Renal Vasculature in Essential Hypertension: Racial Differences

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In an attempt to explain the greater morbidity from essential hypertension in the black as compared with the white race, we evaluated the intrarenal vasculature of 27 patients with hypertension (19 white and 8 black). All patients had mild-to-moderate hypertension (mean arterial pressure, 110 to 125 mm Hg), normal renal function, and minimal target-organ damage. All patients had selective renal angiograms, which were evaluated for arterial nephrosclerosis. Additionally, renal blood flow was estimated by the clearance of para-aminohippurate. Patient age, blood pressure, and plasma renin activity did not differ between the two races. Black hypertensives had significantly ($P < 0.01$) more severe nephrosclerosis than the white patients. Renal blood flow was lower ($P < 0.05$) in black patients (390 ± 35 ml/min · m² body surface area) than white patients (473 ± 19 ml/min · m² body surface area). These findings may help to explain racial differences in morbidity and mortality from essential hypertension.

A VARIETY OF MORPHOLOGIC ABNORMALITIES, known collectively as nephrosclerosis, have been reported in the kidneys of patients with essential hypertension (1, 2). The presence of these lesions, especially in the interlobar and arcuate arteries, has been shown in vivo by arteriography of the hypertensive kidney (3). Although it is possible that in most patients these abnormalities are the consequence of hypertension, the possibility remains that in certain patients nephrosclerosis may have a primary role in the pathogenesis of the hypertension (4). Epidemiologic surveys have disclosed that hypertension occurs more frequently and is associated with greater morbidity and mortality in the black race as compared with the white race (5). Recently, we have begun a multifactorial investigation of hypertensive patients designed to define the (pathophysiologic) differences that may explain these findings. As part of these studies a group of black and white patients with mild-to-moderate essential hypertension have been studied by renal angiography. We have further evaluated their kidneys by measuring the clearance of para-aminohippurate as an index of total renal blood flow. Additionally, we have included measurements of plasma renin activity because a previous study has reported an inverse relation between this enzyme and renal blood flow (6).

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Methods

PATIENTS

Twenty seven men (19 white and 8 black) were referred to the Diagnostic and Treatment Unit of the San Diego Veterans Administration Hospital for initial evaluation of hypertension. All subjects were screened twice before hospitalization and were required to have a supine mean arterial pressure (diastolic blood pressure plus $1/3$ pulse pressure) of at least 110 mm Hg but less than 125 mm Hg on each measurement. None of the patients had previously been evaluated for secondary causes of blood pressure elevation, and only two patients had been treated for hypertension; in both instances medication was omitted for 3 weeks prior to enrollment in the study. Subjects gave informed written consent, and the Committee on Human Experimentation of the University of California, San Diego, approved the protocol.

Each subject was admitted to the hospital for 12 days. The evaluation consisted of a history and physical examination; multiple measurements of blood pressure (*see* below); routine blood chemical studies; blood count; a urinalysis and culture; chest roentgenogram; and an electrocardiogram. Optic fundi were evaluated for hypertensive changes by the criteria of Keith and Wagener (7), and the presence or absence of left ventricular hypertrophy was assessed by standard criteria (8). Blood pressure was measured with the arm cuff method each morning of the first 3 days of hospitalization. Reported blood pressures represent the average of these determinations. All patients whose mean arterial pressure was at least 110 mm Hg but less than 125 mm Hg were further evaluated with a rapid-sequence intravenous urography and measurement of the 24-h urinary excretion of 17-hydroxycorticosteroids, metanephrines, catecholamines, and vanillylmandelic acid. In no case was a known secondary cause of blood pressure elevation suggested by this evaluation. Renal function was normal in every case as judged by 24-h creatinine clearance and urinalysis. Urine culture was sterile in all cases.

