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The Neuropathology Associated with the Psychoses of Aging

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THE NEUROPATHOLOGY ASSOCIATED WITH THE PSYCHOSES OF AGING

Neuropathology of Cerebral Arteriosclerosis

To describe the pathologic changes in cerebral arteriosclerosis accurately, it is necessary to separate the pathology of the large cerebral blood vessels from that of the small blood vessels, arterioles, and capillaries. In all the blood vessels involved, the ultimate result will be an obstruction to the blood supply of a given area, thus resulting in softenings of variable dimensions, or in the extravasation of blood leading to red softenings, or to the rupture of a blood vessel leading to massive hemorrhages.

Before describing the pathology of the vascular changes, it may be well to consider the fact that the clinical symptoms of cerebral arteriosclerosis are related to the extent of the branching of the blood vessels participating in brain-tissue damage caused by the softening or by the hemorrhage. Large softenings or hemorrhages are evidently more apt to result in neurological symptoms, whereas smaller softenings or blood extravasations are more apt to result in mental symptoms. Furthermore, from a neurological standpoint, the extent of the focal damage in the territory of the various blood vessels involved will determine the extent of the neurological symptoms.

It is not my task to discuss the clinical neurological and psychiatric

aspects of cerebral arteriosclerosis, but it is not out of place here to mention briefly that the brain is supplied by the superficial and deep branches of the three main cerebral arteries, the anterior, the medial, and the posterior cerebral arteries, which represent the offshoot of the anatomical branching of the blood vessels participating in the formation of the circle of Willis. Very briefly, the superficial territory of vascular irrigation of the anterior cerebral artery covers in general the mesial surface of each cerebral hemisphere, that of the middle cerebral artery covers their external surface, and that of the posterior cerebral artery covers their basal surface. The neurological symptoms which follow softenings or hemorrhages in the territory of the superficial or deep branches of these arteries constitute the various clinical pictures of hemiplegia, monoplegia of the upper or lower extremities, hemianopsia, alexia, apraxia, aphasia and the like, according to the damaged cerebral territory.

I see no need to report the details of the macroscopic appearance of the brain damage in relation to the occlusion or rupture of each individual branch of the three main cerebral arteries, and will limit myself to illustrating the gross appearance of some of the focal softenings connected with the occlusion of some of the branches of the anterior, middle, and posterior cerebral arteries. Figure 4-1(a) illustrates the macroscopic appearance of a large area of softening in the region supplied by the calloso-marginal branch of the anterior cerebral artery; Fig. 4-1(b) the macroscopic appearance of a large

area of softening in the region supplied by the anterior-parietal artery, a branch of the middle cerebral artery; and Fig. 4-1(c) the macroscopic appearance of a large area of softening in the region supplied by two other branches of the middle cerebral artery, the anterior temporal and the temporo-occipital arteries. Figure 4-2 illustrates the macroscopic appearance of a large bilateral area of softening in the region supplied by the parieto-occipital artery, a surface branch of the posterior cerebral artery.

Figure 4-3 illustrates, better than any description, the sclerotic appearance of some of the larger branches of both the anterior cerebral artery (Figure 4-1(a)) and the middle cerebral artery (Figure 4-1(b)) which discloses thickening of their walls, tortuosity, and nodosity. The pathologic process involving the large cerebral blood vessels is generally designated as "atherosclerosis" a process characterized by patches of yellowish material deposited along the internal surface of the artery, but often visible from the outside because of the translucency of the blood-vessel walls. These patches, which impart a beady nodular appearance to the sclerotic vessels, result in various degrees of narrowing of their lumen, because of their projecting knobs under the intima layer of the vessel. Consequently the blood vessel walls become irregularly dilated and at the same time lose their normal elasticity. In addition to their local damaging effects, these changes evidently contribute to the wider disturbance of the cerebral hemodynamic equilibrium.

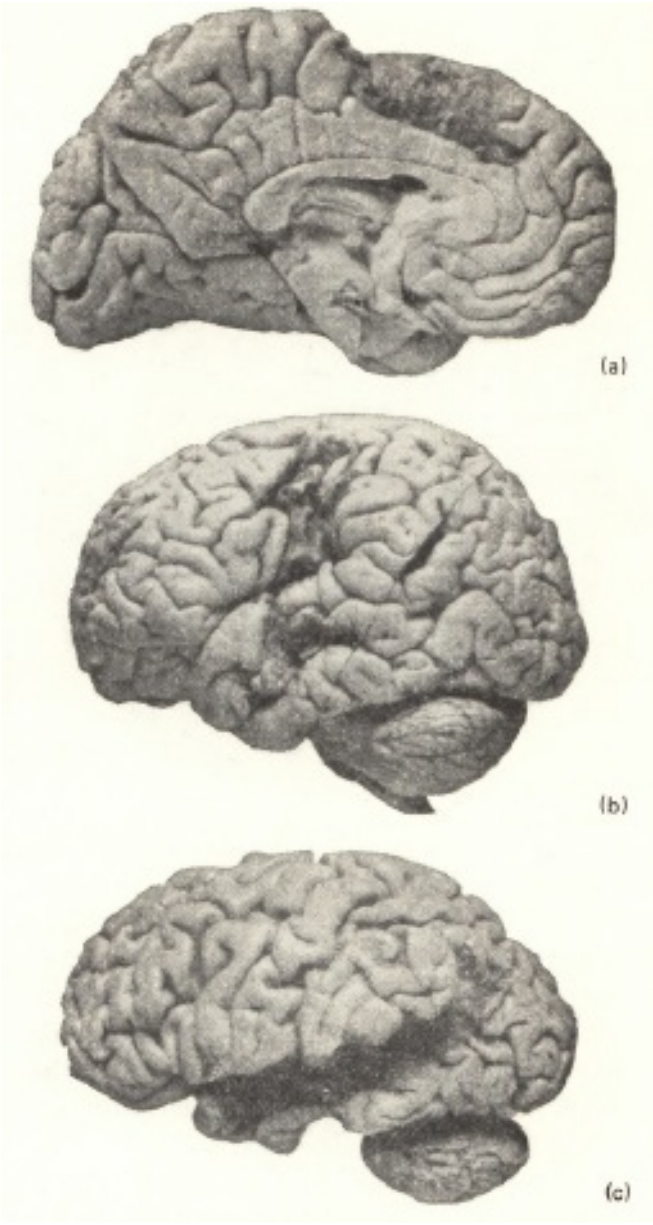

(a)
(b)
(c)

Figure 4-1.

(a) Macroscopic appearance of a large area of softening in the region supplied by the callosomarginal artery, (b) Macroscopic appearance of a large area of softening in the region supplied by the anterior parietal artery, branch of the middle cerebral artery, (c) Macroscopic appearance of a large area of softening in the region supplied by the anterior temporal and the temporo-occipital arteries, branches of the middle cerebral artery.

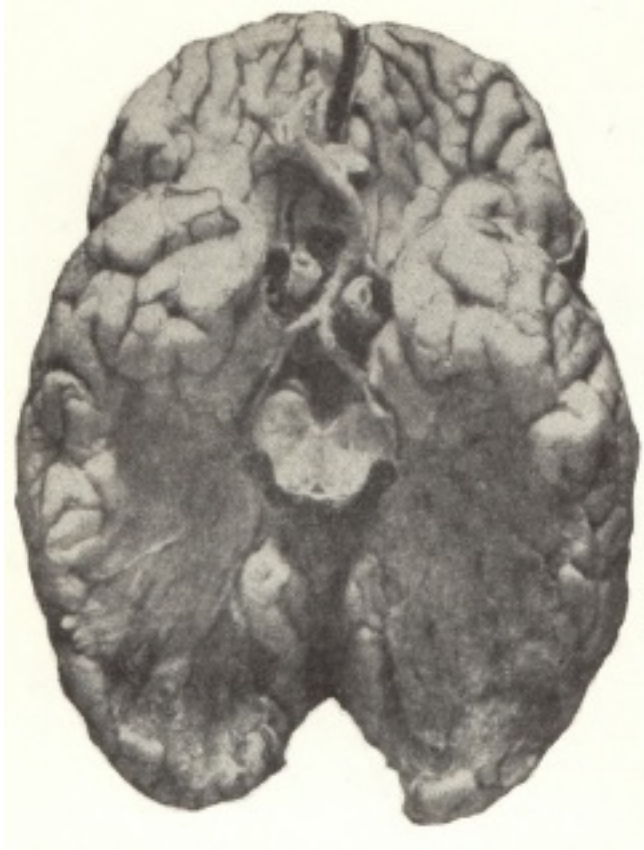


Figure 4-2.

Macroscopic appearance of a large bilateral area of softening in the region supplied by the parieto-occipital artery, surface branch of the posterior cerebral artery.

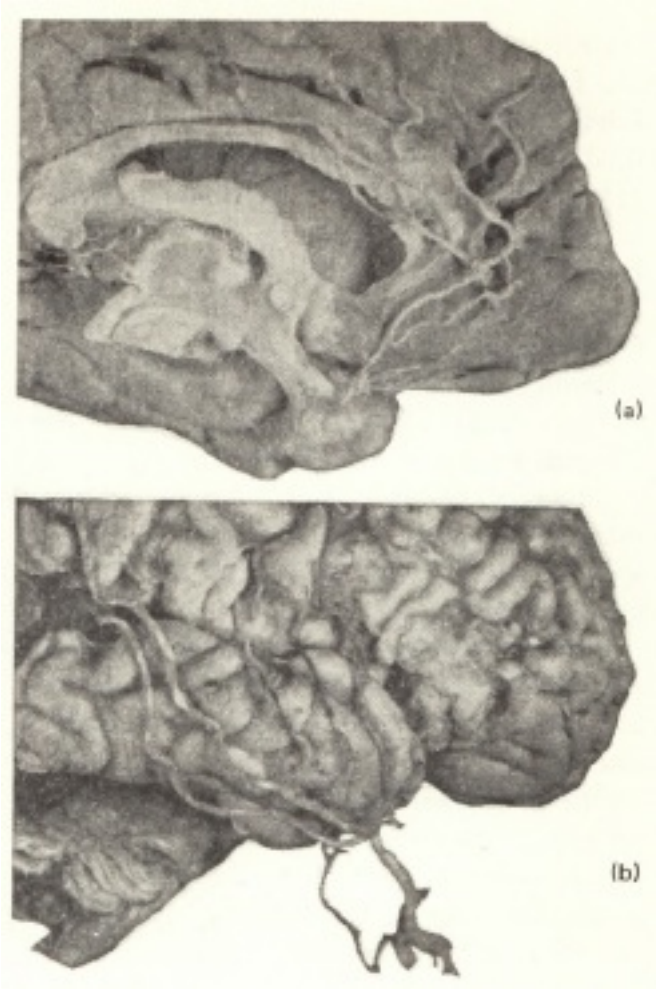


Figure 4-3.

(a) Macroscopic appearance of arteriosclerotic changes in branches of the anterior cerebral artery, (b) Macroscopic appearance of arteriosclerotic changes in branches of the middle cerebral artery. Note thickening, tortuosity, and somewhat nodular appearance of the diseased blood vessels.

Microscopically the focal yellowish thickenings of the large blood vessels, also designated as "atheromas," consist of fatty substances, hyperplastic connective tissue, a thickened endothelial layer, and a thickened internal elastic membrane. The lipids in the intima consist predominantly of lipoproteins, cholesterol and its esters, 10 percent phospholipids and 30 percent natural fats. Hyaline and calcium deposits may also be found in the midst of the atheromatous tissue undergoing necrosis. Figure 4-4 (a) illustrates the fibrotic thickening of the walls of a sclerotic blood vessel and their fatty degeneration, and Fig. 4-4(b) the lumen of a vessel reduced by accumulated fat and elastic tissue, resulting from the splitting of its elastic membrane.

The atheromatous changes of the large blood vessels in humans are, with the exception of necrosis, quite similar to the changes produced experimentally in rabbits, hens, cockerels, and dogs fed high cholesterol diets, which result in a gradual shutting off of the blood circulation in the involved area. However, this similarity of experimental pathology in humans and animals, resulting from high cholesterol diet, applies only to blood vessels outside the cerebral ones, inasmuch as, according to some investigators, the

latter do not seem to participate in the pathologic process as do the blood vessels of other organs.

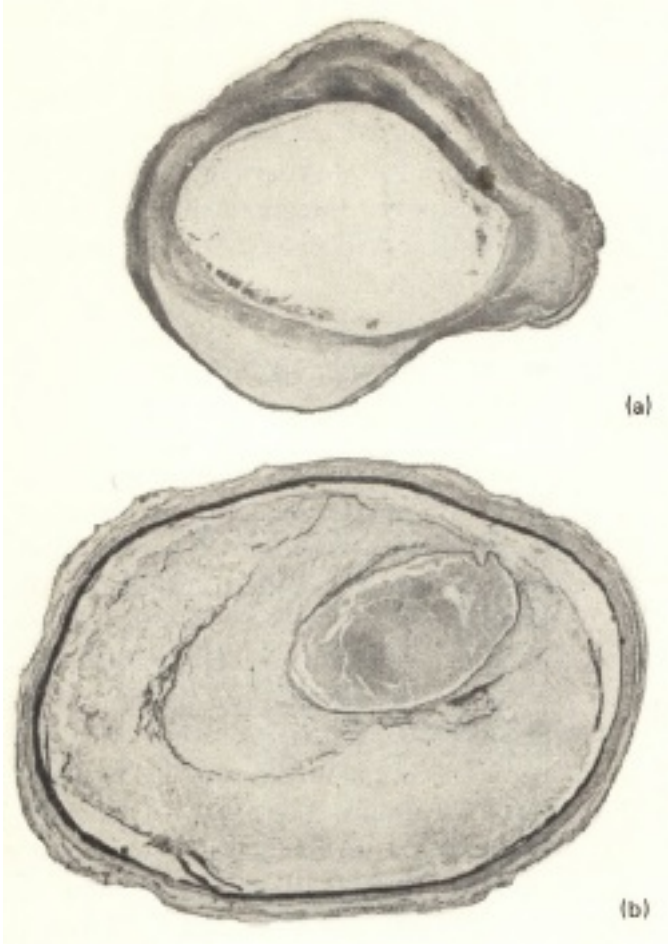


Figure 4-4.

Microscopic atherosclerotic changes in a large blood vessel, (a) Fatty degeneration and fibrotic thickening of the vessel walls, (b) Fatty degeneration, splitting of the elastic membrane, and marked reduction of the blood-vessel lumen.

Microscopic Changes in the Small Blood Vessels

In the small blood vessels the pathologic process has been designated not as atherosclerosis but as "diffuse hypertrophic arteriosclerosis" by Evans, Ophuls, and Moschkowitz, or "arterio-capillary" fibrosis by Gull and Sutton, or "arteriolosclerosis" by Neuburger, Hall, and others. In the diffuse hypertrophic type the early pathologic changes consist in the proliferation of the endothelial lining cells of the intima, followed later by an increase in the fibrous tissue and a delamination of the elastic membrane. In both small arteries and arterioles, the process is a diffuse one which may lead not only to a thickening of the media, but later to the hyaline degeneration of the entire vessel wall. In this variety the increase in number of the cells of the intima, and their concentric lamellation, produce what has been referred to as "an onion-skin-like" appearance of the cross section of the vessel.

In the second variety of arteriosclerosis of the small blood vessels, the "arteriolosclerosis," Hall described as the outstanding feature the hypertrophy of the muscular fibers of the media associated with increased collagen, resulting in the thickening of the vessel wall with the exception of the intima. A third variety is represented by "hyalinization" in which deposit of hyaline material in the subintimal layer is the primary feature. Hyalinosis

may then extend gradually to the whole wall, leading at first to a decreased contractility of the small blood vessel and ultimately to the reduction of its lumen or even occlusion. According to Herburt, hyaline degeneration, a frequent occurrence in cerebral arteriosclerosis, occurs when the arteriolar lesion develops slowly, and such a change may be seen associated at first with splitting, reduplication, and fragmentation of the internal elastic membrane.

Hyaline degeneration is, however, diffuse and prominent also in cerebral hypertension. Without entering into the discussion of the general relationship of hypertension to cerebral arteriosclerosis, the fact remains that it is in association with severe hypertension that the most severe and diffuse hyaline degeneration of the cerebral blood vessels has been reported and related to imbibition of the blood vessel walls by protein substances due to disturbed permeability of the vascular endothelium.

Anders and Eicke, reviewing their cases of hypertension, stress that the occurrence of hyalinosis, which originates in the subendothelial layers, may invade the whole wall of the vessel, protrude in its lumen and end in a global fatty degeneration of the whole wall. They proposed for this condition the term “arteriopathia hypertonica.” Rosenberg, in his studies of the blood vessels in malignant hypertension, stresses however the point that a thickening of all three layers of the small blood vessels with splitting of the internal elastic membrane, and resulting reduction of the lumen of the blood

vessel, is as frequent an occurrence. Because of the difficulty of drawing a distinct separation between hyaline degeneration, as an expression of cerebral arteriosclerosis, and severe hyaline degeneration related only to hypertension, one may consider general hyaline degeneration to be a variety of arteriosclerosis fitting into the general picture of cerebral arteriosclerosis. Figure 4-5 illustrates an advanced stage of hyaline degeneration in the midst of other vascular changes in a case clinically and pathologically diagnosed as cerebral arteriosclerosis.

