# A Morphometric Study of Arterial Intimal Thickening in Kidneys of Dialyzed Patients

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**Arterial intimal thickening is common in the end-stage kidneys of patients maintained on hemodialysis. We measured the intimal thickening in patients dialyzed for varying periods and in patients with the malignant phase of essential hypertension and with scleroderma-associated renal failure. The ratio of intimal area to medial area in intrarenal arteries was used as a measure of intimal thickening. In the dialysis groups, intimal thickening was relatively constant in arteries of all sizes and correlated with duration of dialysis, particularly in larger arteries. In the malignant hypertension and scleroderma groups, the intimal thickening was greatest in arteries less than 200 $\mu$ in diameter and least in those over 500 $\mu$ in diameter. There was much less intimal thickening in arteries of all sizes in kidneys of patients with end-stage polycystic disease than in other end-stage kidneys from patients with a similar diastolic blood pressure and similar duration of dialysis. We believe that the intimal thickening in dialyzed patients is probably a disuse type of change and may be related to reduction in the area of the renal microvascular bed. (Am J Pathol 95:597–610, 1979)**

IT HAS BECOME APPARENT that kidneys from patients who have been treated with chronic dialysis for end-stage renal disease show a variety of changes, including a pronounced widespread cellular intimal thickening of the arteries.[1–4] There has been little attempt to study these changes in detail. The present investigations were designed to examine by morphometry the severity and distribution of the arterial intimal thickening in end-stage kidneys removed prior to transplantation. Correlations were sought between these quantitative measurements and factors such as length of dialysis and height of blood pressure. Light microscopy was used to study the character of the change, and electron microscopy was performed in selected cases. Because there are great similarities between the intimal changes seen in interlobular arteries in the malignant phase of essential hypertension and in scleroderma with renal failure, a similar study was made in patients with these two conditions. The purposes were twofold: a) to compare the arterial changes in these two conditions with the post-dialysis kidneys and b) to see if any light could be shed on the relationship of hypertension to changes in intrarenal arteries, an old but still unresolved problem.

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Supported in part by USPHS Grant HL 07835. Dr. Nishi was supported by an Eli Lilly International Fellowship.

Accepted for publication January 16, 1979.

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0002-9440/79/0607-0597$01.00

## Materials and Methods

Material from 108 patients with end-stage renal disease who had their kidneys removed or who died between 1962 and 1976 was obtained from the autopsy and surgical pathology files of The Johns Hopkins Hospital. The kidneys were obtained at autopsy in 34 cases and at surgery in 74 cases. They were divided into eight groups (Table 1). Group I (n=17) consisted of 10 end-stage kidneys from autopsied patients who had never been dialyzed and 7 surgically removed kidneys from patients who had been dialyzed for less than 1 month. Groups II (n=21), III (n=15), and IV (n=10) consisted of surgically removed end-stage kidneys from patients who had been dialyzed for 1 to 3 months, 3 to 6 months, and 6 to 30 months, respectively. The pathologic diagnoses in Groups I to IV were chronic glomerulonephritis (28 cases), chronic pyelonephritis (8 cases: 3 of the obstructive type and 5 of the nonobstructive variety), hereditary nephritis (2 cases), uremic medullary cystic disease (1 case), diabetic nephropathy (1 case), and end-stage kidney, not further classified (13 cases). These diagnoses were more or less evenly distributed among the four groups. The frequency of the different diseases in Group I through IV does not reflect the true prevalence of the various renal conditions which cause chronic renal failure because patients in our dialysis–transplant program with a clinical diagnosis of pyelonephritis routinely have their kidneys removed, while other patients usually undergo nephrectomy only if they are hypertensive. Groups V (n=12) and VI (n=11) consisted of kidneys from patients with the malignant phase of essential hypertension (MPEH); the patients in Group V (autopsy group) had not received dialysis, whereas those in Group VI (surgical group) had been dialyzed for an average of 3.0 ± 0.9 (SEM) months (range, 1 to 11 months). Group VII (n=12) consisted of kidneys from autopsied patients with scleroderma, all of whom had terminal renal failure but who had not been dialyzed: 9 of these patients were hypertensive (diastolic blood pressure above 90 mmHg) and 3 were not. Group VIII (n=12) was made up of surgically removed end-stage kidneys from patients with the adult form of polycystic kidney disease; duration of dialysis averaged 10 ± 1.33 (SEM) months (range, 2 to 37 months). This group was studied separately because of the possibility that the arterial changes in polycystic kidneys might differ from those in the much smaller end-stage kidneys in the other dialysis groups (I, II, III, and IV).