STUDY DESIGN

Patients were fed a diet that contained 10 meq/24 h of sodium and approximately 80 meq/24 h of potassium. After at least 5 days on this diet a 24-h urine collection for creatinine and sodium was obtained. Concurrent with the 24-h urine collection, a blood sample was obtained for measurement of plasma renin activity after the patient had ambulated for 4 h. Measurements of plasma renin activity were done with the method of Haber and associates (9) by means of the radioimmunoassay of angio tensin I generated after incubation at pH 5.5 for 1 h at 37 °C. Simultaneous blanks were determined at 4 °C. Reagents were purchased from New England Nuclear, Boston, Massachussetts. All assays were done in duplicate, and the values were required to fall within ± 15% of the mean. Reproducibili-

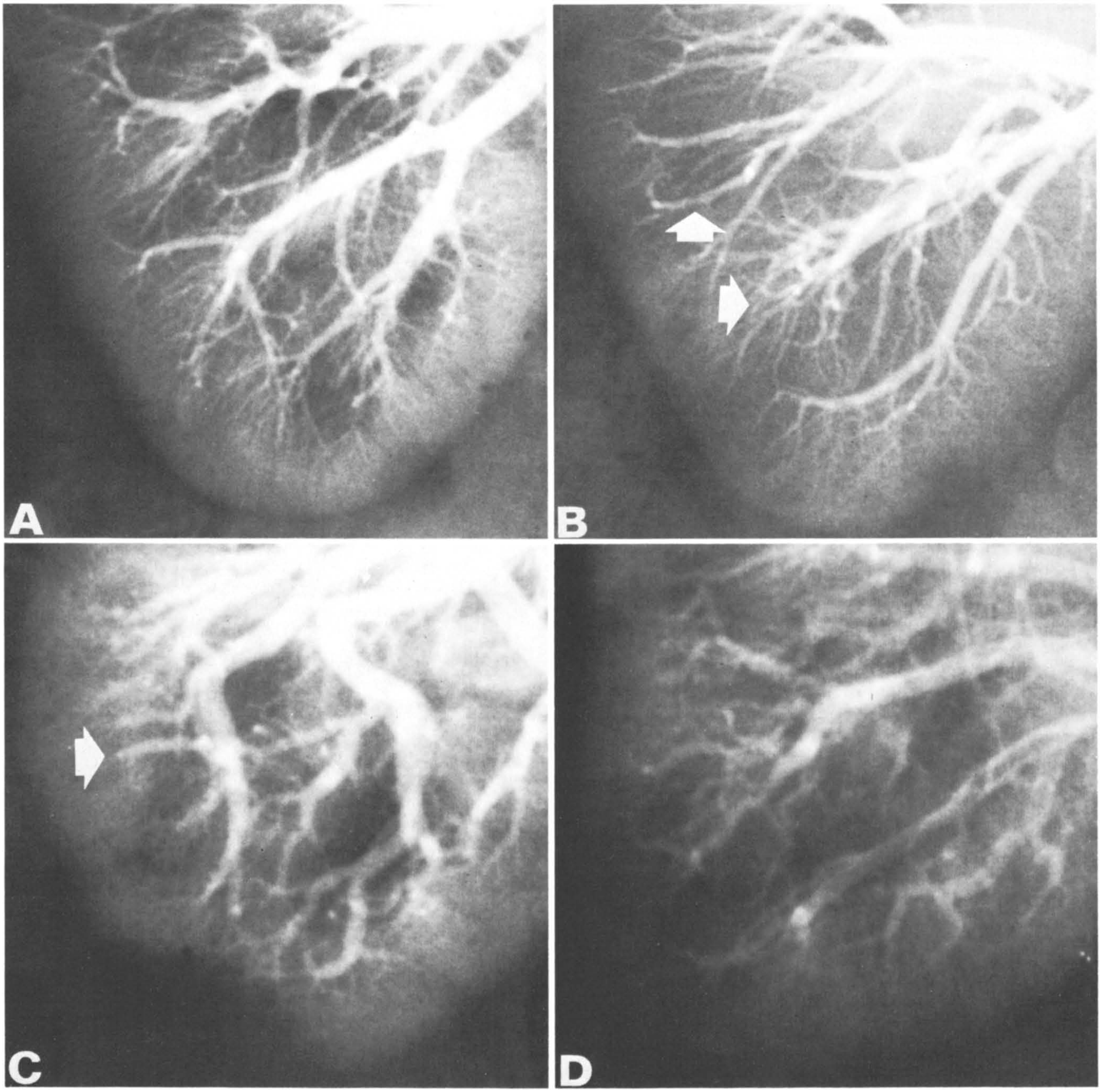

Figure 1A. Grade O: normal arteriogram, gradual tapering from segmental to interlobular arteries, no tortuosity or focal obstructions. **B.**Grade 1+: minor tortuosity of some (*arrows*), but not all arcuate arteries, no occlusions, tapering still normal. **C.**Grade 2+: tortuosity of more than 30% of arcuate arteries, tapering now abnormal with abrupt decrease in caliber at distal arcuate artery level (*arrow*). **D.**Grade 3+: marked tortuosity of all arcuate arteries with abrupt termination of some branches, opacification of peripheral cortex is uneven reflecting focal perfusion deficit.

