# STRUCTURE OF THE SMALL CEREBRAL ARTERIES IN HYPERTENSION*

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In a previous publication,[1] a study was made of the normal histology of the small cerebral arteries and of the changes that occur in their walls with advancing age. With these observations available for comparison it seemed of interest to study the vascular alterations resulting from hypertension. In reviewing the literature on the structure of small cerebral arteries in hypertensive persons, one is impressed by the paucity of reports. There is a definite lack of agreement as to the exact character of the changes.

Johnson [2] and Ewald [3] described a medial hypertrophy occurring within the arterioles throughout the body. These investigators, however, made no special reference to the cerebral vessels.

Jores [4] recorded a widespread intimal hyalinization occurring within most of the arterioles, excluding those within the skeletal muscles.

Keith, Wagener and Kernohan [5] studied the arterioles in four cases of malignant hypertension. They described a marked intimal hyperplasia with hypertrophy of the internal elastic lamina and of the media. There was some perivascular fibrosis.

Rosenberg [6] reported changes in the brain in seventeen patients suffering from malignant hypertension. He found a thickening of the walls of the arterioles with an associated reduction in the caliber of the lumens. Intimal proliferation occurred but was not constant. The elastica interna was frequently hypertrophied, frayed and reduplicated. The media was increased in thickness.

Moritz and Oldt [7] found the small cerebral arteries altered in but 8 per cent of their cases of hypertension. The changes consisted primarily of a medial hypertrophy and of an endothelial hyperplasia with an increase in the elastic elements.

With these investigations in mind, 53 cases of severe hyperten-

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sion were selected from our autopsy service for study. The diagnosis was substantiated by the blood pressure record, the heart weight, or both. The age groups of these individuals were as follows: 5 cases from 11 to 30 years of age; 5 cases from 31 to 40 years; 13 cases from 41 to 50 years; 17 cases from 51 to 60 years; 4 cases from 61 to 70 years; and 9 cases over 70 years of age. No attempt was made to differentiate between the malignant and the slowly progressive nonmalignant type of hypertension, as was done by Rosenberg.[6] Most of the cases, however, were probably not examples of malignant hypertension, since 31 of the 53 had symptoms lasting more than 2 years prior to death; in 16 the symptoms had been present for 5 years or more. This is in direct contrast to Rosenberg's cases in which the average duration of life after the onset of symptoms varied from 4 to 18 months.

Blocks of tissue were taken from various regions of the brain. These blocks were selected from apparently uninvolved areas. The sections were stained with hematoxylin and eosin, with Weigert's elastic tissue stain, with the Mallory-Heidenhain technic (azocarmine) and with the Bodian stain. As in our previous study,[1] the Mallory-Heidenhain technic has proved invaluable for the study of muscle and fibrous tissue because it demonstrates even the smallest amount of these elements.

Since the structure of the normal small cerebral arteries differs from that of similar-sized vessels elsewhere in the body, it might be of advantage to review their structure briefly at this time. Only arteries varying in size from 50 to 150 $\mu$ in diameter will be considered. The internal elastic lamina is both relatively and absolutely thicker than in similar vessels elsewhere in the body. This relative thickness of the elastica tends to persist even into the smallest arteries. The media is composed primarily of a foundation of radially arranged collagenous fibers. This collagenous tissue comprises a surprisingly large portion of this layer and in many cases makes up the major part of the vessel wall. Throughout this connective tissue there are found, in varying numbers, obliquely arranged muscle cells. As the vessel decreases in size, the muscle tissue rapidly disappears and is often difficult to find in vessels under 70 $\mu$ in diameter. With increasing age, there results a progressive reduction in the quantity of the elastic and muscular elements of the media. This change is conspicuous and is nearly

complete early in life. When fibrosis is complete it is usually impossible to differentiate the media from the adventitia, the two merging to form a single structure. The adventitial layer of the small cerebral arteries is variable in size. In some cases it is composed only of a few strands of tissue, while in others it is equal in thickness to the adjoining media. As a rule it is composed of a loose network of collagenous fibers.

The cases in the present study were divided into those under 40 years of age and those over this age limit. This particular differential point was chosen because normally only a minimal degree of vascular alteration occurs prior to this age. One can detect normally some medial fibrosis, but most of the intimal and medial changes occur in individuals past the third decade of life.