Diastolic blood pressure was determined as the mean of at least three measurements within the last 6 months before nephrectomy or autopsy. In the dialysis patients, blood pressures taken immediately before individual dialysis sessions were used. The mean ages

Table 1—Information on 108 Patients With End-Stage Renal Disease

| Group | | No. of Cases | Age (yr)* | Diastolic BP (mmHg)* |
|---|---|---|---|---|
| I | 0 or <1 month dialysis | 17 (7 S; 10 A) | 41.1 ± 4.1 | 105.0 ± 3.1 |
| II | 1-3 months dialysis | 21 S | 26.3 ± 2.3 | 94.5 ± 2.6 |
| III | 3-6 months dialysis | 15 S | 32.5 ± 2.7 | 100.0 ± 4.8 |
| IV | 6-30 months dialysis | 10 S | 35.3 ± 3.9 | 104.8 ± 5.2 |
| V | MPE hypertension, no dialysis | 12A | 42.1 ± 2.0 | 136.7 ± 2.6 |
| VI | MPE hypertension 1-11 months dialysis | 11 S | 40.1 ± 1.9 | 135.9 ± 2.2 |
| VII | Scleroderma with renal failure, no dialysis | 12 A | 46.0 ± 2.3 | 103.3 ± 6.0 |
| VIII | Polycystic kidneys, 2-37 months dialysis | 10 S | 44.7 ± 3.5 | 83.0 ± 4.6 |

* Values are expressed as mean ± SEM.

S = surgical nephrectomy; A = autopsy; MPE hypertension = malignant phase essential hypertension.

of the patients in the various groups were not significantly different ($P > 0.05$), except for Group II, which had a significantly lower mean age than Group I ($P < 0.05$), Group VII ($P < 0.01$), and Group VIII ($P < 0.01$) (Table 1). There were no significant differences between the mean diastolic blood pressures of Groups I through IV ($P > 0.05$) (Table 1).

### Histologic and Electron Microscopic Studies

Slides of kidney from each case stained with hematoxylin and eosin, periodic acid–Schiff (PAS), Masson's trichrome, phosphotungstic acid–hematoxylin (PTAH), and Verhoeff–van Gieson's stains were examined for histologic features. The kidneys from 4 normotensive or mildly hypertensive patients on chronic hemodialysis were used for electron microscopic studies. These 4 patients ranged in age between 13 and 31 years, had blood pressures of 120/70 to 170/90, and had been dialyzed for 3 months to 1 year. The tissues were fixed initially in 3% glutaraldehyde, rinsed in phosphate buffer (pH 7.3), postfixed in 1% osmium tetroxide, and embedded in araldite. In addition, tissues from 1 case were also fixed and stained with ruthenium red for demonstration of proteoglycans, using the method of Luft [5] as modified by Wight and Ross.[6] Using a Porter–Blum M.2. ultramicrotome, thin sections containing the arteries with intimal thickening were prepared, stained with lead citrate and uranyl acetate, and examined with an AEI-801 electron microscope.

### Morphometric Studies

Using a modified camera lucida technique, a drawing was made of all suitably cross-sectioned arteries in one slide from each case. (Three slides per case were used in Group VIII because there were few arteries per slide.) Efforts were made to select only those arteries in which the internal elastic lamina was complete and smooth muscle fibers of the media were circularly arranged throughout. From the drawings of the cross sections, the external diameter (D) of each artery was determined and intimal and medial areas were measured using a polar planimeter. The ratio of intimal area to medial area (i/m) was used as the index of the degree of intimal thickening. Mean i/m was determined for each case and for three ranges of D; $D < 200\ \mu$, $200\ \mu \leq D < 500\ \mu$, and $D \geq 500\ \mu$. In general these three ranges appeared to correspond anatomically to small interlobular arteries, large interlobular and small arcuate arteries, and large arcuate arteries and interlobar arteries, respectively. Only arteries with an identifiable internal elastic lamina were measured; thus, arterioles are not included in the study. Vessels in the small infarcts seen in Groups V and VII were not measured.

