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Two Variants of Nephrosclerosis Separately Related to Age and Blood Pressure

**RICHARD E. TRACY, MD, PhD,
MARCOS-VELEZ-DURAN, MS,
THOMAS HEIGLE, BS,
and MARGARET C. OALMANN, PhD**

From the Department of Pathology, Louisiana State University Medical School, New Orleans, Louisiana

Two variants of nephrosclerosis, roughly corresponding to the arterial and the arteriolar forms, have been examined in a series of autopsy kidneys by five observers using quantitative morphometry. These two variants are both marked by fibroplastic intimal thickening and medial wastage in the arteries, but one of these affects vessels of sizes that are closer to the heart, whereas the other affects sizes that are more remote from the source of arterial pressure. Both types of nephrosclerosis were found to increase with aging in subjects without hypertension. Each year of aging added 0.15 units of intimal thickening to the close vessels and 0.11 to the remote vessels. Each millimeter of mercury of elevated blood pressure was equivalent to 1 year of aging in the close and 2 years in the remote levels of the arterial tree. The four variables, age, blood pressure, remote level intimal thickness, and close level intimal thickness, were found to hold complex curvilinear interrelationships when examined by regression analysis. A dynamic model was suggested by the following findings: The earliest changes shown by young normotensives are in the close vessels, possibly because of the aging effect of the normal pulse wave. Later, the changes extend into the remote level, perhaps because the thickened intima is rigid and propagates the pulse wave abnormally far into the smallest arteries. Hypertension could then be viewed either as a cause for an exaggeration of this normal process or as a consequence of its extension into the remote level vessels where resistance to blood flow is greater or both. The objective morphometric method showed good agreement in the findings by independent observers and is considered to be suitable for epidemiologic studies of nephrosclerosis. (Am J Pathol 1988, 131:270–282)

THE KIDNEYS of elderly patients at autopsy reveal structural differences from those of youth in the arcuate and interlobular arteries. Patients with hypertension tend to manifest these features in such a degree as to appear older than nonhypertensives. In youth, the small and smallest arteries (outer diameter [OD] 80–300 μ in sections of immersion-fixed tissue) have no intima other than an endothelium sitting upon the internal elastic membrane. In midlife, some vessels form a collagenous intima, which is sparsely invested with longitudinally oriented spindle-shaped cells. At first, the media is altered little or not at all. Later, the media withers and disappears, while the intimal thickening increases, and this process extends to all vessels.

Morphometric methods to quantitate these aging changes have been developed in a number of laboratories.[5–12] All of these methods rely upon measuring the dimensions of vascular profiles in paraffin sections of immersion- or perfusion-fixed specimens. In the course of exploring these various methods, it became apparent that vessels of different sizes are not alike in their relationships with age and blood pressure (BP). BP was found to relate better to intimal thickening in vessels of OD 80–140 μ than to thickening in OD 150–300 vessels; the reverse was found for age.[13] Relative to each other, the smaller size range vessels, being remote from the major arteries, are thought to offer greater resistance to blood flow, and the larger, being closer to the source of arterial pressure, to have more of a conduit function.[14]

The former studies of different size vessels were car-

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Address reprint requests to Richard E. Tracy, MD, PhD, LSUMC, Department of Pathology, 1901 Perdido Street, New Orleans, LA 70112.

ried out with subjects who were mainly in the age range of 55–92 years.[13] Subsequently, another series of 40 cases of ages 25–44 has become available. The two sets of cases together allow an exploration of arterial dimensions in relation to BP over a range of ages 25–92 years.

Materials and Methods

Selection of Cases

Three collections of cases were combined for this study. In two of these collections, subjects examined at autopsy in the LSU service of Charity Hospital in New Orleans and at the University of Oregon in Portland, Oregon, were screened for inclusion in this series.[15] If the hospital chart contained at least one BP reading in an outpatient visit or hospital admission workup in each of the 3 years preceding death and at least ten readings altogether, then the subject was accepted. From 1965 to 1967, 37 cases were assembled in Oregon; from 1968 to 1972, 89 cases were assembled from LSU Charity Hospital, yielding 30 black men, 23 white men, 46 black women, and 27 white women. In a third collection from 1968 to 1978, all black and white male residents age 25–44 in Orleans Parish who died and were autopsied were examined by a standardized protocol.[16] Of 1296 subjects in this collection, 40 had sufficient records of BP for inclusion here, ie, at least three readings prior to terminal hospitalization. The age structure of the combined samples of 166 cases is given in the tables; only 4 women were under age 45.

Cause of Death

Each case was assigned to a single category on the basis of the pathologist's decision (Observer B) as to the underlying cause of death. The diagnosis of coronary heart disease required the presence of coronary thrombosis or of arteriosclerotic occlusion plus myocardial scar. In many cases of chronic heart failure, evidence was not sufficient to distinguish between ischemia, hypertension, cardiomyopathy, or other specific conditions as underlying the cause of death. In subsequent analyses, subjects with chronic heart failure tended to parallel those with coronary heart disease. These cases were therefore combined into a pool of "heart disease" cases. In the New Orleans series, 1 case of rheumatic and 1 case of syphilitic disease were also placed into the heart disease pool. Subjects with cerebrovascular or chronic renal or aortic diseases were combined into a pool of atherosclerosis-related disorders.

Blood Pressure Records

Mean pressure (one-third pulse pressure plus diastolic) was calculated for every reading. This average is an estimate of physiologic mean pressure.[17] Unlike the systolic and diastolic BP, which change with age because of widening pulse pressure, the mean BP is independent of age as a measure of hypertension. A series of averages was computed and subjected to the *t* test. The average of the first two was compared with the average of all remaining values; the average of the first three was compared with all remaining values; and so on. In this sequence of *t* tests, the *t* having the smallest *P* value was taken as the place to call "transition point." Only 2 cases, both of them in the Community Pathology series, failed to provide "before transition" as well as "after transition" values. The inherent properties of a series of BP readings that justify this way to identify the transition point were extensively discussed elsewhere.[15] The average of the mean pressure before (P_b) and after (P_a) transition and the duration of P_a (D_{ur}) were tested for relationship with lesion measures and age. A cutpoint of 115 mm Hg for mean pressure was identified for separating hypertensive from normotensive subjects in a previous analysis of these data.[15] This convention is retained here.

Processing of Tissues

Paraffin-embedded corticomedullary tissue cut perpendicular to the capsular surface was sectioned at 6 μ and stained with alcian blue–PAS–metanil yellow.[15] One to six sections were available in these cases, representing both kidneys. Areas of focal involvement by scar, abscess, tumor, cyst, etc., were avoided.