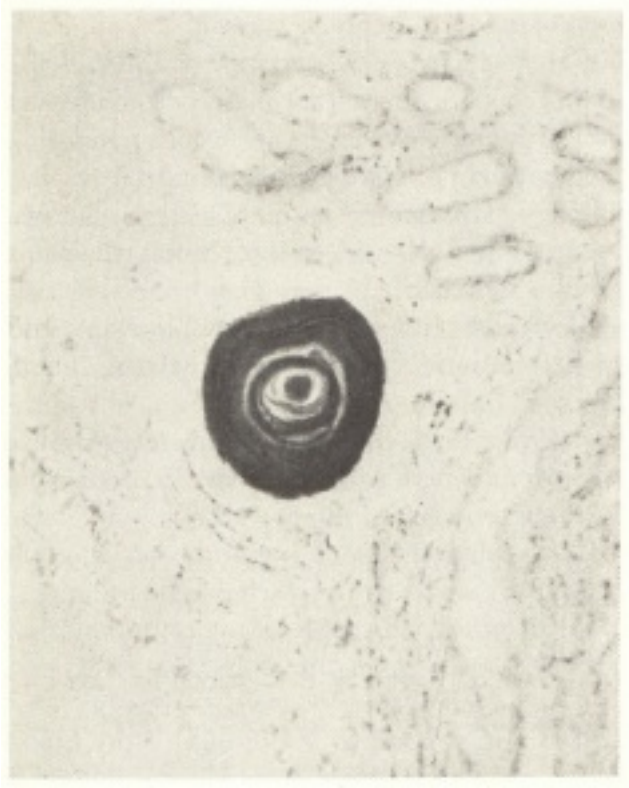


Figure 4-5.

Marked hyaline degeneration of all the three layers of the walls of a blood vessel.

A fourth variety of arteriosclerosis of the small blood vessels is the one described by Scheinker, as “obliterative cerebral arteriosclerosis” found particularly in older patients (sixty-eight to ninety-four years). He differentiated this condition from the “diffuse hyperplastic variety” because in

obliterative cerebral arteriosclerosis, the pathologic changes are limited to the intima in terms of a proliferation of the subendothelial connective tissue, though accompanied by hyalinosis or of fatty degeneration of the vessel walls.

"Capillary fibrosis," a special aspect of cerebral arteriosclerosis, has also been considered as being related to other specific endogenous or exogenous toxic or infectious diseases of the brain outside the field of cerebral arteriosclerosis.

Microscopic Changes in the Brain Parenchyma

Those changes could be divided into two categories: the changes following occlusion or rupture of large cerebral blood vessels, and the changes which follow the involvement of small blood vessels. However, this would repeat the basic description of the parenchymal change, which does not differ in the two categories, as far as softenings and hemorrhages are concerned, except in the severity and the extension of the lesions, the depth of the damage, and the degree of the reparative process. It goes without saying, that a large area of softening or hemorrhage is less apt to undergo repair capable of reestablishing the functionality of the damaged tissue and its continuity with the surrounding tissue.

Referring to a rather large area of softening of relatively recent occurrence, the basic microscopic changes consist in the presence, in that

area, of a mixture of necrotic nervous tissue in the midst of which blood cells may still be found. If the lesion is an older one, blood cells may be absent, though residues of blood pigments may still be seen. If the softening is an older one, the progressive removal of the necrotic tissue may result in the formation of small or larger cavities in which remnants of the disintegrated tissue may still be present, most of it having been removed by phagocytosis. A certain amount of fluid may be present in such necrotic cavities. Figure 4-6 illustrates the microscopic appearance of such an area.

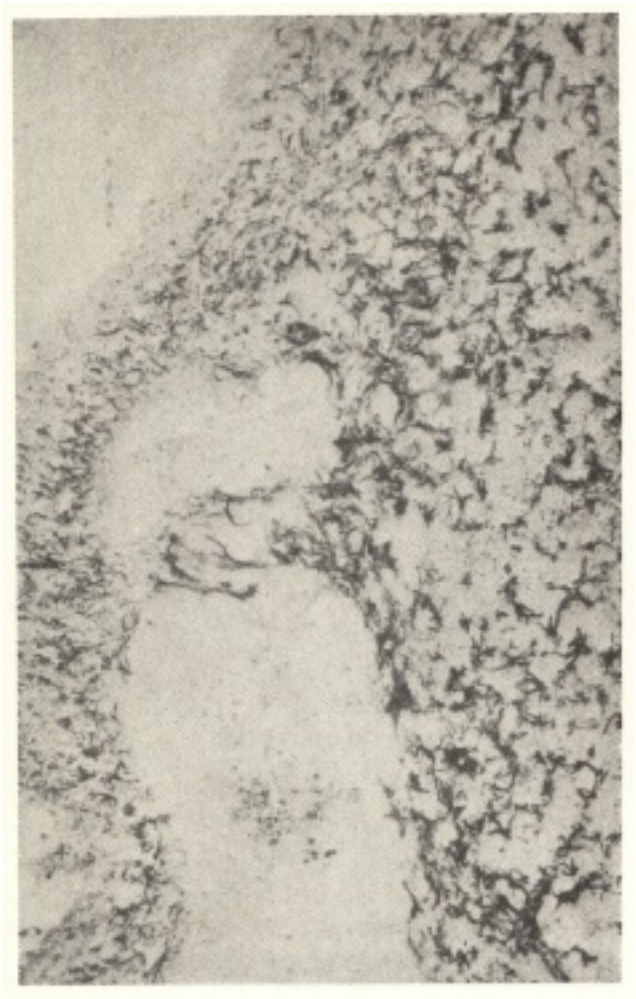


Figure 4-6.

Microscopic appearance of an area of softening which has resulted in two cystic formations because of the inadequate process of repair. Note the reparative activity of the astrocytes at the periphery of the cavities. Cajal's gold sublimate method for

astrocytes.

Without reference to the size of the ischemic softening, I may briefly state that an area of softening is characterized by a more or less complete process of disorganization or destruction of the nervous parenchyma. The destructive process involves all the neural elements, nerve cells, nerve fibers, and glia cells, as well as the vascular and mesodermic elements of support. Nerve cells undergoing all gradations of degenerative changes may be seen, from the severe type of Nissl's "liquefaction," to the Spielmeyer "ischemic type" of degeneration. Reparative activities soon take place. They begin with the reaction of the microglia cells, which multiply, invade the degenerated tissue, and disclose all stages of transformation into compound granular corpuscles, intended to clear the disorganized areas from the remnants of degenerated tissue (Figure 4-7). Concomitantly the mesodermic elements of the nervous tissue, which constitute the blood vessel walls of the region, begin to proliferate and gradually form a visible mesenchymal net.

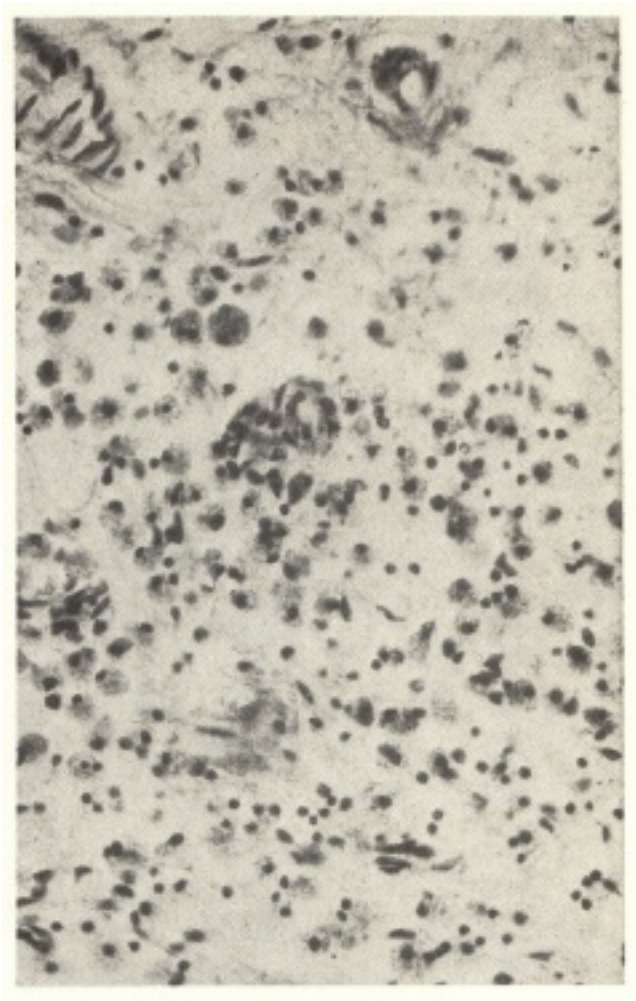


Figure 4-7.

Microscopic appearance of an area of softening disclosing the presence of a large number of compound granular corpuscles. Nissl stain.

In the first stage of the process of repair, the mesenchymal reaction is predominant. In a subsequent phase, the astrocytes participate very actively in that process through their hyperplasia and hypertrophy leading gradually also to the increased number of glia fibers, which, intermingling with the connective tissue elements, form the ultimate scar tissue. In the final phase of the process, the glia reaction is the dominant element, the scar tissue being ultimately formed by a preponderance of glial fibers.

On the other hand, if the vascular occlusion has been a minor one, or of a temporary nature as in the case of transitory vascular spasms, the structural damage is much less intense. As a matter of fact, morphologic evidence of parenchymal destruction may be lacking completely, if the spasm was of a very short duration. Only if it lasts longer, will the blood deficiency result in irreversible structural changes, and in the case of the cortex, in small patches of the tissue, or in a more selective way in the involvement of individual nerve cells of a given cortical area. This "neuronal or selective neurosis," as Scholz labeled it, is characterized mainly by the "ischemic type of degeneration" of individual nerve cells. Their collective presence may result in the formation of areas of different size and distribution in the midst of which bleaching of the nerve cells constitutes the only indication of the ischemic damage. Figure 4-8 illustrates the low-power microscopic appearance of spotty areas of bleaching in the brain cortex resulting from the paling of the nerve cells in the affected areas. At times the ischemia of a cortical area determines a necrosis

of nerve cells along a certain well-defined cortical layer and is called “laminar necrosis.” That transitory vasospasms may determine focal necrosis or laminar necrosis has been documented by Neuburger in his cases of cardiac arrest of no more than a few minutes.

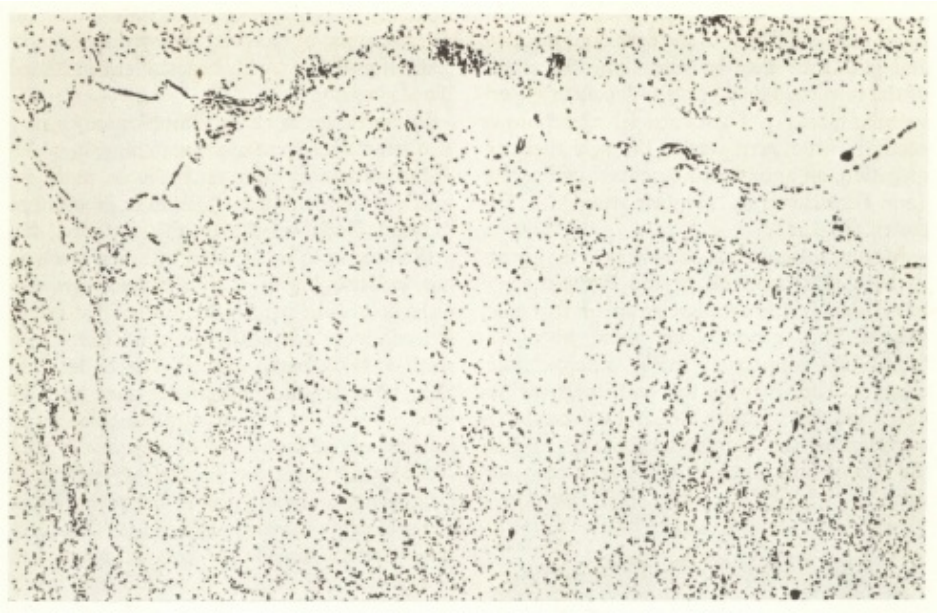


Figure 4-8.

Microscopic appearance of spotty areas of cellular bleaching in the brain cortex resulting from rarefaction, and paling of most of the nerve cells which are undergoing an ischemic type of degeneration. Nissl stain.

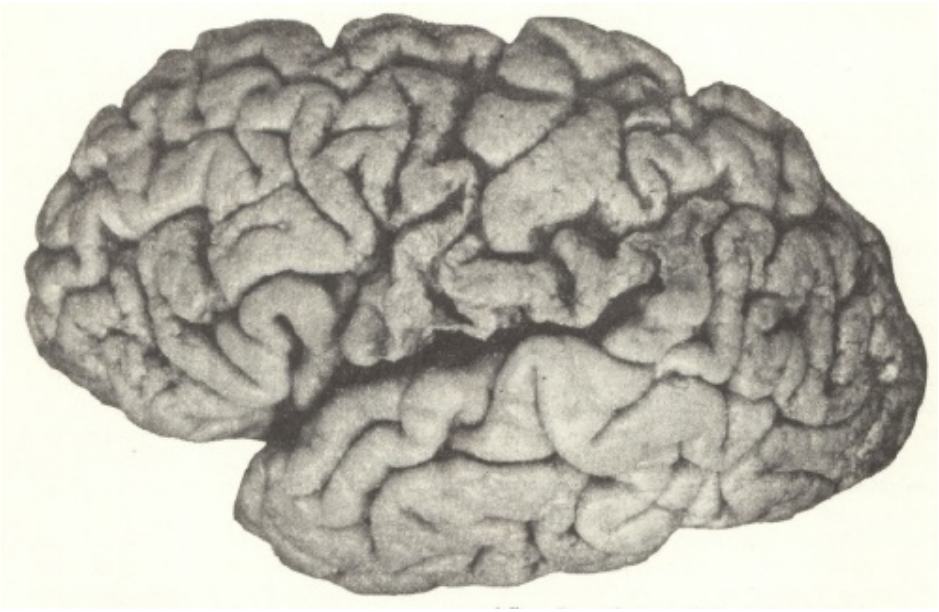


Figure 4-9.

Macroscopic appearance of a diffuse "granular atrophy" of the cerebral cortex resulting from numerous cicatricial cortical retraction of the tissue.

In cases of "patchy neuronal necrosis," the process of repair differs from the one taking place in larger or smaller areas of typical softenings. The reparative process in these cases is mainly one of glia repair, without participation of the mesodermic tissue. Glial proliferation of astrocytes and glial fibers represent the dominant elements in the resulting glia scars which can be observed along the course of individual vessels (Alzheimer's Perivascular Gliosis). Whatever the nature of the scar tissue affecting the

cortex may be, the aggregation of several cicatricial areas may ultimately result in the macroscopic appearance of what Spatz has described as "Granular Atrophy of the Cortex." Figure 4-9 illustrates the macroscopic appearance of a diffuse "Granular Atrophy of the Cortex" resulting from numerous minute cortical retractions due to scar tissue. The patchy type of ischemia, as well as the laminar type of cortical degeneration, are evidently of greater interest to the psychiatrist than to the neurologist, inasmuch as they generally are not accompanied by appreciable neurological signs but are more apt to result in mental symptoms.

Intracerebral hemorrhages may occur in both atherosclerosis of the larger blood vessels and arteriosclerosis of the small vessels. They generally are found more frequently in connection with atherosclerotic changes. They may fill the ventricular cavities (Figure 4-10) or a cavity which they create by compressing the surrounding tissue, so that the loss of brain tissue is only apparent.

Figure 4-10.

Macroscopic appearance of a massive hemorrhage in the left lateral ventricle.

In the past it was thought that massive hemorrhages in the brain were primarily the result of a ruptured blood vessel related to high blood pressure, or to a ruptured aneurysm. Later Rosenblath refuting, as most other investigators did, the exclusive concept of Charcot, pointed to the coexistence of advanced renal diseases in cases of cerebral hemorrhages. He advanced the theory that under such circumstances an enzyme is elaborated, leading first to autolysis of the brain tissue around the blood vessels, which as a point of lowered resistance facilitates their rupture.

Westphal and Baer felt that cerebral hemorrhages arising from diseased intracerebral arteries are the result of a progressive necrosis of the walls of the blood vessels themselves, a condition which they termed “angio-necrosis.” Globus and Strauss and, later on, experimentally, Globus and Epstein established the fact that ischemic changes surrounding diseased blood vessels are the important determinants of cerebral hemorrhages, especially if associated with a concomitant increased blood pressure.