ty was established by replicate analyses of single plasma samples ($n = 22$) with "high" and "low" plasma renin activity. The interassay coefficients of variation (expressed as one standard deviation per mean) were 11% and 15% for the "high" and "low" samples respectively. All results are expressed as nanograms of angiotensin I generated/ml · h. Patients were classified by the method of Laragh and colleagues (10) into normal, low, or high "renin subgroups" by relating their plasma renin activity to the normal range of renin for the concurrent 24-h sodium excretion.

On the day after plasma renin activity measurement, renal blood flow was estimated by the method of constant infusion of para-aminohippurate without urine collection (11). Renal blood flow was calculated by the formula: renal blood flow = para-aminohippurate clearance/1-hematocrit, and is expressed per meter-squared of body surface area.

ANGIOGRAPHY

On the next day renal angiography was carried out. All patients initially had renal aortography with 40 ml of sodium-meglumine diatrizoate (Renografin® 76%) followed by bilateral selective renal arteriography using 6 to 10 ml of the same agent injected at 6 to 8 ml/sec to approximate renal blood flow. The

Table 1. Subject Characteristics of the Two Racial Groups

Racial Group	Age	Mean Arterial Pressure	Creatinine Clearance	Urinary Na^+ Excretion	Plasma Renin Activity
	yrs	*mm Hg*	*ml/min · m² body surface area*	*meq/24 h*	*ng AI/ml · h*
Black	41.7 ± 3.6	118.3 ± 1.5	59.4 ± 1.9	14.2 ± 2.6	9.7 ± 3.0
White	41.6 ± 2.3	115.7 ± 1.1	58.6 ± 1.6	15.0 ± 2.3	11.8 ± 2.8

catheter was 6.5 French polyethylene (Formocath, Becton Dickinson, Rutherford, New Jersey) with no side holes. The main and segmental renal arteries were free of stenosis in all patients.

Based on a previous angiographic study in which the severity of arterial nephrosclerosis was related to aging in nonhypertensive patients (13), we graded the arcuate arteries for signs of arterial nephrosclerosis using the following criteria: Grade O (normal), arcuate arteries of normal caliber, tapering gradually into interlobular arteries with no tortuosity or abrupt terminations (Figure 1*A*); Grade 1 +, tortuosity of some (< 30%) arcuate arteries, but normal tapering of these arteries (Figure 1*B*); Grade 2 +, tortuosity of more than 30% of the arcuate arteries, with sudden tapering or abrupt termination of some (Figure 1*C*); Grade 3 +, tortuosity of all arcuate arteries with focal obstructions, poor tapering, and focal small regions of nonperfusion (Figure 1*D*).

Each patient's selective arteriograms were evaluated independently by two observers (LBT and MNC) without knowledge of the patient's age, race, or clinical findings. Both kidneys were evaluated separately by both observers, and in several instances one kidney was believed to have more severe disease than the other. In these instances, the angiographers recorded the average grade of the two kidneys.

Statistics

Student's *t* test was done using standard techniques (12). Nonparametric techniques (Wilcoxon rank sum test and rank correlation) were used when appropriate. All results are expressed as the mean ± standard error of the mean (± SEM), unless otherwise stated.