Morphometry

A microscope with 10× and 40× objective lenses and mechanical stage controlled by the left hand was equipped with an eyepiece ruler marked in units equivalent to 10 μ under the 10× objective lens. All arterial profiles in the section were examined systematically. The OD of the least axis of the elliptic profile was measured under the 10× objective lens, excluding the adventitia, and measuring from one outer media to the other. The thicknesses of intima and of the total wall were measured under the 40× lens, also along the least axis, with the better presented of the two opposite

walls (ie, lacking tangential sectioning, branch ostium, or artifact). The lumen is the outer diameter minus twice the wall thickness. This is essentially the method of Short[10] adapted to immersion-fixed tissues. It differs from that of Kernohan[7] by the use of elliptic as well as circular profiles. These modifications were made to maximize the numbers of observations that can be made with limited amounts of tissue. However, unlike the methods of either Short or Kernohan, who studied mesentery and skeletal muscle, wherein small arteries typically lack an intima, these studies of the kidney require that the intima be measured as well as the media. Vessels with ODs less than 80 μ (ie, arterioles) were excluded because they often hyalinize, thus obliterating the intima and media. Vessels over 300 μ were excluded because it is impractical to obtain them in sufficient numbers in all specimens.

Observers

Samples of renal tissue were separated into two replicate sets. Observer A carried out measurements of both sets, Observers B, C, and D examined only the first set, and Observer E examined only the second set. Observer A is a medical student who was a premedical college student at the time of these studies. Observer B is the first author of this paper and the instructor for the other four observers. Observers C, D, and E are graduate students in pathology who hold MD degrees from foreign medical schools. Each of the observers A, C, D, and E received approximately 2 hours of instruction on the technique for making measurements, followed by occasional suggestions during a 10-hour training period. Thereafter, all measurements were made independently without further discussion or consultation, and with no effort to obtain consensus. Diagnoses of specific renal diseases were made solely by Observer B. Other observers did their measurements without knowledge of these diagnoses. The unweighted averages of the 5 observers were used in the analyses reported here, except for Table 2, in which complete data for only Observers A and C had been keyed into the computer for this purpose.

Each case yielded 20 data points, four variables recorded by each of five observers. Correlations between observers ranged from 0.69 to 0.97, with 63% of the tests being over 0.85. By components of variance analysis, the ratio of "specimens" to "error" variance for the four variables were R_r:3.8, R_c:4.0, W_r:4.7, W_c:4.8. These represent, in a sense, the signal/noise ratios. It should be noted that these do not represent the maximum values attainable under ideal conditions. Many of the slides were less than optimal in their technical preparation, and many also offered undesirably small samples of tissue. Values similar to those given above should be easily achieved under most practical circumstances.

Clinical Features

Heart failure was coded as present if the clinical record, at any time, carried this diagnosis. *Digitalis* was coded as being in use if some form of this medication was prescribed at any time. *Antihypertensive medications* were coded as being in use if any form of these medications was prescribed at any time; diuretics used for treatment of edema were included in this list. *Diabetes* was coded as present if the diagnosis appeared anywhere in the record, but was also coded separately if insulin was in use.

Kidney Diseases

A variety of specific renal diseases were diagnosed at autopsy. The categories encountered, followed by the numbers of cases, were diabetic nephropathy, 7; atheroembolus, 5; malignant nephrosclerosis, 5; chronic nonsuppurative pyelonephritis, 14; and glomerulonephritis, 1.

Statistical Descriptions

Basic descriptive statistics are presented in Table 1, along with a key to the symbols. These linear correlations should be used with caution because multiple linear regression reveals significant curvatures and interactions in the data. Equations that are of special interest are listed here. To generally validate these equations is beyond the scope of this paper; rather, they are stated here as empirical descriptions of the data which can in future studies be opened to general validation. It is sometimes desirable to use kidney tissue at autopsy in estimating the status of hypertension in subjects who lack records of blood pressure.[16] The equations offered here represent a first step toward the development of equations that are generally useful for this purpose. The cubic form $y = (k_1x_1 + k_2x_2 + k_3)^3$ was expanded, and different assortments of the variables from Table 1 were substituted for x_1, x_2, and y. Simplified versions of these equations, eliminating the

Table 1—Mean, Standard Deviation, Pearson Correlation Coefficients, and Key to Variable Symbols for Selected Variables

				Correlation coefficients†									
Variable*	Symbol	Mean	SD	R_c	W_c	R_r	W_r	D_i	L	P_a	P_b	P_p	D_{ur}
Age		60.3	16.9	0.52	0.37	0.37	0.23	0.50	[−0.11]	0.15	0.29	0.53	[0.02]
Close intima	R_c	14.9	5.9	—	0.90	0.87	0.79	0.47	−0.73	0.57	0.45	0.53	[0.09]
Close total wall	W_c	24.8	5.4		—	0.77	0.86	0.40	−0.87	0.54	0.40	0.52	[0.10]
Remote intima	R_r	10.4	6.6			—	0.88	0.50	−0.70	0.62	0.51	0.46	[0.10]
Remote total wall	W_r	22.6	5.5				—	0.41	−0.86	0.61	0.45	0.51	[0.12]
Diameter (outer)	D_i	137.8	12.4					—	[−0.03]	0.25	0.22	0.40	[0.10]
Lumen	L	74.4	14.3						—	−0.52	−0.38	−0.41	[−0.07]
Mean BP after	P_a	109.6	18.9							—	0.55	0.56	0.22
Mean BP before	P_b	108.8	18.5								—	0.42	[−0.08]
Pulse Pressure after	P_p	65.7	22.0									—	[0.00]
Duration of P_a	D_{ur}	5.1	5.2										

* Age and duration in years; close and remote total wall and intima in percentage of outer diameter; diameter and lumen in micrometers; blood pressure in millimeters of mercury.

† Correlations in brackets are *not* significantly different from zero, $\alpha = 0.05$.

terms that were not significant ($\alpha = 0.05$), are reproduced here.

$$P_a = 84.3 + 7.55R_r - 0.0577R_r^2 - 0.133R_rAge + 0.000972R_rAge^2; R^2 = 0.433 \quad (1)$$

$$P_a = 71.0 + 6.79R_c + 0.00872Age^2 - 0.154R_cAge + 0.0042R_c^2Age - 0.00441R_c^3; R^2 = 0.372 \quad (2)$$

$$R_r = 0.201P_a + 0.109Age - 18.2; \quad R^2 = 0.461 \quad (3)$$

$$R_c = 0.156P_a + 0.153Age - 11.4; \quad R^2 = 0.512 \quad (4)$$

$$D_i = 104 + 0.118P_a + 0.344Age; \quad R^2 = 0.277 \quad (5)$$

$$L = 117 - 0.39P_a; \quad R^2 = 0.270 \quad (6)$$

$$W_r = 0.171P_a + 0.047Age + 1.1; \quad R^2 = 0.390 \quad (7)$$

$$W_c = 0.140P_a + 0.092Age + 4.0; \quad R^2 = 0.371 \quad (8)$$

Results

The intimal thickness of interlobular arteries was found to increase with age in nonhypertensive subjects. Hypertensive subjects manifested severe degrees of intimal thickening, so that they appeared to be older than comparable nonhypertensives. Vessels of different sizes were not entirely alike in these relationships. Vessels of OD 80–140 μ relative to those of 150–300 (measured to the nearest 10 μ) are referred to, respectively, as "remote" and "close" level vessels, designated in relation to the heart. For vessels of the close level, each year of aging adds to the intimal thickness 0.15 percent of the OD; each millimeter of mercury of elevated BP is equivalent to *1 year* of aging (Equation 4). At the remote level, each year of aging adds 0.11 percentage units to the intima; each millimeter of mercury of pressure corresponds to *2 years* of aging (Equation 3). These findings imply the existence of two variants of nephrosclerosis, the close and the remote level variants, which may relate to the arterial and the arteriolar forms of nephrosclerosis as given in some classical descriptions. This report discusses ways to quantitate these pathologic conditions.