Smaller hemorrhages in cerebral arteriosclerosis may also assume the form of what is termed “red softening” in which the disintegration of the nervous tissue is more intimately related to extravasation of blood from diseased vessels. In such instances, diapedesis seems to be the most

important mechanism, related however to the same prehemorrhagic conditions of an altered perivascular tissue. Red softenings, which are generally related to a more general cardiovascular deficiency, occur indeed more frequently in connection with small arteriosclerotic vessels, as pointed out by Wilson et al. and Neuburger. Vascular insufficiency may play a far more important part in the pathogenesis of both softenings and hemorrhages than does local vascular pathology. Loss of blood and myocardial and circulatory failure may result in insufficient blood supply, resulting in a slowing down of the local circulation which creates a prestasis or stasis around the blood vessels, thus facilitating the development of white or red softenings. Red softenings are generally localized in the more richly vascularized gray matter where diapedetic hemorrhages take place not only from capillaries, but also from small veins, thus pointing out the importance also of the veinous circulation in the pathogenesis of hemorrhages.

Histopathogenesis of Cerebral Arteriosclerosis

Large Blood Vessels. Generally the accepted theories of atherosclerosis of the larger cerebral blood vessels are the same as those which apply to the other large blood vessels of the body. They stem mostly from the experimental work of Ignatowski, Saltikow, Wesselkin, and Anitschkow, who induced atherosclerosis in animals and related it to cholesterol deposits in the blood vessel walls. However, in 1856, Virchow had already advanced the

theory that atherosclerosis was related to fatty imbibition of the blood vessel walls, secondary to necrobiotic processes in the connective tissue cells and ground substance of the intima, a theory later on accepted by Aschoff, Ignatowski, Katz and Stamler, and most other investigators.

According to Wilens both intimal thickening and lipids deposits are concomitant facts in atherosclerosis.

Klotz believes that an increase, between the endothelial cells, of the ground substance which becomes hyaline-mucoid in character, precedes the deposits of lipids in the intima.

Leary held that cholesterol-laden macrophages accumulate in the Kupffer's cells of the liver, and their analogues in the adrenals. These pass into the blood and lymph stream, through the lining filter, and become deposited in the intima of the arteries. From there they migrate through the endothelial cells into the subintima.

Duguid held that cholesterol-laden macrophages accumulate in the intima of the arteries and remain in place, but soon become incorporated within the artery's walls by the endothelium growing over the cell mass, and give origin to intramural thrombi which may gradually increase in size.

Winternitz et al. feel that the greater vascularity of the blood vessel's

walls, resulting from local deposits of fats or intramural thrombi, is an important contributing factor to the production of atheromatous changes, a thesis upheld by Geiringer's findings.

Hueper contends that a film of fatty substances deposited on the surface of the intima, because of altered colloid composition, interferes with the proper oxidation metabolism of the intima, and results in changes which are secondary to nutritional deficiency.

Small Blood Vessels. The histopathogenesis of the arteriosclerosis of the small blood vessels may or may not have a direct relationship to the atherosclerotic changes reported in the large blood vessels.

Are the hyperplastic changes of the small vessels an integral part of atherosclerosis? It would be interesting, indeed, to investigate cases of cerebral arteriosclerotic changes of the small blood vessels, and relate them to the presence of severe or light atherosclerotic changes of the large arteries, or more so, to the absence of such changes. Unfortunately the various histopathogenetic theories of cerebral arteriosclerosis, mainly concerning studies of the small blood vessels, have been advanced without any attempt by their authors to correlate them with the pathology of the large blood vessels.

Thus, Eros, studying the small cerebral blood vessels, with no reference

to the large ones, emphasized that the primary and most important arteriosclerotic changes take place in the elastic tissue, especially in the internal elastic membrane. All other degenerative changes, such as fatty and mucoid degeneration, calcification, fibrous proliferation, and hyalinization, are only secondary to the changes in the elastic tissue. In general he distinguished two main types of the alterations of the elastic tissue: (1) the hyperplastic degenerative type; and (2) the hypoplastic degenerative type.

The hyperplastic degenerative type is characterized by the initial proliferation and splitting of the elastic membrane (Figure 4-11). As the process advances, the elastic fibers gradually lose their individual outlines and tend to fuse with each other, giving the membrane a thicker appearance. While increased fibroblasts and collagenous fibers become more prominent, they are subsequently followed by fat and calcium deposits and by hyalinization and mucoid degeneration.

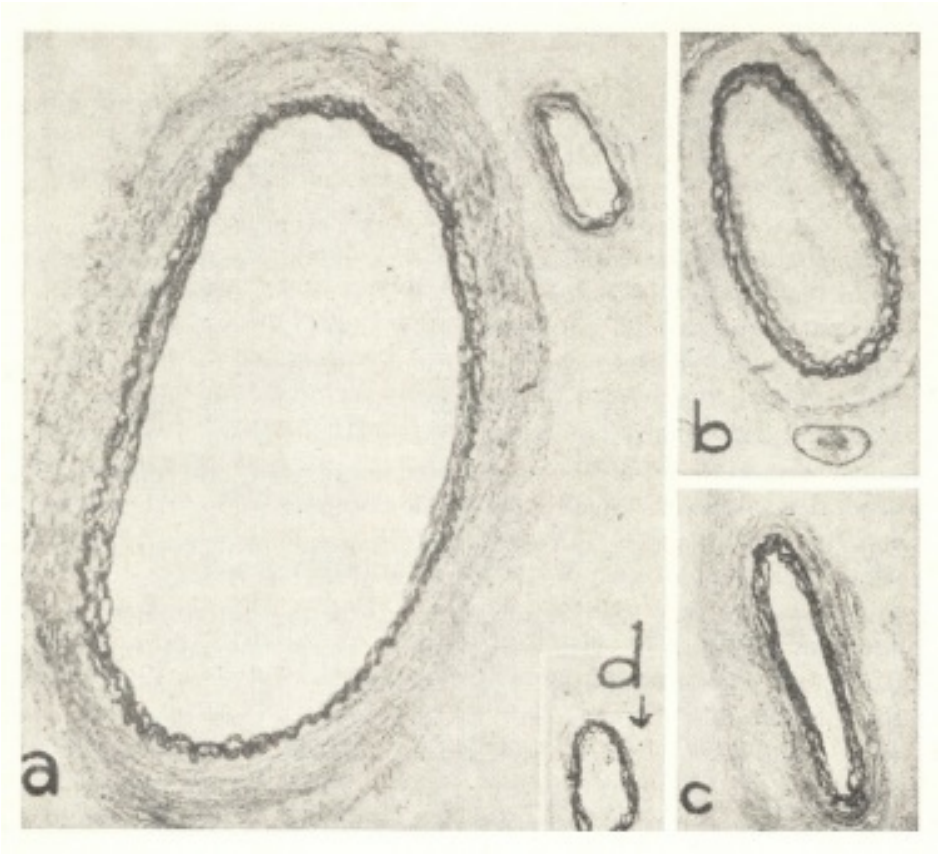


Figure 4-11.

Hyperplastic type of cerebral arteriosclerosis; (a), (b), and (c) are pial arteries; (d) is an intracerebral artery. Note the proliferation of the elastica membrane, and the beginning degeneration of the hyperplastic tissue. Weigert stain for elastic tissue. (Courtesy Dr. G. Eros and the J. Neurophatol. Exp. Neurol.)

The hyperplastic degenerative type is characterized by either a very

slight tendency to proliferation of the elastic membrane, or none at all. In the early stages the elastic membrane stains very poorly, loses its sharp outlines and soon fades out (Figure 4-12). No split in the membrane occurs, and there is only a slight tendency to fibrous proliferation of the intima proper. The secondary degenerative changes start early, with fat appearing in the loosened elastic membrane. Hyaline degeneration follows. Thrombosis is much rarer.

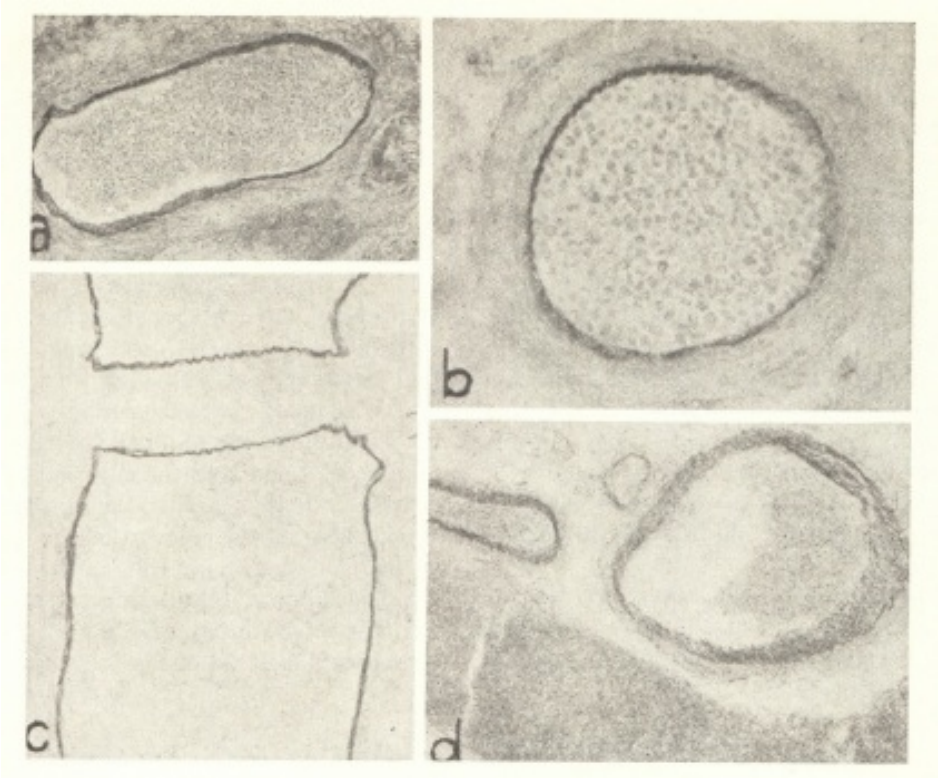


Figure 4-12.

Atrophic type of cerebral arteriosclerosis. Note the atrophic appearance, the thinning of the elastic membrane and the dilation of the blood vessel lumen, and the degeneration of the blood vessel walls. (Courtesy Dr. G. Eros and the *J. Neurophatol. Exp. Neurol*.)

Bruetsch makes a distinction between the histopathology of the large blood vessels of the circle of Willis and the histopathology of the small cerebral blood vessels. He does not however discuss the quantitative or qualitative relationship of the two pathologic changes. He stated that the lesions in the large cerebral arteries are predominantly fatty in type, owing to an accumulation of cholesterol and lipids in the arterial walls. In the small cerebral arteries, on the other hand, endothelial proliferation alone with lipids deposits predominates, while in the smallest blood vessels, hyaline degeneration often associated with endothelial and fibroblastic proliferation is a frequent feature (Figure 4-13(a)). In both large and small blood vessels, Bruetsch stressed the point that the fibroblastic proliferation is related to the presence of what he calls “embryonic foci of cellular proliferation” in all the involved blood vessels. These consist of a wall of loosely arranged cells, from one to fifteen deep, of a variety of cellular elements (young fibroblasts, lymphocytes, or Maximow’s undifferentiated mesenchymal cells) which may erupt at any time and lead to further fibroblastic growth (Figure 4-13(b)). Rapid proliferation of endothelial cells may entangle red cells and form an occluding mass, although not a true thrombus. According to Altschul, the endothelial cells which line the inner wall of the arteries of all sizes—large,

small, and even capillaries—are the progenitors of the foam cells found in the midst of the arteriosclerotic changes, cells which morphologically resemble closely mesenchimal or reticular cells if indeed they are not identical with them. The intima of the larger arteries shows an additional feature not clearly seen in the smallest vessels, namely thickening of the intima with consequent narrowing of the lumen. Formation of foam cells and of the mesenchimal and reticular cells must be considered together. The next stage of atheromatosis in the larger vessels is the disintegration of the foam cells which help to form the atheroma proper.

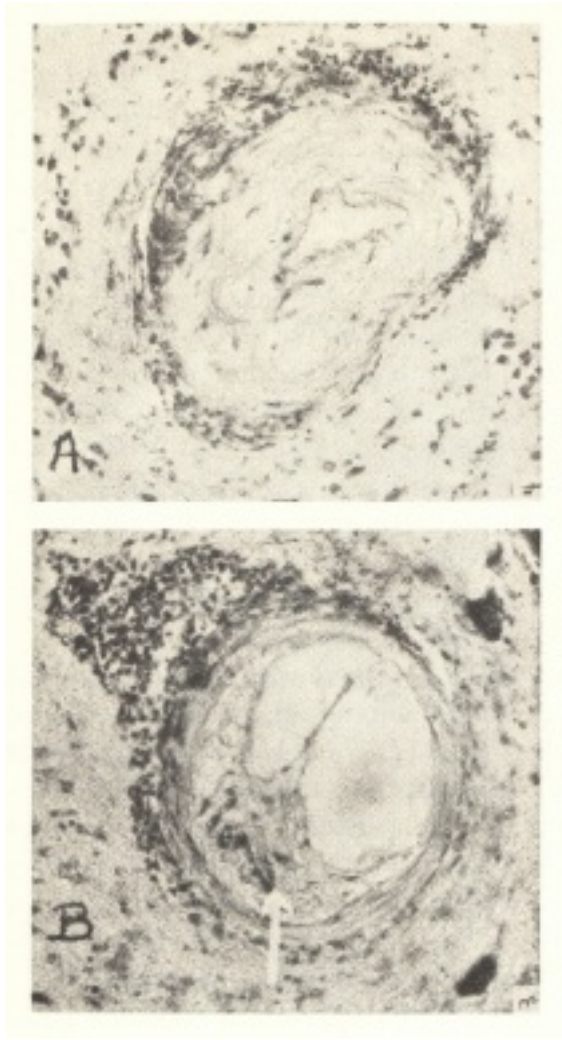


Figure 4-13.

(a) Small cortical artery. The lumen is filled with hyaline tissue. Toluidine blue stain, (b) Small artery of the substantia nigra showing a focus of embryonic cellular proliferation,

sending a tongue of cytoplasma containing minute hyperchromatic nuclei through the lumen. (Courtesy of Dr. W. L. Bruetsch.)

Tuthill contends that arteriosclerosis is not a disease of primary fat absorption. The first histopathological change is an increase in the height and extension of the areas of split elastica, and collagen increase at the specific sites of the branching of the large and of many small cerebral blood vessels. These primary areas are present from birth, and may remain unchanged through adult life. Deposits of fats and their absorption follow the primary process of the splitting of the elastica and of the increase of the collagen fibers. Hydrostatic changes at these levels of narrowing, related to the changes in blood volume, constitute a contributing mechanical factor to the genesis of arteriosclerosis.

Relationship between the Arteriosclerotic Changes and the Clinical Symptoms

The important aspect of the clinico-pathologic relationship, particularly from the psychiatric standpoint, has been merely touched upon and by only a few authors, though if properly developed it might furnish us with valuable information. According to Eros, focal neurological symptoms were more prevalent in cases of hyperplastic cerebral arteriosclerosis than in the hypoplastic type. Out of twenty-six cases of the hypertrophic type of arteriosclerosis, fifteen disclosed predominantly neurological focal symptoms, whereas predominantly mental symptoms were present in

eighteen out of twenty-four cases of the hypoplastic type.

In the hypoplastic type the mental symptoms were usually much more severe than in the hyperplastic. Delusions and hallucinations were more often encountered in the hypoplastic type, while they were rather rare in the hyperplastic. In the hyperplastic type the more severe mental symptoms developed late in the course of the disease; at the beginning only irritability, nervousness and emotional instability were predominant. In the hypoplastic type, severe mental symptoms, often resembling schizophrenia, developed rather early.

In the earlier stages therefore, according to Eros, some indications as to the pathologic type of cerebral arteriosclerosis can be established on the basis of the presence of focal symptoms and the severity and character of the mental symptoms. In the later stages, when the damage of the parenchyma is already far advanced and deterioration sets in, the clinico-pathological distinction is difficult in the absence of focal neurological signs.

Physiopathology of Cerebral Arteriosclerosis

It has been assumed by most investigators that physiopathogenetic mechanisms determining atherosclerosis in the large cerebral blood vessels do not differ from the ones involved in atherosclerosis of the aorta, coronary arteries, and other important blood vessels.

A very comprehensive review of the whole subject can be found in Katz and Stamler's book *Experimental Atherosclerosis.* These authors state that cholesterol is primarily and not secondarily involved in experimental atherogenesis. They feel that transintimal filtration from blood plasma is the mechanism whereby lipids (lipoprotein complex) enter the arterial wall. They also feel that the state of aggregation of cholesterol in plasma must be a key factor influencing the extent and rate of transudation of lipids into the arterial walls.

Although hypercholesterolemia is a factor in the production of the disease, an important element is the ratio between the cholesterol content of the blood and its phospholipids. The normal ratio in question is 0.8, i.e., 200 mg. of cholesterol per 100 to 250 cc. of phospholipids. The higher the ratio, the higher the incidence of atherosclerosis, especially of the coronary arteries. The lower the ratio, the more likely is the avoidance of atherosclerosis. Thus, the more the phospholipids are increased, as compared to the total cholesterol increase, the more protection exists against atherosclerosis. Without any altered lipid metabolism, little or no atherosclerosis develops, regardless of any other alterations of the arterial walls, including senescent changes.