Areas were compared in an attempt to overcome the two main problems encountered when attempting a quantitative evaluation of the degree of intimal thickening in histologic sections: First, the intimal thickening is frequently irregular and eccentric. Second, arteries show varying degrees of wall contracture, probably due to agonal and postmortem changes as well as to fixation.[7-10] Thickness of intima and media are altered depending on the degree of wall contracture,[9] but these difficulties can be overcome by measuring the area of the intima and media, since these areas remain relatively constant when an artery contracts.[7,10] Also, areas can be determined accurately even when the intimal thickening is eccentric. The ratio of intimal area to medial area (i/m) was used as a measure of intimal thickening, since absolute values for intimal (and medial) area would be influenced in any cross section by deviation of the cut from the perpendicular plane.[11] In five kidneys selected at random, there was no significant difference between i/m measurements in different slides from the same kidney.

## Results

### Histologic and Electron Microscopic Studies

In the dialysis groups (II, III, and IV) the thickened intima contained many somewhat elongated cells (Figures 1 and 2). In addition, there was a

loose stroma which contained proteoglycans, as revealed by Alcian blue staining, and fine collagen. There was little evidence of fibrin in the intima. The thickening usually affected the entire circumference of the vessel; and the lumen was virtually occluded in many instances, particularly in arteries with D < 200 $\mu$ and D between 200 and 500 $\mu$.

In Groups V and VII there were the usual changes associated with the malignant phase of hypertension and scleroderma. These consisted of fibrin in the wall and lumen of arterioles and cellular intimal thickening, sometimes containing fibrin, in the intima of arteries less than 500 $\mu$ in diameter. Small cortical infarcts were present in 8 of the 12 cases of Group VII and in 1 of the 12 cases of Group V; this is a striking difference and is difficult to explain in light of the virtually identical morphometric findings in arteries. As noted earlier, arteries within the infarcts were excluded from the study. Cellular intimal thickening was not noted to any great extent in arteries over 500 $\mu$ in diameter in Groups V and VII; in those cases in which intimal thickening occurred in vessels of this size, it was mainly fibrous, with a scanty cellular component.

Group VI (malignant phase of essential hypertension plus dialysis) had fundamentally the same histologic lesions as the other dialysis groups just described except that there were more examples of fibrin in the thickened intima. On the other hand, this latter change was less pronounced than in Groups V and VII.

Group VIII (polycystic kidneys plus dialysis) showed minor degrees of intimal thickening which, in general, was relatively acellular.

On electron microscopy, the thickened intima of four kidneys from dialysis patients consisted of smooth muscle cells embedded in a matrix of collagen fibers, elastic fibers, and a large quantity of ground substance. The smooth muscle cells had characteristic myofilaments and dense fusiform bodies (Figure 3).[12,13] The ground substance contained proteoglycans (acid mucopolysaccharide) with characteristic dense polygonal granules 200 to 500 Å in diameter on ruthenium red staining (Figure 4).[6] These proteoglycan granules with fine processes appeared to be distributed predominantly along the collagen fibers.

#### Morphometric Studies

The results of the morphometric study of Groups I through VII are summarized in Table 2 and Text-figure 1. In Groups I through IV, i/m for the full range of D was significantly higher ($P < 0.05$) in Group IV (0.615± 0.047 SEM), compared with Groups I (0.429 ± 0.041), II (0.409 ±0.025), and III (0.486 ± 0.037) despite the absence of significant difference in age or diastolic blood pressure between Group IV and the

Table 2—i/m in Different Vessel Size Ranges

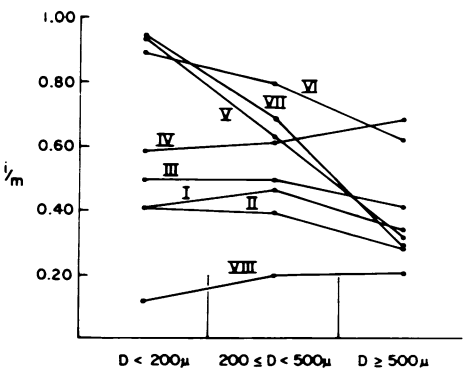
| Group | Full range | D < 200 μ | 200 μ ≤ D < 500 μ | D ≥ 500 μ |
|---|---|---|---|---|
| I | 0.429 ± 0.041 | 0.407 ± 0.045 | 0.464 ± 0.030 | 0.340 ± 0.045 |
| II | 0.409 ± 0.025 | 0.408 ± 0.036 | 0.397 ± 0.028 | 0.281 ± 0.033 |
| III | 0.486 ± 0.037 | 0.500 ± 0.041 | 0.498 ± 0.036 | 0.414 ± 0.044 |
| IV | 0.615 ± 0.047 | 0.589 ± 0.053 | 0.613 ± 0.046 | 0.685 ± 0.076 |
| V | 0.734 ± 0.043 | 0.932 ± 0.063 | 0.630 ± 0.063 | 0.320 ± 0.059 |
| VI | 0.833 ± 0.051 | 0.897 ± 0.065 | 0.800 ± 0.061 | 0.623 ± 0.069 |
| VII | 0.743 ± 0.058 | 0.937 ± 0.073 | 0.681 ± 0.060 | 0.274 ± 0.056 |

D = external diameter of the arteries (μ).
All values are expressed as mean ± SEM.

