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Review Article

Nephrosclerosis from childhood to old age, a viewpoint

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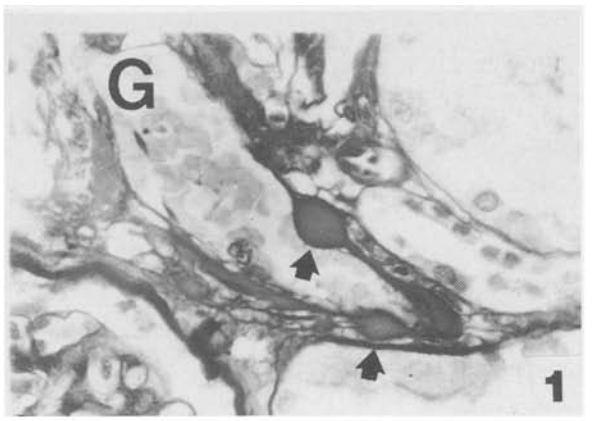
Abstract

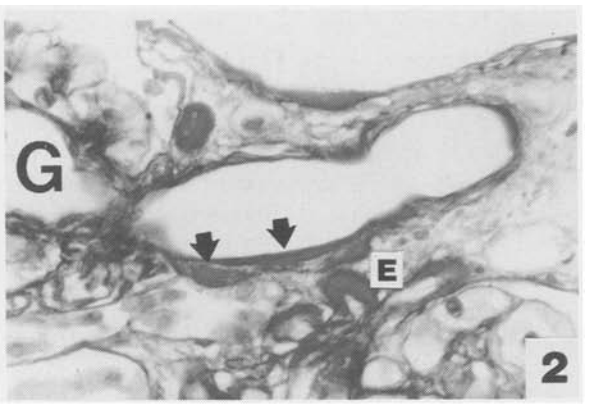
Cortical arteries of the kidney in benign nephrosclerosis are characterized by arterial intimal fibroplasia whereas arterioles are affected by hyalinization; these features overlap in the tiniest terminal arteries. In malignant nephrosclerosis, the characteristic lesions are mucoid edema and fibrinoid necrosis respectively. A fifth kind of vasculopathy is marked by reduced calibre and increased wall thickness to diameter ratio; although this is often called "hypertrophy", wall mass may not be increased, and the name "structural autoregulation" has been proposed in its place. Fibroplasia is found to some degree in every elderly person, even those who never experienced high blood pressure; blood pressure is elevated in those who manifest more than what is usual for the age. A review of reports concerning hypertension in subjects who lack evidence of nephrosclerosis suggests that such subjects may be statistical outliers who are likely to demonstrate regression to the mean in blood pressure rather than subsequent progression of renovasculopathies. It is proposed that uneven sclerosis of arteries may cause heterogeneity of nephrons so that some nephrons are sufficiently ischemic to evoke elevation of blood pressure by Goldblatt mechanisms, while other nephrons have structural autoregulation. A kidney with a small population of ischemic nephrons may show normal overall average function by available clinical methods. The etiology of arterial intimal fibroplasia in aging normotensives is unknown. That unknown etiology could, in theory, explain hypertension as merely the consequence of the more extreme degrees of benign renovasculopathies. A novel kind of epidemiological approach is proposed for pursuing clues to the unknown etiology.

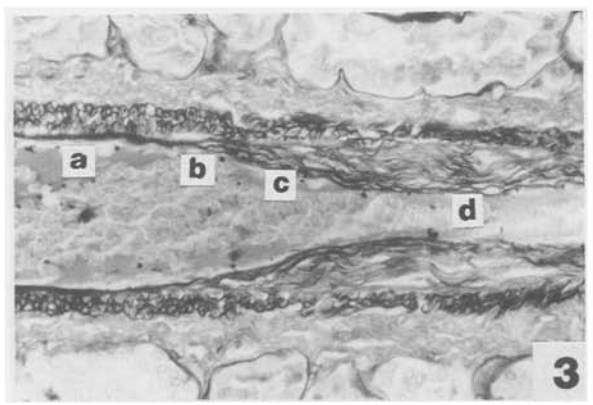
As the healthy human kidney ages in the absence of hypertension, the arteries and arterioles within the renal cortex show changes in structure (Figs. 1-3). The afferent and efferent arterioles, ranging from 10 to 30 μm in outer diameter in immersion fixed specimens, show more or less replacement of the medial musculature with hyaline masses; fibrosis of the media or of a newly formed intima is extremely rare in the absence of infarction or pyelonephritis (Fig. 1). The small arteries, designated interlobular, range in outer diameter from 80 to 300 μm in the collapsed state as seen in usual immersion-fixed postmortem or biopsy material. These vessels show a progressive replacement of youthful medial musculature with elderly fibrotic intima (Fig. 3); it is an extreme rarity to see hyaline masses in the walls of these small arteries [1-5]. The size range 30 to 80 μm is an ambiguous region which is sometimes included with the arterioles [2, 4] and sometimes with the small arteries [1, 3]. These terminal arteries frequently manifest hyalinization, intimal fibroplasia, or both coexisting together, thereby ambiguously displaying pathological characteristics of both arteries and arterioles. Benign nephrosclerosis is marked by hyalinization and fibroplasia of the vasculature in excess of what is expected for the age.

