation progressive de GFR, et TRBF qui reste relativement bas, *4)* et une amélioration de GFR qui est associée à une augmentation progressive et parallèle du débit absolu de perfusion du cortex superficiel. Ces résultats suggèrent que le processus de récuparation survient en deux étapes. A la première étape, la récupération du débit cortical superficiel et de la fonction rénale précède la récupération de TRBF et de la fonction tubulaire qui constitue la deuxième étape.

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Over the past 25 years a great deal of attention has been focused on the clinical, pathologic, and physiologic aspects of acute renal failure. Some investigators have emphasized the role of tubular obstruction and necrosis, while more recently the importance of the renin-angiotensin system, the no reflow phenomenon, and renal vascular changes have been extensively investigated [1–7]. These studies have suggested that increased vascular resistance and decreased cortical blood flow play an important role in the pathogenesis of acute renal failure. Since these previous observations are based, in large part, on studies of the initial phase of acute renal failure, the present experiments were designed to evaluate the interrelationship between functional and hemodynamic factors during the recovery phase of acute renal failure.

Methods

Experiments were performed on male, Sprague-Dawley rats (Charles River Breeding Laboratory, Wilmington, MA), weighing 200 to 300 g. Two groups of animals were studied. In the first group, which consisted of 45 animals, acute renal failure (ARF) was induced by the s.c. injection of an aqueous solution of potassium dichromate in a dose of 15 mg/kg of body wt. The second group, consisting of 30 animals, received an equal volume of normal saline and served as sham-injected control animals. Following s.c. injection, the animals were returned to their cages, allowed free access to food and water, and studies were performed one, four, seven, and 14 days later on different animals of each group.

At the designated interval after injection, glomerular filtration rate (GFR), total renal blood flow (TRBF), and outer cortical perfusion were determined by using the following techniques. The animals were anesthetized (Inactin, 80 to 100 mg/kg of body wt, i.p.), placed on a heated animal board to maintain temperature between 36.5 to 37.5°C, a tra-

cheostomy was performed, and polyethylene catheters (PE-50) were secured into the external jugular vein and bladder. After replacement of surgical losses with isotonic saline (1% of body wt), a priming dose of 10μCi of ^{3}H-methoxy-inulin (New England Nuclear Co.) was given and followed by a sustaining infusion of 10μCi/hr in a volume of 1.2 ml. After a 45-min equilibration period, inulin clearance was determined by the average of three 10-min urine collections. Blood samples were obtained from the tail at the mid-point of each urine collection; and at the end of the third clearance period, a sample was obtained from the left renal vein. The concentration of ^{3}H-methoxy-inulin was determined using a Tri-carb liquid scintillation counter (Packard model #3320), and the inulin clearance and total renal blood flow were calculated by using a standard formula [8].

At the conclusion of the clearance studies, proportional flow to the outer cortex was determined using radioactive microspheres (3M Corporation, St. Paul, MN), as previously described [6, 9]. An incision was made from the tip of the xiphoid process, parallel to the last rib bilaterally. The internal mammary arteries were ligated and care was taken to prevent bleeding. Microspheres, 15 ± 5 microns in diameter, labelled with strontium-85 (^{85}Sr) were dissolved in 10% dextran containing three drops of Tween 80. After the microspheres were mixed for one minute with an ultrasonic dismembrator (Artek Systems Corp., Farmingdale, NY), the xiphoid was gently retracted upward allowing visualization of the heart through the diaphragm, and 0.1 cc (60,000 microspheres) of the microsphere mixture was injected directly into the left ventricle. The kidneys were removed, the capsule stripped and sectioned sagitally. Each half was placed separately, cut-surface down, cortex up, on a Stadie-Riggs microtome, and the outer 0.5 mm of cortex was removed and placed in a preweighed vial. The remainder of the kidney was placed in a separate vial, and the weights of each slice and remainder piece determined. The vials were then counted in a properly calibrated scintillation counter, and the specific activity (counts/min/gm) of each 0.50 mm of outer cortex and whole kidney was determined. The relative proportional flow to the outer cortex (OC/TC) is expressed as:

$$\frac{\text{counts/min/g of outer 0.5-mm cortex}}{\text{counts/min/g of whole kidney}}$$

The absolute flow to the outer cortex could be estimated from the expression: perfusion/g of outer cortex = renal blood flow × proportion of flow to outer cortex ÷ weight of 0.5-mm outer cortical slice. All values are mean ± SEM and Student's t test was used to determine significance of differences.