That cholesterolemia alone is not responsible for atherosclerosis is indicated by the fact that hypercholesterolemia is not always found in

atherosclerosis. This is why Katz and Stamler state that it is not only the level of cholesterol in the plasma that is important for atherogenesis, but also the quantity of exogenous cholesterol the body must transport, turn over and metabolize.

Further investigations on the relationship between cholesterol and atherosclerosis, carried on by Gofman and his associates, established that in man, a high concentration of plasma cholesterol bearing lipoproteins (Sf 10-20) (Svedberg units of flotation) not directly correlated with the plasma total cholesterol concentration is associated with atherosclerosis. The Sf 10-20 constitute the less dense components, isolated by ultracentrifugation. These lipoproteins diminish on a restricted fat and cholesterol diet, even if no decrease of total cholesterol concentration follows.

The cholesterol is generally bound to the beta-lipoproteins. The more beta-lipoproteins, the more susceptibility to atherosclerosis. Kendall and others feel, therefore, that atherosclerosis is the result of an elevated beta-lipoprotein level, perhaps combined with other localizing factors. Furthermore, individual situations as a result of which the plasma is unable to hold a greater concentration of sterols in solution, may lead to the precipitation of cholesterol in the blood stream.

Altered metabolism of lipids, so important in the production of

atherosclerosis, cannot be separated from its interplay with other factors of exogenous or endogenous origin. Without entering into details, I will mention some which may lead to the precipitation or aggravation of either arteriosclerosis or atherosclerosis. They are: (1) hypervitaminosis; (2) pyridoxine deficiency; (3) excessive vegetable proteins diet; (4) adrenalinemia; (5) excessive adrenal steroids; (6) hypothyroidism; (7) Diabetes mellitus; and (8) hypertension.

It has not yet been established whether the same physiopathologic mechanism or precipitating factors in the production of atherosclerosis in the large cerebral blood vessels apply also to the small and very small cerebral blood vessels. On the whole, with the exception of a few attempts on a small scale, very little attention has been paid to the more general problem of the relationship of cerebral atherosclerosis to the lipid metabolism, and even less attention to the relationship of that metabolism to the arteriosclerosis of the small cerebral blood vessels. Investigations along such lines may furnish us with valuable data on the significance of the pathological lesions of the small blood vessels of the brain.

The various psychiatric hospitals all over the United States contain a wealth of clinical and autopsy material waiting to be studied by a well-organized team of research workers.

Beckenstein and Gold reported that in 1942 at the Brooklyn State Hospital (New York) the number of deaths for arteriosclerosis and senile psychoses was 703, that is, 77.5 percent of the total number of deaths in the hospital for that same year. Out of these 703 deaths, 384 were cases of psychoses associated with cerebral arteriosclerosis.

Constitution and Heredity

Several investigators have pointed out that a certain constitutional physical makeup is more apt to be found among patients suffering from arteriosclerosis and hypertension. Moschkowitz states that hypertensive patients are generally soft-muscled individuals, pudgy, short-necked, ungraceful, nonathletic, and overweight. Badia found that the megalosplancnic type of Viola, or pycnic type of Kretschmer, discloses a tendency to chronic changes in the blood vessels of the heart, to hypertension, to precocious development of arteriosclerosis, and to cerebral hemorrhages. This view is shared by Larimore and Fishberg.

From the point of view of heredity, it has often been reported that siblings and parents of patients suffering from arteriosclerosis also disclose a history of cardiovascular disease. I will only refer to Allbutt's case of a patient with hypertension, whose paternal ancestors for three generations had died of apoplexy—a total of four generations.

Studies by Boas et al. of fifty families of arteriosclerotic patients whose cholesterol values in the blood exceeded 300 mg. per 100 cc., revealed the existence of abnormal cholesterol metabolism in 30 percent of all the families. Within these, all or most of the siblings showed an elevation of serum cholesterol. In addition, in nine of the fifty families, half of the examined members exhibited hypercholesterolemia.

Studies by Weitz, Nador-Nikititis, Curtius and Korkhaus, and others on the occurrence of arteriosclerosis, hypertension, and cerebral hemorrhages in identical pair of twins reared in different environmental situations, support the contention that heredity plays an important part in this type of vascular pathology. Weitz feels that the predisposition to hypertension behaves in the genetic sense as a Mendelian dominant character.

Differential Diagnosis from a Neuropathologic Standpoint

A few authors have been unwilling to accept a separation between psychoses associated with arteriosclerosis and senile dementia (Tanzi and Lugaro), basing their view on the assumption that arteriosclerosis and senility are almost always associated. Meyer, discussing arteriosclerosis and mental diseases, wrote that: “We have no means to speak of arteriosclerotic insanity, but only of insanity of senile or prematurely senile involution. . . . the real arteriosclerotic nature is only revealed by the course, and by the nervous

and collateral symptoms, of focalized or general arteriosclerosis."

However, if one studies reports from clinical material, one does not encounter such a constant combination of senile dementia and arteriosclerosis. Simchowitz in a study of twenty-three cases of senile dementia, found only eight in which well-developed arteriosclerosis was present. Bonfiglio in a study of thirty-three cases of senile dementia, reported only eight in which well-developed arteriosclerosis was present.

From a pathologic standpoint, one must not consider as characterizing arteriosclerosis the mere presence, here and there, of small vessels disclosing changes assignable to this condition. If this were the case, one should diagnose as arteriosclerosis all sorts of mental disorders occurring in old age, and also the changes found in the brain of mentally normal individuals who die at an advanced age and whose vascular system shows occasional incipient sclerosis.

One must also keep in mind the fact that senile changes of the small blood vessels may lead ultimately to hyalinization and sclerosis of their walls. A certain amount of overlapping of vascular pathology is therefore to be expected. More characteristic of senile vascular changes are, according to Baker, the splitting of the elastic membrane, a diminution of the muscular elements, and fibrosis of the media, with increased collagenous substance.

Loss of elasticity, tortuosity, and dilatation of the blood vessels seem to occur more frequently in senility. Furthermore, one finds numerous senile plaques in senile psychoses, and also nerve cells disclosing the so-called Alzheimer's neurofibrillar disease—findings missing as a whole in cerebral arteriosclerosis. In arteriosclerotic brains, senile plaques were found in only one out of six cases by Simchowitz and in two out of nine cases by Bonfiglio.

Of additional assistance in the differential pathologic diagnosis between senile and arteriosclerotic psychoses, is the frequent finding in arteriosclerosis of vascular damage in the remainder of the cardiovascular system and in the kidneys (cardiac hypertrophy, myocardial infarcts, passive congestion of organs, and infarcts of the kidneys). Furthermore, the presence of cerebral red or white softenings of various intensity and extension, and involving well-known cerebral vascular territories, favors the diagnosis of arteriosclerosis.

Neuropathology of Senile Psychoses

There is no direct correlation between cerebral pathological findings in senile psychoses, and the development of mental symptoms. Contrary to Simchowitz, who believed that senile dementia was merely an exaggeration of the normal senium, Gellerstedt has shown that anatomically it is not a simple quantitative difference which characterizes normal and pathological senium, an opinion shared by Grünthal, Cerletti, Critchley, Bonfiglio, Rothschild, and others. Moreover, in cases of pathological senility, there is a lack of correlation between the severity of the cerebral structural change and the severity of the intellectual impairment. Conversely, marked alterations are occasionally found in the brains of old persons of normal mentality. Therefore, tissue damage alone is not responsible for the onset of the psychosis.

The following macroscopic and microscopic changes are in general encountered in cases of senile psychoses:

Macroscopic Changes

Cranial Changes. The calvarium in old age is usually thicker than normal, the density being generally uniform. Atrophy of the skull bones, cranium, and face may be encountered much less frequently. Occasionally the process of atrophy is localized particularly in the parietal region, and

hyperostosis of the inner table has been reported.

Brain. One of the general characteristics of the brain is a marked shrinkage resulting from both atrophy and loss of lymphatic fluid. Instead of an average weight between 1200 and 1400 g., weights of 1100 and 1000 g. are often reported. Weights as low as 912 g. and 815 g. have been reported by Grünthal and by Critchley.

Along with the shrinkage of the brain tissue, there follows a marked difference of 23 to 24 percent, between the volume of the brain and the volume capacity of the cranial cavity, instead of a normal difference of 12 percent. On the other hand, brains of normal old individuals may also undergo marked shrinkage and loss in weight (1002 g. in a case reported by Grünthal), whereas brains of severe cases of senile dementia may differ only slightly from the normal average.

When shrinkage is present, as in most cases, the process is usually generalized, although at times it is more prominent in the frontal area, and the middle portion of the posterior area of the brain. The shrinkage of the nervous tissue itself is reflected in the widening of the brain sulci and thinning of the convolutions (Figure 4-14). As the result of a marked shrinkage of the brain parenchyma, an internal hydrocephalus may develop.

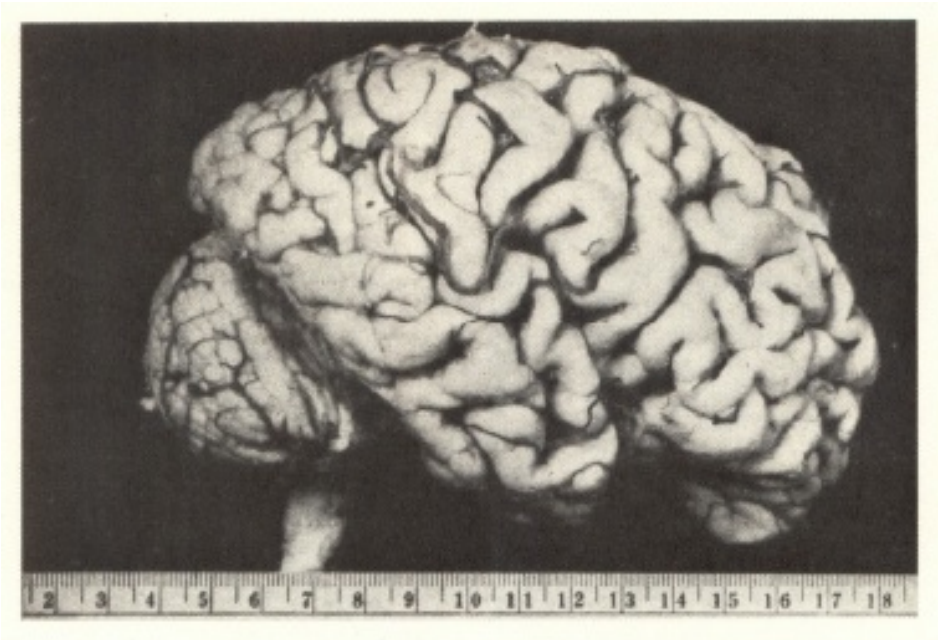


Figure 4-14.

Macroscopic aspect of a senile brain in which shrinkage is moderate. The cerebral convolutions are thinned and the sulci are slightly widened.

The dura matter is almost always thickened and, in many cases, adherent to the inner table of the skull. Longitudinal densification of that covering may be seen following the course of the external blood vessels. The pia is generally three to four or more times thicker than normal.

Subdural hematomas are occasionally found in from 8 to 9 percent of the cases (Campbell) and Leri has reported occasional perforations of a thick

and edematous pia.

Microscopic Findings

The brain cortex generally discloses a reduction in size because of an actual reduction in the volume of the nerve cells which appear smaller and closer to each other, and because of an actual loss in their number.

In general, phylogenetically older parts of the cortex, such as the motor areas, are less involved than are the parts developed later. The upper cellular layers of the cortex, particularly the third one, show the greatest damage in most cases, though not marked enough to disturb considerably the layering of the cortical lamination. In some cases that lamination is, however, greatly disturbed. In some areas the nerve cells still present may occasionally give the impression of being even more numerous because of the shrinkage of their interstitial tissue. In the same cortical convolutions, one may find areas of marked shrinkage, i.e. volume reduction of most of the nerve cells and marked disturbed lamination, near-by areas in which the cells are better preserved, and the cytoarchitecture close to normal (Figures 4-15 to 4-18).

The pathological process which involves the individual nerve cells is generally known as “shrinkage” of the nerve cell. Shrunken nerve cells, which in the past were designated as “chronically diseased cells,” are seen scattered in the various cortical areas. Most of the cells undergo a gradual process of

necrobiosis, which leads to their gradual disappearance. Remnant shadows of such cells are dispersed here and there. Only occasionally, cells undergoing a simple acute swelling, or conversely the “acute severe type of degeneration” described by Nissl, are encountered. The shrinkage of the nerve cells which results in their deeply stained appearance is the most frequent finding.

Among the preserved nerve cells, many disclose an increase in pigmentation, particularly of the yellow type which may invade the whole of the cellular body, and at times spread into some of its processes. The extreme degree of such a change may lead to the “pigment atrophy” of the nerve cell, a pathologic feature which seems to predilect the nerve cells of the inferior olivary bodies, and at times the nerve cells of the dentate nucleus. In contrast to the excessive pigmentation, a loss of the normal melanin pigment of the cells of the substantia nigra has been reported by Stief, and by Grünthal. In the basal ganglia, particularly in the striatum, a loss of the larger nerve cells has been reported, and in the cerebellum the Purkinje nerve cells appear diminished in size and in number.

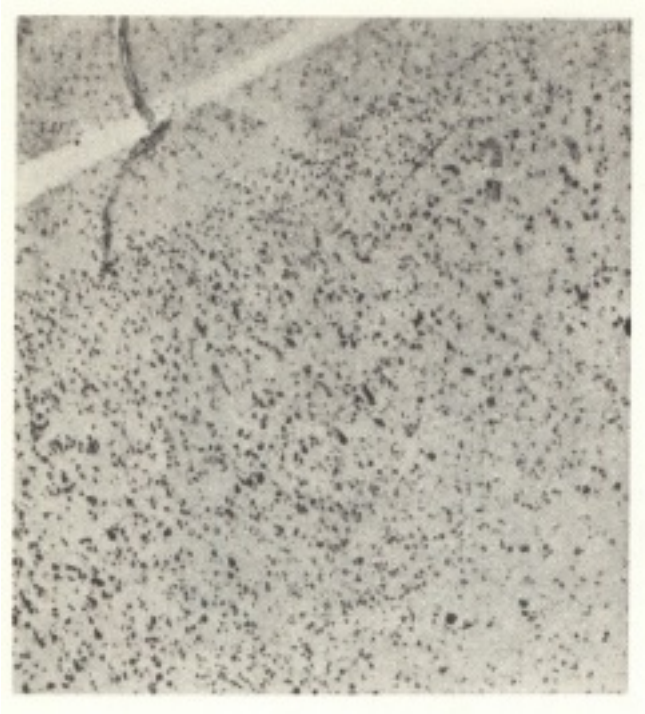


Figure 4-15.

Reduction in the number of nerve cells and considerable shrinkage of their body, particularly in the inner cortical layers. Nissl stain.

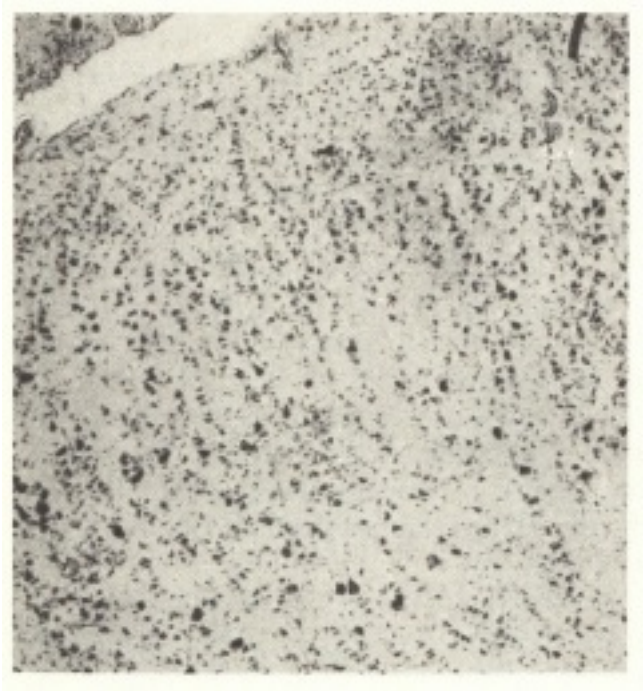


Figure 4-16.

Patchy area, in which nerve cells are reduced in number, and reduction in the volume of the cell bodies is noticeable in the middle cortical layers. Nissl stain.

Figure 4-17.

Marked reduction in the number of nerve cells in all of the cortical layers and marked shrinkage in the cell body of the remaining ones. Nissl stain.