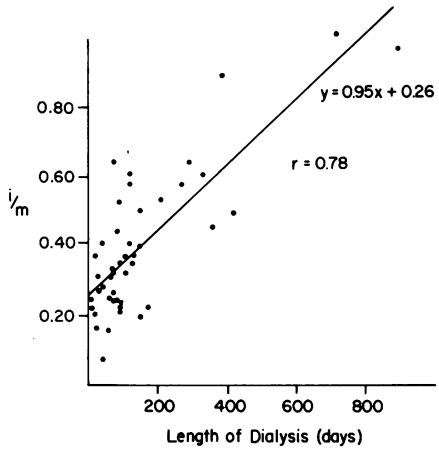
others. The difference of i/m between Group IV and Groups I, II, and III at the three ranges of D was most pronounced ($P < 0.01$) in the range of D > 500 μ (Table 2). In the dialysis groups (II, III, and IV) there was an increase of i/m with increasing length of dialysis in each of the three vessel size ranges.

For the full range of vessel size there was a significant correlation between i/m and duration of dialysis ($r=0.59$, $P \ll 0.001$) and the correlation coefficient (r) was higher for larger vessels ($D \geq 500\ \mu$, $r=0.78$, $P \ll 0.001$) (Text-figure 2) than for smaller vessels ($D < 200\ \mu$, $r=0.42$, $P < 0.005$; $200\ \mu \leq D < 500\ \mu$, $r = 0.50$, $P < 0.005$). There was no correlation between length of dialysis and diastolic blood pressure ($r=0.22$, $P > 0.05$) or between i/m in vessels with $D > 500\ \mu$ and diastolic blood pressure ($r = 0.26$, $P > 0.05$).

In Groups V, VI, and VII, there was no significant difference in i/m for the combined ranges of D. In Groups V and VII, i/m was much higher ($P < 0.01$) in the range of $D < 200\ \mu$ compared with i/m in the ranges of $200\ \mu \leq D < 500\ \mu$, and $D \geq 500\ \mu$. The pattern of intimal thickening in




TEXT-FIGURE 1 —Mean ratio of intimal area over medial areas in arteries with different ranges of external diameter. The Roman numerals refer to the eight experimental groups.




TEXT-FIGURE 2 —Relationship between duration of dialysis in days and severity of intimal thickening (intimal area over medial area) in arteries with an external diameter of $\geq 500\ \mu$ in the dialysis groups (I through IV).

Groups V and VII was in sharp contrast to that in the dialysis groups, in which intimal thickening was quite similar in the three ranges of D. Group VI, compared with Group V, showed significantly higher i/m ($P < 0.01$) in the range of $D \geq 500\ \mu$ despite the absence of significant differences in age and diastolic blood pressure.

The results from the patients with polycystic kidneys (Group VIII) are given in Table 3. These are compared with 9 patients drawn from Groups III and IV whose blood pressures were similar to those in Group VIII. Although the mean duration of dialysis was greater in Group VIII, the i/m ratios are significantly lower for all sizes of artery.

## Discussion

There are many interesting facets of the finding of extreme intimal thickening in arteries in the kidneys of patients on chronic dialysis, and several possible explanations exist, including a) that it represents in-

Table 3—Intimal Thickening in Polycystic Kidneys and Nonpolycystic Kidneys From Dialyzed Patients With Diastolic BP < 100 mmHg

| | Polycystics | Nonpolycystics |
|---|---|---|
| Number | 10 | 9 |
| Duration of dialysis | 10.1 ± 3.3 months | 7.4 ± 1.4 months |
| Blood pressure (diastolic) | 83 ± 5 mmHg | 83 ± 5 mmHg |
| i/m full range | 0.187 ± 0.048* | 0.491 ± 0.055 |
| i/m $D < 200\ \mu$ | 0.115 ± 0.045* | 0.489 ± 0.069 |
| i/m $200\ \mu < D < 500\mu$ | 0.196 ± 0.050* | 0.505 ± 0.049 |
| i/m $D > 500\ \mu$ | 0.205 ± 0.070* | 0.517 ± 0.062 |

* Significantly different from nonpolycystic group ($P < 0.01$)

creased arteriosclerosis; b) that it is the effect of hypertension; c) that it is somehow a direct effect of metabolic or hemodynamic changes brought about by dialysis; and d) that it is a form of disuse endarteritis.