Intimal Thickness in Arteries of Different Sizes

The intima, expressed as a percentage of OD, tended to be markedly thinner in vessels of decreasing size below an OD of 150 μ. In subjects of varying age and blood pressure, the details of this relationship are complex (Table 2). Certain simplifications, however, seem justified. The vessels of sizes 150–300 μ OD can be approximately described as sufficiently similar to each other to be combined into a pool. The vessels of sizes 80–100 and 110–140 were combined into a second pool, which differed conspicuously from the 150–300-μ vessels.

The average close level intimal thicknesses of elderly normotensives (15.0–18.0 %OD) resemble those of young hypertensives (15.0–18.4). These results are seen in Table 2 where ages 55–92 at BP < 115 can be compared with ages 25–44 at BP > 115 in vessels of OD 150–300. No such overlap was seen at the remote level, where elderly normotensives averaged 8.6 to 11.8 %OD, compared with 12.1–15.0 for young hypertensives. *These results imply that the gap between normotensives and hypertensives is greater in the remote than in the close levels.* This conclusion is illustrated with photographic examples in Figure 1. Four cases were drawn from the positions marked a, b, c, and d in Table 2. Representative examples of remote (lo) and close (hi) level vessels were chosen from these 4 cases to illustrate typical appearances, in the sense

Table 2—Means of Intima/Diameter Ratios by Age According to Size of Artery, for Two Levels of Mean Blood Pressure, in 14,920 Arterial Profiles Measured by Two Observers

	Outer diameter (μ)						
	80–100		110–140	150–180	190–220	230–260	270–300
Mean BP < 115 mm Hg							
Age							
25–44	3.0		4.6	7.8	9.1	9.8	9.1
45–54	3.2	a_{lo}	6.5	9.4	13.0	a_{hi} 12.7	9.1
55–74	9.6		11.8	15.2	16.5	15.3	15.0
75–92	8.6	c_{lo}	11.5	16.2	16.6	c_{hi} 18.0	16.7
Total	7.6 D		9.9 C	13.6 B	14.9 A	14.7 A	14.4 AB
Number of observations	2805		2738	1564	825	584	398
Mean BP > 115 mm Hg							
Age							
25–44	12.1		15.0	18.4	16.2	16.7	15.0
45–54	15.7	b_{lo}	20.1	25.5	19.5	b_{hi} 16.9	15.1
55–74	13.3		16.6	19.1	21.0	19.4	17.8
75–92	16.0	d_{lo}	19.3	23.9	22.6	d_{hi} 21.7	22.3
Total	13.7 E		17.0 D	20.2 AB	20.4 A	19.3 B	18.1 C
Number of observations	1788		1680	1061	577	449	351

The symbols a, b, c, and d with subscripts lo and hi correspond to the labels in Figure 1. These photographs illustrate specific instances of what is "typical" in the sense of having nearly average ratios of intimal thickness to OD, R = T/D, at these positions in the Table.

Letters A, B, C, D, and E beside row means in the "total" rows refer to Duncan multiple range test results; means with the same letter do not differ significantly.

of having approximately average intimal thicknesses. The comparison of c_{hi} with b_{hi} in Figure 1 shows the similarity between elderly normotensive and young hypertensive close vessels in the magnitude of intimal thickness, T. The contrast between c_{lo} and b_{lo} illustrates the substantial gap between these classes of subjects in the remote level vessels.

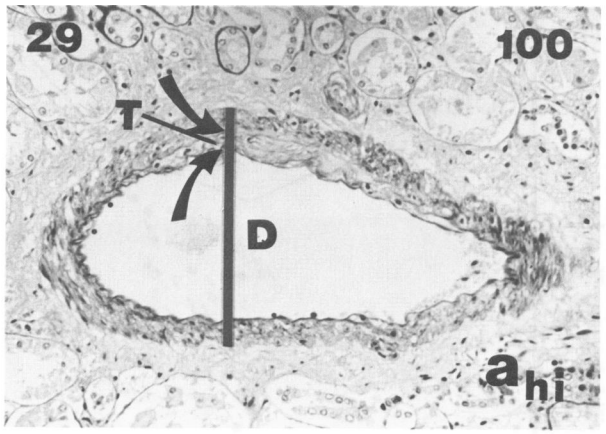
Intimal Thickening With Age in Nonhypertensives

Whereas the cutpoint of 115 was used in Table 2 to separate hypertension and normotension, for the construction of Figure 2 a more stringent criterion was applied. Subjects whose recent mean BPs (P_a) averaged below 104 mm Hg were taken to constitute the nonhypertensives. This level could represent a reading such as 138/87 for systolic/diastolic, providing a conservative upper limit of normal for this analysis. Some of these subjects had past records of mean BP averaging above the 104 cutpoint, whereas others had no such past record. *Intimal thickness in these nonhypertensive subjects was seen to increase with age, and this was true even with absence of elevated BP in documents from the past.* The 22 subjects receiving medication for heart failure or high BP were not notably different in this respect from the 40 subjects not receiving such medication. Only the most extreme instances of intimal thicknesses attained by some of the elderly nonhypertensives were within the range for the average hypertensives.

Intimal Thickness and Blood Pressure

BP tended to increase with intimal thickening in both remote and close level vessels (Table 1). However, the curve that describes this relationship in the remote level vessels was different from the comparable curve for the close level. Thickening of the intima from 0 to 8% of diameter at the remote level was accompanied by a rising of mean BP from about 85 to 115 mm Hg in young subjects. The rise that accompanied close level thickening from 0 to 8% OD was modest, from about 85 to 99 mm Hg. With thickening from 8 to 30 percentage units, the situation was reversed: BP rose more steeply with close level than with remote level thickening. The lower right quadrant of Figure 3 (P_a < 100, intimal thickness > 10%) holds 8 cases in the remote level plot and 32 cases in the close

