SUMMARY Characteristic medial damage occurs in the distal lenticulostriate arteries in patients with hypertensive cerebral hemorrhage. Medial changes were studied in the proximal and distal lenticulostriate arteries and cortical circumsiplex arterioles. Additionally, intramyocardial coronary, gastric submucosal and renal interlobular arterioles were examined in hypertensive patients. Hypertensive medial damage consisted of irregular atrophy and paucity of smooth muscle with accumulation of nonfatty debris and basement membranes. These changes were diffuse, extensive and not uniform, and were unrelated to atherosclerosis or bifurcation. By electron microscopic morphometry smooth muscle occupied 28% of the media in the distal lenticulostriate arteries of hypertensive patients as compared with 80% in controls. The proximal lenticulostriate and cortical branches in hypertensive patients showed values higher than 50%, as did the coronary, gastric and renal arterioles. Massive primary hemorrhages are prevalent in the area supplied by the distal lenticulostriate artery, 150-660 μm in diameter. Fibrinoid necrosis and microaneurysm occur in more peripheral arterioles, 70-200 μm. Thus, hypertensive medial damage with significant reduction of the smooth muscle area to less than 50% of the total media is viewed as an additional important factor which predisposes to sudden arterial rupture and massive cerebral hemorrhage.

MASSIVE CEREBRAL HEMORRHAGE is prevalent among hypertensive patients. The mechanism for this primary hemorrhage remains poorly understood. Despite the inherent technical difficulties in investigating the arterial rupture causing hematomata, several mechanisms and lesions have been described as pathogenic or associated. An extensive review has been summarized by saying that the most likely cause of primary cerebral hemorrhage is rupture due to arteriosclerotic change in the intracerebral arteries combined with reduced tensile strength. However, fibrin infiltration, exhibited by the vessel wall, and or any subclinical perivascular hemorrhage can also lead to such a rupture. 1

The current understanding of pathogenesis is similar; two lesions often discussed are fibrinoid necrosis and microaneurysm. Causative relationships have been questioned, however, between fibrinoid necrosis and hypertension and between fibrinoid necrosis and miliary aneurysm formation. 2 No definitive answers have been proposed as to whether fibrinoid necrosis is primary or secondary to hemorrhage. Unanswered questions include the puzzling fact that 30% of all miliary aneurysms occur in the subcortical white matter despite the low incidence of primary hemorrhage at this location. 1

Prior ultrastructural studies suggest that massive cerebral hemorrhages are caused by severe medial damage and rupture near bifurcations of the distal lenticulostriate arteries with a diameter of 150 to 660 μm. 3 The viable segments adjacent to the presumed rupture show characteristic damage of the media. This medial damage of the distal lenticulostriate artery, descriptively termed moth-eaten change, is present on the non-ruptured side in the same patients as well as in hypertensive patients without cerebral hemorrhage. Normotensive controls do not show this medial damage. The distribution of medial damage in hypertensive patients correspond to the site of predilection of massive cerebral hemorrhage. Angionecrosis, fibrinoid change and microaneurysm involve the arterioles of much smaller calibers, 70 to 200 μm. 19 20 Some of the microaneurysms observed in our earlier series, furthermore, appeared to be secondary to prior perivascular hemorrhages in various stages of organization. 1

Hypertensive medial damage has been observed, on the other hand, in the visceral arteries of hypertensive patients and mammals. 14 16

In the current studies we evaluated the degree and extent of medial damage in selected cerebral, coronary and visceral arteries in hypertensive patients. Cerebral arteries of normotensive patients served as controls. This report emphasizes the medial damage of intact (nonruptured) arteries in hypertensive patients. Ultrastructural morphometry data indicated a substantial reduction of the % area of smooth muscle per whole media of the distal lenticulostriate arteries in patients with hypertensive cerebral hemorrhage as compared with controls and with other arteries in hypertensive patients. The significantly poor preservation of the distal lenticulostriate artery in patients with hypertensive cerebral hemorrhage, 28% vs 81% in controls, suggests structural predisposition to necrosis and sudden hemorrhage. Hypertensive medial damage in other cerebral, coronary and visceral arteries was significantly less than that in distal lenticulostriate artery: in the cerebral, coronary and visceral arteries the % area of smooth muscle per whole media was always more than 53%.
Materials and Methods

Hypertension in this series was defined as persistent diastolic pressure higher than 95 mm Hg; hypertensive patients examined had either a history longer than 1 year or complications usually attributable to hypertension.