The first of these ideas is worthy of consideration because there is alleged to be a high frequency of occlusive vascular disorders in patients on chronic hemodialysis,[14] possibly arising from abnormal lipid concentrations in the blood in such patients [15,16] and the existence of high blood pressure, two well-accepted causes of accelerated arteriosclerosis. It should be noted that these claims of severe arteriosclerosis in patients on chronic dialysis have recently been challenged.[17,18] We are in no position to comment on the status of the vasculature in other organs in our dialysis patients because kidney was the only tissue available for examination. We do not, however, believe arteriosclerosis to be the cause of the intimal arterial thickening in the kidney because the changes are unlike those seen accompanying generalized arteriosclerosis. In such patients the intrarenal arteries show intimal thickening due to increased amounts of fibrous tissue and elastica [19]; in any event, the degree of intimal thickening is hardly ever of the magnitude seen in the kidneys under discussion.

The second idea, that of hypertension being the causative factor, is more commendable. In patients with hypertension the intrarenal arteries and arterioles show thickening with luminal reduction, and it might be expected that dialysis, by prolonging life, would allow hypertension to exert its effects over a longer period. The mean blood pressures of the patients in Groups II, III, and IV are 94.5, 100, and 104.8 mmHg, respectively. The individual pressure readings on which these means are based were taken just before the dialysis session began; these would of necessity be the highest pressures experienced by the patients. Such levels of diastolic blood pressures would be associated with intimal thickening caused by reduplication of the internal elastic lamina, not with cellular intimal thickening, such as is the case in the malignant range as exemplified by Group V. The size of vessel affected is also evidence against hypertension being a principal cause of the dialysis lesion. Whereas, even in the severe grades of hypertension experienced by the patients in Group V, the changes in arteries over 500 $\mu$ in diameter are not great, Group IV (6 to 30 months of dialysis) shows considerable involvement in this size of vessel, and Group III (3 to 6 months of dialysis) shows more change than Group V. This argument is underlined by the considerable increase in degree of involvement in vessels of this large size when dialysis is instituted for 1 to 11 months in patients with the malignant phase of essential hypertension (Group VI). Lastly, when the i/m ratios of 9 patients with normal blood pressures (used for comparison with patients with polycystic

disease) are examined (Table 3), it will be seen that appreciable levels are reached, especially in the case of vessels over 500 $\mu$ in diameter. Thus, an elevated blood pressure is not necessary for the appearance of the dialysis lesion. In summary, there is little evidence for hypertension being an appreciable factor in the production of the cellular intimal thickening seen after dialysis.

The third possibility, ie, that dialysis in some way directly causes the intimal thickening, is largely speculative. However, the possibility must be considered that the hemodynamic (blood volume and blood flow) or metabolic changes which occur during the dialysis procedure contribute in some unknown way to the intimal thickening observed.

The fourth possibility to consider is that of disuse endarteritis being the principal factor in the development of the arterial lesion. Analogy can be drawn with the behavior of arteries in the postmenopausal uterus and ovaries,[20] in which, as the organs become atrophic, the arteries undergo a concomitant obliteration of their lumens. In a kidney undergoing progressive atrophy from continuation of the basic process, such as glomerulonephritis, capillaries and arterioles will become increasingly obliterated as life is supported by artificial means. The resistance of the microvascular bed will increase markedly, and perhaps as a result of this increased resistance to blood flow the arteries supplying the microvascular bed will undergo intimal thickening as a means of cutting down this supply. The behavior of the polycystic kidney gives support to this idea. Polycystic kidneys do not appear to undergo any great reduction in size as renal failure sets in and progresses. It is likely that the volume of the microvascular bed does not decrease substantially in these kidneys and, therefore, the stimulus for intimal hyperplasia is lacking. The mild degree of intimal thickening in the still enormous kidneys of patients undergoing dialysis for polycystic disease is in striking contrast to the other groups studied.