Figure 1—Four cases were chosen because they typify the average intimal thicknesses observed in young and old hypertensive and normotensive subjects at the close and remote levels. Age is in the upper left and mean BP (P_a) in the upper right of each frame. Outer diameter (*D*) is approximately 220 μ in the upper four frames, and 100 μ in the lower; these exclude the adventitia. Intimal thickness (*T*) excludes the media. (PAS–Alcian blue, ×135 above, ×270 below).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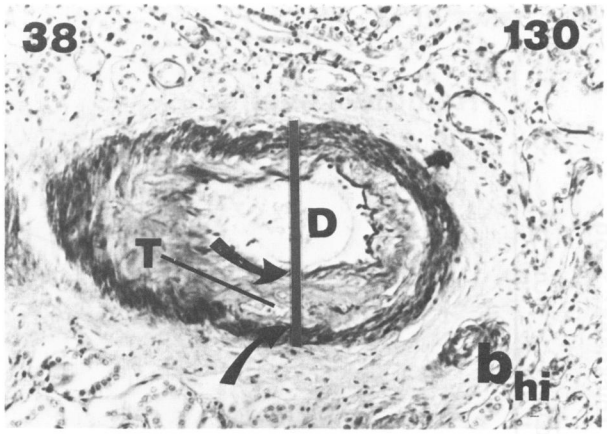
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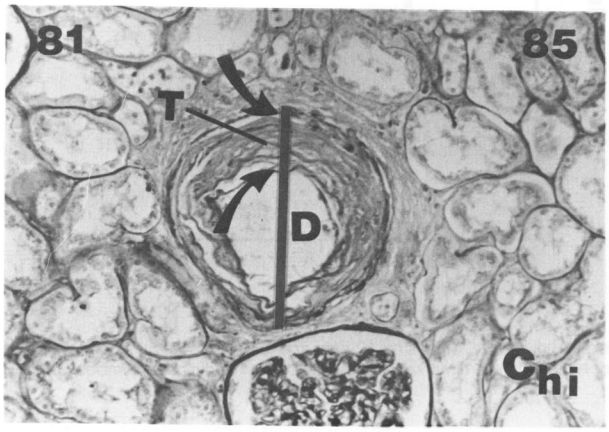
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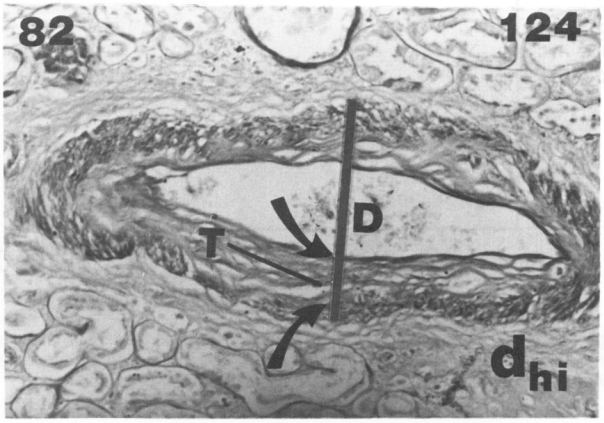
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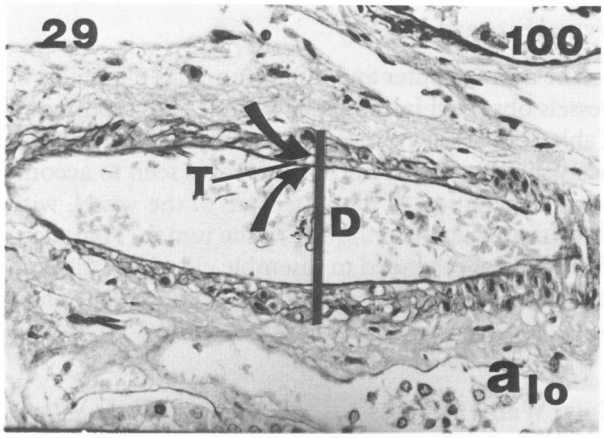
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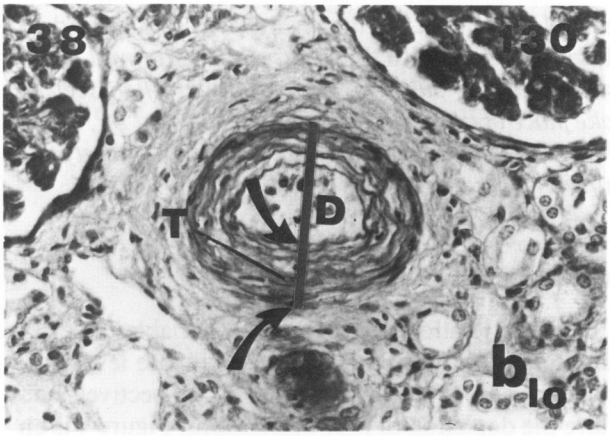
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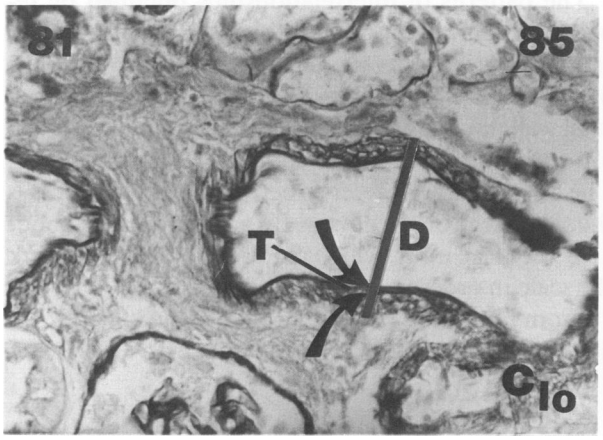
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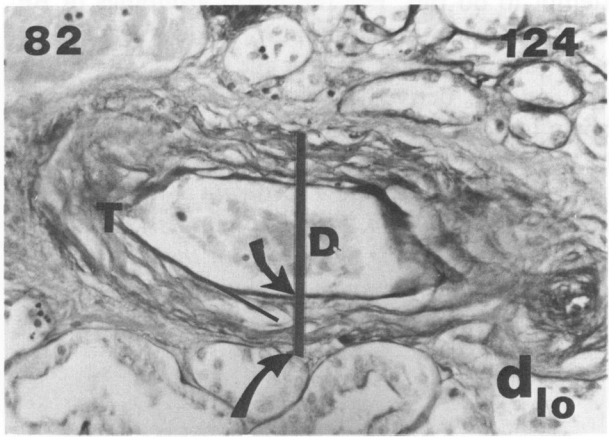
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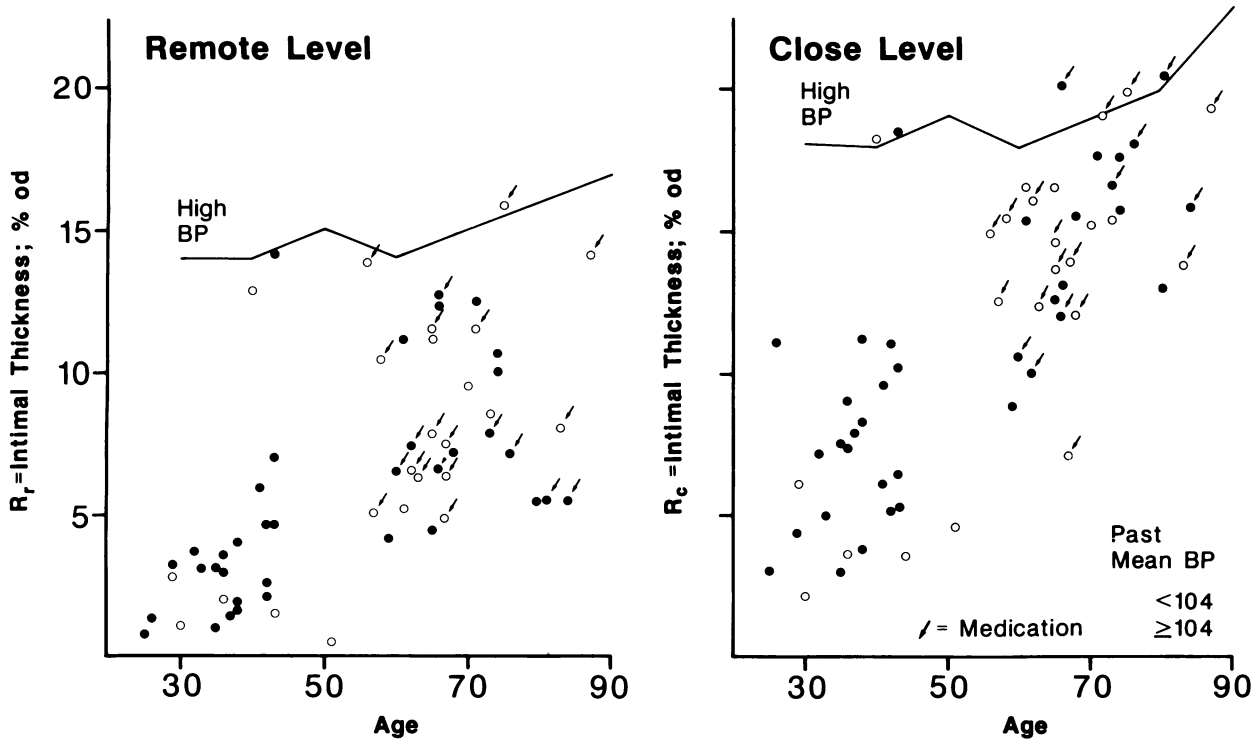