Results

The number of animals in each group and the characteristics of each group at one, four, seven, and 14 days after s.c. injection are shown in Table 1. In the sham-injected control animals, all values at each interval are similar (P = NS). Mean arterial blood pressure was similar in both experimental and control animals and averaged 105 ± 8 mm Hg. Since inulin clearance and extraction were used to estimate total renal blood flow, it is important to point out that the variation in percent of inulin extraction in these studies was similar in all groups of animals, and the coefficient of variation of this measurement was consistently less than 20% (range, 12 to 16%).

Table 1. Characteristics of groups after s.c. injection of potassium dichromate

	One day after		Four days after		Seven days after		Fourteen days after	
	Sham-injected (N = 8)	Dichromate-injected (N = 10)	Sham-injected (N = 7)	Dichromate-injected (N = 12)	Sham-injected (N = 7)	Dichromate-injected (N = 13)	Sham-injected (N = 8)	Dichromate-injected (N = 10)
UFR, $\mu l/min/100\ g\ BW$	1.61 ±0.30	1.62 ±0.22	1.46 ±0.20	2.55 ±0.15	1.51 ±0.16	2.70 ±0.26	1.60 ±0.20	1.74 ±0.24
GFR, $\mu l/min/100\ g\ BW$	1040.0 ±30.0	233.0 ±10.0	1050.2 ±20	449.4 ±25.7	973.7 ±29.5	646.9 ±29.3	975.2 ±20.1	955.7 ±29.2
Inulin extraction, %	40.1 ±2.1	16.0 ±0.8	39.2 ±1.8	28.5 ±1.4	38.2 ±2.0	34.4 ±1.4	38.1 ±1.8	39.2 ±1.7
TRBF, $\mu l/min/100\ g\ BW$	5150.0 ±140	3350.5 ±220	5029.3 ±150	3284.1 ±153.6	5217.3 ±244.2	3474.3 ±229.7	5100.3 ±160	4904.9 ±162.1
U_{In}/P_{In}	627.0 ±5.64	148.5 ±21.1	648.3 ±48.2	230.8 ±22.2	637.5 ±70.0	352.0 ±50.1	671.8 ±38.6	535.2 ±48.8
OC/TC	1.67 ±0.03	1.30 ±0.04	1.68 ±0.04	1.92 ±0.04	1.65 ±0.04	1.98 ±0.02	1.63 ±0.05	1.68 ±0.04

[a] Abbreviations used are: UFR, urine flow rate; GFR, glomerular filtration rate; TRBF, total renal blood flow; U_{In}/P_{In}, ratio of urine to plasma inulin clearance; OC/TC, proportional outer cortical perfusion; N, number of animal used.

Although the experimental animals were not oliguric, the typical pattern of acute renal failure was seen one day after dichromate injection. Glomerular filtration rate (GFR) fell 80% ($P < 0.01$) and total renal blood flow (TRBF) was reduced 35% ($P < 0.01$) compared to the sham-injected group. In addition, the proportional flow to the outer cortex (OC/TC) was diminished from 1.67 ± 0.03 in the sham-injected animals to 1.30 ± 0.04 in the dichromate-treated animals; and the ability to reabsorb water, as reflected by the urine to plasma (U/P) inulin ratio, was also impaired in the experimental group.

The early recovery phase, days four and seven, was characterized by the following findings: There was a progressive rise in GFR from 449.4 ± 25.7 μl/min/100 g of body wt on day four to 646.9 ± 29.3μl/min/100 g on day seven. This sequential increase in GFR was associated with a mild, but signifcant ($P < 0.01$), diuresis on day four (2.55 ± 0.15μl/min/100 g) and day seven (2.70 ± 0.26 μl/min/100 g) in the experimental animals. Of particular note was the finding that TRBF, which had been reduced to 65% of control values on day one, remained essentially unchanged during the recovery period, 3284.1 ± 153.6μl/min/100 g on day four and 3474.3 ± 229.7μl/min/100 g on day seven (P = NS, compared to dichromate-injected day one animals, but $P < 0.01$ compared to respective sham-injected animals). In these dichromate-injected animals, however, the recovery of GFR and the mild diuresis were associated with a significant increase in proportional flow (OC/TC) to the outer cortex: OC/TC was 1.92 ± 0.04 on day four and 1.98 ± 0.02 on day seven, which exceeded the control values of 1.68 ± 0.04 and 1.65 ± 0.04, respectively ($P < 0.01$). Since total renal blood flow remained relatively constant during this interval, this observation would suggest that a preferential increase in outer cortical perfusion occurred during the early recovery phase in the dichromate-injected animals. In addition, the urine/plasma inulin ratio remained low during this interval, indicating continued tubular dysfunction.