Of the various ideas suggested to account for the intimal thickening, we believe that of disuse endarteritis to be the most likely, but we have little idea of the pathogenesis of the change. We have shown that the predominant cell in the intima is the smooth muscle cell, but the precise stimulus for its increase in numbers is unknown. Perhaps the elevated serum lipid levels play a contributory role in some way, but we can only speculate on this. We have found little evidence that intravascular coagulation and subsequent organization play a part and have been unable, except in the occasional artery, to demonstrate fibrin in the arterial intima or lumen by either fluorescent antibody technics or by staining with PTAH in Groups II through IV. This is in contrast to the kidneys in

Groups V and VII, in which luminal fibrin or fibrin in the vessel wall is a common feature.

As part of the study it was decided to do histologic and morphometric studies on kidneys from patients with the malignant phase of hypertension and scleroderma with renal failure; the former contained patients without dialysis (Group V) and with dialysis (Group VI), while the scleroderma group (Group VII) contained patients with and without hypertension. In the overall analysis of results no attempt was made to separate the cases of scleroderma into those with and those without hypertension, because the numbers of those without were so small. Reference has been made to the ways in which Groups II through IV differ from Groups V and VII, the main differences being in the arteries $\geq 500\ \mu$ and in the paucity of fibrin in vessel walls in Groups II through IV. We were particularly interested in seeing if a comparison of Groups V and VII could help resolve the old question of whether intrarenal arterial changes in the malignant phase of hypertension are a cause or a consequence of hypertension. It is generally believed, largely on experimental grounds,[21-23] that the vascular changes are caused by the hypertension. However, when Groups V and VII are compared it is found that not only are the histologic changes in the arterioles and arteries indistinguishable but the kidneys cannot be distinguished when morphometry is applied to the arteries. In fact, the only difference between the two conditions seems to be the greater number of small infarcts in scleroderma. The similarities of the two conditions are seemingly in conflict with the idea of hypertension causing the vascular changes, because of the 12 patients with scleroderma, 3 had a normal blood pressure, and of the 9 with hypertension, only 3 had diastolic pressures over 130 mmHg, a level that was approximately the mean for the malignant phase kidneys (Group V). Certainly, then, in the scleroderma group it would be impossible to postulate hypertension as the cause of the vascular lesions, and by analogy it could be argued that the identical lesions in the malignant phase of hypertension are not the consequence of the high blood pressure. We had originally hoped that there would be sufficient cases of scleroderma with a normal blood pressure to enable us to compare them with cases with high blood pressure. We found only 3 of the 12 patients to have normal pressures and do not feel we are justified in coming to too many conclusions. It might be said, however, that from a morphometric point of view these 3 were no different from the 9 with hypertension. It is tempting to suggest that the hypertension in the scleroderma cases is a result of the severe arterial narrowing, and clinical experience would support this, since several patients became hypertensive over the duration of the terminal illness, an

observation made by others.[24,25] Whether the findings in scleroderma can be extrapolated to the malignant phase of hypertension is questionable. But sufficient morphologic similarities are present to raise the question of some event taking place in essential hypertension, eg, an episode of intravascular coagulation, that leads to narrowing of intrarenal arteries and the acceleration of hypertension to the malignant phase. The presence of fibrin in the lumen and walls of arterioles and in the intima of small arteries is consistent with this idea, but the stimulus that triggers the episode is unknown. The findings in this study suggest that the morphologic changes in arteries in scleroderma are responsible for the hypertension that may develop in that condition and that by analogy the same sequence could take place in the malignant phase of essential hypertension.

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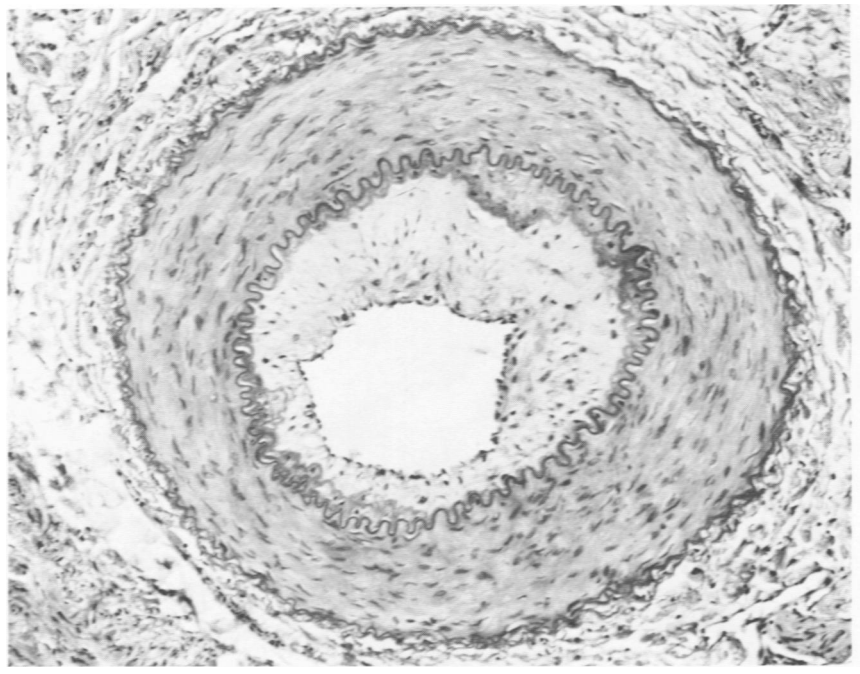
[*Illustrations follow*]