Results

Subject characteristics are given in Table 1. Black patients ranged in age from 28 to 57 years with a mean age of 41.7 ± 3.6 years, similar to white patients whose mean age was 41.6 ± 2.3 years (range, 25 to 57 years). Black patients had an average mean arterial pressure of 118.3 ± 1.5 mm Hg similar ($P > 0.10$) to the white patients 115.7 ± 1.1 mm Hg. One of eight black patients exhibited electrocardiographic evidence of left ventricular hypertrophy, but none of the white subjects had this abnormality. Ocular fundi were believed to manifest grade II or less hypertensive disease in all patients. The mean score for blacks (1.63) was similar to that of the white subjects (1.47). Thus, there were no significant ($P > 0.10$) differences in the incidence or severity of "target-organ" damage (optic fundi and heart) between the two racial groups. Creatinine clearance was greater than 50 ml/min · m² body surface area in every patient, and urinary sodium excretion was less than 20 meq/24 h in each instance. There were no racial differences in the mean results of these two determinations (Table 1). Black patients had plasma renin activity of 9.7 ± 3.0 ng angiotensin I/ml · h, not significantly ($P > 0.10$) different from the white hypertensive patients (11.8 ± 2.8 ng angiotensin I/ml · h). One black patient and one white patient had "high" plasma renin activity, whereas two blacks and three whites had "low" plasma renin activity. Thus, the distribution of renin subgroups between the races was similar.

Results of measurements of renal blood flow and angio-graphic evaluations of the renal vasculature are given in Table 2. Black patients had a mean renal blood flow of 390 ± 35 ml/min · m² body surface area, significantly ($P < 0.05$) less than white hypertensive patients whose mean renal blood flow was 473 ± 19 ml/min · m² body surface area. In 21 of the 27 cases, both observers graded the renal angiograms in a similar fashion. In six instances, angiographic evaluations differed between observers, but in no case did the evaluations differ by more than one grade. In these instances, the average of the two observers' evaluations were used to permit a racial comparison. The mean grade of severity of arcuate artery nephrosclerosis was 1.84 ± 0.25 in blacks compared with 0.89 ± 0.14 in white patients. By rank-sum analysis, whites have significantly ($P < 0.01$) milder arcuate artery disease than their black counterparts.

We further evaluated our results by attempting to correlate (by rank correlation) renal blood flow and angiographic score with each other, with patient age, with mean arterial pressure, and with plasma renin activity for each of the two racial groups. We did not observe a significant correlation coefficient for any of the pairings ($P > 0.10$).

Discussion

The finding of important biologic differences between the black and white races is not without precedent. A well-known example would be the frequency distribution of erythrocyte enzyme deficiencies among the different races (14). More pertinent to the present study, several lines of evidence support the concept that essential hypertension may have different characteristics in the two racial groups. Variably defined "low renin hypertension" occurs more frequently in blacks (15) and accelerated hypertension is found more commonly among the black population (16). Our own preliminary findings indicated that the black hypertensive patient may have a greater plasma volume than his white counterpart (17), and, more recently, we have noted deficient activity of the renal kallikrein-kinin system (renal vasodilators) in black hypertensive patients studied during dietary sodium restriction (18). In the present study, a group of black and white patients with mild-to-moderate essential hypertension (mean arterial pressure between 110 and 125 mm Hg) were selected for evaluation. Blacks and whites were matched for age and magnitude of hypertension. All patients exhibited normal renal function, no patient had greater than grade II retinopathy, and only one patient had electrocardiographic evidence of left ventricular hypertrophy. Despite these clinical similarities, substantially more severe disease of the arcuate arteries was observed in the black hypertensive patients. In addition, there was a parallel decrease of para-aminohippurate clearance as an index of renal blood flow. In contrast to the present findings, a previous study (18) has shown that renal blood flow is similar between black and white normotensive subjects.

Previous reports of renal angiographic abnormalities in essential hypertension have not included racial analyses. Hollenberg and coworkers (3) did renal angiography in 66 patients with essential hypertension. They found significant correlations between interlobar and arcuate artery abnormalities and the age of the patient and the duration and severity of the hypertension. These findings differed from our own, but many of Hollenberg's patients had more severe hypertension than those in the present study. The relation they described between blood pressure and arcuate artery disease appears to be a weak one in patients with "mild" hypertension and is stronger in patients with more severe disease. We were unable to document duration of hypertension in most of the patients and thus cannot relate angiographic findings to duration of disease. The relation reported by Hollenberg between age and severity of nephrosclerosis appeared to reflect to some extent the correlation between age and duration of hypertension. A lack of correlation between age and duration of mild hypertension in our series would provide a possible explanation for our inability to relate patient age to severity of nephrosclerosis.