During the interval between days seven and 14, the late recovery phase, all parameters returned to control values in both groups of animals.

The interrelationship between changes in glomerular filtration rate, total renal blood flow, and absolute outer cortical perfusion for the dichromate-injected animals are shown in Figure 1 as a percent of sham-injected values. One day after dichromate injection, a concurrent decrease in total renal blood flow and proportional flow to the outer cortex results in a marked fall in absolute flow to the outer cortex from 10.1 ± 0.6 ml/min/g in dichromate-treated animals ($P < 0.01$). This ischemia of the outer cortex is associated with a profound decrease in GFR on day one. Although total renal blood flow remains relatively constant during the early recovery phase (days four and seven), an increase in the proportional flow to the outer cortex to above control values results in progressive increases in outer cortical perfusion which are associated with a concomitant and parallel increase in GFR. Consequently, there is a dissociation between improvement in renal function and changes in total renal blood flow during the recovery phase. GFR increases progressively, while renal blood flow remains relatively fixed. Thus, improvement in GFR was associated with increased perfusion of the outer cortex and a mild diuresis. The changes in GFR and absolute outer cortical perfusion precede changes in total renal blood flow. By day 14, GFR, RBF, and outer cortical perfusion have all returned to control values.

Discussion

Over the past several years, many investigators have focused attention on the initial phase of acute renal failure. In large part, these studies have dealt with the role of various factors in the pathogenesis of the oliguria, and a variety of models of acute renal failure have been studied. While some investigators have favored the role of tubular obstruction and the passive back diffusion of tubular fluid [4], others have argued in favor of vascular and vasomotor phenomena [1–3]. It seems likely that no single mechanism can account for the various observations in different models at different stages of development. The rela-

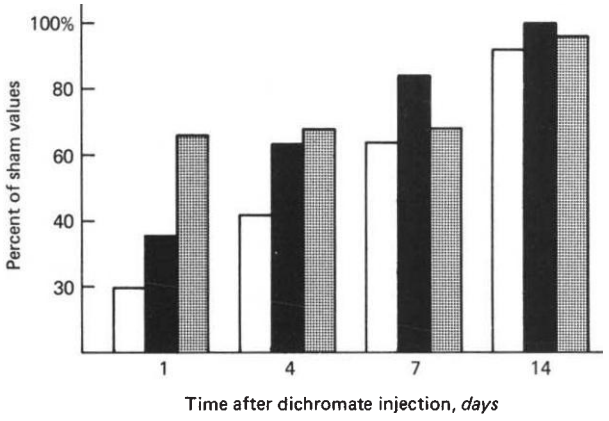

Fig. 1. *The interrelationship between glomerular filtration rate (GFR) (clear bars), absolute outer cortical perfusion (solid bars), and total renal blood flow (RBF) (hatched bars) during the recovery phase of dichromate-induced acute renal failure.* Although RBF remains constant, there is a concomitant and parallel increase in the absolute perfusion of the outer cortex and the GFR during the early recovery phase (days four and seven).

tive role of a number of different factors in a variety of animal models has been recently reviewed [2–5, 7].

Significant and consistent hemodynamic changes have been described in both experimental and human acute renal failure [7, 10]. Recent studies from our laboratory have employed several different techniques to study the role of hemodynamic factors in the development and recovery phases of postischemic acute renal failure [6]. In animals exposed to renal ischemia for 60 min, a decrease of total renal blood flow and a redistribution of blood flow away from the outer cortex were a consistent observation. The persistence of renal cortical hypoperfusion, however, could not be related to endothelial damage or the "no reflow" phenomena. Arteriolar lesions demonstrated by electron microscopy suggested that arteriolar vasoconstriction which preferentially effected the superficial cortical vessels was responsible for the persistence of the cortical ischemia. Previous studies from our laboratory concerning the initial phase of dichromate- or globin-induced acute renal failure [1] had suggested that the decreased reabsorptive capacity, decreased glomerular filtration rate, and reduced glomerular capillary pressure were apt to be the result of renal cortical ischemia, which could be modulated by the renal content of renin. Thus, it becomes apparent that increased vascular resistance and decreased cortical perfusion play an important, if not predominate, role in the maintenance of acute renal failure in a variety of different models and that the hemodynamic changes may not strictly correlate with the severity of tubular injury or the nature of the initial insult.