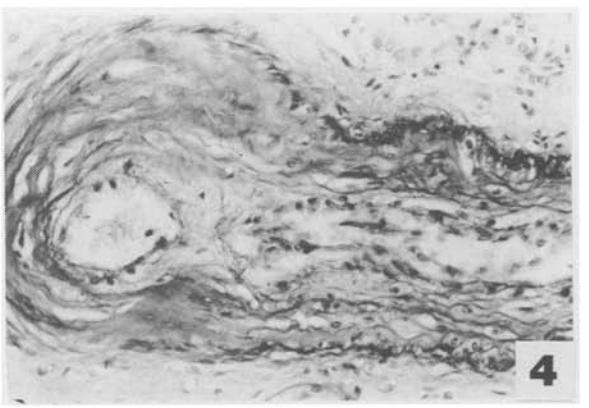
The histology of renovasculopathies

Youthful small arteries are composed of an orderly medial musculature, internal elastic lamella, and an adventitia of indefinite boundaries that blend









Figs. 1–4. Arrows mark hyaline deposits in the afferent arterioles of immersion fixed left kidney (Fig. 1) and perfusion fixed right kidney (Fig. 2) of an autopsied subject; "G" indicates glomerulus, "E" is a cluster of hyalinized efferent arterioles. Site "a" in Figure 3 illustrates the "youthful" structure of small artery walls, where orderly, circumferentially arranged smooth muscles cells, separated by thin and uniform basement membranes, compose a media that is delimited by an internal elastic lamella and a loose areolar adventitia. Site "d" illustrates progression toward the "elderly" wall structure where multiple layers of dense, cell-poor collagenous intima replace the withering media. Sites "b" and "c" illustrate intermediate stages of progression toward the elderly pattern. Figure 4, a "malignant" lesion, exemplifies the intrusion of hypercellular, mucin-rich edema into an intima that previously was of the fibrotic elderly pattern. PAS-Hematoxylin, X750 in Figs. 1 & 2, x 300 in Figs. 3 & 4.

into interstitial areolar tissues (Fig. 3, "a"). Endothelium is typically missing in postmortem preparations. Elderly arteries are characteristically composed of multiple intimal layers of dense collagenous material with reduction or absence of medial musculature (Fig. 3, "d"). The earliest stage of this fibroplasia is thought to be splitting of the internal elastica (Fig. 3, "b") followed by further splitting of the new layers ("c"). Cells are few, and are either longitudinally oriented smooth muscle or flat, stellate cells. These may represent relocated medial cells; no evidence of cell proliferation has been forthcoming. Elderly fibrotic arteries are "rigid" in the sense that they collapse less than youthful muscular arteries in postmortem specimens, and distend less upon perfusion fixation [6]. If this principle applies in vivo, then these arteries could be incapable of vasodilation or constriction.

Hyaline deposits in arterioles, as seen in immersion fixed specimens, often seem beaded after the manner of liquids (Fig. 1). With perfusion fixation, the beaded look is usually lost, and the masses are flattened into the walls of the arterioles (Fig.

2). Although hyalinization of arterioles is often called "sclerosis", no evidence has ever been offered that it is actually hard. Observations like those in Figures 1 and 2 might suggest the name "arteriolomalacia". Historically, it seems likely that the term "arteriolosclerosis" originally referred to the artery–like intimal fibrosis that affects terminal arteries (which most observers called arterioles); that term, as currently used, ordinarily refers to hyalinization. The meaning of "arteriolosclerosis", like the meaning of "arteriole", is ambiguous and must be inferred from each author's context. Some early workers proposed that the hyalin in arterioles may have a semifluid character [2]. That suggestion has since been seldom heard, although the matter has never been critically investigated.

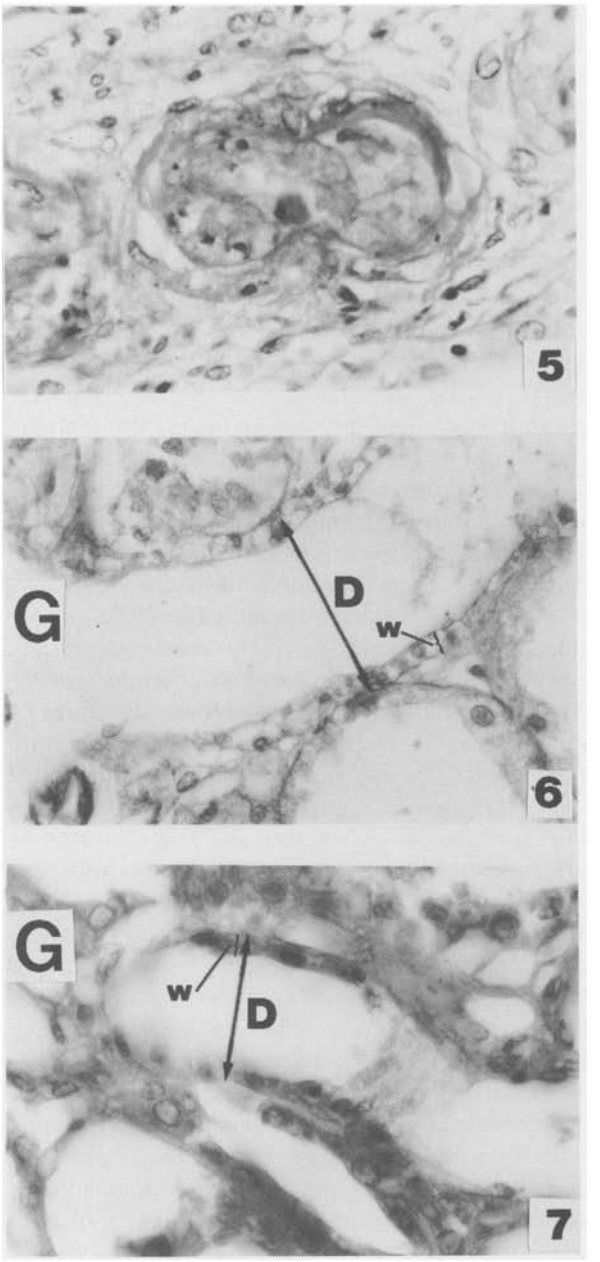
With malignant hypertension, small arteries take on a unique appearance that is often called "mucoid edema". This condition is marked by the presence of many large cells of an active appearance within an abundant matrix of acidic proteoglycans [5]. Since this usually strikes previously fibroplastic arteries, the residue of the former condition is usually the background for the mucoid edema (Fig. 4). Arterioles can acquire "fibrinoid necrosis" (Fig. 5). Terminal arteries uniformly share the mucoid edema with the small arteries but can also show fibrinoid necrosis like that in arterioles [5, 7–9]. Here, again, the terminal arteries of sizes 30 to 80 μm can ambiguously share properties of both small arteries and arterioles. Muirhead and Pitcock [7] have noted that the kind of fibrinoid necrosis that was commonly seen in the era before effective antihypertensive therapies is seldom seen in more recent specimens, whereas the mucoid edema remains as the characteristic finding. The experience in New Orleans with 43 autopsies of end stage renal disease (18 due to malignant nephrosclerosis) is in agreement with this observation; it was possible to find only one subject showing fibrinoid necrosis to photograph for inclusion here in Figure 5. It is well established that the mucoid edema and fibrinoid necrosis of malignant hypertension can be reversed and prevented by effective antihypertensive interventions (sometimes including hemodialysis or kidney transplant) [10–11]. Patients rescued in this way, however, may not be protected from continued progression of benign nephrosclerosis into ESRD [12–15].