### Age Group 11 to 40 Years

Material from 10 hypertensive patients in the age group 11 to 40 years was studied. In 3, the small cerebral arteries showed extensive changes, while in the remaining 7 they presented little, if any, alteration. A review of the history of the 3 cases showing arterial change revealed the course of the hypertension to have been very rapid. They probably belong to that group described by Keith, Wagener and Kernohan,[5] and Rosenberg[6] as malignant hypertension. Since the alterations of the elements of the vessel wall in these cases were very pronounced, they warrant some detailed description.

*Intima.* Many vessels showed a marked endothelial proliferation even to the extent of complete vascular occlusion. The usually solid, thick, elastic lamina was irregularly frayed with many tiny fibrils projecting from various portions of the membrane into the adjacent media. Reduplication of the elastica, which does not normally occur until the fifth and sixth decades, was already very extensive. The reduplicated elastic elements occasionally extended inward to narrow or occlude the vessel lumen. Certain segments of the elastica interna showed a definite thickening; other segments were swollen and had lost much of their normal tinctorial properties. These swollen areas occasionally projected inward, producing a definite narrowing of the lumen.

*Media.* There was a partial to complete reduction of the elastic and muscular elements within the media. In those arteries where

the replacement of the muscle had been complete the fibrosed media merged with the adjacent adventitia, making a separation between them very difficult. The media was much thicker than normal due to the increased fibrous tissue. Normally, a mild fibrosis can be observed in the small arteries of nonhypertensive individuals during the third decade of life; however, it never appears as extensively as in the cerebral vessels of these cases of rapidly progressive hypertension. The medial elements of many of the arteries showed either a diffuse or a patchy hyalinization and loss of their tinctorial properties. These changes seemed to begin in the outer portion of the media and then to spread into entire segments of the vessel wall. Often the hyalinization was complete, replacing all elements (Fig. 1). This hyalinization is very unusual at such an early age since normally it does not occur in the cerebral arteries until the fifth or sixth decades.

*Adventitia.* The adventitial changes resembled closely those described in the media. In most vessels the adventitia was thicker than normal.

The extreme fibrosis and hyalinization of these small arteries appeared to weaken them to such an extent that erythrocytes often broke through the frayed elastica and fibrosed media and escaped into the perivascular space where they formed a ring-hemorrhage around the vessel.

The 7 remaining cases in this age group were from individuals suffering from chronic hypertension. There was no striking alteration in any of the small cerebral arteries. In an occasional artery there was seen a mild fraying of the elastica interna. Usually, however, this membrane appeared as a deeply staining, thick, compact, laminated structure with only a few regular waves and no signs of reduplication. The media of these vessels was also uninvolved. Although, as is normally the case, the bulk of this layer was composed of collagenous tissue, still the muscular elements were surprisingly prominent. In some of the arteries it appeared that even the normal degree of fibrosis was lacking and the vessels seemed more compact and muscular than is usually the case. Likewise, the adventitia was unchanged. Hyalinization and tinctorial alterations were minimal in this group of cases, although occasionally a mild patchy homogeneity appeared in a few of the collagenous fibers.

From these observations it can be concluded that in this early age group, patients with so-called malignant hypertension present most extensive alterations in the small cerebral arteries, while in the more slowly progressive and chronic cases the arteries are entirely free of visible alteration. In fact, in many vessels in those of the latter group the normal vascular fibrosis is retarded by the hypertensive process.

### Age Group 41 to 60 Years

Thirty cases were available for study. In these the findings were much more difficult to evaluate, since normally in this age group extensive changes occur within the small cerebral arteries in the form of reduplication and fraying of the elastica, and fibrosis and hyalinization of the media and adventitia. In none of the hypertensive cases were the alterations in the vessel walls any different from those in normal individuals. Probably the most common observation was a fraying of the elastica interna. The media in most cases contained very little muscle tissue. It was composed almost entirely of collagen and showed a moderate degree of hyalinization. The adventitia was moderately thickened, often frayed and partially hyalinized. Many of these small arteries were surrounded by red cells that had passed through the weakened, frayed elements of the wall and had accumulated within the perivascular spaces.