Table 2. Comparison of Renal Blood Flow and Renal Angiographic Findings in the Black and White Races

Subject Number	Angiographic Evaluation*			Renal Blood Flow
	Observer 1	Observer 2	Average of No. 1 and No. 2	*ml/min/m² body surface area*
Black patients				
1	1	1	1	408
2	3	3	3	544
3	2	2	2	400
4	2	2	2	355
5	2.5	2.5	2.5	227
6	2	2	2	484
7	1	1	1	303
8	1	1.5	1.25	402
Mean ± SEM			1.84 ± 0.25	390 ± 35
White patients				
9	1	1	1	376
10	1	1	1	500
11	0	0	0	394
12	1	1	1	373
13	1	2	1.5	578
14	1	2	1.5	389
15	1	1	1	560
16	1	1	1	469
17	0	0	0	397
18	0.5	0.5	0.5	430
19	1	1.5	1.25	396
20	0	0	0	399
21	0.5	0	0.25	624
22	1	2	1.5	499
23	2	2	2	532
24	0.5	0.5	0.5	483
25	0	0	0	607
26	0	0	0	477
27	2	2	2	521
Mean ± SEM			0.89 ± 14†	473 ± 19‡

* *See* text for description of evaluation technique.
† Whites have less severe abnormalities than blacks, $P < 0.01$.
‡ Renal blood flow is greater in whites than in blacks, $P < 0.05$.

Our findings of only two patients with "high" renin levels and the lack of correlation between plasma renin activity and the state of the renal vasculature confirm a previous report that renal oligemia of this degree is not associated with increased renin secretion (6). In the present study, blacks did not have greater plasma renin activity than whites. Thus, we are unable to explain our results on the basis of the proposed vasculotoxic effect of the renin-angiotensin system (19).

We did not find statistical correlation of angiographic assessment with reduction of renal blood flow by a clearance technique. In a previous study, Hollenberg and coworkers (3), using a xenon washout method, observed normal total renal blood flow in subjects with essential hypertension with normal or minimally diseased renal vasculature (by angiography). It was only in the patients with more extensive vascular changes that impaired renal blood flow was found. Reasons for these differences between the two studies are not established, but our exclusion of patients with more severe hypertension may explain the lack of correlation between our clearance and angiographic results. It is also possible that the difference between techniques for measurement of renal blood flow may be responsible for some of the discrepancies between our results and those of Hollenberg and coworkers.

The pathophysiologic meaning of the racial differences in the renal vasculature has not been established by the present study. Many investigators appear to favor the concept that renal vascular abnormalities observed by angiography or assessed at postmortem examinations occur secondarily to elevated blood pressure (20). Thus, black patients may have had more severe arterial changes because their renal vasculature is more sensitive to elevated blood pressure. Alternatively, they may have had more severe or prolonged hypertension than the white group, although our measurements of blood pressure and assessment of other target-organ damage would not support this latter proposal. It has been suggested that disease of the renal vasculature and elevated renal vascular resistance may initiate certain cases of "essential hypertension" (4, 21). If this theory is correct, it may be that inherent racial differences in renal blood vessels may contribute to the increased frequency and severity of hypertension in the black population. The present study does not distinguish between fixed organic lesions and functional lesions (abnormal renal vascular tone) (22). Thus, alterations in one or more renal vasoactive substances may account for some of our findings (18).

Some authors have suggested that milder forms of arterial hypertension warrant more vigorous treatment in the black patient (23). The present study affords experimental support for such an approach. Accelerated ("malignant") hypertension is frequently characterized by a vicious cycle of impaired renal perfusion, leading to activation (6) of the potentially vasculotoxic renin-angiotensin system. Early treatment of hypertension in the black patient might stabilize the already compromised renal circulation and prevent a decline in renal perfusion below the critical level that induces renin release.

Thus, potentially important racial differences exist in the renal vascular abnormalities observed by angiographic examination of the patient with essential hypertension, and analogous differences in renal blood flow occur between the black and white hypertensive patient. The meaning of these findings is uncertain at present, but it is clear that future studies should consider important variations that may exist between the races (24). A prospective analysis of these sorts of factors might elucidate further the pathophysiology of essential hypertension.