Besides the vasculopathies of benign nephrosclerosis (arterial intimal fibroplasia and arteriolar hyalinization) and of malignant nephrosclerosis (mucoid edema and fibrinoid necrosis), a fifth kind has been described in company with hypertension. The fifth kind of vasculopathy has most often been called medial hypertrophy or hyperplasia [16–17]. These vessels show reduction of calibre from normotensive sizes, and increased ratios of wall thickness, w, to vessel diameter, D. Short [18–19] has demonstrated in an elegant way that the increased wall: lumen ratio, w/D, does not require an increased number or size of medial muscle cells. In hypertension, there is a scaling down of the denominator of this ratio, and, even without a change in the mass of the vessel wall, a compensatory increase in the numerator (w). Short's data on perfusion fixed mesenteric and intestinal vessels led to the conclusion that wall mass was, although demonstrably increased in macroscopic arteries, unchanged in the microscopic arteries of hypertensives. Kamal & Campbell [20] gathered data in a manner similar to that of Short, but analyzed the outcome in a different way; they concluded that wall mass was increased in hypertensive vessels. Inspection of their data, however, does not indicate any inconsistency, but rather a surprisingly good agreement with Short; the conclusion would best be reexamined using the same statistical methods. A similar study of afferent arterioles in perfusion fixed human kidneys [21] tends to support Short: hypertensives demonstrated a reduced calibre in vessels with no demonstrable qualitative or quantitative change in the wall structure. This finding is illustrated by representative examples of perfusion fixed afferent arterioles of a normotensive (Fig. 6) and a hypertensive subject (Fig. 7). Although the ratio w/D is increased in the hypertensive, because of the reduced caliber of the vessel, it scarcely seems reasonable to call the smaller vessel in Figure 7 "hypertrophied" in comparison with the larger vessel in Figure 6.

Folkow [17, 22] and others [23–24] have examined blood flow in the arms and hands of normotensives and hypertensives. They consistently find that maximum vasodilatation by pyrogen or other agents does not wholly reverse all of the vasoconstriction of hypertension. From this they conclude that "structural autoregulation" has

reduced the sizes of resistance level vessels, but without impairing their functional capabilities to dilate and constrict appropriately within the hypertensive range of blood pressures that they deal with. These findings are in good keeping with the anatomical studies that were just discussed. Folkow's "structural autoregulation" is an apt descriptive term for the observed condition of diminished lumen with increased wall: lumen ratio (Fig. 7), and might prove to be more accurate than the term "hypertrophy" which is not fully justified by existing data.

In the 19th century, histologic techniques were crude. Some observers saw medial muscular hypertrophy in the walls of hypertensive small arteries [25] while others saw fibrohyaline and arteriocapillary fibrosis [26]. Both groups of observers then made essentially the same mistake. Each of them insisted that all arteries of all organs and tissues must be affected alike, and that only one type of vasculopathy exists, the other being attributed to defective observation. It was subsequently demonstrated that this is not the case. The fibroplastic and hyaline types of vasculopathy often affect the solid splanchnic viscera, kidney, spleen, pancreas, adrenal gland, and liver; they are rarely seen in skin, fat or muscle (including the heart), and are usually of minor degrees in the hollow viscera [1–4]. Hence, anatomically rigid sclerosis of arteries is often widespread and severe in the kidneys of hypertensives and aging normotensives, but is of trivial degree in the vast vascular beds of the bulk tissues of the body. The great mass of body tissues, which largely determine the overall "peripheral resistance" to blood flow, show structural autoregulation, like that in Fig. 7, instead of sclerosis and hyalinization, like those of Figs. 1–5, in the small arteries and arterioles. Unfortunately, these fundamental facts seem not to be well known, and advocates of one or the other nineteenth century position can still be found.



Figs. 5–7. A terminal artery of 50μm outer diameter in this immersion fixed specimen illustrates fibrinoid necrosis (Fig. 5). Perfusion fixed afferent arterioles of a normotensive (Fig. 6) and a hypertensive subject (Fig. 7) are seen entering their respective glomeruli "G". Outer diameter, D, is diminished in the hypertensive, but wall thickness, w, is not altered compared with the normotensive, thereby raising the w/D ratio in the hypertensive. The designation "structural autoregulation" has been proposed for this feature of hypertensive arterioles. PAS-Hematoxylin, x 700.

Arterial intimal fibroplasia with aging and hypertension

The trends of progression of arterial intimal fibroplasia with normal aging are illustrated in Figure 8, where the data from three studies are summarized (data from references 27–29). In those

studies, autopsies on subjects having no evidence of cardiovascular diseases supplied kidney samples. Fibroplasia was quantified by measuring %od, the percentage of outer diameter (od) formed by the intimal thickness, in many vessels from each kidney. Arteries of outer diameter 150 to 300 μm were evaluated separately from those of 80 to 149 μm. Fibroplastic intima was found in some vessels in children of ages 5 to 15 years, with slow increases in quantity up to age 25 years. The rate of progression was greatest from ages 25 to 54 years, after which the rate of increase slackened into old age. For vessels of outer diameters 150 to 300 μm, the three studies seem to show good agreement, whereas the agreement is less good for smaller vessels. A similar graph showing data for hyalinization of arterioles is nearly identical to the sigmoid pattern of growth seen in Figure 8. It is perhaps not a coincidence that the ages of most rapid progression of fibroplasia, 25 to 54 years, are the ages in which nearly all cases of malignant hypertension are encountered.