Thurau and Boylan [5] have recently suggested that these glomerular and hemodynamic alterations resulting in oliguria are appropriate homeostatic responses to maintain glomerular tubular balance. They postulate that since tubular injury is accompanied by decreased tubular reabsorption, the feedback control of glomerular filtration results in a decrease in nephron GFR. Such a mechanism could result in a redistribution of blood flow if superficial cortical glomeruli contain more renin or if they are more sensitive to the action of the feedback control mechanism.

In contrast to the large body of information concerning the initial phase of acute renal failure and the role of hemodynamic factors in the pathogenesis of acute renal injury, relatively little is known about the interrelationship between functional and hemodynamic factors during the recovery phase. Ayer et al [11], using the xenon washout technique in the glycerol-induced myohemoglobinemic model, have demonstrated a severe cortical hypoperfusion at the height of oliguria that gradually disappeared in parallel with the functional recovery of the kidney. Employing micropuncture techniques, Oken, DiBona, and McDonald [12] demonstrated that when the BUN had fallen 20% below its peak value following the intramuscular injection of glycerol, significant defects in proximal tubular water reabsorption persisted after individual nephron GFR had returned to normal and the volume of fluid collected was supernormal. On the basis of these studies, these investigations concluded that recovery from acute renal failure reflected the recruitment of function in increasing numbers of nephrons which had minimal glomerular function during the oliguric phase. Subsequently, Chedru, Baethke, and Oken [13], using the hydrogen washout method in the same model, showed that an increase in cortical blood flow was associated with a concomitant parallel rise in whole kidney GFR. In these studies, however, the sequential pattern of hemodynamic and functional changes during the recovery phase was not determined. Recent studies in our laboratory have demonstrated that animals studied 24 and 48 hr after 30 min of bilateral renal ischemia have marked improvement in GFR which was best associated with a significant restoration of outer cortical perfusion [6]. Other investigators have suggested that renal blood flow returns to normal or supernormal values relatively promptly in post-ischemic acute renal failure [14–16]. In these studies, the model of unilateral renal ischemia was examined, and factors such as tubular obstruction and back-leak of filtrate appear to predominate. The modifying effects of the presence of a normal contralateral kidney were not evaluated in these experiments. Marked differences in renal blood flow and cortical blood flow distribution have been observed in our studies comparing unilateral and bilateral ureteral obstruction [9, 17] and the rather special nature of unilateral injury may account for the apparently conflicting observations regarding the return of cortical perfusion following acute renal failure.

In interpreting the present data, a number of methodological considerations must be addressed. Several recent studies [18, 19] have questioned the validity of measuring cortical blood flow distribution using microspheres. These studies have emphasized that axial streaming of microspheres in the circulation would lead to an overestimation of outer cortical blood flow and an underestimation of juxtamedullary blood flow. A systematic error in these directions would make the actual differences between the experimental and control groups even more distinct than the values observed in the present studies. In addi-

tion, the potential contribution of streaming artifact has not been demonstrated to be different under varying conditions [20, 21] and would, therefore, not negate the use of microspheres as a comparative measure of changes in blood flow distribution between experimental and control groups.

Total renal blood flow was calculated using the direct Fick method with corrections for urine volume. Since this method is dependent on measuring a difference in concentration of a marker substance between the renal artery and vein, the imprecision of the method as reflected in the coefficient of variation increases significantly with very small arteriovenous differences. Munck [22] examined this problem and found that the coefficient of variation was 92% in patients with acute renal failure as compared to 8% in control normal subjects. The coefficient of variation of our determinations was in the range of 15% for animals with either high or low renal blood flows. Care was taken to avoid contamination of the renal venous blood with systemic venous blood at the time of collection, and the lack of difference in the coefficients of variation between the two groups, ($0.3 < P < 0.4$) suggests that no consistent error in collection, determination, or calculation of the samples was present.