Figure 2—Sixty-two cases with recent mean BP (P_a) less than 104 mm Hg are plotted individually. Means by 10-year age group (*solid lines*) are plotted for subjects with high BP (P_a > 115). Subjects receiving medication for hypertension or heart failure are marked with *arrows*. *Open* and *closed* symbols refer to subjects with average mean BP over and under 104 mm Hg, respectively.

level plot; for $P_a < 90$, the result was 1 remote and 13 close level cases with thickness > 10%. *Intimal thickening in aging subjects, therefore, was often seen to take place at the close level without elevated BP, but at the remote level early intimal thickening rarely occurred without rising BP.*

Intimal Thickness and Age

The interrelationships of the four variables age, BP, remote level intimal thickening, and close level intimal thickening (age, P_a, R_r, and R_c, respectively) require the depiction of four dimensions. Figure 4 is an attempt to do this. For the broad groupings of BP above and below the cutpoint $P_a = 115$, means of R_r and R_c are plotted for 10-year age groups. The values of R_r and R_c derived from Equations 3 and 4 are shown in dotted lines, which plot against each other the two parametric functions of age and BP.

The patterns in Figure 4 illustrate that young normotensives (age 25–44, $P_a < 115$) manifest greater intimal thickness in the close than in the remote level vessels, and that subsequent thickenings in aging normotensives are of approximately equal proportions in vessels of all sizes.

Vessel Size and Age

The average outer and inner (luminal) diameters of vessels observed in the tissue samples are reported in Table 3. In these averages, the intimal thickening that occurs with aging in normotensives is seen to accompany a dilatation of the outer size of the vessel, with little or no change in the size of the lumen. Hypertensives of all ages tended to resemble elderly normotensives in average OD, but showed a consistently narrower lumen irrespective of age.

Total Wall Thickness

The patterns of interrelationships obtained by replacing total wall for intimal thickness in the analyses are nearly the same as already described. Figure 5 presents the plots relating close level to remote level total wall thicknesses, W_c and W_r, respectively, for the same age and blood pressure groupings as in Figure 4. The only striking difference between the two figures is the shift of the origin downward and leftward by about 16 percentage units, which requires the artist to shrink the scale in order to display the findings.

From Equations 7 and 8, W_r and W_c had $R^2 = 0.390$ and 0.371, respectively, compared with 0.461 and

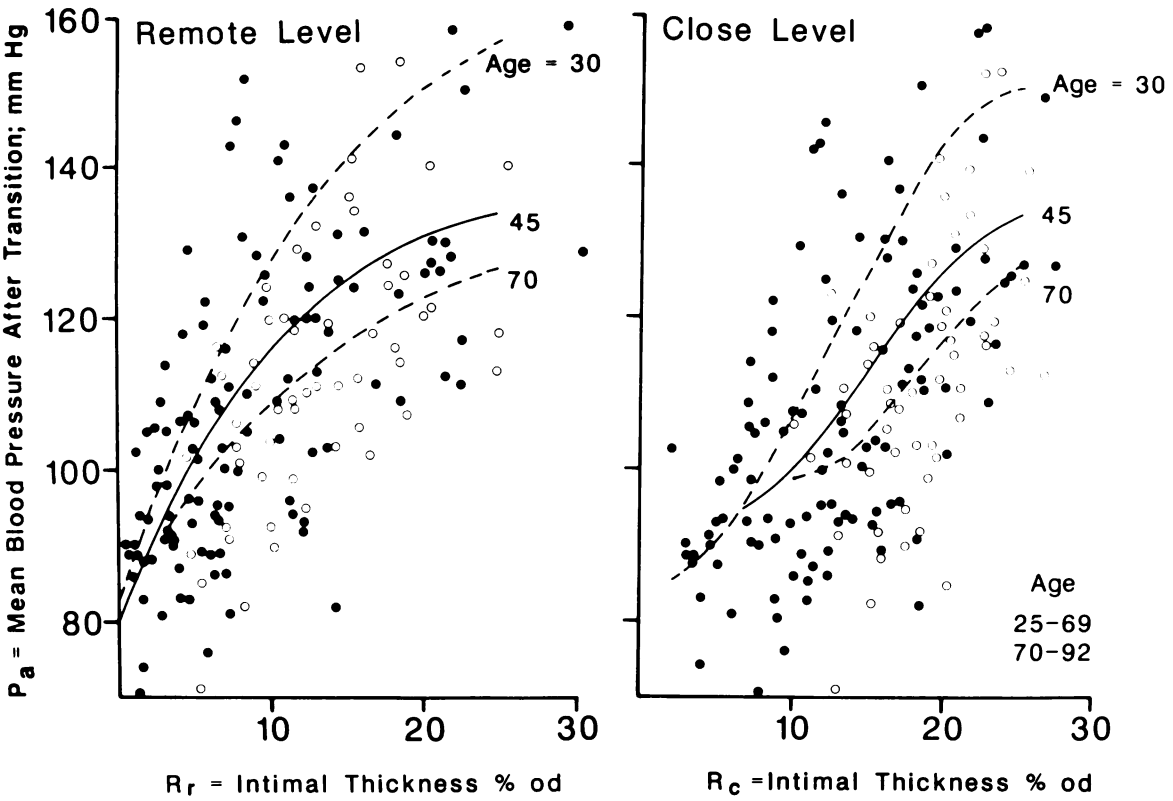

Figure 3—One hundred sixty-six cases are plotted individually. Regression lines with P_a as dependent variable are plotted for selected values of age. *Open* and *closed* symbols refer to subjects over and under age 70, respectively.

