STRUCTURE OF THE SMALL CEREBRAL ARTERIES AND THEIR CHANGES WITH AGE *

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Many histologists believe that the arteries of the brain are anatomically different from those in other parts of the body; others feel that they are essentially the same. In reviewing the literature on the structure of normal cerebral vessels one is impressed by the paucity of reports. It was for this reason that our attention was directed to the investigation of the histology of the small cerebral vessels and the changes that occur in their walls with advancing age.

Triepel [1] in 1897 first described in detail the histological structure of the cerebral vessels. He suggested that they differed from similar sized vessels elsewhere in the body in three features: in the great prominence of the internal elastic lamina; in the slight development of the elastic tissue in the circular musculature of the media; and in the striking decrease in the longitudinal elastic fibers of the adventitia. He believed that as the artery decreased in size the elastica interna decreased in thickness until it finally disappeared entirely in the precapillary stage, leaving a vessel composed simply of a few strands of muscle fibers lined by a layer of endothelial cells.

Schäfer's [2] description in 1912 agreed with that of Triepel.

Binswanger and Schaxel [3] in 1917 studied the cerebral arteries in brains of individuals from birth to 60 years of age and concluded that at birth the structure of all arteries is complete and the later changes are those of quantity alone. As age advances the elements vary in their growth. By middle life the elastic tissue of the media and the elastica interna has stopped increasing. The muscle of the media continues to grow up to the 60th year. The collagenous tissue continues to increase and retains the greatest growing power. In older people, therefore, the cerebral vessels would show considerable increase in connective tissue at the expense of the rest of the wall elements. As the vessels decrease in size there is a decrease in the

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quantity and quality of the elements in the walls. The elastic fibers in the media disappear first, then the muscle fibers decrease, only the collagenous tissue remaining to surround the arteriole to the precapillary stage. This is in disagreement with Triepel who believed that muscle fibers could be detected around precapillaries.

Spielmeyer [4] in 1922 and Jacob [5] in 1927 agreed in their description of the cerebral vessels with Binswanger and Schaxel. However, they differed in their description of the capillaries which they believed contained an intima, elastica interna and a few adventitial fibers. Jacob described the cerebral arterioles as containing definite oblique muscle cells within their media.

Hackel [6] in 1928 studied the cerebral arteries in 13 cases varying in age from 15 days to 50 years, and described a structure quite similar to that described by Triepel. Hackel emphasized the relative scarcity of elastic fibers in the media as compared to the adventitia.

In 1931 Tuthill [7] made a study of the elastic layer of the cerebral arteries in 2 stillborn infants and in 24 children varying in age from birth to 14 years. He believed the size of the vessel determined the presence and the thickness of the elastica interna at birth. In the smaller arteries the elastic layer increases in thickness chiefly during the first 5 years, although it continues to grow throughout childhood, becoming quite a prominent part of the vessel wall.

With these earlier investigations in mind the present studies were undertaken in order to determine the normal histology of the cerebral vessels, as well as the normal variations in structure that may be encountered in the routine observation of normal brains in any single age group. For this investigation 70 apparently normal brains were selected, from our coroner's service, from individuals all of whom died of some extracerebral condition such as gunshot wound of the abdomen, crushed chest, and so on. The age groups of these individuals were as follows: 6 cases up to 10 years of age; 21 cases from 11 to 30 years of age; 20 cases from 31 to 50 years of age; 16 cases from 51 to 60 years of age; and 7 cases over 60 years of age.

During the early part of this investigation many blocks of tissue were taken from the various regions of the brain. It was necessary, therefore, to study a great many slides in each case. It was soon observed that the structure of the small cerebral arteries was quite constant in the various blocks studied, and that adequate observations could be made on fewer sections. Therefore, single blocks were taken from representative areas throughout the cerebral cortex and the white substance and fixed in formalin. Sections were stained with the Weigert-Van Gieson stain, by the Mallory-Heidenhain technique (azocarmine), with Weigert's elastic tissue stain, and with the hematoxylin-eosin stain. For the study of muscle and fibrous tissue in the cerebral vessels staining by the Mallory-Heidenhain technique is invaluable since it demonstrates even the smallest connective tissue and muscle fibers. However, it does not differentiate between elastic and collagenous fibers. For this purpose Weigert's elastic tissue stain serves very well. Hematoxylin-eosin and Van Gieson stains were used to study the cellular structures.