In the present studies, several observations concerning the recovery process in dichromate-induced acute renal failure are of particular importance: *1)* There is a mild but significant diuresis during the recovery phase in this model of acute renal failure, and such a diuresis is characteristic of the recovery phase of this syndrome in man. *2)* This diuresis is associated with a progressive improvement in GFR and an increase in the proportional flow to the outer cortex which actually exceeds control values. *3)* There is a dissociation between improvement in renal function and changes in total renal blood flow since GFR increased progressively while total renal blood flow remained relatively fixed. *4)* Improvement in GFR is associated with a progressive and parallel increase in absolute perfusion of the outer cortex, and restoration of renal function and outer cortical perfusion precede changes in total renal blood flow.

During the recovery phase in the experimental animals, the preferential reperfusion of the previously ischemic outer cortical nephrons resulted in a marked diuresis with a progressive increase in glomerular filtration rate. This polyuria which characterizes the recovery phase of acute renal failure in both experimental animals and man may be the result of an inability of the damaged tubules to reabsorb a proportional amount of filtrate, indicating glomerular tubular imbalance as a result of a restoration of perfusion and glomerular filtration before a return of tubular function. The disproportionate increase in the perfusion of the short-looped outer cortical nephrons might accentuate this imbalance by presenting these nephrons with a greater proportion of the solute load. Altered glomerular hemodynamics might also result in an inability to attain filtration equilibrium because of a loss of peritubular oncotic gradients in a manner similar to that seen in isotonic volume expansion [23].

In our interpretation of the present studies, inulin clearance has been equated with glomerular filtration rate. This requires that filtered inulin is not returned to the circulation in significant quantities by movement across the tubule wall. Several studies have emphasized that the integrity of the tubular wall is damaged in certain models of acute renal failure, resulting in an increased permeability of the tubules [4, 16, 24]. If significant inulin back-leak had occurred, an alternative interpretation of the present data during the recovery phase would propose that *1)* glomerular filtration rate may return relatively promptly to normal levels, *2)* the reduction in inulin clearance is the result of a back-leak of inulin across abnormally permeable nephron segments, and *3)* the recovery phase actually represents changes in nephron permeability to inulin and a return to normal tubular integrity. An inulin back-leak has been detected by microinjection studies and by observation of extravasation of dye in models of acute renal failure, in which intrarenal tubular obstruction played a prominent role and in which elevated intratubular pressure and oliguria were usually present during the initial phase. Previous micropuncture studies from our laboratory [1] have demonstrated that dichromate-induced polyuric acute renal failure is not associated with significant intrarenal tubular obstruction or elevated tubular pressures. Lissamine-green, which had been injected directly into the tubules in these studies, was not seen to extravasate into the interstitium, and no dye was seen remaining in the interstitium after the tubules cleared, suggesting that tubulorrhexis is not a prominent feature in this model of acute renal failure. Although microinjection studies were not performed in the present experiment, it seems unlikely that obstruction and back-leak played a significant role since the animals were not oliguric on day one and were polyuric during the recovery phase. In addition, since inulin extraction was used to measure total renal blood flow, significant changes in the permeability or integrity of the tubule to inulin would be expected to have been seen as concomitant and parallel changes in urine volume, GFR, and TRBF. The changes in GFR and TRBF occurred,

however, independently of one another during the polyuric phase of recovery (days four and seven), suggesting that improvement in inulin back-leak played an insignificant role in the recovery process.

Based on the present observations, the recovery process following dichromate-induced ARF appears to occur in two stages. The first stage or early recovery period is characterized by *1)* a progressive fall in renal vascular resistance, *2)* a preferential reperfusion of outer cortical nephrons, *3)* a restoration of glomerular perfusion and filtration prior to a return of tubular function, and *4)* a diuresis with decreased sodium and water reabsorption. The second stage or late recovery period is characterized by *1)* a progressive return of tubular function, *2)* a restoration of glomerular-tubular balance, and *3)* a return of renal function to normal values.

A similar pattern of recovery has been observed in our laboratory in animals with ischemia-induced acute renal failure [6] and in animals undergoing a postobstructive diuresis following the release of bilateral ureteral occlusion [9, 17]. Therefore, the pattern of recovery observed in this study may not be specific for dichromate-induced acute renal failure but represents a pathophysiologic mechanism which occurs during the recovery phase, in a number of conditions, which are characterized by a decrease in outer cortical perfusion during the acute renal injury.