Arterial specimens were obtained from a total of 34 autopsy, 8 surgical and 150 renal biopsy cases. Autopsy cases consisted of 12 patients with hypertensive cerebral hemorrhage, 11 hypertensive heart disease, 3 malignant hypertension, 5 normotensive subarachnoid hemorrhage, and 3 ruptured arteriovenous malformations in the brain.

Seven of the 12 hypertensive patients had lateral cerebral hemorrhage and 5 median hemorrhage; 8 were men and 4 were women. The age ranged from 39 to 65 years, the mean ± standard deviation being 53.8 ± 7.2. Six of the 11 patients with hypertensive heart disease were men and 5 were women, 51- to 63-year-old (56.3 ± 3.3). The surgical cases consisted of gastric resection in 5 men and 3 women, 38- to 58-year-old (51.3 ± 7.2), for chronic peptic ulcer of the stomach (1), of the duodenum (5), and gastric carcinoma (2). Two men, 36- and 41-year-old, and a 32-year-old woman died with malignant hypertension. Renal biopsy specimens were obtained from 98 patients with renal hypertension, 32- to 65-year-old (38.2 ± 10.1), 46 patients with essential hypertension, 32- to 61-year-old (41.3 ± 8.1), and 6 with malignant hypertension, 30- to 41-year-old (32.2 ± 6.3). The sex ratio of the last group was 1.7 males and 1.0 females. Five normotensive controls died with subarachnoid hemorrhage: 4 men and 1 woman, 41- to 58-year-old (48.3 ± 4.2). A 28-year-old woman and 48- and 49-year-old man died with ruptured arteriovenous malformation.

Renal biopsy specimens were immersion-fixed in 1.4% glutaraldehyde in phosphate buffer, pH 7.4. All the remainder of specimens were perfusion-fixed with phosphate buffer 1.4% glutaraldehyde at 90 to 100 mm Hg for 20 minutes. The interval for autopsy averaged 1½ hours, and that for gastric resection 15 minutes. The lenticulostriate arteries and cortical circumflex arteries were divided into the side with hemorrhage and the intact side. The coronary, gastric and renal arteries were divided into two groups similar in caliber and number. One group of vessels was routinely processed for paraffin embedding. Paraffin sections were stained with hematoxylin eosin, Weigert's elastic fiber, PAS & PAMS stains. Arteries and arterioles similar to those examined by light microscopy were dissected from the other group of wet tissues and processed routinely for electron microscopy. These arterioles and arteries ranged from 100 to 1,000 μm in diameter, and were embedded in epoxy resin (Epon 812 and Spurr's low viscosity embedding medium).

At least 10 epoxy blocks each per patient were sampled from the proximal and distal lenticulostriate arteries, cortical circumflex arterioles, intramyocardial coronary arteries and gastric submucosal arterioles. At least 3 interlobular arteries were examined per renal biopsy. One-μm epoxy sections were stained with alcian blue-methylene blue-basic fuchsin, and were used for evaluation of general features.

Ultrathin sections were double-stained with uranyl acetate and lead citrate, and examined in an electron microscope (JEM 100C). Electron micrographs at the original magnification of 1,000 to 3,000 × were analyzed with a modified digitizer (RS 232, NEC, Tokyo) coupled with a desk computer (NEC PC-8001). The areas occupied by the medial smooth muscle cells and of the total media were traced with the digitizer and the measurements were recorded by the computer. The distinction between the arterial media and adventitia and the line of demarcation between them are described in Results. The ratios of the areas of smooth muscle cells and the whole media were expressed as %, using 10 electron micrographs per epoxy block, and 10 to 20 epoxy blocks per artery. Values were tabulated and statistical significance was evaluated using Student’s t-test.