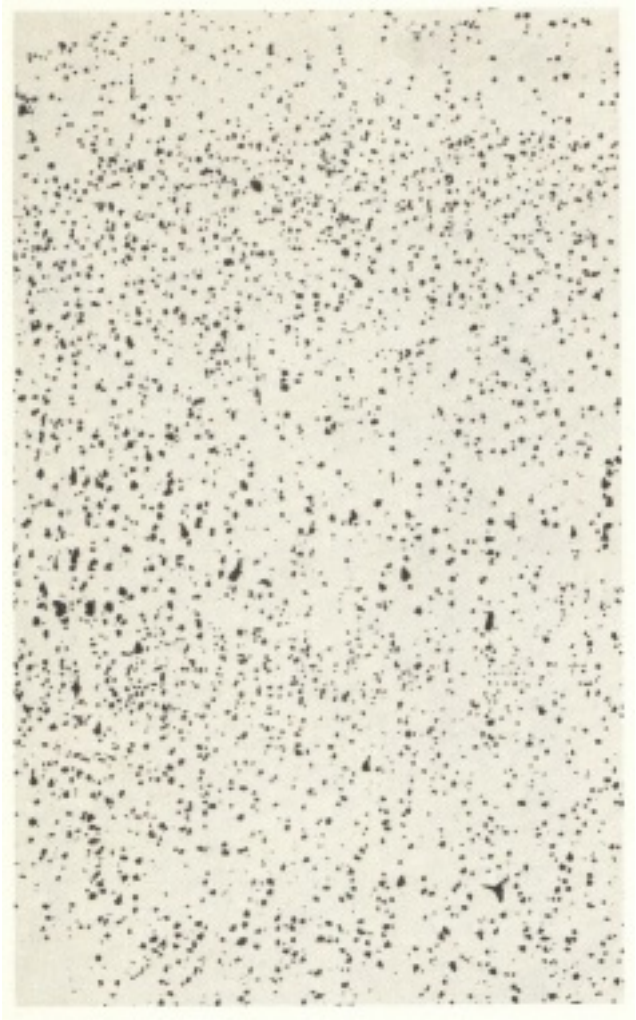


Figure 4-18.

Uneven distribution of shrunken nerve cells and uneven reduction of their number, mostly in the middle and outer layers. Nissl stain.

A special type of nerve-cell pathology first described by Simchowitz, the so-called "granulo-vacuolar degeneration" has been reported in cases of senile psychoses, particularly in the large pyramidal cells of the hippocampus, though present also in other cortical areas (Piazza). The process consists in the appearance of granules scattered in the cytoplasm of the nerve cells, each granule being generally surrounded by a vacuole (Figure 4-19). According to Simchowitz these granules do not contain fat tissue, a statement which is contested by Piazza.

Another characteristic cellular change often found in senile dementia is the so-called "Alzheimer neurofibrillar disease of the nerve cells," a condition first described by Alzheimer in a variety of ageing diseases of the brain, but considered more closely related to that variety of presenile psychoses designated Alzheimer's disease. Within the nerve cells the neurofibrils coalesce and condense, thus assuming various peculiar aspects such as convolutions, spirals, loops, knots, and clumps within the cytoplasma (Figure 4-20), none of which are found in normal cells.

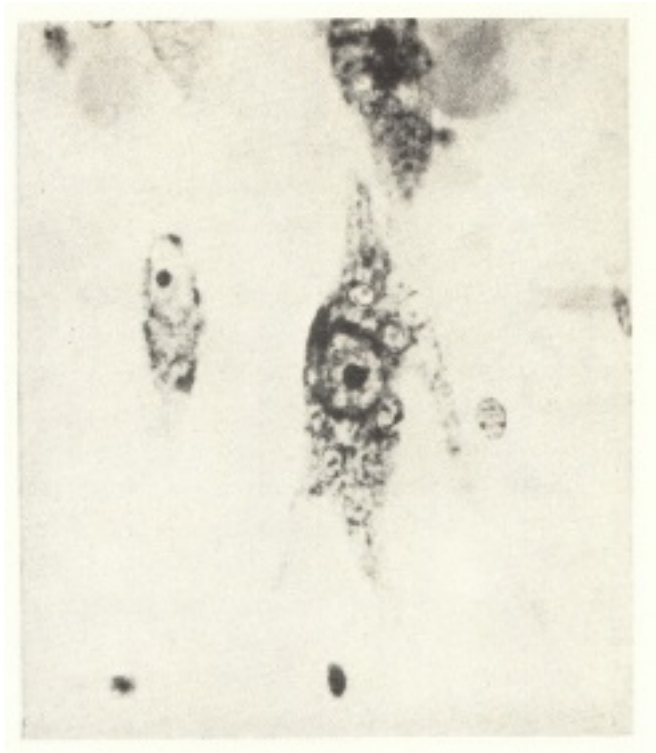


Figure 4-19.

Nerve cells disclosing the granulo-vacuolar degeneration of Simchowitz; granules surrounded by vacuoles in the midst of the cellular cytoplasm. Nissl stain.

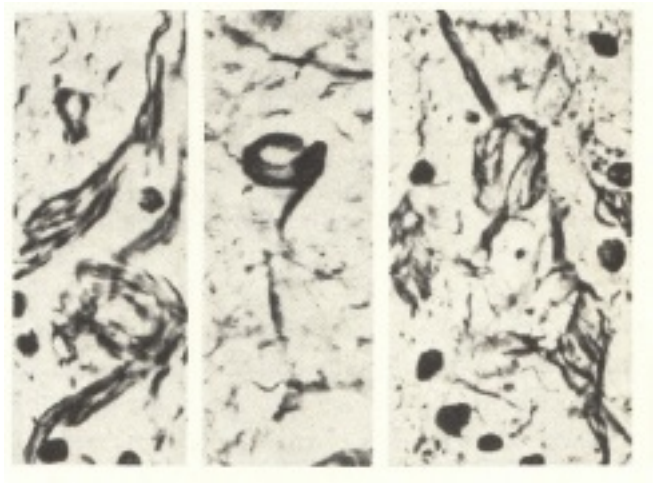


Figure 4-20.

Various morphologic aspects of nerve cells disclosing the so-called Alzheimer neurofibrillar disease. Silver carbonate impregnation method of Del Rio Hortega.

These unusual formations, which have also been described as surrounding certain nerve cells, have been considered by the majority of investigators as resulting from degenerating neurofibrils within the nerve cells. However, this point of view is not shared by Achucarro and Gayarre, Del Rio Hortega, Lafora, or Divry, who have shown that the same changes occur in the pericellular, the neuroglial, and the syncytial reticulum of Held, and even in astrocytes, especially if undergoing ameboid degeneration, data which seem to point to a wider physicochemical disturbance of the amyloid and hyaline metabolism.

The association of Alzheimer's neurofibrillar disease with the other pathologic changes in the brain of senile psychotics occurs in 17 per cent of the cases according to Simchowitz, but in less than 6 percent according to Tiffany. On the other hand, according to Cerletti, Costantini, Fuller, Ley, and Gellerstedt, neurofibrillar change has been found in a few nerve cells of the brain of normal aged individuals.

Nerve cells showing the so-called Alzheimer's fibrillar disease are now, however, very numerous in senile dementia, and also in the presenile type of psychosis designated "Alzheimer's disease," where Perusini first and Jervis more recently, found that respectively one out of six and one out of two or three cells disclosed that change.

The most striking microscopic pathological feature in the brain in cases of senile psychosis is the presence of the so-called "senile plaques." These plaques were first described by Blocq and Marinesco, in a case of epilepsy in 1892, as neuroglia nodules; in 1898, Redlich called them miliary sclerosis, and Fisher, in 1907, described them as "spherotrichia cerebri multiplex." It was Simchowitz who, in 1911, proposed the now generally accepted term of "senile plaques." They represent small areas of tissue degeneration, generally of a roundish aspect, in the midst of which granular or filamentlike detritus is recognizable in addition to other products of degeneration.

Senile plaques are scattered throughout the cortex from the frontal to the occipital pole, as shown in Figures 4-21 to 4-23. The frontal lobes and the Ammon's horn seem to be seats of predilection. According to Tiffany, senile plaques are found in the frontal, hippocampal, central, paracentral, occipital convolutions, and basal ganglia in that order of frequency. Rothschild found them in abundance in the amygdaloid nucleus, in small numbers in the putamen and caudate nucleus, and less frequently in the thalamus and the substantia nigra.

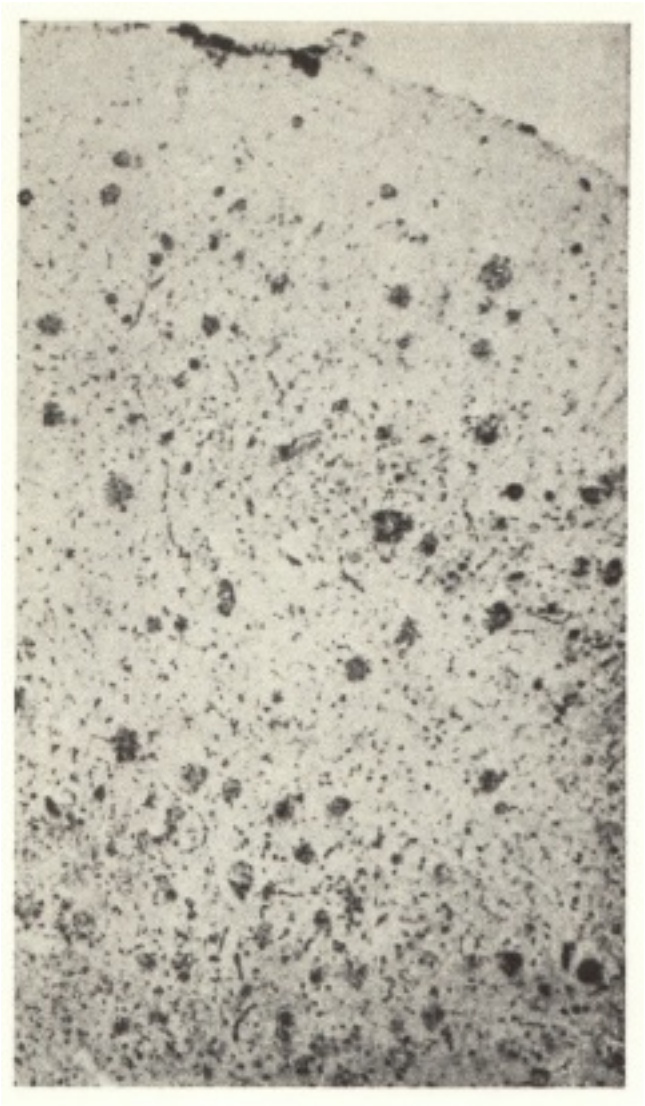


Figure 4-21.

Numerous senile plaques distributed in various cortical layers. Silver carbonate impregnation method of Del Rio Hortega.

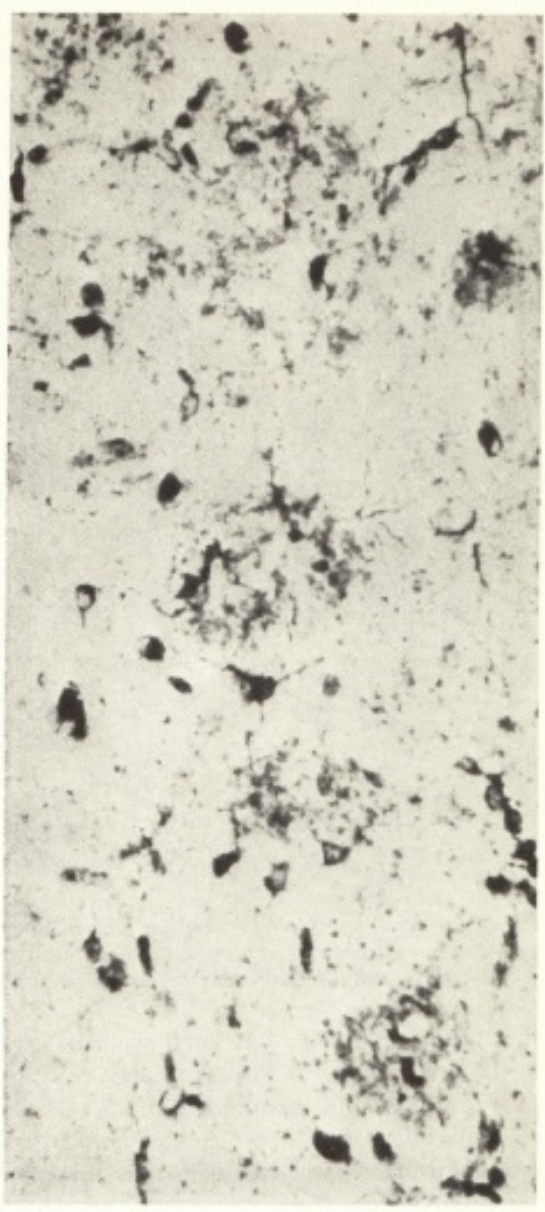


Figure 4-22.

High-power magnification of senile plaques, illustrating their grandular and filamentous structure. Silver carbonate impregnation method of Del Rio Hortega.

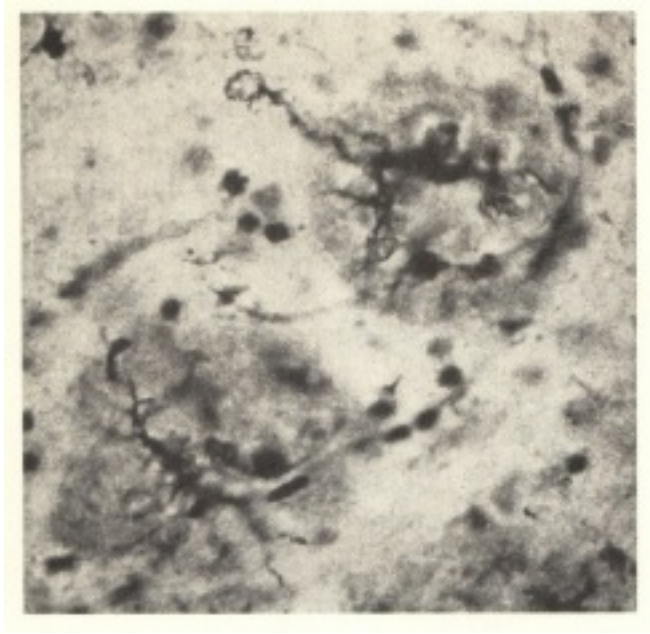


Figure 4-23.

High-power magnification of two senile plaques in the midst of which reacting microglial cells are clearly visible. Silver carbonate impregnation method of Del Rio Hortega.

According to Simchowitz, the number of plaques is the best index of the severity of the senile process in the cortex. The more plaques, the more severe is the process. Such a contention, although generally accepted, is

refuted by a few authors who feel that a pathological diagnosis of senile dementia may be acceptable even in the absence of senile plaques. Simchowitz and Perusini feel however, and I agree with them, that if a detailed examination of the brain of a senile psychotic is undertaken, one will never fail to find plaques, and their absence justifies a doubt as to the diagnosis of senile dementia.

An important corollary to that statement concerns the presence of plaques in normal senile brains. Such a question seems to have been disposed of, because normal senile brains do show senile plaques, occasionally in substantial numbers, and sometimes as many as in senile dementia. Gellerstedt detected senile plaques in 84 percent of normal aged brains, neurofibrillar alterations in 87 percent, and granulo-vacuolar degeneration in 40 percent. In each case, however, such findings were scarce, and at times detectable only after very careful examination.

The senile plaques have been considered as deriving from various individual structures of the nervous tissue. Some authors believe that they originate from neuroglia elements; others consider them as derived from the nerve cells. Still others assert that the disintegrated intercellular structure and the neuroglia reticulum constitute the elements from which senile plaques develop; Marinesco feels that they originate from deposits of abnormal material.

In 1922, Ley first expressed the opinion that in the formation of the senile plaques, microglia elements take part, a view later upheld by Verhaart, and Urecchia and Elekes. My own investigation on the histogenesis of the senile plaques has led me to conclude that senile plaques are formations that indeed may originate not only from degenerating microglia cells, but also from oligodendroglia cells and even directly from degenerating nerve cells (see Figure 4-24). A detailed bibliography on the histogenesis of the senile plaques may be found in my paper on this subject.

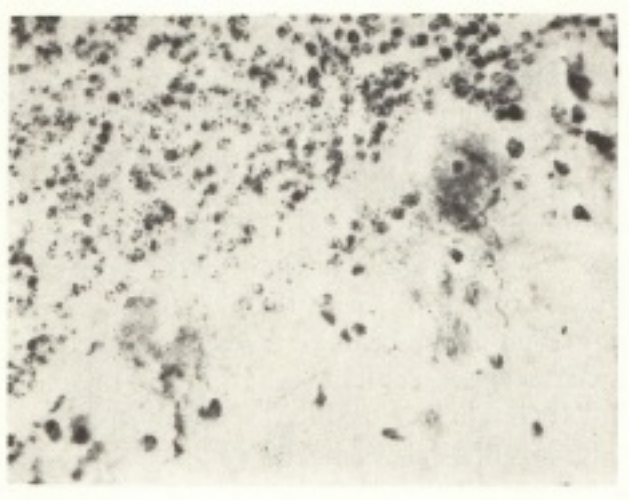


Figure 4-24.

Two Purkinje cells of the cerebellum undergoing individual degenerative changes leading to the formation of senile plaques. Silver carbonate impregnation method of Del Rio Hortega.

The histochemical process that governs the transformation of a cellular element into a senile plaque is as yet somewhat obscure. All that can be said is that it leads to the formation of a granular argyrophilic substance which according to Divry represents a miliary hyalino-amyloidosis. The so-called nucleus of the plaques, that is, its central portion, shows the staining properties of an amyloid metachromatic substance which reacts in a brown-reddish color to Lugol's solution, which stains in red with Congo red, and which above all is birefringent at polarized light.