Clearly, the progression over time of fibroplasia in renal cortical arteries does not require any degree of blood pressure elevation, since it happens to some degree in everyone. However, when hypertensive subjects are also examined, they typically show greater intimal thickenings than normotensives of the same ages [1–4]. Figure 9 shows individuals of ages 70–92 years from a study in New Orleans (spots and solid regression line) and the comparable regression line for Japanese American men in Hawaii. Also shown is the dotted regression line representing New Orleans subjects of ages 25 to 54 years. Of special interest is the finding that older subjects have greater thicknesses of intima than younger subjects of comparable blood pressure levels, ie the solid regression line is shifted rightward from the dotted line. This may be a consequence of the decreasing renal mass with age, so that a fibrotic artery may be supplying less tissue in the old compared with the young. Hyalinization of arterioles was less well correlated with blood pressure than was arterial intimal fibroplasia in these studies, although two small Japanese studies contradict this result by showing equally close correlations [30–31].

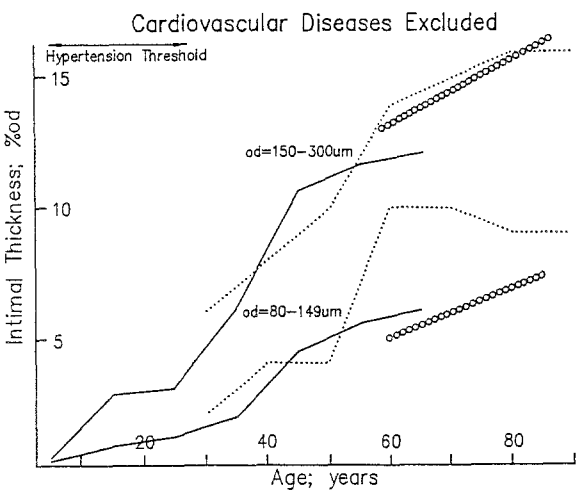


Fig. 8. Means of 10-year age groups are drawn from a New Orleans coroner's series (solid lines, ref. 29), and a New Orleans hospital series (dotted lines, ref. 27). Also shown are regression lines drawn from a series of Japanese-American men in Hawaii (lines of circles, ref 18). Intimal thicknesses, such as those at sites "b", "c", or "d" in Figure 3, measured as percent of outer diameter (%od) and averaged over many arteries per case, are plotted on the vertical. All cases having cardiovascular diseases were excluded from these analyses.

The term "nephrosclerosis" was introduced by Fahr [32], presumably to replace the previous name, chronic interstitial nephritis, which erroneously implied an inflammatory basis of the disorder. The new term correctly suggests the existence of interstitial fibrosis replacing functional renal tissue; it does not, however, invoke an image of vasculopathies that underlie the disorder. Our data now in editorial review have clearly documented that arterial fibroplasia and arteriolar hyalinization can be seen in severe degree in the absence of important interstitial fibrosis, and these forms of vasculopathy continue to dominate the picture through varying degrees of renal destruction. The data therefore demonstrate that vasculopathies with intact nephron structure comprise one end of a continuum that extends into varying degrees of nephrosclerosis at the other end of the continuum. Nephrosclerosis is the important consideration in cases of failing renal function and progression toward end stage renal disease (ESRD). Vasculopathy, however, is the important concern in hypertension. Some observers reserve the term "essential hypertension" for cases without measurable impairment of overall renal function [33], although the usual custom is to use the term irrespective of the severity of nephrosclerosis. A distinction between "nephrosclerotic hypertension" in instances of impaired renal function and "essen-

tial hypertension" in subjects with overall average normal renal function would go far to remove much confusion in comparing the results of different studies with each other, but this distinction has not been universally established. Although many of those essential hypertensives who lack nephrosclerosis can be shown to carry significant degrees of occult vasculopathies, it is not yet clear whether all of them do so.

Heterogeneity of nephrons

The anatomic studies just reviewed suggest that the small arteries and arterioles of the hypertensive kidney can participate in either structural autoregulation or fibroplastic sclerosis, some nephrons showing one feature and some the other. A number of function studies have been developed to search for this kind of nephron heterogeneity in living subjects [34]. Inert gases, such as krypton or xenon, have the ability to diffuse rapidly into and out of tissues. When a bolus of 133Xe is introduced into the renal artery, the gas is taken up by the renal tissue, to be delivered back into the renal vein blood over the next 5 to 15 minutes. The load of label in the kidney can be followed by external scintillation counting, thereby generating a curve to depict the washout of the label. Following the results in dogs, the washout curve is typically resolved into a series of four linear exponential terms that are said to represent the blood flow through the renal cortex, medulla, pelvis and capsule, and surrounding fat. Results from use of this method in subjects with nephrosclerotic hypertension have generally been interpreted as showing diminished flow through the cortex, but with unchanged flow through the medulla [35–37]. Since the method measures blood flow per gram of renal tissue, the diminished flow can be attributed to ischemia, and not just to loss of renal substance. Ladefoged [38] has noted, however, that, "In patients with severe kidney disorders, an inhomogeneous distribution of the blood flow through the renal cortex may occur . . . . It is possible that areas in the cortex with low perfusion may be represented in the second component of the wash–out curve, and likewise parts of the outer medulla may contribute to the first component." Hollenberg et al. [39] favored this view; "The presence of a normal flow rate per unit mass in the rapid component of most of these patients suggests that portions of the kidney, presumably some parts of the renal cortex, were perfused at a normal rate. The other cortical areas in which the flow rate per unit mass was reduced were represented as slower flow components . . ."

The use of albumin bound dyes, however, has raised into question the existence of nephron heterogeneity [40–41]. This crucial finding has not been reconciled with other data, and argues for caution before acceptance of nephron heterogeneity.

Does hypertension sometimes precede renovasculopathies?

A number of observers have identified the existence of some hypertensive subjects whose kidneys on biopsy [42–43] or necropsy [3, 8] show minimal degrees of vasculopathy. Figure 9 shows two such individuals at position "a". These observations have been used to argue that ". . . hypertension precedes structural changes in the kidney vasculature" [42]. However, the existence of such unusual hypertensives does not necessarily mean that they can be expected to experience rapid progression of renovasculopathy. This notion is a guess that could only be tested through the kinds of prospective studies that have never been reported.