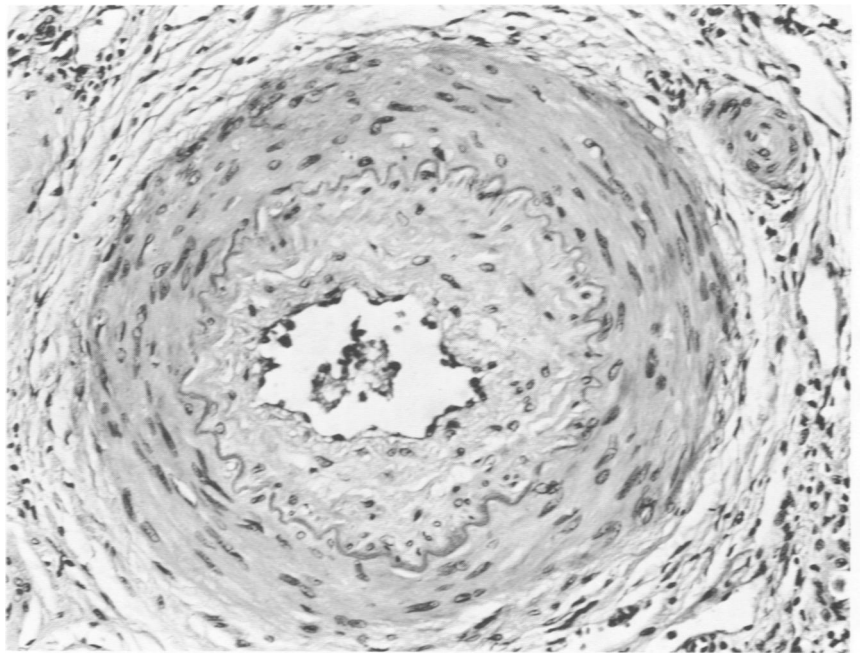


**Figure 1**—Extensive intimal thickening in an interlobar artery from the kidney of a patient who had been dialyzed for 7 months. (H&E, ×125) **Figure 2**—Intimal thickening in an arcuate artery from a patient dialyzed for 13 months. (H&E, ×170)

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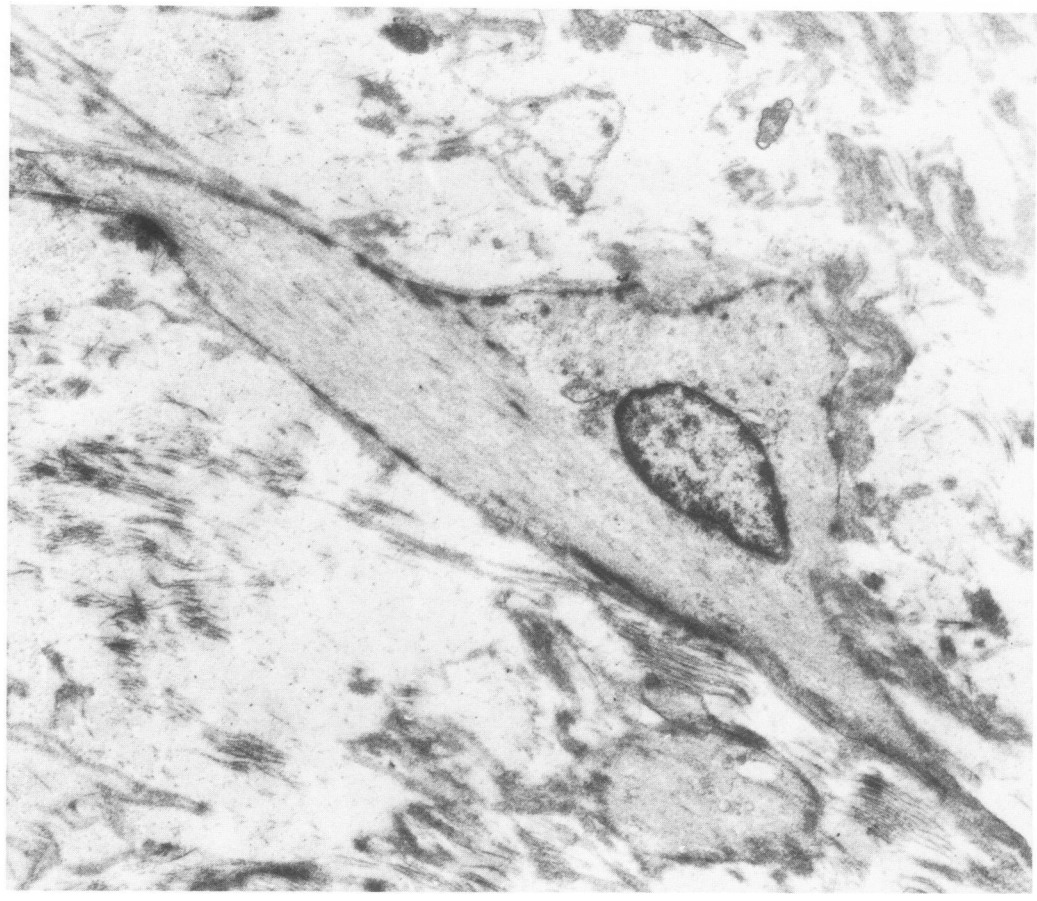