Divry is also of the opinion that the so-called Alzheimer's neurofibrillar disease is the result of amyloid degeneration related to some colloidal disruption, that is, of a flocculation of the fibrinoplastic cellular substance, a process akin to syneresis. Morel and Wildi felt that the amyloid degeneration in the plaques themselves, within the blood vessels or outside their walls, is the result of an altered protein metabolism (paraproteinemia) associated with impaired vascular permeability.

Free amyloid bodies are also frequently seen in senile dementia. They are scattered in various cortical areas, in the white substance, in the subependymal layer of the ventricular cavities, and more abundantly in the external lamina of the Ammon's horn. Various theories such as the neurogenic, gliogenic, lymphogenic, hematogenic, and postmortem, have been advanced for their histogenesis. After an investigation which Damon and I

carried out in this connection, we concluded that mostly microglial and oligodendroglial elements contribute to the origin of said bodies, through an amyloid degeneration of their cell bodies. Figure 4-25 illustrates amyloid bodies impregnated by the silver carbonate method in the course of their amyloid degeneration, and Figure 4-26 illustrates the genesis of amyloid bodies from clusters of oligodendroglia cells, which still retain some of their processes. An extensive literature on this subject is found in my publication on this subject.

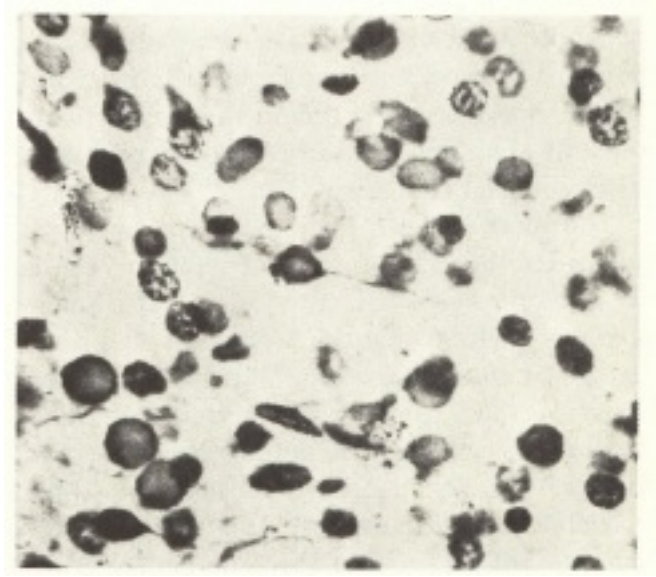


Figure 4-25.

Numerous amyloid bodies diffusely distributed. Silver carbonate impregnation method of Del Rio Hortega

Neuroglial Tissue

With the atrophic process, which involves not only the cortex but also the white matter, there is a moderate neuroglia reaction of the progressive type—astrocytic reaction—which if present, is found in the outer layers of the cortex in the form of marginal gliosis. Hypertrophy of isolated astrocytes is observed here and there in the white and gray matter, but much less frequently an increase in their number (hyperplasia). Clasmatodendrosis of the glial fibers as well as reticulocystic degeneration of the astrocyte bodies is also found occasionally.

Deposits of free iron are common in the brain of aged people, localized particularly in the perivascular spaces of either the cortex or the white substance. A seat of predilection is generally the globus pallidus where free deposits of iron seem to be found, independently from their immediate relationship to the blood vessels. No specific relationship has been established from the quantitative standpoint between iron deposits in normal and pathological senility.

Myelin Sheaths and Nerve Fibers

In the brain cortex, the myelin sheaths do not seem to be substantially involved, except for a slight diminution of the myelinated fibers in the tangential layer, and a questionable diminution of fibers in the radiate and

supra-radiate layers. In the white matter, areas of patchy myelin rarefaction may be observed.

The axis cylinders, corresponding to the areas of myelin involvement, show occasional fragmentation, but nothing compared with that observed in the midst of the senile plaques and in their immediate vicinity.

Blood Vessels

Cerletti first described in the senile atrophic tissue of the brain the presence of vascular loops and vascular knots, resulting from the elongation of the blood vessels which have lost their elasticity and which furthermore have to adjust themselves to the narrower space offered by the shrunken tissue. Aschoff reports ectasia of the blood vessels, widening of their lumen, some increases of the internal elastic membrane and some twists in the course of the blood vessels which he attributed to fibrosis of the muscular elements.

Simchowitz described what he termed “simple senile changes” of the small blood vessel: degenerative changes of the endothelial lining cells, fibrosis of the media, and slight reactive proliferation of the adventitial cells. According to Baker, in old age the internal elastic membrane discloses fraying, and the muscular fibers of the media are replaced by connective tissue which later may become hyalinized. Hyalinization may, according to

Binswanger and Schaxel, spread to the adventitia. In the course of that process, the elastic fibers disappear first, followed by the muscular fibers of the media. Collagenous tissue is ultimately found surrounding the arterioles and the capillaries.

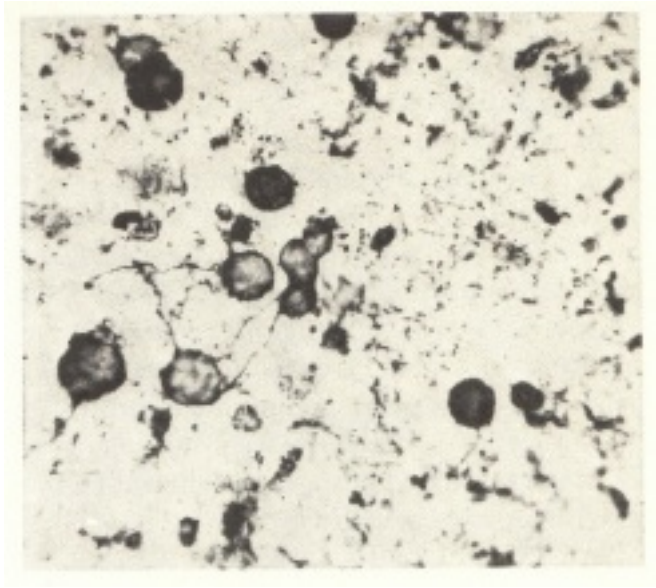


Figure 4-26.

Oligodendroglial cells undergoing amyloid degeneration. Some of the cells still disclose a few of their disintegrating processes. Silver carbonate impregnation method of Del Rio Hortega.

In eight cases of arteriosclerosis associated with pronounced senile changes, Eros reported that in seven of them, the blood vessels showed

hypoplastic degenerative changes of the elastic membrane. Recently Fisher has reported, in cases of senile dementia, arteriosclerotic changes leading to more or less marked occlusion of the internal carotid arteries. He feels that a relationship may exist between these findings and the clinical picture exhibited by these patients.

In cerebral blood vessels, Scholz has described a degenerative condition of the media, occurring in very old people, which he termed *Drusige Entartung.* This condition termed *degenerescence grumeuse* by Lafora, consists on the infiltration of the media by a substance of homogeneous appearance, which according to the latter, shows the staining properties of the amyloid substance (Figures 4-27 and 4-28) and particularly of its birefringence.

In the choroid plexus the most common findings are the proliferation of the connective tissue, vacuolization and pigmentary degeneration of its epithelial cells, and the presence of calcareous hyaline and psammomatous bodies.

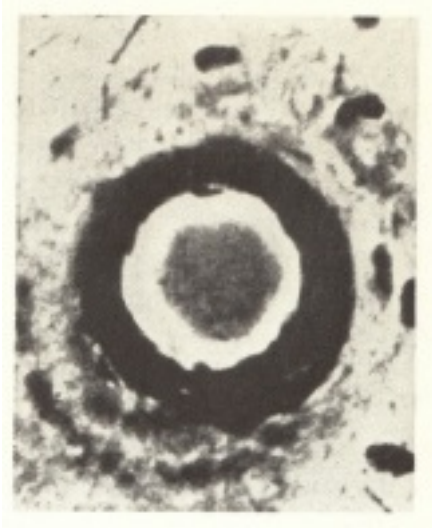


Figure 4-27.

Amyloid degeneration within the walls of a blood vessel.

Figure 4-28.

Birefringence of amyloid substance along the longitudinal course of a blood vessel.

Spinal Cord

Its meninges are thickened and calcareous plaques may be seen attached to the pia arachnoid. Ossification is only rarely found. The spinal cord itself is generally shrunken and the myelin sheaths somewhat rarefied, particularly in the posterior and lateral columns. Astrocytic proliferation may be noticed around the blood vessels and in the areas of myelin involvement.

Accumulation of yellow pigment is often seen in the ganglion cells.

Occasionally “Alzheimer’s fibrillar disease” has been reported.

The blood vessels may show a combination of simple senile degenerative and mild arteriosclerotic changes. Amyloid bodies generally surrounding the blood vessels seem to be prominent along the spinal cord septi and mostly in the zone entrance of the posterior roots.

Electroencephalographic Studies

Luce and Rothschild reported a slowing of the predominant rhythm in their cases of senile psychoses, especially in those showing a more severe intellectual impairment. Diffuse dysrhythmia of brain waves in senile psychoses have been reported by Silverman, Busse, and Barnes. These investigators found a correlation between diffuse dysrhythmias and decreased facility to communicate, lower clarity of perception, increase in concrete concept formations, and greatly reduced psychomotor speed. When focal dysrhythmia was associated with diffuse abnormalities, organic deterioration was clearly noted. McAdam and McClatchey felt that probably an impaired cerebral blood flow was the important factor in the abnormal electroencephalographic tracings. They too reported a high correlation between slow rhythm activity and intellectual deterioration.

Neuropathology of Presenile Psychoses

Alzheimer's Disease

It may be said in general that the same findings are reported in senile dementia and in Alzheimer's disease, a condition first described by Alzheimer in 1907. Perusini in 1910 and in 1911 contributed substantially to its clinical and pathological aspects, as a result of which the disease called Alzheimer's disease in Germany became known as Alzheimer-Perusini disease in Italy.

The atrophy of the brain tissue is more pronounced than in senile dementia, the reduction in volume of the convolution and the widening of the sulci being more marked (Figures 4-29 and 4-30). The process of atrophy, generally involving most of the lobes, is occasionally more pronounced in some of them—the frontal, temporal, parietal, or occipital. Circumscribed atrophy in one lobe only is rare, and cases of this type may constitute variants of Pick's disease rather than genuine cases of Alzheimer's disease.

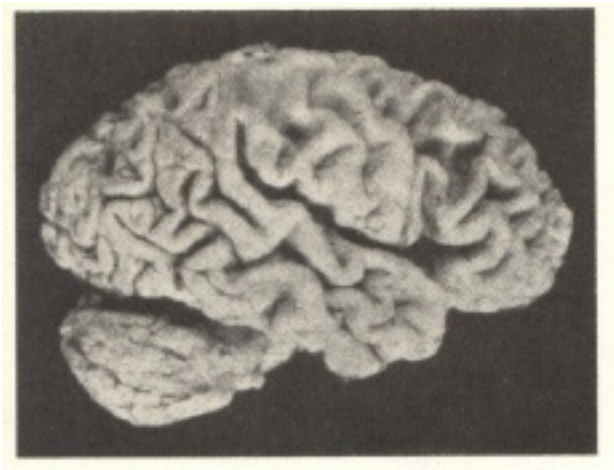


Figure 4-29.

Macroscopic appearance of the right cerebral hemisphere in a case of Alzheimer's disease. Note the widely distributed shrinkage of the cerebral convolutions in most of the lobes and the markedly enlarged fissures and sulci.

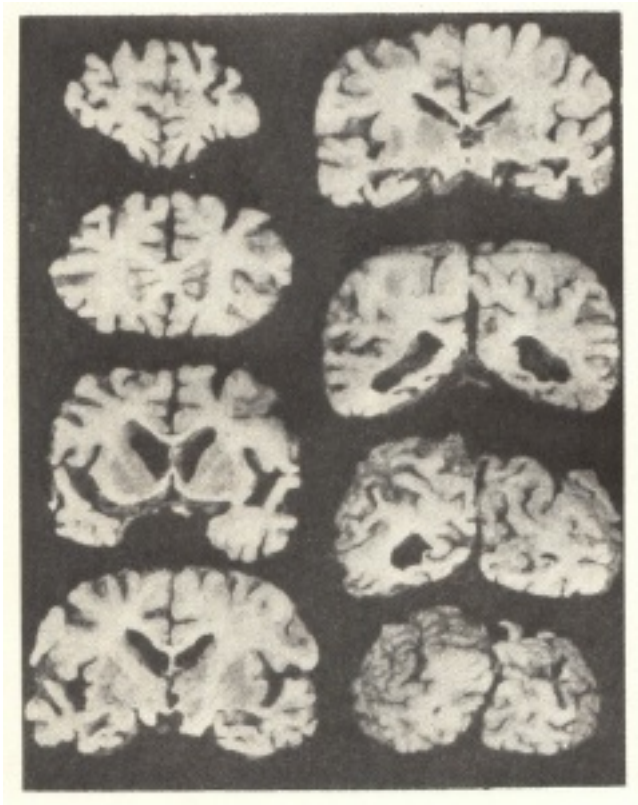


Figure 4-30.

Macroscopic appearance of gross vertical sections of brain of Figure 4-29, illustrating the cerebral atrophy and the widening of the sulci from the frontal to the occipital pole and the dilatation of the lateral ventricles.

Histologically the process of atrophy is represented by a diffuse disappearance of nerve cells and by a resulting disturbed cortical lamination. No particular cortical layers are involved, the cellular atrophy being more

pronounced at times in the outer layers (Figure 4-31), at times in the middle layers, (Figure 4-32), and at other times indiscriminately in all cortical layers (Figure 4-33). On the whole, there seems to be no predilection for any special cytoarchitectural field; cortical areas of more recent ontogenetical development are as involved as are others of older organization. The involved areas are irregular, and generally no clear-cut boundaries exist between normal and pathological areas. Occasionally, though, a sharp boundary is apparent between atrophic areas and the better preserved ones.

Figure 4-31.

Shrinkage and disappearance of nerve cells involving mostly the outer cortical layers. Nissl stain.

Figure 4-32.

Shrinkage and disappearance of nerve cells involving predominantly the middle cortical layers. Nissl stain.

Corresponding to the areas of cortical cellular atrophy, there occurs an increase of glia cells. In the white matter, one finds also that increase which may represent an actual numerical increase in the number of the glia cells, or a relative one resulting from the shrinkage of the white substance. This glial increase may constitute one of the differential features from the senile psychoses, where gliosis, if present, rarely reaches an appreciable degree. Occasionally, fibrillar gliosis may be seen in some of the areas of the white substance, even though in those areas the myelin sheaths appear to be preserved.

The most common individual type of the degenerative change of the involved nerve cells is that of shrinkage, or pyknosis; these nerve cells appear reduced in size, and deeply stained; their processes appear distorted and tortuous. Their intracellular pigment is generally increased, particularly in the lamina terminalis and the presubiculum of the Ammon's horn. However, one may also encounter a few nerve cells undergoing the severe acute type of degeneration of Nissl, consisting in their swollen appearance, poverty of the Nissl's substance, a marked vacuolization and peripheral disintegration. At times, a few nerve cells are encountered, undergoing the ischemic type of cellular degeneration, particular in the vicinity of the blood vessels. Many

distorted shadows, remnants of nerve cells, are detected, giving the impression that a slow progressive vascular mechanism contributes to the atrophic process. Only occasionally has the granulo-vacuolar degeneration of Simchowitz, frequently encountered in the senile psychoses, been reported in Alzheimer's disease.

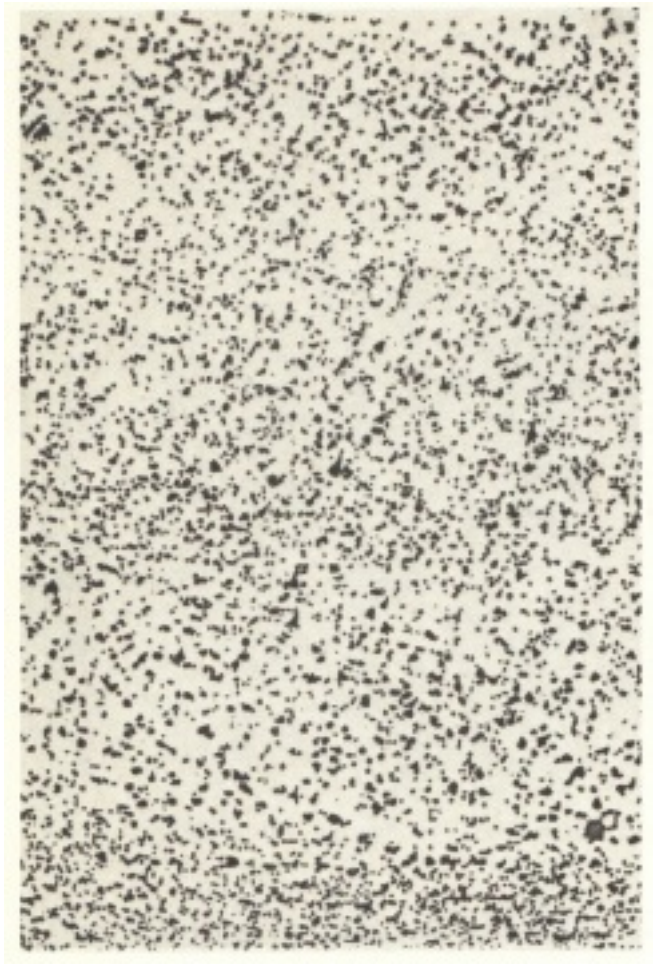


Figure 4-33.