The preceding argument is statistical, and perhaps should be reviewed in a statistical way: Healthy young people with intact renal function manifest a "normal range" of blood pressure. Elderly persons with minimal renovasculopathy likewise manifest what might legitimately be called a normal range. In the lower left quadrant of Figure 9, for instance, mean blood pressure is seen to range from about 70 to 110 mmHg in the elderly subjects with the least renovasculopathy – roughly what would be found in persons of age 20 years. Elderly subjects with maximal degrees of renovasculopathy, seen in the upper right quadrant of Figure 9, also manifest a range of readings, from about 110 to 150 mmHg. Hence, the average aging person is seen to manifest a level of blood pressure

that is linked to the severity of arterial intimal fibroplasia, as described by the solid regression line. Upon this average tendency is imposed a degree of individual variation that may represent nothing more than a persistent "normal range". The total variation of blood pressure among individuals is therefore, in statistical jargon, resolved into a nephrosclerosis linked component (along the regression line) and a residual component (vertical deviation from the line). It seems paradoxical to suggest that subjects of differing blood pressure with similar degrees of vasculopahty, e.g. those at positions "c" and "d" in Fig. 9, are advancing the vasculopathy at different rates, or that subjects with little fibroplasia are progressing at the same rate as those with much fibroplasia when blood pressure levels are alike, e.g. positions "a" and "b" in Fig. 9. The hypothesis that blood pressure governs the rate of progression of renovasculopathy is not required to explain the data in Fig. 9.

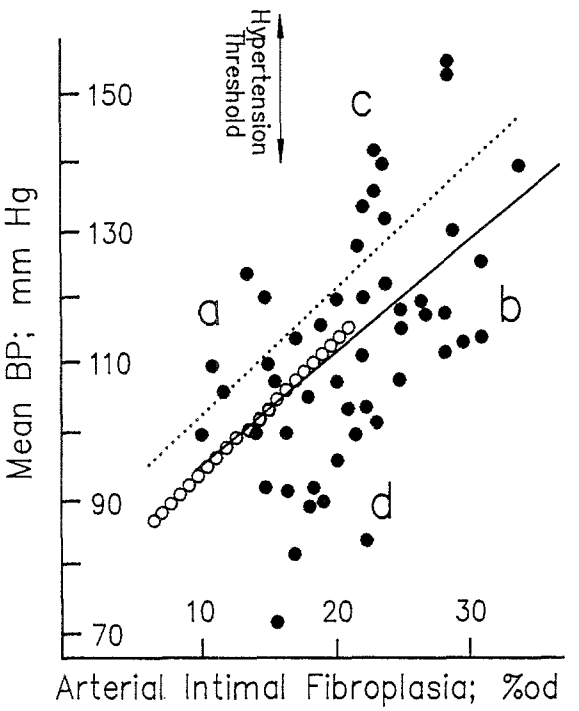


Fig 9. Hospital patients followed in the outpatient clinics with recordings of blood pressure over many years, were examined at autopsy for renal arterial intimal fibroplasias such as those in Figure 3. Spots represent subjects of ages 70-92 years, and the solid line is the regression fit to these spots. The dotted line is the comparable regression line fit to the subjects of ages 25-54 years. The line of circles is the regression line drawn from the study of Japanese-Americans in Honolulu. Letters a-d are introduced to aid discussion

An exception to the foregoing argument occurs with the onset of malignant hypertension. The autoregulatory capacity for nephrons to restrain blood flow within a narrow range spans mean blood pressures of about 60 to 180 mmHg [44]. When a patient experiences pressures in excess of the upper limit of this range, rapidly progressive arterial strictures (mucoid edema) can be induced which activate Goldblatt mechanisms to further elevate blood pressures, and so on. This vicious cycle, as expected, goes rapidly to completion, unless interrupted by medical intervention. Benign hypertension, on the other hand is marked by a striking absence of such a rapidly self completing vicious cycle. As noted by Coleman et al [45], "In contrast, essential hypertensives often show a relatively stable pressure over several decades." The data of Figure 8 also argue against such a vicious cycle in the causation of benign nephrosclerotic vasculopathies. The progression of arterial fibroplasia was most brisk in younger age groups, who generally average low levels of blood pressure, and actually slowed in the elderly, who tend to average higher blood pressures. Instead of an acceleration of the process in its later stages, a slackening was seen.

It is well known that some hypertensives can be shown to manifest a "hyperdynamic" state, with high cardiac output, normal peripheral resistance, and normal or increased renal blood flow [46–48]. Yet, here again we have reason to wonder what may be the future course for these uncommon kinds of hypertensives. Statistically, we would anticipate that these "outliers", represented at positions "a" and "c" in Figure 9, would "regress to the mean" of their vasculopathy defined groups, represented by the solid regression line. The logical probabilities are that blood pressure should decline toward average over time in those subjects who have temporarily strayed into the high range. This is, after all, the origin of the name "regression line".

Some indirect data reviewed by Schmieder et al. [49] would seem to verify this statistical expec-

tation: Those authors reviewed 19 reports in which some hypertensive subjects had antihypertensive medications withheld or withdrawn after variable periods of administration; they found, "Most study groups have observed that some formerly treated hypertensive patients remain normotensive after drug withdrawal for months or even years . . . in two prospective studies blood pressure values in the control groups have been observed to regress toward the normotensive range without therapy." (the latter two studies were those which included a placebo group). We do not know, of course, that the unmedicated hypertensives who showed regression toward the mean were of the "hyperdynamic" type. It would be statistically expected, however, that these cases with regressing high blood pressure are not experiencing progression of renovasculopathy, and that they are not instances of hypertension preceding nephrosclerosis as they are often summarily assumed to be.

The data from anatomical and functional studies, as just reviewed, indicate that some small percentage of subjects with high blood pressure can show persuasive evidence that renal ischemia is absent. These results, however, do not argue that such hypertensives are destined to acquire renovasculopathies. Rather, those exceptional subjects seem instead to be temporarily above their usual range of blood pressure, and are likely to regress over time toward average. This matter, however, has not been tested by the necessary prospective studies.