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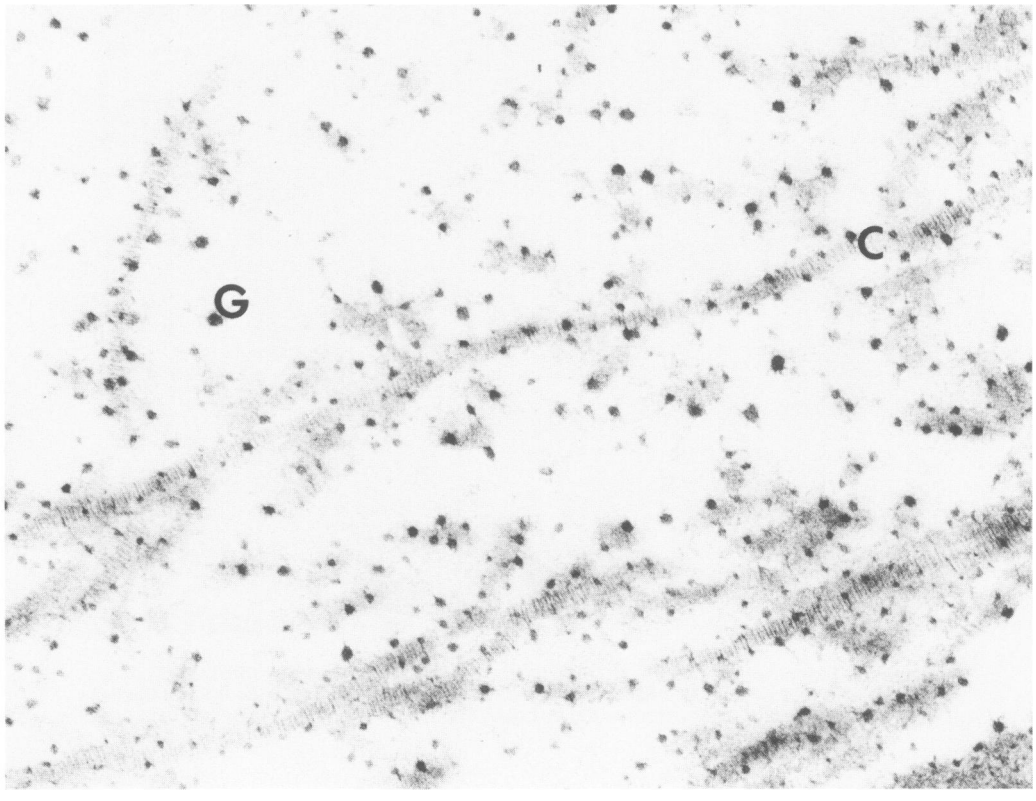


**Figure 3**—Electron micrograph of smooth muscle cell from the thickened intima of an arcuate artery from a dialyzed patient. (×21,000) **Figure 4**—High-magnification electron micrograph from same artery as Figure 4. Proteoglycan granules (*G*) and collagen fibers (*C*) are seen. (Ruthenium red staining, ×52,500)