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References

1. SALTZ M, SOMMERS SC, SMITHWICK R: Clinicopathologic correlations of renal biopsies from essential hypertensive patients. *Circulation* 16:207-212, 1957
2. SOMMERS SC, RELMAN AS, SMITHWICK RH: Histologic studies of kidney biopsy specimens from patients with hypertension. *Am J Path* 0134:685-715, 1958
3. HOLLENBERG NK, EPSTEIN M, BASCH RI, MERRILL JP: "No man's land" of the renal vasculature. *Am J Med* 47:845-854, 1969
4. GOLDBLATT H: Hypertension due to renal ischemia. *Bull NY Acad Med* 40:745-755, 1964
5. *Vital Statistics of the United States 1967*, Vol. II, Part A, Section 6. Mortality Statistics, United States Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Division of Vital Statistics
6. HOLLENBERG NK, EPSTEIN M, BASCH RI, COUCH NP, MERRILL JP, HICKLEY RB: Renin secretion in essential and accelerated hypertension. *Am J Med* 47:855-859, 1969
7. WAGENER HP, KEITH NM: Diffuse arteriolar disease with hypertension and the associated retinal lesions. *Medicine (Baltimore)* 18:317-320, 1939
8. GOLDMAN MJ: *Clinical Electrocardiography*, 7th ed. Los Altos, California, Lange Medical Publications, 1970, pp. 98-107
9. HABER E, KOERNER T, PAGE LB, KLIMAN B, PURNODE A: Application of a radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. *J Clin Endocrinol Metab* 29:1349-1355, 1969
10. LARAGH JH, BAER L, BRUNNER HR, BUHLER FR, SCALEY JE, VAUGHN ED: Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease. *Am J Med* 52:633-642, 1973
11. COLE BR, GIANGIACOMO J, INGLEFINGER JR, ROBSON AM: Measurement of renal function without urine collection. *N Engl J Med* 287:1109-1114, 1972
12. BLISS EI: *Statistics in Biology*. New York, McGraw-Hill Book Company, 1970
13. DAVIDSON AJ, TALNER LB, DOWNS WM: A study of the angiographic appearance of the kidney in an aging normotensive population. *Radiology* 92:975-983, 1969
14. MARKS PA: Erythrocyte GGPD differences between negroes and caucasians with respect to this genetically determined trait. *J Clin Invest* 38:2253-2262, 1959
15. KAPLAN NM, KEM DC, HOLLAND OB, KRAMER NJ, HIGGENS J, GOMEZ-SANCHEZ C: The intravenous furosemide test: a simple way to evaluate renin responsiveness. *Ann Intern Med* 84:639-645, 1976
16. FREIS ED: Age, race, sex and other indices of risk in hypertension, in *Hypertension Manual*, edited by LARAGH J. New York, Yorke Medical Books, 1975
17. LILLY J, HSU L, STONE R: Racial disparity of plasma volume in hypertensive men. *Ann Intern Med* 84:707-708, 1976
18. LEVY SB, LILLEY JJ, FRIGON RP, STONE RA: Urinary kallikrein and plasma renin activity as determinants of renal blood flow: the influence of race and dietary sodium intake. *J Clin Invest* 60:129-138, 1977
19. BRUNNER HR, LARAGH JH, BAER L, NEWTON MA, GOODWIN FT, KRAKOFF LR, BARD RH, BUHLER FR: Essential hypertension: renin and aldosterone, heart attack and stroke. *N Engl J Med* 286:441-449, 1972
20. KAPLAN NM: *Clinical Hypertension*. New York, Medcom Press, 1973, p. 48
21. HOLLENBERG NK, ADAMS DF: The renal circulation in hypertensive disease. *Am J Med* 60:773-784, 1976
22. HOLLENBERG NK, ADAMS DF, SOLOMON H, CHENITA WR, BURGER BM, ABRAMS HL: Renal vascular tone in essential and secondary hypertension: hemodynamic and angiographic responses to vasodilators. *Medicine (Baltimore)* 54:29-44, 1975
23. KAPLAN NM: *See* Reference 20, p. 112
24. ENTWISLE G, APOSTOLIDES AY, HEBEL JR, HENDERSON MM: Target organ damage in black hypertensives. *Circulation* 55:792-796, 1977