The present study was limited to arteries varying in size from 20 to 150 μ in diameter. A detailed description of the larger vessels will be given, followed by a discussion of the various modifications that occur in the wall elements as the vessel decreases in size.

Normal Cerebral Arteries

The small cerebral arteries are characterized by the thinness of their walls. In arteries measuring 150 μ in diameter the vessel wall is frequently less than 15 μ in thickness. The walls of these vessels may be divided roughly into the three coats ordinarily described for arteries, namely, interna, media and externa, although microscopic study of these vessels does not always reveal clear-cut divisions between these layers. The middle layer shows the greatest departure from the structure usually observed in the average small artery. It will, therefore, be described in some detail in a later paragraph.

Intima: The inner coat or intima is composed of an endothelial lining and an elastica interna. The latter is a thick, compact laminated structure and exhibits only a few fairly regular waves that project into the vessel lumen. This internal elastic lamina is both relatively and absolutely thicker in the cerebral vessels than in similar vessels elsewhere in the body. This relative thickness of the elastica interna tends to persist even into the smallest arteries. In many of these smaller vessels, although this structure retains its relatively large proportions, it frequently reveals certain changes in its tinctorial properties. Irregular segments of the elastica may fail to stain. In the smallest of vessels the elastic membrane decreases rapidly in thickness until it finally consists of a few strands of fibers that appear as granules in cross section.

Media: The media of most small extracerebral arteries is usually thick relative to the size of its lumen and consists mostly of circularly arranged flat bundles of smooth muscle. Numerous elastic fibers appear between the muscle cells forming a wide meshed network. Delicate collagenous strands, although present within the media, are few in number. They tend to follow the ramifications of the elastic fibers into the adventitia. The basic tissue within the media of the average small artery of a young individual consists, therefore, of smooth muscle, and the collagenous fibers are usually few and inconspicuous. The latter tissue does increase with advancing age, but only in vessels of very old individuals does it become a dominant element in the media. The middle layer of the small cerebral arteries presents quite a different picture. It is composed of a foundation of radially arranged, fine and coarse collagenous fibers which seem to fuse with one another. The collagenous tissue comprises a surprisingly large proportion of this lamina and in many cases makes up the greatest bulk of the wall (Fig. 1). Throughout this connective tissue there are found varying amounts of obliquely arranged muscle cells and nuclei. The muscle tissue is usually quite irregular in occurrence and is often entirely absent from a part or from the entire vessel wall. The elastic elements in the media are scarce.

There is a striking change in the middle layer as the vessel decreases in size. The structure of the wall becomes more simple. The elastic and muscle tissue rapidly disappear and are often difficult to find in vessels of 70 μ in diameter. Often only an occasional muscle cell nucleus can be detected within an almost solid collagenous wall. Thus in the smaller vessels the entire media, regardless of the age of the patient, appears to be composed of collagenous connective tissue, which merges imperceptibly with the adventitia. At this stage, with the azocarmine stain, this lamina is a solid blue staining layer of tissue.

The media of the small cerebral arteries, therefore, possesses certain features that are quite different from those of similar sized vessels elsewhere in the body, namely, a relative paucity of both elastic and muscle tissue and a predominance of collagenous fibers. In all the smaller vessels, as well as in many of the larger ones of apparently normal young adults, the media is composed almost strictly of collagenous tissue. So striking is the appearance of this layer, especially when stained by the Mallory-Heidenhain technique, that at first it was believed to be of pathological significance. Its uniform occurrence in the smaller arteries demonstrates that what appears to be fibrosis of the media is normal for cerebral arteries.

Adventitia: The adventitial layer of the small cerebral arteries is quite 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 quite thin and made up of a loose network of longitudinally and circularly arranged collagenous fibers. This lamina is well supplied with elastic fibrils. In the smaller arteries this outer layer of collagen becomes less and less distinct as an individual structure. It merges with the adjacent fibrous media to form a single layer.