Blood pressure in kidney transplant recipients

About 50% of patients who receive successful renal transplants manifest some degree of hypertension [50–54]. Factors which are associated with elevated blood pressure include elevated serum creatinine, cadaveric rather than related donor, number of rejection episodes, excess body weight, presence of native kidneys, stenosis of the transplant renal artery, therapy with corticoids, and more recently, the vasospastic effect of cyclosporine [50, 52–54]. Conspicuous for its lack of effect on posttransplant blood pressure is the operative diagnosis of nephrosclerosis. Subjects whose ESRD resulted from "essential hypertension" of maximal degree ending in decompensated benign nephrosclerosis had no degree of hypertension beyond what was expected from their status as donor recipients. Subjects with nephrosclerotic hypertension, therefore, had no impetus to high blood pressure beyond what could be attributed to malfunctioning kidneys or the therapy used for them. This evidence leaves little reason to think that nephrosclerotic hypertension has any cause other than what emanates from disordered kidneys.

Progression of nephrosclerosis in treated hypertensives

It is well documented that lowering of blood pressure in hypertensives by use of medications improves their outlook for avoiding heart failure, stroke, and to a lesser degree, coronary events. Whether such medications may retard the progression of benign nephrosclerosis or its associated vasculopathies, however, has not been determined. Part of the problem in such determinations is that ESRD is a rare complication of nephrosclerotic hypertension. The number of hypertensives in the USA is often said to be about 60,000,000 [55]. Yet the annual rate of newly discovered nephrosclerotic ESRD is about 9,000 (plus 10,000 attributed to diabetes) [56]. In the Hypertension Detection and Follow–up Program [57], 10,940 recruited hypertensives were followed for as much as 8.3 years; 43 deaths were attributed to renal diseases, but the numbers entering chronic hemodialysis are not given. In a review of six prospective trials of therapy for hypertension with over 20,000 patients years of followup, Whelton & Klag [58] tabulated 35 "renal disease outcome events" as judged by progressive azotemia; 17 of these cases occurred in placebo treated controls. "Two of the six trials reported proteinuria, and in both trials, proteinuria was less common during active therapy." An improvement of microalbuminuria in treated hypertensives was seen in one [59] but not another [60] of two recent series. If high blood pressure acts to worsen renal ischemia, thereby further elevating the blood pressure in a vicious cycle, then surely the cycle should quickly end in decompensated benign nephrosclerosis more often than these data indicate.

Treated hypertensive subjects often experience

progressive deterioration of renal function as measured by serum creatinine levels [55, 60] or by clearance methods [59]. (A negative report in this regard was designed in a way that would permit regression to the mean in the test subjects [61].) These observations would seem to suggest that subjects with advanced renovasculopathy continue to show faster than average progression, even when blood pressure levels have been normalized by medication. The conclusion is tenuous, however, because few properly controlled studies have reported the changes in renal condition during medication for high blood pressure. Moreover, it is possible that continuing deterioration of renal function might be due to glomerulosclerosis induced by hyperperfusion and hyperfiltration, perhaps fostered by medicinal vasodilatation in the structurally autoregulated nephrons [62–65].

Animal models

Animal experimentation has demonstrated that high blood pressure can induce vasculopathies, and hyperperfusion types of glomerulopathies, that closely mimic the features of malignant hypertension in man [66–70]. No such model has ever produced vasculopathies that resemble benign nephrosclerosis, as illustrated in Figures 1 & 3 [5, 33, 70–71]. Indeed, the only model that shows arterial structures in the renal cortex reminiscent the intimal fibroplasia of Figure 3 is the chronic rejection of organ transplants by incompletely immunosuppressed hosts [51, 72].

The search for etiology

Most instances of arterial intimal fibroplasia and arteriolar hyalinization seen in the kidneys of elderly people cannot be explained by any purported effect of hypertension, because those subjects never manifested high blood pressure (cf Figures 8 & 9). Therefore, an unknown cause related in some way to normal aging must be invoked to explain what is seen in aging normotensives. Having been invoked, the unknown cause is then found to be sufficient, in theory, to explain hypertension as merely the consequence of the more extreme degrees of benign renovasculopathies, by way of well known Goldblatt mechanisms. A posited effect of blood pressure as an agent to accelerate the process is undocumented and unnecessary.

Unique evidence of a new sort has recently become available to offer clues about the possible nature of the unknown etiologic factors. North American black and white men and women have been compared with men in Guatemala and Tokyo and with women in Tokyo [73–74]. Sigmoid curves like those in Figure 9 relating renovasculopathies to age were found in all of these populations. Intimal thicknesses of the interlobular arteries with 150–300 μm outer diameters (od) reached an average of 9.0 %od in black females of North America at age 35 years, but only 6.1 %od in Guatemalan men. These are, so far, the greatest extremes yet observed between populations.

These epidemiological data offer, for the first time, clear evidence that the progression of intimal fibroplasia in renocortical arteries, although strongly age related, may not be an inescapable feature of the human condition, because the Guatemalan males do escape the very rapid rates of "aging" seen in the black females of North America. The recent evidence has also identified the years of pubertal growth as a time of especially great importance in establishing population differences in renovasculopathies. Clues of this kind are only now becoming available to aid in a search for the etiologies of the renovasculopathies that may underlie most cases of essential hypertension. In the meantime, these etiologies will remain distressingly unknown.