0.512 from Equations 3 and 4. As a measure of intimal thickness, the total wall thickness loses information because of incorporating the media, which has a contrary trend of decreasing with age and BP. *It is the intimal thickness, not the total wall thickness, which statistically relates best to age and BP.*

Past Levels and Duration of Recent Levels of Blood Pressure

In the relationships of intimal thickness to age and recent BP, past records of BP were statistically of no interest (Table 4). Whether the recent habitual level was attained from a previous high or low level was of no consequence to the measures of intimal thickness. Similarly, the duration of the recently attained levels did not influence the intimal thicknesses. The results given for remote level vessels in Table 4 were not appreciably different for the close level.

Heart Failure, Digitalis, and Antihypertensive Medications

These clinical features had no appreciable influence upon the relationships of intimal thickness to age and BP. This result was obtained by carrying out three-way analysis of variance (ANOVA) upon residuals from regression equations as done for Table 4. Again, this result implies that rising or falling of BP over a period of years in accompaniment with heart failure or medication was associated with changes of the intima/diameter ratios with no measureable lag. These results were the same for the remote and close level vessels.

Cause of Death

Cerebrovascular disease was considered to be the cause of death in 16 cases. The average mean blood pressure in these 16 cases was 12.5 mm Hg too high for their ages and intimal thickness. This was shown by ANOVA of residuals from Equation 1. Residuals from Equation 2 indicated 13.1 mm Hg of excessive blood pressure in these subjects. These blood pressure measurements were obtained over a period of years prior to the terminal event and therefore do not reflect acute changes taking place during the fatal vascular accident. No other cause of death group was exceptional in this respect.

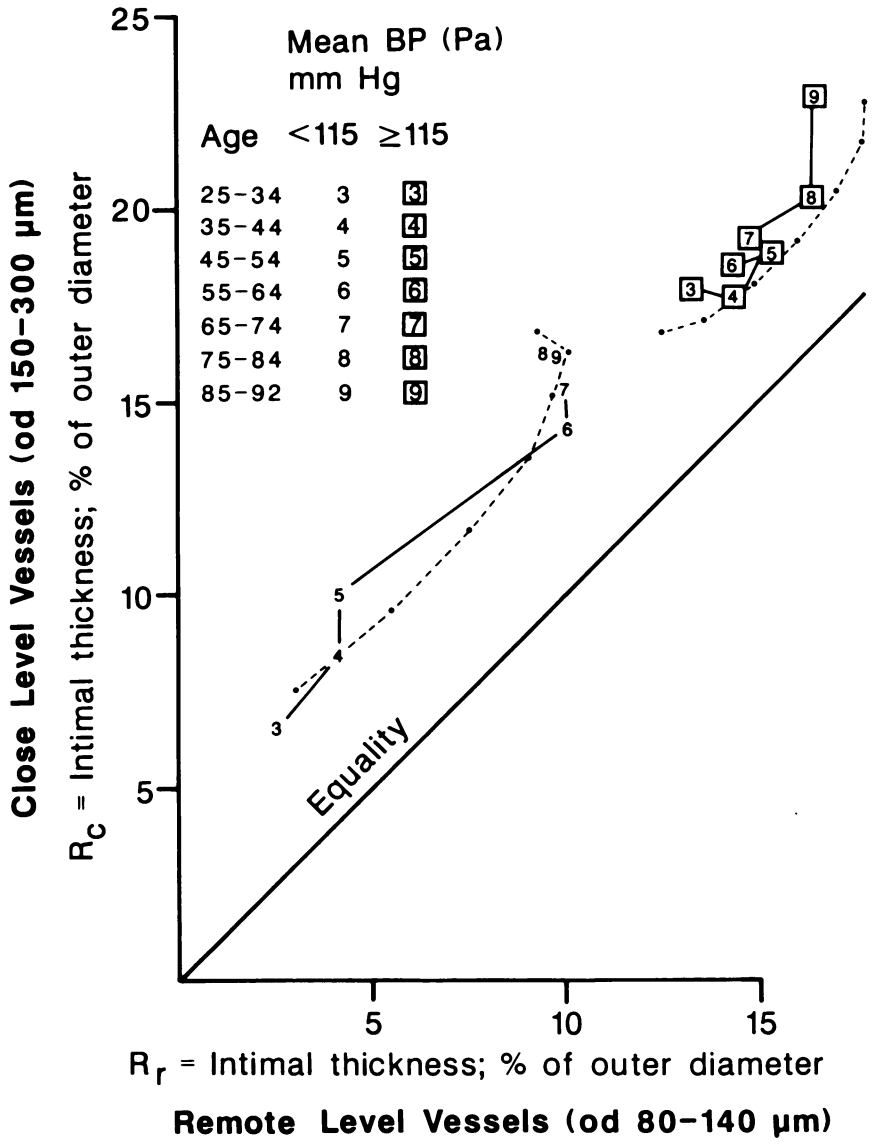

Figure 4—Means of R_c and R_r by 10-year age group are plotted for subjects with mean BP above and below 115 mm Hg. Regression equations relating R_c and R_r to age and BP were used as parametric functions to compute the *dotted lines* representing selected values of age with P_a = 100 and P_a = 135. The *circles* along the *dotted lines* represent ages 30, 40, 50, 60, 70, 80, and 90 as substitute values in these equations.

Specific Kidney Diseases

The 25 subjects having either chronic nonsuppurative pyelonephritis, glomerulonephritis, malignant nephrosclerosis, or atheroemboli showed excessive intima/diameter ratios. This was shown by ANOVA of residuals from regression as in Table 4. The average excess was 3.4 %OD at the close and 4.2 %OD at the remote level. Diabetics, with or without glomerulopathy, had no such excess intimal thickness.

Race, Sex, and Source of Specimens

Residuals from Equations 1, 2, 3, and 4 were examined by three-way ANOVA. A significant race difference was found for R_r and R_c, and a sex difference was seen for R_c. All other comparisons, including interactions, lacked statistical significance. When adjusted to age = 60.3 and P_a = 109.6, the 109 blacks had R_r = 11.3 and R_c = 15.6, compared with R_r = 8.7 and R_c = 13.5 for the 57 whites. The 73 women had R_c = 15.6, compared with 14.4 in the 93 men.