In a few cases the small arteries were conspicuous by the absence of even those changes normally expected for the age. The elastica was not reduplicated and even its fraying was minimal or entirely absent. Although these vessels were composed predominantly of collagen, throughout this connective tissue there were varying amounts of obliquely arranged muscle cells (Fig. 2). The muscle elements were naturally quite irregular in occurrence but were definitely more prominent than in normal vessels of the same age group. The adventitia was unaltered. Tinctorial changes or hyalinization was not observed. The vessel walls were not thickened and their lumens were not narrowed.

### Age Group 61 to 90 Years

Thirteen cases were studied in this group. In these the small arteries showed the same changes as are seen normally at this age.

Reduplication and fraying of the elastica were very pronounced. The media was composed almost entirely of loose bands of collagenous fibres. Curiously enough, in an occasional case even in the eighth decade, the arteries contained a few muscle fibers and cells scattered irregularly through the vessel wall. Their presence was never observed in the vessels of the control series. Tinctorial impairment was very frequent in this group. These tinctorial changes seemed to begin in the center of the vessel wall and gradually spread in all directions to involve large segments of the wall. In some cases only a faint outline of the original vessel could be made out. Hyalinization was also extensive and seemed to follow the same pattern as the tinctorial changes.

In view of the striking absence of definite alterations in the small arteries of these patients with long-standing hypertension, a study was made of the larger cerebral vessels in some of the same cases. Only those were studied in which the smaller vessels were exceptionally free of change. In direct contrast to the smaller arteries, the larger ones (over 300 $\mu$ in diameter) showed most extensive alterations, primarily in the form of severe intimal and medial changes. Areolar tissue eventually underwent degeneration with hyalinization. This process produced a marked irregular narrowing of the vessel lumen and in many of the vessels an extensive reduction of the blood flow through the vessel (Fig. 3).

## Discussion

In the present study, one is immediately impressed by the paucity of the actual alteration occurring within the small cerebral arteries in cases of long-standing hypertension. In fact, it appears that in certain cases the structure of such vessels in hypertensive patients is spared the routine wear and tear that occurs with increasing age. On the other hand, the larger arteries show definite and often far advanced arteriosclerotic changes with a marked narrowing of their lumens. It is generally believed that protracted hypertension might favor the development of a fairly severe arteriosclerosis, even though in many cases the blood pressure may be elevated for many years without resulting in excessively severe sclerotic changes. In an attempt to explain or correlate the paucity of changes in the smaller arteries and the exten-

sive changes in the larger ones, one could assume that, as the larger vessels become sclerotic and narrowed, there results a reduced blood pressure in the smaller arteries with a corresponding reduction in the wear and tear upon their walls. This might help preserve their normal architecture even in the face of a long-standing hypertension. A phenomenon of this type is not without its parallel in the human body. It has already been shown by Zon [8] that in severe aortic stenosis the base of the aorta shows much less sclerosis or other change associated with age than is normally the case. These aortas have an elasticity corresponding to that of individuals 20 years younger. It was assumed by Zon that the narrowed aortic orifice protected the base of the aorta from the usual wear and tear to which it was exposed.

The present findings may also lend further evidence on the question whether the hypertension or the vascular pathology is the primary event. In view of the above findings it becomes apparent that, as far as the cerebral arteries are concerned, hypertension may exist for years with little or no effect upon the small arteries.

Attention may also be called to the fact that in some of our patients death was due to uremia; correspondingly, definite changes had occurred within the arterioles of the kidney and yet similar changes within the small arteries of the brain were not present. Apparently the arteriolar changes throughout the various organs of the body are not correlated.

## Conclusions

1. The average small cerebral artery in cases of long-standing hypertension shows very little structural alteration.

2. The larger arteries often present definite arteriosclerotic changes with a marked narrowing of their lumens.

3. It is possible that the narrowing of the larger vessels reduces the wear and tear upon the smaller ones, thus preserving their normal architecture in the face of the long-standing hypertension.

4. In so-called malignant hypertension, the small arteries show extensive alterations. The elastica interna becomes reduplicated and the media undergoes a rapid fibrosis and patchy hyalinization.