References

1. Evans G. A contribution to the study of arteriosclerosis, with special reference to its relation to chronic renal disease. Q J Med 1920; 14: 215–82.
2. Fishberg AM. Anatomic findings in essential hypertension. Arch Int Med 1925; 35: 659–68.
3. Bell ET, Clawson BJ. Primary (essential) hypertension. A study of four hundred and twenty cases. Arch Path 1928; 5: 939–1002.
4. Moritz AR, Oldt MR. Arteriolar sclerosis in hypertensive and non-hypertensive individuals. Am. J Path 1937; 13: 679–728.
5. Stoddard LD, Puchtler H. Human renal vascular lesions and hypertension. Pathol Annu 1969; 4: 253–68.
6. Tracy RE, Heigle TJ, Velez-Duran M. Evidence for the

failure of the Laplace law as a sole explanation for wall thickening of arteries in hypertensive and aging normotensive kidneys. Arch Pathol Lab Med 1989; 113: 342–9.
7. Muirhead EE, Pitcock JA. Histopathology of severe renal vascular damage in blacks. Clin Cardiol 1989; 12: IV–58–65.
8. Kimmelstiel P, Wilson C. Benign and malignant hypertension and nephrosclerosis. Am J Pathol 1936; 12: 83–97.
9. Burkholder PM. Malignant nephrosclerosis. Arch Path 1965; 80: 583–9.
10. McCormack RE, Beland JE, Schneckloth RE, Corcoran AC. Effects of antihypertensive treatment on the evolution of the renal lesions of malignant nephrosclerosis. Am J Pathol 1958; 34: 1011–8.
11. Jespersen B, Eiskjaer H, Christiansen NO, Olsen S, Pedersen EB. Malignant arterial hypertension. Relationship between blood pressure control and renal function during long–term observation of patients with malignant nephrosclerosis. J Clin Hypertens 1987; 3: 409–18.
12. Woods JW, Blythe WB, Huffines WD. Management of malignant hypertension complicated by renal insufficiency. New Eng J Med 1974; 291: 10–14.
13. Mitchell HC, Graham RM, Pettinger WA. Renal function during long–term treatment of hypertension with minoxidil. Comparison of benign and malignant hypertension. Ann Intern Med 1980; 93: 676–81.
14. Nicholson GD. Long–term survival after recovery from malignant nephrosclerosis. Am J Hypertens 1988; 1: 73–5.
15. Patel R, Ansari A, Grim CE. Prognosis and predisposing factors for essential malignant hypertension in predominantly black patients. Am J Cardiol 1990; 66: 868–9.
16. Kernohan JW Anderson EW, Keith NM. The arterioles in cases of hypertension. Arch Intern Med 1929; 44: 395–423.
17. Folkow B. "Structural factor" in primary and secondary hypertension. Hypertension 1990; 16: 89–101.
18. Short D. Morphology of the intestinal arterioles in chronic human hypertension. Br Heart J 1966; 28: 184–92.
19. Short D. The vascular fault in chronic hypertension with particular reference to the role of medial hypertrophy. Lancet 1966; 1: 1302–4.
20. Kamal MF, Campbell ACP. Medial hypertrophy in the small intestinal arteries in systemic hypertension, renal and essential. J. Pathol 1979; 129: 99–110.
21. Tracy RE, Overl EO: Arterioles of perfusion–fixed hypertensive and aged kidneys. Arch Pathol 1966; 82: 526–34.
22. Folkow B. "Structural autoregulation" – local adaptation of vascular beds to chronic changes in pressure. Development of the Vascular System (CIBA Foundation Symposium 100). Pittman Books, London: 1983: 56–79.
23. Sivertsson, Hansson L. Effects of blood pressure reduction on the structural vascular abnormality in skin and muscle vascular beds in human essential hypertension. Clin Sci Molec Med 1976; 51: 77S–79S.
24. Ashton H. Critical closing pressure in hypertension. Clin Sci 1962; 22: 89–94.
25. Johnson G. On the changes in the blood–vessels and in the kidney, in connection with the small red granular kidney. Trans Path Soc London 1877; 28: 381–94.
26. Gull S, Sutton HG. On the artrio–capillary system in connection with kidney disease. Trans Path Soc London 1877; 28: 361–81.
27. Tracy RE, Velez–Duran M, Heigle T, Oalmann MC. Two variants of nephrosclerosis separately related to age and blood pressure. Am J Pathol 1988; 131: 270–82.
28. Tracy RE, MacLean CJ, Reed DM, Hayashi T, Gandia M, Strong JP. Blood pressure, nephrosclerosis, and age. Autopsy findings from the Honolulu Heart Program. Mod Pathol 1988; 1: 420–7.
29. Tracy RE, Berenson G, Wattigney W, Barrett TJ. The evolution of benign arterionephrosclerosis from age 6 to 70 years. Amer J Pathol 1990; 136: 429–39.
30. Katafuchi R, Takebayashi S. Morphometrical and functional correlations in benign nephrosclerosis. Clin Nephrol 1987; 28: 238–43.
31. Yamaguchi T, Omae T, Katsuki S. Quantitative determination of renal vascular changes related to age and hyper Effros RM, Demeester M, Chasis H, Baldwin DS, Gomez DM. The distribution of intrarenal blood flow in normal and hypertensive man. Circulation 1967; 35: 250–9.
32. Fahr Th: Uber Nephrosklerose. Virchows Arch 1919; 26: 119–78.
33. Goldblatt H. The renal origin of hypertension. Physiol Rev 1947; 27: 120–65.
34. Sealy JE, Blumenfeld JD, Bell GM, Pecker MS, Sommers SC, Laragh JH. On the renal basis for essential hypertension: nephron heterogeneity with discordant renin secretion and sodium excretion causing a hypertensive vasoconstriction–volume relationship. J Hypertens 1988; 6: 763–77.
35. Nomura G, Kurosaki M, Inasaka T, Takabatake T, Dohi K , Takeuchi J. Intrarenal blood flow in essential hypertension. Nephron 1974; 13: 114–24.
36. Ladefoged J, Pedersen F. Renal blood flow in patients with hypertension. Clin Sci 1969; 37: 114-24.
37. Gatta A, Merkel C, Pessina AC, Milani L, Sacerdoti D, Zuin R. Renal haemodynamics in essential hypertension assessed by 133–xenon washout and selective renal angiography by 133–xenon washout and selective renal angiography. Angiology 1982; 33: 818–24.
38. Ladefoged J. Measurements of the renal blood flow in man with the 133xenon wash–out technique. A description of the method. Scand J Clin Lab Invest 1966; 18: 299–315.
39. Hollenberg NK, Epstein M, Basch RI, Merrill JP. "No man's land" of the renal vasculature. An angiographic and hemodynamic assessment of the interlobar and arcuate arteries in essential and accerlerated hypertension. Am J Med 1969; 47: 845–54.
40. Lowenstein J, Steinmetz PR, Effros RM, Demeester M, Chasis H, Baldwin DS, Gomez DM. The distribution of intrarenal blood flow in normal and hypertensive man. Circulation 1967; 35: 250–9.
41. Kioschos JM, Kirkendall WM, Valenca MR, Fitz AE. Unilateral renal hemodynamics and characteristics of dye–dilution curves in patients with essential hypertension and renal disease. Circulation 1967; 35: 229–48.
42. Sommers SC, Relman AS, Smithwick RH. Histologic studies of kidney biopsy specimens from patients with hypertension. Am J Pathol 1958; 34: 685–702.