Results

Most of the proximal and distal lenticulostriate arteries from normotensive controls were normal except for occasional fibromuscular thickenings in older patients. Ultrastructural features of the media adjacent to the thickened intima were normal and similar to those of the segments with a thin intima. There was no significant difference in the thickness of the media with or without intimal thickening. Medial smooth muscle cells in cross-sectioned arteries were round, oval to polygonal cells with the central nucleus fusiform densities, myofilaments and other organelles. The basement membrane was circumferential and distinct. The internal elastica was largely continuous and constituted the demarcation between the intima and the media. The cells in the adventitia were stellate and spindle-shaped fibroblasts with no basement membrane, fusiform densities or myofilaments. There was no external elastica in the cerebral and most of the coronary and visceral arterioles examined. The major matrix material of the adventitia was collagen.

The total area of the media was defined as the area between the outer margin of the internal elastica and the line connecting the outermost zone of the smooth muscular basement membrane facing the adventitia. The total area of medial smooth muscle cells was defined as the aggregate of areas within the plasmalemma of smooth muscle cells.

The ratios of the areas occupied by the medial smooth muscle cells and the whole media were similar in the proximal and distal lenticulostriate arteries in normotensive controls, mean ± SD being 83.2% ± 5.1 and 80.8% ± 4.1, respectively (fig. 1). This small difference was statistically insignificant.

Intimal changes of the cerebral, coronary and visceral arteries in hypertensive patients ranged from fibromuscular thickening to atheromatous lesions with extracellular stainable lipids and foam cells. These intimal lesions were present in most of the sections. The renal arterioles in all hypertensive patients showed marked stenosis due to laminar fibrosis of the intima.
The media was clearly demarcated in large part from the intima by the internal elastica. There was no apparent extension of fatty deposits into the media from atherosclerotic intimal lesions. The medial thickness in the segments with intimal lesions were similar to that in adjacent segments without intimal lesions.

The cerebral, coronary and visceral arteries and arterioles examined showed diffuse medial damage. This medial damage was similar to that which had been termed moth-eaten change previously. This moth-eaten appearance was not apparent in H-E-stained paraffin sections, except for sparsity of smooth muscle cells. Electron microscopy revealed irregular atrophy and sparsity of medial smooth muscle cells accompanied by accumulation of granular and vesicular debris and basement membrane densities. Stainable lipids did not participate in the medial damage. This moth-eaten change was distinct from fibrinoid necrosis due to the absence of characteristic electron-dense fibrillary deposits with typical 250 Å periodicity in appropriate plane of sections, or characteristic eosinophili smudging. Fibrinoid change was focally present in peripheral arterioles more distal to the distal lenticulostriate arteries with moth-eaten change.

The degree of this moth-eaten change was not uniform within the segments and also varied according to the location. The severity did not correlate with that of the intimal lesions, but coincided with the vulnerability to rupture and massive hemorrhage. The distal lenticulostriate arteries invariably showed the most severe damage in a given hypertensive patient, the proximal segments and cortical circumflex arterioles showing distinctly less damage (figs. 2, 3 and 4).

Figures 1A and 1B summarize the result of electron microscopic morphometry of the area of medial smooth muscle cells per whole area of the media expressed as a percentage of the mean. The number of arterial specimens examined and patients are specified in the figures. Both the proximal and distal lenticulostriate arteries in hypertensive patients showed significantly lower values, 56.7% ± 11.2 and 27.7% ± 13.4, than corresponding control values with respective p values of less than 0.01 and 0.001. The distal lenticulostriate arteries showed a significantly lower value than those of both the proximal segment and further distal cortical circumflex arterioles (p < 0.01).