Shrinkage and disappearance of nerve cells involving, indiscriminately, all cortical layers. Nissl stain.

A most characteristic change of the nerve cells is the so-called Alzheimer's neurofibrillar disease. Contrasting with senile dementia, this type of cellular change has been reported by Lafora as being always present in Alzheimer's disease. Figure 4-34 illustrates various aspects of Alzheimer's neurofibrillar disease in individual cortical nerve cells. Occasionally, round argyrophylic masses, resembling the inclusions described in Pick's disease, have been reported in the cytoplasm of a few cortical nerve cells.

A diagnosis of Alzheimer's disease has been, however, considered compatible with the absence in the nerve cells of the characteristic neurofibrillar change, a statement contested by the majority of the investigators. Indeed, if one considers the difficulty of establishing a differential clinical diagnosis between senile dementia, Alzheimer's disease and Pick's disease, one is justified in insisting—for a correct diagnosis of Alzheimer's disease—on the presence in the brain of the whole typical pathology, including the Alzheimer's neurofibrillar changes.

The proportion of the nerve cells showing Alzheimer's neurofibrillar change to normal cells is as high as 1 to 2, or 1 to 3. It is precisely the large number of nerve cells disclosing that special intracellular change which characterizes Alzheimer's disease pathologically. There is, however, no parallelism between the number of nerve cells so diseased and the cortical atrophy, some severely atrophic areas lacking at times the presence of nerve

cells disclosing the neurofibrillar changes. Such changes are infrequent in the basal ganglia (striatum and thalamus), but numerous in the Ammon's horn, particularly in the Sommer's sector.

The pathogenesis of the Alzheimer neurofibrillar disease is a debated question. Although the majority of the investigators still maintain that the Alzheimer's changes result from degenerated neurofibrils, others do not share this view, having demonstrated that the same argyrophilic incrustation of the neurofibrils in the cells are seen in the pericellular reticulum of the nerve cells, in the neuroglia reticulum, in the sincytium of Held, in the protoplasma of the cells of the choroid plexus, in the ependymal glio-epithelial cells and even in the cytoplasm of astrocytes, especially of those undergoing the so-called ameboid degeneration. These incrustations may, therefore, originate not only from neurofibrils, but also from the thickening of the spongioplasm of many other cells in the nervous tissue.

Alzheimer's neurofibrillar disease, although generally essential for the pathologic diagnosis of Alzheimer's disease, is not pathognomonic of the latter. It may be found in senile dementia, particularly of the presbyophrenic variety. It has also been reported in other neuropsychiatric conditions, such as chronic epidemic encephalitis, familiar spastic paralysis, amyotrophic lateral sclerosis, disseminated sclerosis, involutional psychosis, Tay-Sachs disease, and Pick's disease. In all such conditions, the number of the nerve

cells showing Alzheimer's changes is, however, very limited compared with the large number of cells involved in Alzheimer's disease. Furthermore, the neurofibrillar disease reported in these various human conditions as well as in some animals, may not be of the same nature as that reported in the Alzheimer disease proper.

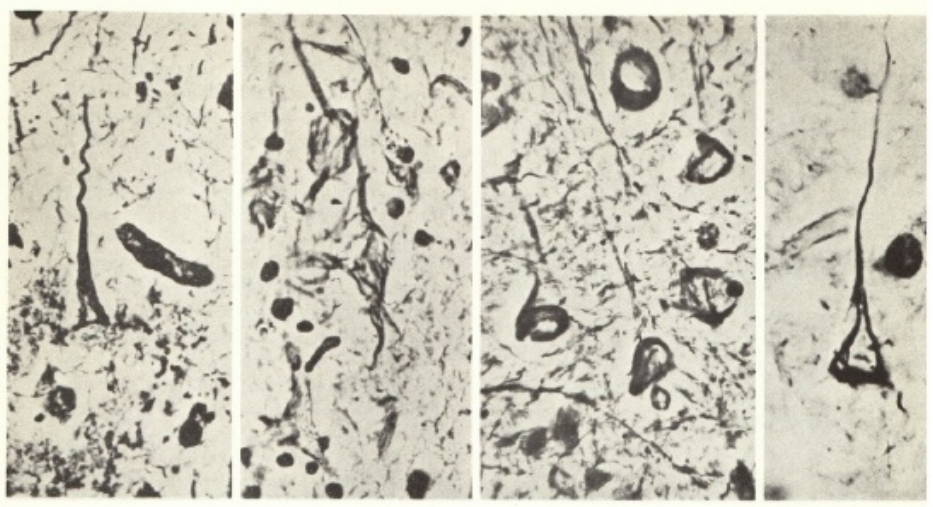


Figure 4-34.

High power view of Alzheimer's neurofibrillary changes. Silver stain.

Senile Plaques

Senile plaques constitute an almost constant finding in Alzheimer's disease, rarely being absent in a typical case. According to Simchowitz, in

Alzheimer's disease the plaques are dominant in the occipital and parietal lobes, in contrast to their predominance in the frontal lobes in senile dementia. In general, however, they are distributed throughout the cerebral cortex, and more so in the subiculum of the Ammon's horn, although they have been reported in large number in the basal ganglia, the brain stem, and the cerebellum. The more diffuse are the senile plaques and the more severe and numerous the Alzheimer's neurofibrillar changes, the more severe, in general, are the clinical symptoms.

Blood Vessel Changes

Most of the vascular changes reported in senile psychoses are generally found also in Alzheimer's disease. The senile atrophic angiopathy (the degenerative changes of the endothelial and aventitial cells of the blood vessel walls) and the so-called "dysphoric angiopathy" (Drusige Entartung of Scholz) have been reported in Alzheimer's disease, although the latter seems commoner in very old patients. The character of the histochemical alterations in such angiopathy does not differ from those described by Divry in senile psychosis, including the birefringence and the staining properties of the material deposited in the walls of the small blood vessels, capillaries and precapillaries and in their surrounding tissues, a material which possesses the properties of the amyloid substance. Even in the senile plaques themselves and in the argentophylic loops, spirals or baskets of the diseased

Alzheimer cells, the same substance was detected by Divry, thus pointing to a general metabolic disorder of which Alzheimer's disease of the brain may be a local expression.

Pathogenesis of the Disease

The close relationship of Alzheimer's disease to senile dementia, as first described by Alzheimer, was soon accepted by Perusini, Bonfiglio, Frey, and Fisher. Rheingold and Reichhardt consider the disease a variety of presbiophrenia.

Runge considers Alzheimer's disease a special form of senility, occupying the same position among the senile psychoses that Lissauer's paralysis occupies in general paresis.

Hilpert, Rothschild and Kasanin, Malamud and Lowenberg, and McMenemy and Pollack consider Alzheimer's disease to be a syndrome which is due to various exogenous or endogenous factors. Senility may be only one of these factors.

Goodman recently advanced the theory that Alzheimer's disease is related to devitalized microglia cells which are unable to fulfill their supposed trophic and nutritional functions. He related the devitalization to a disturbance in the cerebral metabolism of the iron which appears increased

in practically all nerve cells.

Endocrine disturbances have also been thought to play a pathologic role in cases where myxedema was found associated with that condition.

A common derivation for the senile and the presenile psychoses has been advocated by Braunmuhl, on the basis of colloidal changes which are common in senile and presenile states. In his opinion, aging of the brain is the result of a change from a highly cellular colloid dispersion to a lesser one, resulting in condensation and coagulation. This process of "protoplasma hysteresis," which may also occur in the presenile stages, does not differ from the one occurring in senility proper under the influence of various precipitating factors, which in Alzheimer's disease may act with greater intensity, thus leading to earlier and more extensive damage.

The vascular involvement, widely rejected in the past as a precipitating factor in presenile psychoses, seems at present to be less reluctantly accepted. Morel and Wildi emphasize the importance of the altered vascular permeability. De Ajuriaguerra speaks of circulatory changes leading to disturbed oxygen utilization, and Lafora speaks of cerebral vascular pathoclisis. It is not, however, a matter of structural vascular damage, inasmuch as this may be absent, but of altered functionality, which may be transitory and recurrent (vasospasm). In Alzheimer's disease, vasospasm may

constitute, indeed, a precipitating element which complicates the underlying senile process, and therefore precipitates and aggravates its expression. This contention is supported by the occurrence of nerve cell atrophy and gliosis, which at times are detected along the longitudinal course of a blood vessel. Furthermore the association of a mild arteriosclerosis with Alzheimer's disease has also been reported.

Von Bogaert summarized the relationship of the vascular permeability to the presence of amyloid substance often reported in the brain in Alzheimer's disease. In his words: "In senile processes and therefore in Alzheimer's disease, an abnormal vascular permeability is found which allows the production of complex substances, which in some cases possess the attribute of the amyloid substance (amyloid angiopathy). If the deposit is limited to the walls of the blood vessel, it is referred to as 'congophilic angiopathy;' if it overflows into the adventitial space, welding it to the glio-adventitial structure and even penetrating into the nervous parenchyma, it is called 'dishoric angiopathy.' These discontinuous deposits tend to occur in areas differing from those where hyalinosis occur—both substances are often formed in the same brain, but in different parts. However, hyalinosis may be closer than is generally thought to the congophilic material." [p. 100] In his opinion, cerebral amyloid angiopathy is a sign of a more general humoral disturbance and of local tissue changes, which characterize "normal involution," but which become more pronounced in pathological senility and

presenility.

Relationship of Alzheimer's Disease to the So-called "Juvenile Type"

The occurrence of Alzheimer's disease in early periods of life has created doubts as to the classification of the disease as a presenile psychosis. Similar doubts resulted also because of the occurrence of the disease in very old age. For the latter, a delayed pathological senility, triggered by delaying precipitating factors, may explain the occurrence of Alzheimer's disease in the course of advanced senium, and may preserve its relationship to it.

Concerning the so-called cases of "juvenile Alzheimer's disease," a critical review of some of these cases, undertaken by Jervis and Soltz, brought out the following conclusions: Four of the ten cases reviewed 84 and 85,155 disclosed insufficient pathological evidence and atypical clinical manifestations and therefore did not justify the original diagnosis of "juvenile Alzheimer's disease." In three other cases although the pathology was characteristic, the clinical symptoms were atypical enough to exclude them from Alzheimer's disease. The four remaining cases were typical from both the clinical and pathological standpoint. These cases occurred late in the fourth decade of life, instead of the fifth, in which presenile psychosis is more common. Jervis and Soltz concluded that this margin is evidently too narrow and insufficient to justify the differentiation of a nosological variety of a

"juvenile type of Alzheimer's disease."

Also the "juvenile familial cases" disclosing a dominant genetic trait, described by von Bogaert et al. and Worster-Drought et al., do not seem to belong to Alzheimer's disease. The paucity of the cerebral changes characteristic of that disease, the mental picture lacking the typical impairment of trans-cortical associative functions, and the presence of outstanding pyramidal, cerebellar, or extra-pyramidal neurological symptoms, indicate a closer relationship of these cases to heredode-generative diseases (spastic spinal paralysis, hereditary ataxia, hereditary chorea) than to Alzheimer's disease.

Genetic Factors

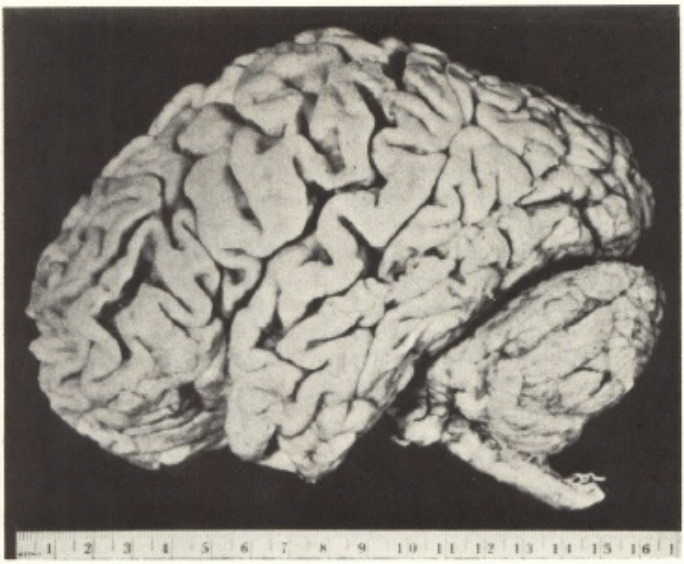
Some cases have been described in support of a direct genetic hereditary link, although serious doubts have been expressed as to their correct clinical diagnosis. Other cases of Alzheimer's disease show more of an indirect hereditary link, inasmuch as, in the same family, cases of senile dementia, schizophrenia, feeblemindedness, or alcoholism have been reported. Studying genetically and clinically sixty-nine cases of Alzheimer's disease, the Sjogrens et al., reported three secondary cases in three families among the parents of the patients, and three secondary cases among the siblings. The authors point out the possibility of a multifactorial inheritance in

Alzheimer's disease, including genetic factors determining premature pathologic aging.

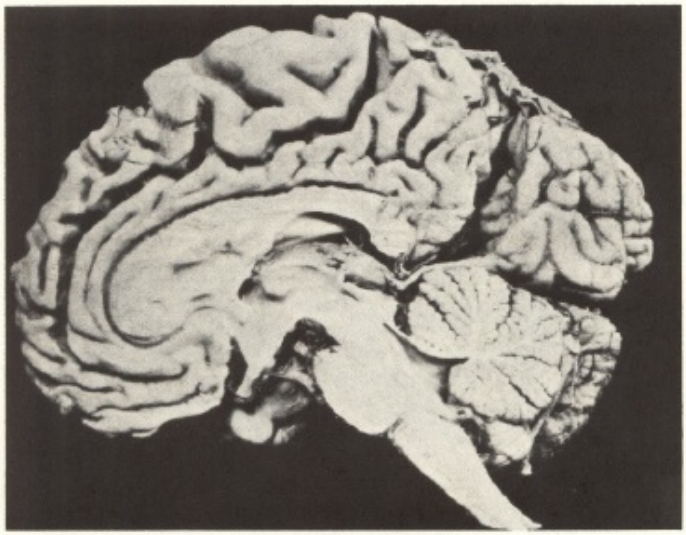
Pick's Disease

Pick's disease is an endogenous disease occurring in the presenile period of life, and is characterized clinically by a state of dementia, in addition to which, because of a primary circumscribed atrophy of the cerebral hemispheres, certain focal symptoms develop. This atrophy is the result of a slowly progressing degenerative process, lacking the character of inflammation or necrosis, and therefore disclosing no appreciable product of the disintegration of the involved tissue. Although Pick, who first described this condition, considered it related to the senile psychoses, other investigators feel that the disease is an entity to be classified among the heredode-generative processes.

The macroscopic appearance of the brain in Pick's disease reveals the presence of a circumscribed lobar atrophy, which is expressed in terms of shrinkage more or less pronounced, of the involved lobes, the marked shrinkage of the individual convolutions (knife-blade appearance) and the broad widening of the cortical sulci.



(a)



(b)

Figure 4-35.

(a) Lateral view of a brain showing the atrophy, circumscribed mainly to the frontal and temporal lobes, (b) Medial aspect of the same brain. Note the well-preserved paracentral lobule.

The cerebral atrophy is generally circumscribed and localized in the orbitofrontal and temporal lobes. It is generally symmetrical but more pronounced over the left hemisphere. Frontotemporal-parietal localization is also encountered. Lobar atrophy limited exclusively to the occipital convolutions lacks postmortem pathological confirmation. In the frontal lobes, the frontal poles are more frequently involved. In the temporal lobes, the convolutions T_2 and T_3 are more frequently involved. The two posterior thirds of convolution T_1 are generally preserved. In the parietal lobe, the gyrus supramarginalis is mostly affected.

According to Spatz, the most resistant cortical areas to the process of atrophy are the occipital convolutions, especially the calcarine area, the central convolutions, the paracentral lobule, the more dorsal portions of the frontal lobes, near the interhemispheric fissure, the temporal convolutions of Heschl, the caudal portion of the first temporal convolution and the Ammon's horn.

Spatz also reports the presence of primary foci from where the atrophic process initiates, diffusing later to the surrounding tissue. One of these

primary foci is to be found in the mediocaudal portion of the orbital lobes (gyrus rectus); a second focus he reported in the insula, a third in the fronto-opercular region, a fourth in the opercular portion of the precentral convolution, and a fifth in the frontal pole.

It is difficult to evaluate the report of Bonfiglio who described a case of Pick's disease with atrophy limited solely to the basal ganglia, or the one of Verhaart, where the predominance of the atrophy was in a cerebellar lobe.