43. Heptinstall RH: Renal biopsies in hypertension. Br Heart J 1954; 16: 133–41.
44. Kiil F. The mechanism of renal autoregulation. Scand J Clin Lab Invest 1981; 41: 521–25.
45. Coleman TG, Guyton AC, Young DB, DeClue JW, Norman RA Jr, Manning RD Jr. The role of the kidney in essential hypertension. Clin Exp Pharm Physiol 1975; 2: 571–81.
46. Dustan HP. Rational therapies for hypertension. Is step 1 of stepped care archaic? Circulation 1987; 75: 96–100.
47. Hollenberg NK, Adams DF, Solomon H, Chenitz WR, Burger BM, Abrams HL, Merrill JP. Renal vascular tone in essential and secondary hypertension: hemodynamic and angiographic response to vasodilators. Medicine 1975; 54: 29–43.
48. Hollenberg NK, Adams DF. The renal circulation in hypertensive disease. Am J Med 1976; 60: 773–84.
49. Schmieder RE, Rockstroh JK, Messerli FH. Antihypertensive therapy: To stop or not to stop? JAMA 1991; 265: 1566–71.
50. Hume DM, Lee HM, Williams GM, White HJO, Ferre J, Wolf JS, et al. Comparative results of cadaver and related donor renal homografts in man, and immunologic implications of the outcome of second and paired transplants. Ann Surg 1966; 164: 352–96.
51. Taylor HE. Pathology of organ transplantation in man. Pathol Annu 1972; 7: 173–99.
52. Kasiske BL. Possible causes and consequences of hypertension in stable renal transplant patients. Transplantation 1987; 44: 639–43.
53. Luke RG. Hypertension in renal transplant recipients. Kidney Int 1987; 31: 1024–37.
54. Curtis JJ. Hypertension after renal transplantation: cyclosporine increases the diagnostic and therapeutic considerations. Am J Kidney Dis 1989; 13: 28–32.
55. Rostand SG, Brown G, Kirk KA, Rutsky EA, Dustan HP. Renal insufficiency in treated essential hypertension. New Eng J Med 1989; 320: 684–8.
56. USRDS. Excerpts from the United States Renal Data System 1990 annual report. Am J Kidney Dis 1990; 16: 18–48.
57. Hypertension Detection and Follow–up Program cooperative group: Persistence of reduction in blood pressure and mortality of participants in the hypertension detection and follow–up program. JAMA 1988; 259: 2113–22.
58. Whelton PK, Kłag MJ. Hypertension as a risk factor for renal disease. Review of clinical and epidemiological evidence. Hypertension 1989; 13 (I Suppl): 19–27.
59. Hartford M, Wendelhag I, Berglund G, Wallentin I, Ljungman S, Wikstrand J. Cardiovascular and renal effects of long–term antihypertensive treatment. JAMA 1988; 259: 2553–7.
60. Samuelsson O, Wikstrand J, Wilhelmsen L, Berglund G. Heart and kidney involvement during antihypertensive treatment. Results from the primary prevention trial in Goteborg, Sweden. Acta Med Scand 1984; 215: 305–11.
61. Pettinger WA, Lee HC, Reisch J, Mitchell HC. Long–term improvement in renal function after short term strict blood pressure control in hypertensive nephrosclerosis. Hypertension 1989; 13: 766–72.
62. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. New Eng J Med 1982; 307: 652–9.
63. Lindeman RD, Tobin JD, Shock NW. Hypertension and the kidney. Nephron 1987; 47: 62–7.
64. Bohle A, Biwer E, Christensen JA. Role of hyperperfusion in different glomerular diseases. Blood Purif 1988; 6: 258–63.
65. Schmieder RE, Messerli FH, Garavaglia G, Nunez B. Glomerular hyperfiltration indicates early target organ damage in essential hypertension. JAMA 1990; 264: 2775–80.
66. Campbell WG, Santos–Buch CA: Widely distributed necrotizing arteritis induced in rabbits by experimental renal alternations. Am J Pathol 1965; 46: 71–83.
67. Heptinstall RH, Hill GS. Steroid–induced hypertension in the rat. A study of the effects of renal artery constriction on hypertension caused by deoxycorticosterone. Lab Invest 1967; 16: 751–767.
68. Ljungqvist A. Intrarenal vascular alternations and the persistence of experimental hypertension. Acta Path Microbiol Scand 1969; 76: 561–74.
69. Helmchen U, Bohle RM, Kneissler U, Groene HJ. Intrarenal arteries in rats with early two–kidney, one clip hypertension. Hypertension 1984, 6 (Suppl III): 92.
70. Mandal AK, Bell RD, Parker D, Nordquist JA, Lindeman RD. An analysis of the relationship of malignant lesions of the kidney to hypertension. Microvasc Res 1977, 14: 279–92.
71. Goldblatt H. Discussion. In Moyer JH editor Hypertension; The first Hahnemann Symposium on hypertensive disease. Phila.: W.B. Saunders Co., 1959: 171–4.
72. Porter KA, Calne RY, Zukoski CF. Vascular and other changes in 200 canine renal homotransplants treated with immunosuppressive drugs. Lab Invest 1964; 13: 809–24.
73. Tracy RE, Bhandaru SY, Oalmann MC, Guzman MA, Newman WPIII. Blood pressure and nephrosclerosis in black and white men and women aged 25 to 54. Mod Pathol 1991; 4: 602–9.
74. Tracy RE, Malcom GT, Oalmann MC, Qureshi U, Ishii T, Velez–Duran M. Renal microvascular features of hypertension in Japan, Guatemala, and USA. Arch Pathol Lab Med 1992. In Press

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