The difference was insignificant between the cortical circumflex (64.7% ± 6.8) and the proximal lenticulostriate arteries (56.7% ± 11.2). The media of intramyocardial coronary, gastric submucosal and renal interlobular arterioles was relatively well preserved. Respective values of the percentage of area occupied by smooth muscle cells of the coronary and gastric arteries in patients with hypertensive cerebral hemorrhage was 60.1% ± 9.2 and 66.2% ± 10.0. The values for the renal arterioles in patients with renal, essential and malignant hypertension were 61.2% ± 9.8, 59.5% ± 10.9 and 52.8% ± 16.1. This lowest value of 52.8% obtained from the patients with malignant hypertension was significantly different from the remainder of the values obtained from the coronary and visceral arterioles (p < 0.01) (fig. 5.). The distal lenticulostriate arteries in patients with hypertensive cerebral hemorrhage were more significantly damaged (27.7%; p < 0.01), however, than the renal arterioles of patients with malignant hypertension, the most severely damaged among the coronary and visceral arterioles.
FIGURE 2. Proximal lenticulostriated artery, 72-year-old woman who died with hypertensive intracerebral hemorrhage. The media consisting of smooth muscle cells and the matrix materials extends from the outer margin of the internal elastica (E) to the outermost zone of smooth muscle cells. Medial smooth muscle cells (*) are relatively well preserved. Small clusters of cellular debris are scattered in the media (†). X3400.

Discussion
Medial damage as quantified in this report, irregular atrophy and paucity of medial smooth muscle cells, have been observed in various arteries of hypertensive patients and non-human mammals.7-12 Similar medial changes have been shown to occur as part of aging.13, 14 What have been illustrated as changes secondary to intimal atherosclerosis1 appear indistinguishable from those reported here in the context of hypertension. Thus, the exact nature of this medial damage is open to dispute and needs to be clarified. The problem is compounded by the frequent association of hypertension and atherosclerosis. The lack of positive correlation, however, between intimal atherosclerosis and the observed medial moth-eaten change supports the importance of hypertension in pathogenesis. Furthermore, this medial damage was most severe in the distal lenticulostriate arteries which are the major vessels for rupture and hemorrhage. The proximal segments are prone to atherosclerosis, but show much less medial damage.

The areas of medial smooth muscle cells in hypertensive patients were higher than 50% in the proximal and cortical circumflex branches and also in the intramyocardial coronary, gastric submucosal and renal interlobular arteries. Among these the interlobular arteries in patients with malignant hypertension showed the lowest value of 52.8%, which was significantly differ-
ent from the lowest value observed in the distal lenticulostriate arteries. The biological significance of this low value in the renal interlobular arteries is not clear. Nonetheless, these extracranial arteries are usually dissociated from hypertensive primary hemorrhage. Thus, the significantly poor preservation of the medial smooth muscle cells seems characteristic of the distal lenticulostriate artery, occupying less than 50% of the whole media area and at ⅓ of the normotensive control value and ⅔ of the proximal lenticulostriate and cortical circumflex branches in hypertensive patients. Such a structural deficit, diffuse and extensive as observed, would predispose the distal lenticulostriate artery to rupture together with the hemodynamic stress and structural peculiarities of the arterial bifurcation.

The pathogenesis of diffuse hypertensive medial damage is yet to be elucidated. Thorball et al.\textsuperscript{15} Nemes et al.,\textsuperscript{16} and Takebayashi, et al\textsuperscript{11} reported focal cytoplasmic necrosis as the underlying process. An abnormal rise in blood pressure would increase the intramural tension. Such an increase, if recurrent and beyond the range controllable by autonomic nervous regulation, could cause focal cytoplasmic damage and whole death of a smooth muscle cell in the media. Such focal cytoplasmic necrosis of smooth muscle cell have been demonstrated by experimental means other than hypertension. These experimental means include repetitive electrical stimulation of the gastric arteries in rabbits,\textsuperscript{5} contraction of pulmonary arterial smooth muscle cells by crotalaria alkaloid in rats,\textsuperscript{17} and restraining stress damaging the gastric submucosal arterioles in rats.\textsuperscript{18} Hypertonicity of the arterial musculature seems important in these experimental models.

Acknowledgment

The author acknowledges with gratitude the contributions made by Dr. Hideshige Imai, Albany Medical College, Albany, NY, in writing the manuscript.

References

Ultrastructural morphometry of hypertensive medial damage in lenticulostriate and other arteries.
S Takebayashi

Stroke. 1985;16:449-453
doi: 10.1161/01.STR.16.3.449

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/16/3/449

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/