Discussion

Renal interlobular arteries were seen in this study to undergo metaplastic replacement of the youthful muscular media with the fibroplastic intima of old age. In the absence of hypertension, this fibrometaplasia was found to progress steadily throughout life. Intimal thickening was delayed in the tiny arteries remote from the arcuate branches, and tended to hap-

Table 3—Mean Ratios of Intima/Diameter and Total Wall/Diameter, Mean Diameter, and Mean Lumen by Age for Two Levels of Mean Blood Pressure in 166 Cases Measured by Five Observers

	Remote (Od 80–140)		Close (Od 150–300)		Mean		
Age	Intima	Total wall	Intima	Total wall	Diameter	Lumen	Number of cases
Mean BP < 115 mm Hg							
25–34	3	16	6	18	124	86	11
35–44	4	18	8	20	129	83	20
45–54	4	18	10	22	130	80	5
55–64	10	23	14	25	137	75	17
65–74	10	21	15	25	139	79	36
75–84	9	21	16	25	144	79	11
85–92	9	21	16	26	150	80	5
Mean BP > 115 mm Hg							
25–34	14	26	18	28	140	65	3
35–44	14	28	18	29	132	60	11
45–54	15	28	19	29	141	63	3
55–64	14	25	18	28	140	67	11
65–74	15	26	19	28	145	69	18
75–84	16	26	20	28	140	67	11
85–92	17	28	23	31	153	60	4

Intimal and total wall ratios are expressed as percentages of the outer diameter; diameter and lumen are in microns.

pen earlier and faster in the somewhat larger vessels closer to the arcuates. Intimal thickening was regularly seen in "close" level vessels of young patients who had no appreciable elevations of BP. The thickening was of marked degree in some elderly subjects who had no elevated BP throughout a lengthy period of documentation. This result is in accord with many prior reports.[1,2,3,5,8,12] When seen in the vessels remote from the arcuate level, however, the same kind of fibrometaplasia was typically accompanied by a degree of blood pressure elevation commensurate with the severity of the structural alteration. The blood pressure was found to be elevated, by and large, in proportion to the degree of fibrometaplasia in excess of what is appropriate to a person's age. The statistically expected magnitudes of these effects can be computed from Equations 1 and 2.

These findings do not resolve the issue of whether the arterial changes are the cause or the consequence of high BP. It seems possible that the "wear and tear" caused by the pulsations of the normal BP might promote an accumulation of fibrometaplasia at some irreducibly minimal rate. The remote level of the arterial tree might at first be protected from this process until the close level is made rigid by "arteriosclerosis"; thereupon, the transmittal of the pulse wave abnormally far into the tiny branches could propagate the process. The rate of the process would be expected to respond to the level of the BP. Alternatively, when "arteriosclerosis" impairs the ability of resistance level vessels to dilate upon adaptive demand, occasional episodes of ischemia here and there in the renal cortex might provide the driving force to propel ever higher and higher elevations of BP. Hence, fibrometaplasia could progress for its own reasons without regard to BP; BP would rise in those patients who progress most quickly, thereby coming to exceed the amount of intimal thickening that is tolerable for the age. Either of these mechanisms, or some combination of them, would yield the same data.

Whatever the mechanism of progression may be, the data suggest the existence of a kind of lethal limit at the level of R_c = 16%OD, such that the average intimal thickness of the close level vessels is 16% of the OD (Figure 4). Of the 32 patients above this value, 27 died of cardiovascular diseases. Survival beyond this degree of involvement seems to be usually brief and accompanied by ill health.

If the severity of fibrometaplasia grows at a rate that is governed by BP, then past levels of pressure would be expected to leave some kind of imprint. Subjects of similar age and BP should show more intimal thickening if past levels of BP were high and less thickening if past levels were low. This result was not found. Rather, these contrasting kinds of cases showed average degrees of fibrometaplasia that did not differ significantly from each other (Table 4). On the face of it, this result would suggest that the kidney is not an end organ for the damaging effects of high BP. Rather, the renal microvasculature could be seen as a register for showing reversible changes that come and go in keeping with current levels of BP, or as the barostat that

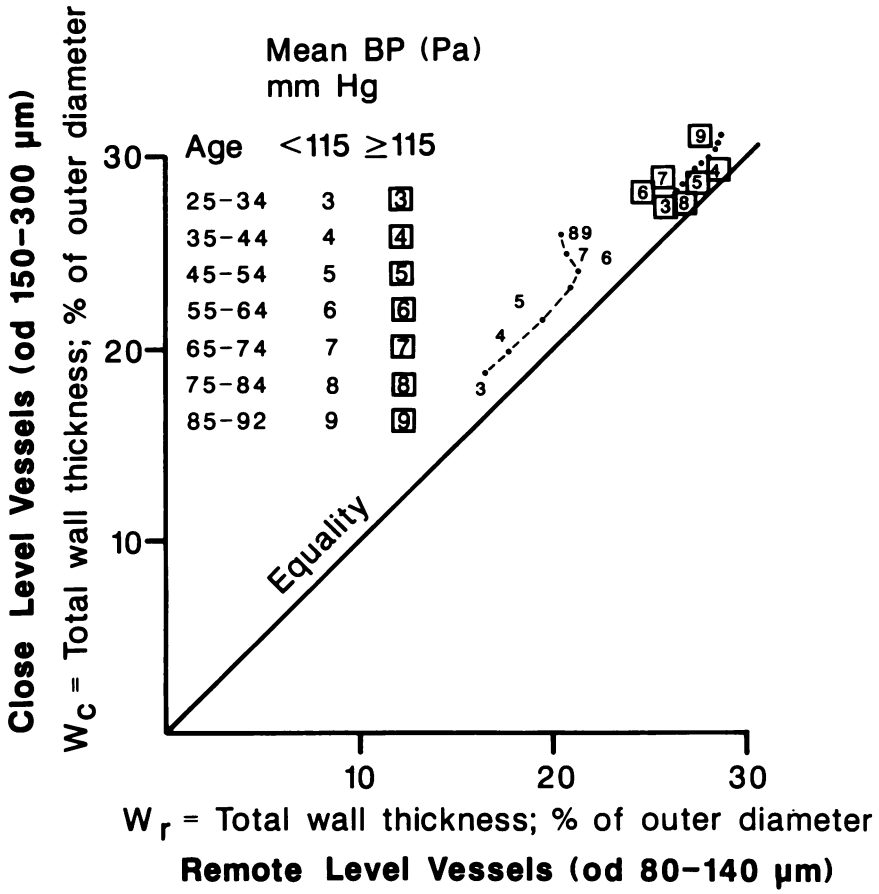

Figure 5—Means of W_c and W_r by 10-year age group are plotted for subjects with mean BP above and below 115 mm Hg. Regression equations relating W_c and W_r to age and BP were used as parametric functions to compute the *dotted lines* representing selected values of age with $P_a = 100$ and $P_a = 135$. The *circles* along the *dotted lines* represent ages 30, 40, 50, 60, 70, 80, and 90 as substitute values in these equations.

sets the pressure levels. There is good reason, however, to hesitate before accepting this conclusion at face value.