Age Changes

Intima: With the advance of age numerous alterations begin to occur in all layers of the cerebral arteries. One of the first structures to show changes is the internal elastic lamina. Whereas this structure is usually a solid uniform band, it begins to show areas of reduplication as early as the latter part of the third decade. At first this consists of an irregular fraying of the solid, thick elastic lamina, forming tiny fine fibrils which project irregularly from various portions of the main lamina. This process results in a pseudoreduplication of the internal elastic lamina. True multiplication of the elastica interna does occur, but usually later in life — during the fourth decade and most frequently during the fifth and sixth decade (Fig. 2). This reduplication, however, is not the only change that occurs within this structure with the advance of age. Changes of equal frequency occur in the tinctorial properties of this membrane. It loses its ability to stain normally with the usual dyes and appears patchy and indistinct (Fig. 2).

Occasionally certain segments of the elastic lamina appear swollen. This swelling usually extends in an outward direction encroaching on the media. It is in these swollen areas that the first changes in the staining properties of this elastic tissue occur.

In advanced age large portions of the elastic membrane lose their normal staining properties. The thickened pale staining membranes, instead of appearing as uniform structures, are split not only into longitudinal structures but often also into transverse fragments. This, no doubt, is a stage in the final disintegration of this membrane.

Media: The earliest change that is noticeable in the media of the cerebral arteries is an alteration quite similar to that which occurs as the vessel decreases in size, namely, a complete reduction in the quantity of its elastic and muscular elements. This change is quite conspicuous and is fairly complete early in life. When fibrosis of the media is complete it is usually impossible to differentiate this lamina from the adventitia, these two layer elements merging with one another to form a single structure. The cerebral vessels usually reveal a complete fibrosis of their media long before any preponderance of collagen begins to be apparent in this layer of the extracerebral vessels. Hence, such vessels in the younger age group must not be considered as a pathological finding but as a normal age process that occurs fairly early in life.

Other age changes occur within this layer. During the fifth and sixth decades many of the vessels show an indistinct staining of the medial elements. The heavy collagenous fibers lose their outline and become hyalinized. Similar changes occur in the adventitia which at this stage usually cannot be separated from the media (Fig. 3).

The extreme fibrosis and hyalinization of the vessel elements often fray the arterial wall and weaken it to such an extent that erythrocytes break through and escape from the lumen through the frayed elastica and vessel wall to the perivascular spaces, forming a ring of red cells around the vessel. It is not uncommon to find red cells scattered among the fragmented elements of a hyalinized vessel wall.

A final and more uncommon alteration that is observed in the media with advance of age is calcification of the wall elements. This change was rarely observed before the fifth decade. The calcium is at first deposited as irregular tiny particles in the outer portion of the media and inner adventitial layers (Fig. 4). The deposition may increase and become so complete that the entire wall is replaced by the calcium particles, which form a solid ring around the uninvolved lumen. This calcification is independent of any other change within the wall and may occur with or without hyalinization or fibrosis of the wall elements.

Adventitia: The age changes in the adventitia of the small cerebral arteries resemble closely those already described in the media. The hyalinization that involves the media spreads also to the adventitia (Fig. 3). Calcification, when it occurs, spreads from within outward, at first involving the portion adjacent to the media but eventually replacing the entire wall (Fig. 4).

In the smallest arteries no differentiation can be made between the middle and outer vessel lamina, since the media early undergoes complete fibrosis and hence merges imperceptibly with the outer lamina.

Basal Vessels: As stated in a previous paragraph, when the small cerebral vessels alone are considered there is very little difference in their structure regardless of the part of the cerebrum considered. There is one possible exception to this statement and that concerns the vessels in the basal nuclei. As a rule these small arteries are thicker walled and contain somewhat more muscle tissue within their medial walls. The small arteries of 50 μ have already lost enough muscle to make them indistinguishable from similar sized vessels elsewhere in the brain.

The age changes already described occur also in the basal vessels, only much more extensively and at an earlier age. Reduplication of the elastica interna can be seen as early as the third decade. The medial musculature disappears very rapidly so that these vessels rapidly assume a fibrous appearance. Hyalinization and calcification of the vessel wall are quite frequent and usually well advanced by the fourth decade. The calcification occurs in the same manner as described for the other cerebral arteries, only it occurs more rapidly and often completely replaces the vessel wall in individuals about 40 years of age.