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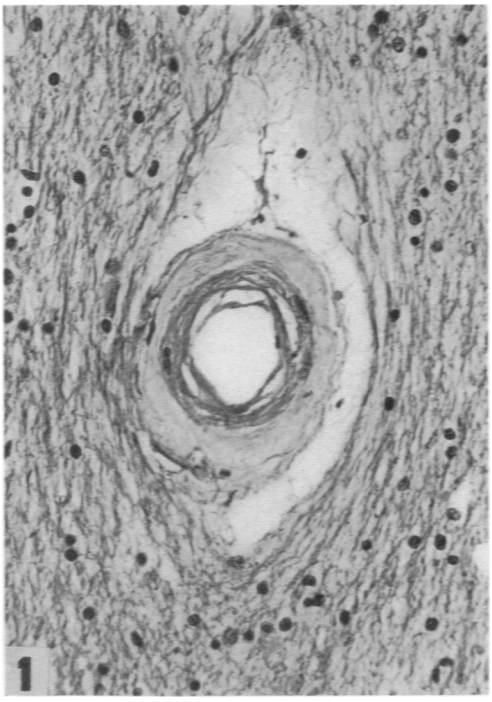
## DESCRIPTION OF PLATE

### PLATE 9

FIG. 1. Hyalinization and tinctorial alterations of a small cerebral artery in a case of malignant hypertension. The hyalinization is complete, replacing all of the wall elements. There is some reduplication and fraying of the intima. Hematoxylin and eosin stain. × 300.

FIG. 2. Structure of a small blood vessel from a chronic hypertensive patient in the fifth decade of life. A few muscle nuclei are still present within the wall elements. Hematoxylin and eosin stain. × 400.

FIG. 3. Structure of a large blood vessel from a chronic hypertensive patient. Note the severe degree of sclerosis. The vessel lumen is greatly reduced in size. Hematoxylin and eosin stain. × 200.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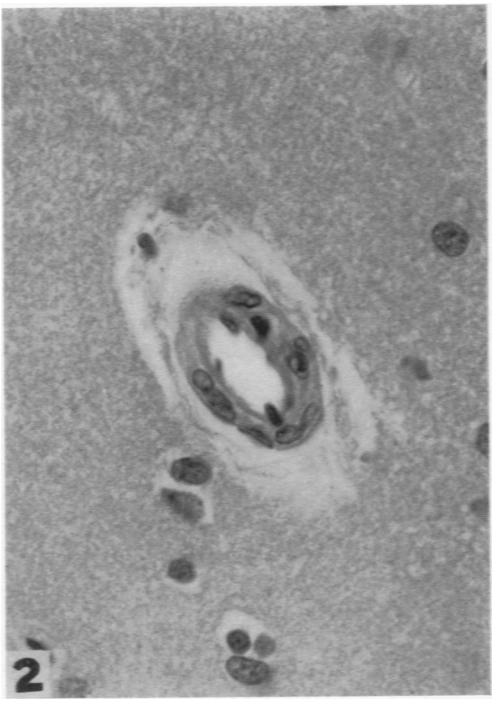
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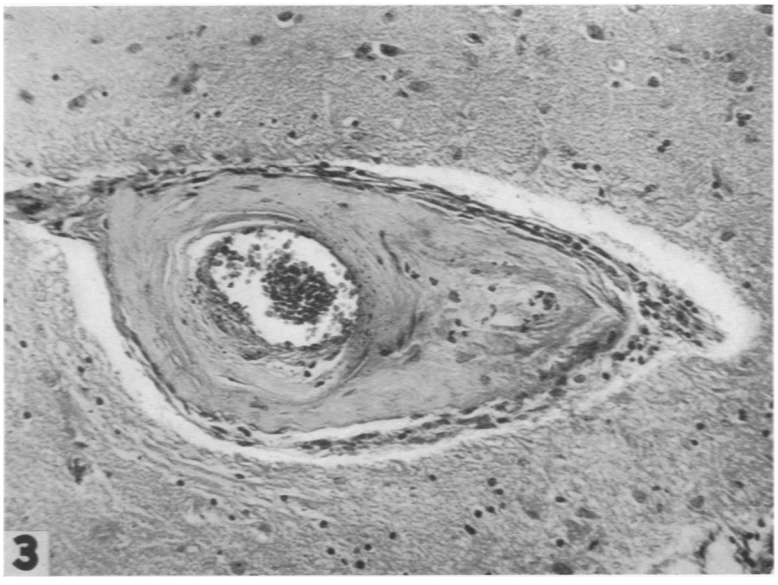
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