The results given here rest upon data that are known to be affected by serious sources of method error. For the estimation of BP, records were used that had been made by a multitude of observers under uncontrolled circumstances during conditions of illness, heart failure, medication, and other perturbing events. In order to minimize these problems, the cases

Table 4—Mean Intima/Diameter Ratios (Adjusted for Age and Recent Blood Pressure) by Duration of Recent Pressure According to Past Levels of Blood Pressure and Two-Way ANOVA

		Duration of recent mean BP					
		<3	3–5	6–12	>12	Total	Number of cases
Past mean BP							
P_b as % P_a							
>109		0.9	−0.5	1.6	—	0.6	51
100–109		0.9	−0.8	−0.4	—	0.4	36
88–100		−0.8	−1.8	−0.2	−2.9	−1.1	33
<88		−1.6	2.4	1.0	0.1	0.3	46
Total		−0.1	−0.2	0.5	−0.7	0.0	66
Number of cases		78	37	36	15	166	
ANOVA	Interactions	0.93 ($P = 0.49$)					
(Type III)	Duration	0.36 ($P = 0.78$)					
	Past mean BP	1.01 ($P = 0.39$)					

Table entries are in units of %OD computed as residuals from the regression equation $R_r = (k_1 \text{ Age} + k_2 P_a + k_3)^3$, which is the unsimplified form of Equation 3. Duration of recent BP (P_a = average mean pressure after transition) is in years. Past mean BP (P_b = average mean pressure before transition) is percentage of the recent level. ANOVA results are from the GLM procedure of SAS.

were highly selected by requiring that the records should include multiple outpatient readings over a period of years. Moreover, the effects of heart failure, medication, and category of illness were examined by analysis of variance to show that they could be treated as negligible. Even so, the records examined in this study were made without a standardized protocol, and represent only a short interval in the lifetime of each patient. For these reasons, we are now in the process of repeating these studies in a prospective study, the Honolulu Heart Project. Equations 1–8, therefore, represent hypotheses to be tested in an independent series of cases.

Another source of methodologic concern is the fact that the dimensions observed in the renal cortical arteries in tissue sections are artifactually affected by postmortem constriction.[9,10,18] Estimates computed from the data show that the average OD tended to increase with age, whereas lumen diameter remained constant, and that OD increased with hypertension, whereas the lumen was constricted (Table 3). Again, these results should be viewed with caution. Age and BP might conceivably bear upon the rigidity of the arteries and thereby correlate with the degree of postmortem constriction. The data given in Table 3 undoubtedly reflect a complex interaction of dimensional and rigidity effects of age and blood pressure. Some of these complex effects might be sorted out by studies of perfusion-fixed specimens, and such studies are under way in this laboratory. However, some sampling problems remain. Because hyalinization often obliterates the vessels less than 80 μ in size, those smallest arteries are not equally represented in the observed sample in all kidneys. By excluding all vessels less than 80 μ from the sample, the impact of this bias is lessened but not entirely eliminated. It seems likely that *in vivo* dimensions will never be accurately assessed by any means in postmortem tissue.

Some important uses of these data, however, do not require accurate preservation of *in vivo* dimensions, or even an understanding of the causal relationship of blood pressure to nephrosclerosis. The studies reported here were originally undertaken with a view toward their epidemiologic applications. Whereas hypertension is known to be a "risk factor" for coronary attacks, heart failure, and stroke, this tells us nothing about *etiology*. If we want to know what factors in a human community are *causing* hypertension, then clearly we can just as well ask what factors are causing nephrosclerosis. Given the close empirical linkages between these two classes of variables, as detailed in Equations 1–8, and in Table 1, the finding of etiology for one class implies the finding of etiology for the other class of variables. It sometimes happens that autopsy tissues are available when BP records are not. By measuring the severity of nephrosclerosis, one can, in a sense, indirectly observe BP, and thus compute correlations with other clinical, pathologic, and epidemiologic variables that would otherwise be difficult or impossible to pursue.

Many thousands of studies have been published comparing BP levels in differently constituted populations of subjects—some of these populations even being followed prospectively after assessment of suspected causative factors. These data on BP, together with vital statistics, provide all the information that we now have concerning the incidence rates of hypertension among populations that are variously exposed to putative etiologic agents. No study has been done for comparison of the severities of nephrosclerosis in samples of kidney tissue brought together from different sources for objective evaluation in a single facility. This laboratory is undertaking such studies for the first time. The method reported here has been shown to be reproducible by five independent observers. The severity of nephrosclerotic arterial fibrometaplasia assessed in this way has been shown to hold a close correlation with age-standardized levels of BP. A strong relationship of fibrometaplasia to cardiovascular diseases as cause of death has also been documented. The technique is "robust," in that small samples of tissue readily available from autopsies require no special handling, which will facilitate its use in a wide variety of circumstances wherein records of BP may be unavailable. For the first time, we are now in a position to undertake an attempt to correlate the severity of nephrosclerosis with whatsoever agents of causation may be proposed, now or in the future.

References

1. Branch A, Linder GC: The association of generalized arteriolar sclerosis with high blood pressure and cardiac hypertrophy in chronic nephritis. J Clin Invest 1926, 3: 299–318
2. Evans G: A contribution to the study of arteriosclerosis, with special reference to its relation to chronic renal disease. J Med 1921, 216–260
3. Fishberg AM: Anatomic findings in essential hypertension. Arch Intern Med 1925, 35:650–668
4. Stoddard LD, Puchtler H: Human renal vascular lesions and hypertension. Pathol Annu 1969, 4:253–268
5. Bell ET: Renal Diseases Philadelphia, Lea & Febiger, 1950
6. Cook TA, Yates PO: A critical survey of techniques for arterial mensuration. J Pathol 1972, 108:119–127
7. Kernohan JW, Anderson EW, Keith NM: The arterioles in cases of hypertension. Arch Intern Med 1929, 66:395–423

8. Moritz AR, Oldt MR: Arteriolar sclerosis in hypertensive and non-hypertensive individuals. Am J Pathol 1937, 13:679–728
9. Nishi T, Bond C, Brown G, Solez K, Heptinstall RH: A morphometric study of arterial intimal thickening in kidneys of dialyzed patients. Am J Pathol 1979, 95: 597–610
10. Short D: Morphology of the intestinal arterioles in chronic human hypertension. Br Heart J 1966, 28:184–192
11. Sommers SC, Relman AS, Smithwicke RH: Histologic studies of kidney biopsy specimens from patients with hypertension. Am J Pathol 1958, 34:685–702
12. Ueda K, Omae T, Hirota Y, Takeshita M, Hiyoshi Y, Nakamura Y, Katsuki S: Epidemiological and clinico pathological study on renal diseases observed in the autopsy cases in Hisayama population, Kyushu Island, Japan. J Chron Dis 1976, 29:159–173
13. Tracy RE, Mercante DE, Moncada A, Berenson G: Quantitation of hypertensive nephrosclerosis on an objective rational scale of measure in adults and children. Am J Clin Pathol 1986, 85:312–318
14. Joyner WL, Davis MJ: Pressure profile along the microvascular network and its control. Fed Proc 1987, 46: 266–269
15. Tracy RE, Tabares Toca V: Nephrosclerosis and blood pressure I. Rising and falling patterns in lengthy records. Lab Invest 1974, 30:20–29
16. Strong JP, Oalmann MC, Newman WP III, Tracy RE, Malcom GT, Johnson WD, McMahan LH, Guzman MA: Coronary heart disease in young black and white males in New Orleans: community pathology study. Am Heart J 1984, 108:747–759
17. Safar ME, Simon AC, Levenson JA: Structural changes of large arteries in sustained essential hypertension. Hypertension 1984, 6 (Suppl III):117–121
18. Pesonen E, Martimo P, Rapola J: Histometry of the arterial wall/A new technique with the aid of automatic data processing. Lab Invest 1974, 30:550–555

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