Discussion

The changes occurring in the cerebral arteries with age have been mentioned in the literature, although in many cases their significance was overlooked. Tuthill,[7] Hackel,[6] and Triepel [1] all described the splitting of the elastica interna with age. Triepel gave a fairly complete description of the elastic reduplication but did not connect this alteration with the age of the patient. Tuthill believed that the abnormalities in the elastica interna were due to the effects of intoxication or infection. Hackel studied the cerebral arteries in 13 cases where the age varied from 15 days to 50 years. He described the splitting of the elastica interna as an old age phenomena.

Rosenblath [8] in studying a series of cases noticed that frequently the small cerebral arteries showed a fibrous tissue increase in their walls. In some vessels this fibrosis was quite extreme and caused the author to suspect that this change might be the cause of various nervous tissue alterations. He believed the fibrosis was caused by some type of chronic inflammation. Binswanger and Schaxel [3] also noticed the fibrous tissue increase in the cerebral arteries of older people. However, they carried their study farther and concluded that the various tissues in the arterial wall possess different growing powers. The collagen retains the greatest growing power and continues to increase after the other elements have ceased. Therefore, in older people the cerebral vessels would show a considerable increase in connective tissue, and a relative absence of elastic and muscle tissue.

It appears from our studies on normal brain tissue that the so-called medial fibrosis is the normal structure for the small cerebral arteries and that this fibrosis merely becomes more extensive with the advance of age. Elastic reduplication, hyalinization and calcification, on the other hand, occur only with advancing age and are not observed in the arteries of young individuals.

Conclusions

1. The average small cerebral artery differs in structure from similar sized vessels elsewhere in the body in that it contains within its media a relative paucity of both elastic and muscle tissue and a predominance of collagenous fibers.

2. The very small cerebral arteries are composed almost strictly of collagenous tissue and may appear as a cerebral fibrosis.

3. With the advance of age the elastica interna of the cerebral arteries becomes reduplicated and frequently loses its normal tinctorial properties. The media undergoes a rapid fibrosis. It frequently shows a hyalinization and more rarely a calcification of all of its elements.

REFERENCES

1. Triepel, H. Das elastische Gewebe in der Wand der Arterien der Schädelhöhle. *Anat. Hefte*, 1897, **7**, 189–214.
2. Schäfer, E. A. Textbook of Microscopic Anatomy. Longmans, Green and Co., London, 1912, 340–341.
3. Binswanger, O., and Schaxel, J. Beiträge zur normalen und pathologischen Anatomie der Arterien des Gehirns. *Arch. f. Psychiat.*, 1917, **58**, 141–187.
4. Spielmeyer, W. Histopathologie des Nervensystems. Julius Springer, Berlin, 1922, 195–199.
5. Jacob, Alfons. Normal und pathologische Anatomie und Histologie des Grosshirns. Mit besonderer Berücksichtigung der Histopathologie der Psychosen und extrapyramidalen Erkrankungen. Franz Deuticke, Leipzig und Wien, 1927, **1**, 179–183.
6. Hackel, W. M. Über den Bau und die Altersveränderungen der Gehirnarterien. *Virchows Arch. f. path. Anat.*, 1927–28, **266**, 630–639.
7. Tuthill, C. R. The elastic layer in the cerebral vessels: studies of newborn and of children. *Arch. Neurol. & Psychiat.*, 1931, **26**, 268–278.
8. Rosenblath. Über die apoplektiforme, nicht embolische und vorwiegend unblutige Hirnerweichung und über "Arterio-capillary fibrosis." *Ztschr. f. klin. Med.*, 1927, **106**, 482–527.