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References

1. Henry LW, Lane CE, Kashgarian M: Micropuncture studies of the pathophysiology of acute renal failure in the rat. *Lab Invest* 19:309–314, 1968
2. Oken DE: Acute renal failure (vasomotor nephropathy): Micropuncture studies of the pathogenetic mechanisms. *Ann Rev Med* 307–319, 1975
3. Oken DE: On the passive back flow theory of acute renal failure. *Am J Med* 58:77–82, 1975
4. Finn WF, Arendshorst WJ, Gottschalk CW: Pathogenesis of oliguria in acute renal failure. *Circ Res* 36:675–681, 1976
5. Thurau K, Boylan J: Acute renal success. *Am J Med* 61:308–315, 1976
6. Siegel NJ, Kashgarian M, Ries AL, DiMeola HJ, Hayslett JP: Hemodynamic aspects in development and recovery phases of experimental postischemic acute renal failure. *Kidney Int* 10 (suppl. 6): S160–S168, 1976
7. Thurau K (editor) Symposium on experimental acute renal failure. *Kidney Int* 10 (suppl. 6): S1–S207, 1976
8. Kaufman JM, Siegel NJ, Hayslett JP: Functional and hemodynamic adaptation to progressive renal ablation. *Circ Res* 36:286–293, 1975
9. Siegel NJ, Feldman RA, Hayslett JP, Lytton B: Intrarenal hemodynamics in postobstructive diuresis. *Invest Urol* 12:172–175, 1974
10. Hollenberg NK, Epstein M, Rosen SM, Basch RI, Oken DE, Merrill JP: Acute oliguric renal failure in man; evidence for preferential renal cortical ischemia. *Medicine* 47: 455–470, 1968
11. Ayer G, Grandchamp A, Wyler T, Truniger B: Intrarenal hemodynamics in glycerol-induced myohemoglobinuric acute renal failure in the rat. *Circ Res* 29:128–135, 1971
12. Oken DE, DiBona GF, McDonald FD: Micropuncture studies of the recovery phase of myohemoglobinuric acute renal failure in the rat. *J Clin Invest* 49:730–736, 1970
13. Chedru MF, Baethke R, Oken DE: Renal cortical blood flow and glomerular filtration in myohemoglobinuric acute renal failure. *Kidney Int* 1:232–239, 1972
14. Cox JW, Baehler RW, Sharma H, O'Dorisio T, Osgood RW, Stein JH, Ferris TF: Studies on the mechanism of oliguria in a model of unilateral acute renal failure. *J Clin Invest* 53:1546–1558, 1974
15. Riley AL, Alexander EA, Migdal S, Levinsky NG: The effect of ischemia on renal blood flow in the dog. *Kidney Int* 7:27–34, 1975
16. Arendshorst WJ, Finn WF, Gottschalk CW: Pathogenesis of acute renal failure following temporary renal ischemia in the rat. *Circ Res* 37:558–568, 1975
17. Siegel NJ, Feldman RA, Lytton B, Hayslett JP, Kashgarian M: Renal cortical blood flow distribution in obstructive nephropathy. *Circ Res* 40:379–384, 1977
18. Yarger WE, Boyd MA, Schrader NW: Measurement of intrarenal "nutrient" and glomerular blood flow in hydropenic rats, in *Proc Am Soc Nephrol*, Washington, D.C. 1976, p. 118
19. Wallin JD, Rector FC, Seldin DW: Effect of volume expansion on intrarenal distribution of plasma flow in the dog. *Am J Physiol* 223:125–129, 1972
20. Stein JH, Ferris TF, Huprich JE, Smith TC, Osgood RW: Effect of renal vasodilatation on the distribution of cortical blood flow in the kidney of the dog. *J Clin Invest* 50:1429–1438, 1971
21. Stein JH, Boonjarern S, Wilson CB, Ferris TF: Alterations in intrarenal blood flow distribution. *Circ Res* (suppl 1) 32 & 33:61–71, 1973
22. Munck O: *Renal Circulation in Acute Renal Failure.* Oxford, Blackwell Scientific Publications, 1958
23. Brenner BM, Troy JL, Daugharty TM, Deen WM, Robertson CR: Dynamics of glomerular ultrafiltration in the rat: II. Plasma-flow dependence of GFR. *Am J Physiol* 223:1184–1190, 1972
24. Tanner GA, Sloan KL, Sophasan S: Effects of renal artery occlusion on kidney function in the rat. *Kidney Int* 4:377–389, 1973