DESCRIPTION OF PLATE

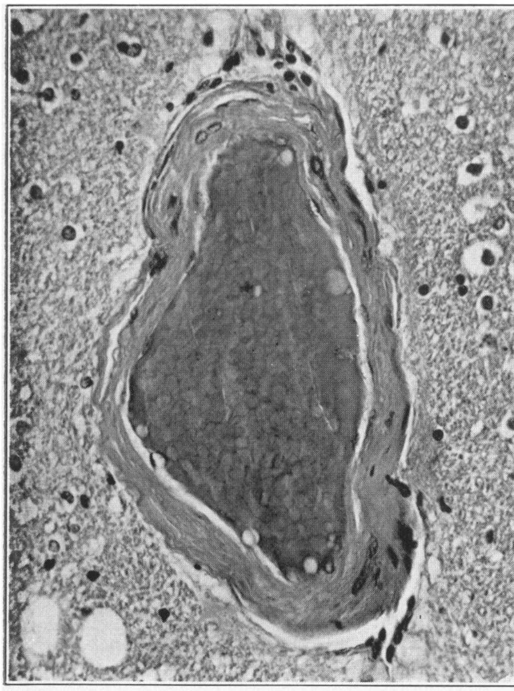
PLATE 80

FIG. 1. Structure of a normal cerebral blood vessel from an individual in the third decade of life. The entire wall is composed of collagenous connective tissue. Only a few cell nuclei are present within the wall elements. Hematoxylin and eosin stain. × 1000.

FIG. 2. Age changes within the elastica interna of a small cerebral artery. Note the reduplication and the patchy and indistinct staining of this membrane. Weigert's elastic tissue stain. × 1000.

FIG. 3. Hyalinization of a cerebral artery. The hyalin is deposited irregularly throughout the vessel wall. Hyalinization is quite extensive in this case and has replaced most of the wall elements. Hematoxylin-eosin stain. × 1000.

FIG. 4. Calcification of a cerebral artery. Note that the deposition of the calcium is limited to the outer portion of the media and the inner layer of the adventitia. The calcium has already formed an almost complete ring within the vessel wall. Hematoxylin-eosin stain. × 1000.



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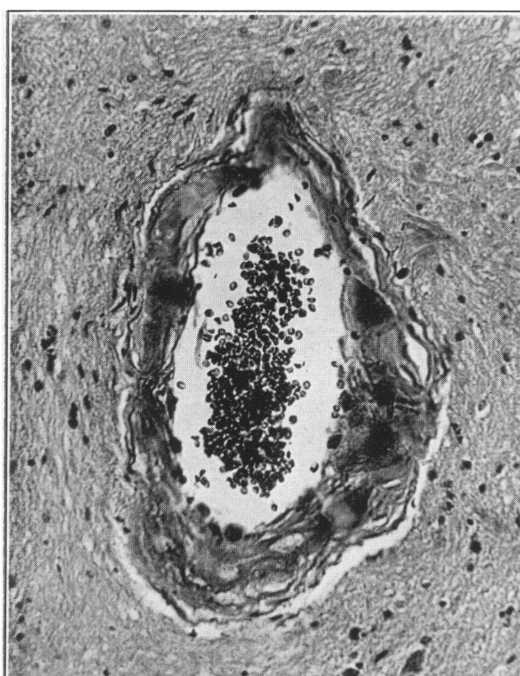

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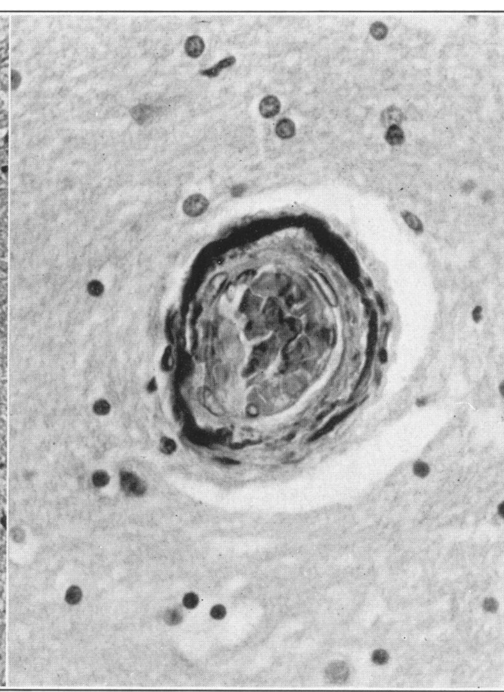

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