Figure 4-35(a) illustrates the macroscopic aspect of the brain in a case of Pick's disease, disclosing a dominant fronto-temporal atrophy. The third frontal, the first temporal, and the pre- and postcentral convolutions are well preserved. The Figure 4-35(b) illustrates the atrophy in the medial aspect of the same brain hemisphere. The frontal lobe is markedly atrophic, whereas the paracentral lobule is well preserved.

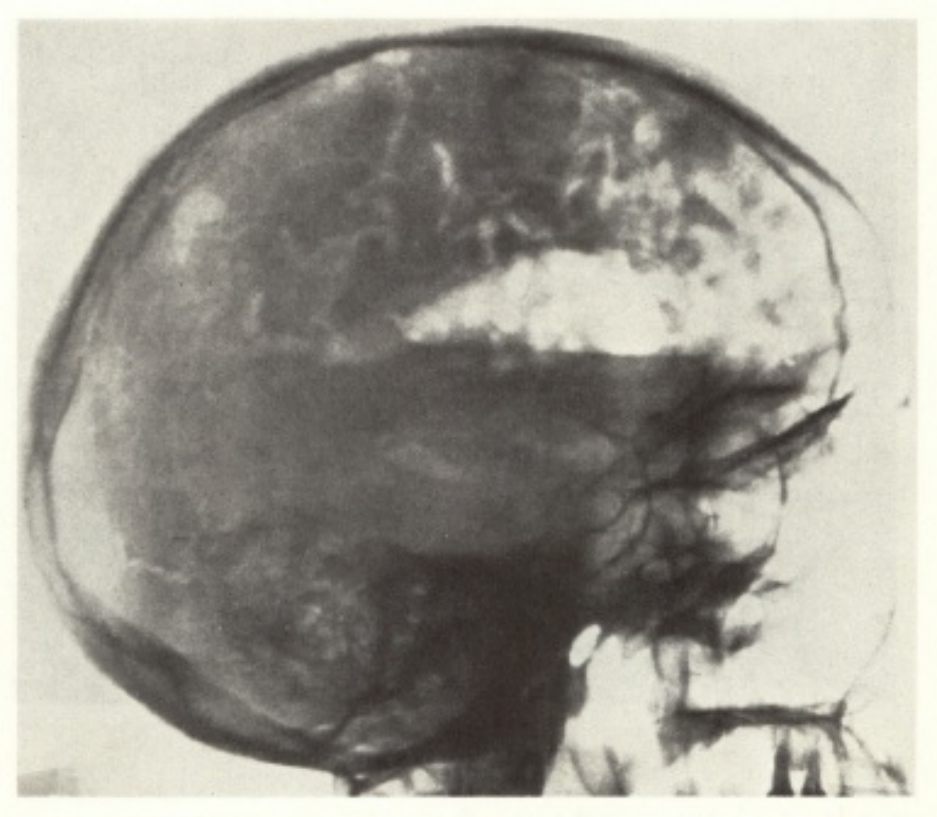


Figure 4-36.

Pneumoencephalogram showing a large amount of air over the frontal lobes and the enlargement of the lateral ventricle.

Microscopic Changes

The meninges appear thicker because of a more or less pronounced

increase in the connective tissue. The main parenchymatous changes consist of a slow progressive process of atrophy of the neurons without appreciable disintegration or necrosis of the nervous tissue, but accompanied by hyperplasia of the glia fibers, and to a lesser degree of the astrocytes themselves.

Spatz, Onari, and Bagh found the atrophy to be systemic, initiating at the distal end of the neuron, and progressing centripetally toward the nerve cell. The intensity and the diffusion of the involvement of the neurons determine the intensity of the shrinkage of the gray and white matter and of the subsequent dilatation of the cerebral ventricles.

Corresponding to the marked lobar atrophy, the encephalogram reveals a collection of air in the corresponding portion of the ventricular cavities. Figure 4-36 illustrates the pneumoencephalographic findings related to the marked frontal atrophy in the case illustrated in Figure 4-35.

The degenerative process of the cortical nerve cells leads to their gradual rarefaction and complete disappearance. This process has no definite predilection, being at times more pronounced in certain cortical layers, and at others involving all of them. In certain cases the cellular atrophy from the outer layers of the cortex invades the middle layers (Figure 4-37); in others it is limited to the external layers; in still others it is more pronounced in the

inner layers. In others it may unevenly involve most of the cortical layers (Figure 4-38). The boundaries between better-preserved areas and areas of major involvement are, at times, sharply demarcated while at others they fade gradually into well-preserved areas. At other times the disappearance of the nerve cells is patchy, and may be seen to follow the longitudinal course of a blood vessel (Figure 4-39).

The predominant type of the cellular involvement is the simple shrinkage of the cell body, with increased pigmentation so that it gradually becomes very pyknotic. Occasionally, however, vacuolation of its cytoplasm is observed, as well as the more specific type of granulo-vacuolar degeneration described by Simchowitz. In a few areas, the ischemic type of cellular degeneration described by Spielmeyer may also be encountered. Occasionally some of the degenerating nerve cells show increased content of fat products.

But the most characteristic aspects of nerve cell degeneration are two special ones which have been considered by some investigators as characteristic of Pick's disease. One type consists in the so-called "cellular swelling" (Blähung of Alzheimer) (Figure 4-40). Since the cytoplasm of these nerve cells has lost most of its Nissl's substance, these swollen cells appear poorly stained except for a thin peripheral chromatine band of the cytoplasm itself or of its nucleus. The nucleus, either swollen or distorted and pyknotic, is excentrically located. This type of cellular lesion seems to have a

predilection for the less severely atrophic cortical areas, and recalls the type of cellular reaction described by Meyer in various mental diseases as “central neuritis.”

Figure 4-37.

Extreme diminution of nerve cells and remnants of others, mostly in the outer cortical layers and extending into the middle layers.

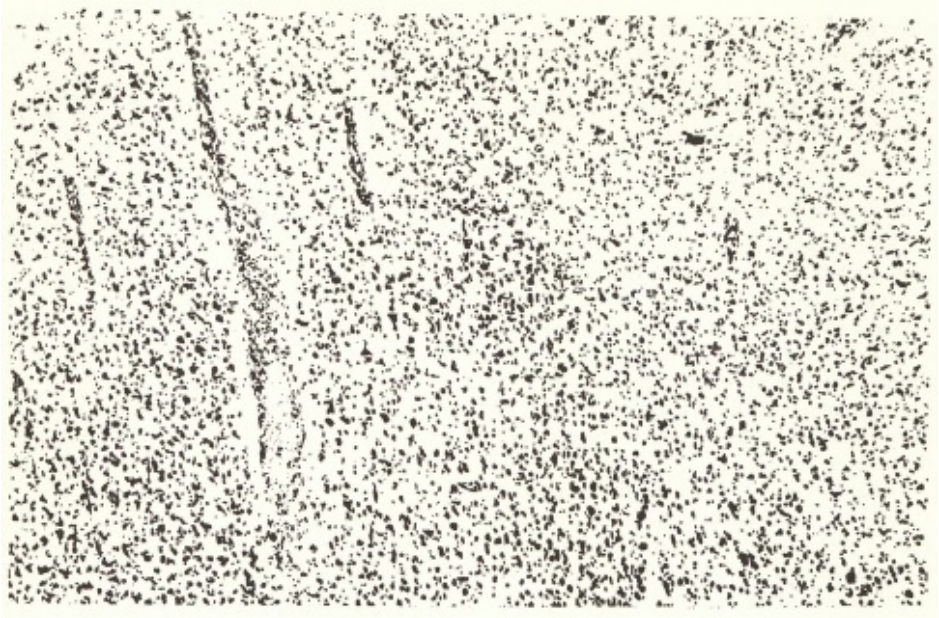


Figure 4-38.

Unevenly distributed nerve cells undergoing atrophy leading to cellular rarefaction in all the cortical layers.

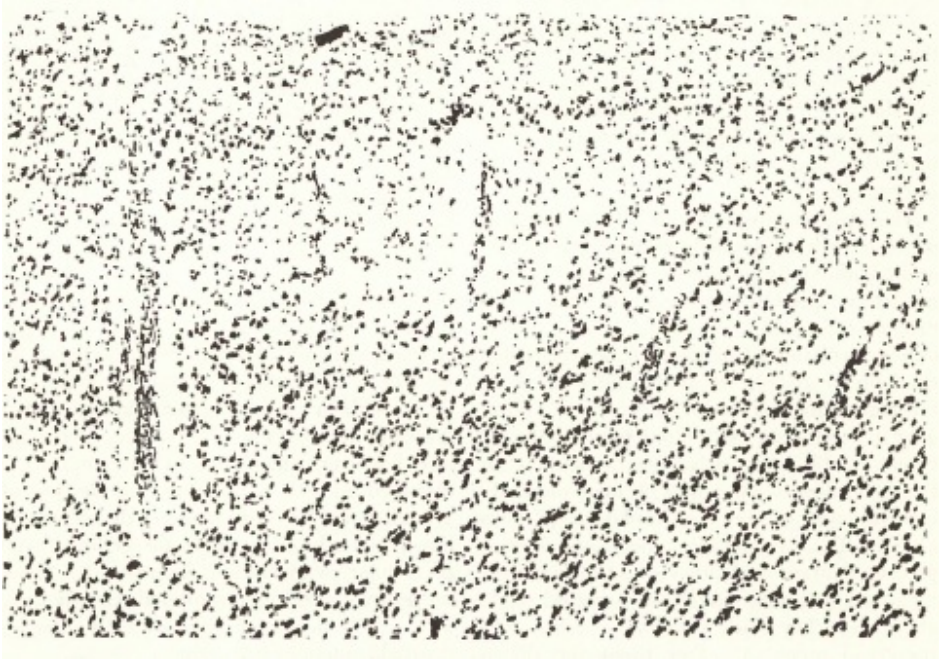


Figure 4-39.

Patchy areas of cellular atrophy and rarefaction of nerve cells along the longitudinal course of some blood vessels. Nissl stain.

Figure 4-40.

Nerve cells of the first temporal convolution undergoing the characteristic swelling (Blähung). Nissl stain.

The other characteristic type of nerve cell change consists in the presence in the nerve cells of intracellular argyrophylic roundish inclusions, particularly numerous in the Ammon's horn. They are known as "cytoplasmic inclusions of Alzheimer" (Figure 4-41). These roundish bodies, which may displace the nucleus, possess metachromatic staining properties in addition

to being argyrophylics. Though they do not stain with Congo Red, or show the optic birefringence of the amyloid substance, Divry considers them to be the expression of colloidal condensation, an early stage of amyloid degeneration.

It is worthy of notice that nerve cells with cytoplasmic inclusions are found at times in large number in the areas where the atrophic changes are of a very moderate degree.

Myelin Sheaths

Involvement of axis cylinders and myelin sheaths varies from area to area, disclosing various aspects of early swelling, of fragmentation, and of granular disintegration accompanied by various degrees of demyelination. The demyelination may extend to the corpus callosum, while in the white substance it spares most of the so-called arcuate fibers. The sheaths of the optic nerves seem also better respected.

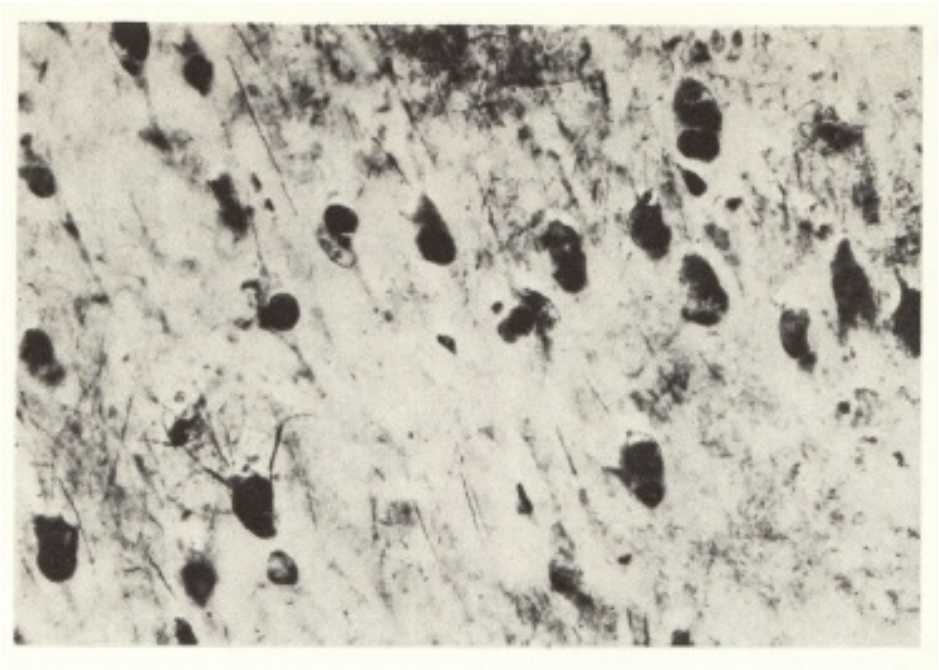


Figure 4-41.

Characteristic argentophilic inclusions in the nerve cells of the Sommer sector of the Ammon's horn. Cajal silver stain.

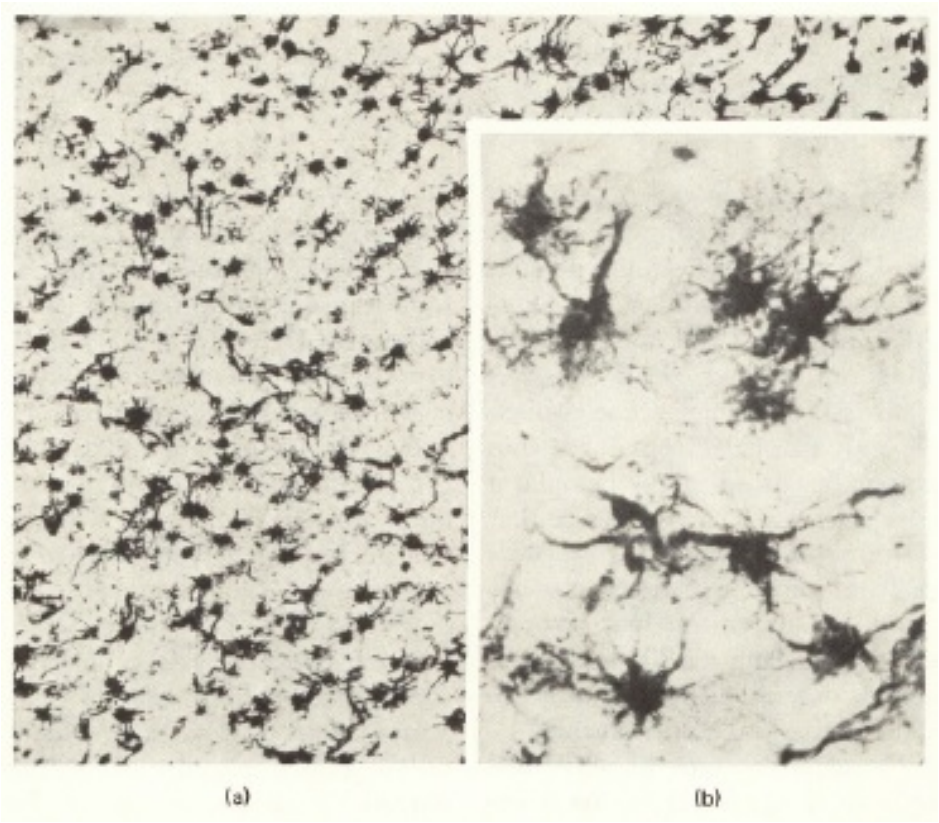


Figure 4-42.

(a) Typical hypertrophy and hyperplasia of astrocytes, (b) Astrocytes undergoing degeneration (clasmatodendrosis). Cajal's gold-sublimate method.

Glial Reaction

The glial reaction in Pick's disease, as opposed to senile psychoses or

Alzheimer's disease, is a major component of the histopathological process. At times there is a definite increase in the number of astrocytes and their related number of glia fibers, plainly visible with the Cajal method of gold sublimate impregnation. In the midst of such a glial astrocytic hyperplasia, hypertrophic cells are found disclosing at higher power, evident signs of clasmatodendrosis. Figure 4-42(a) illustrates an area of glia hypertrophy, and Figure 4-42(b) shows cells undergoing swelling and fragmentation of their processes (clasmatodenrosis). Oligodendroglia cells appear individually normal, but they give the impression of being abnormally numerous in the white matter. This is presumably related to the shrinkage of the white matter and does not necessarily represent an absolute numerical increase. As already mentioned in the definition of the disease, there are little or no fatty degeneration products in the atrophic areas, either free in the tissue or embedded in the microglia cells.

A common finding in relation to the reaction of the glia reaction in the areas disclosing a severe demyelinating process (Figure 4-43(a)) is the presence of an outstanding glial fibrosis (Figure 4-43(b)). Another impressive change is the very marked increase in the number of glial nuclei, detectable by the staining method, in the midst of some atrophic areas. Particularly interesting is the great increase of those nuclei which I have reported in a typical case, along the course of various small branches of small blood vessels which appear to be surrounded by a heavy collection of glial nuclei (Figure 4-

44). Such a marked reaction surrounding the blood vessels seems to indicate the participation of a vascular factor in the pathogenesis of the disease.

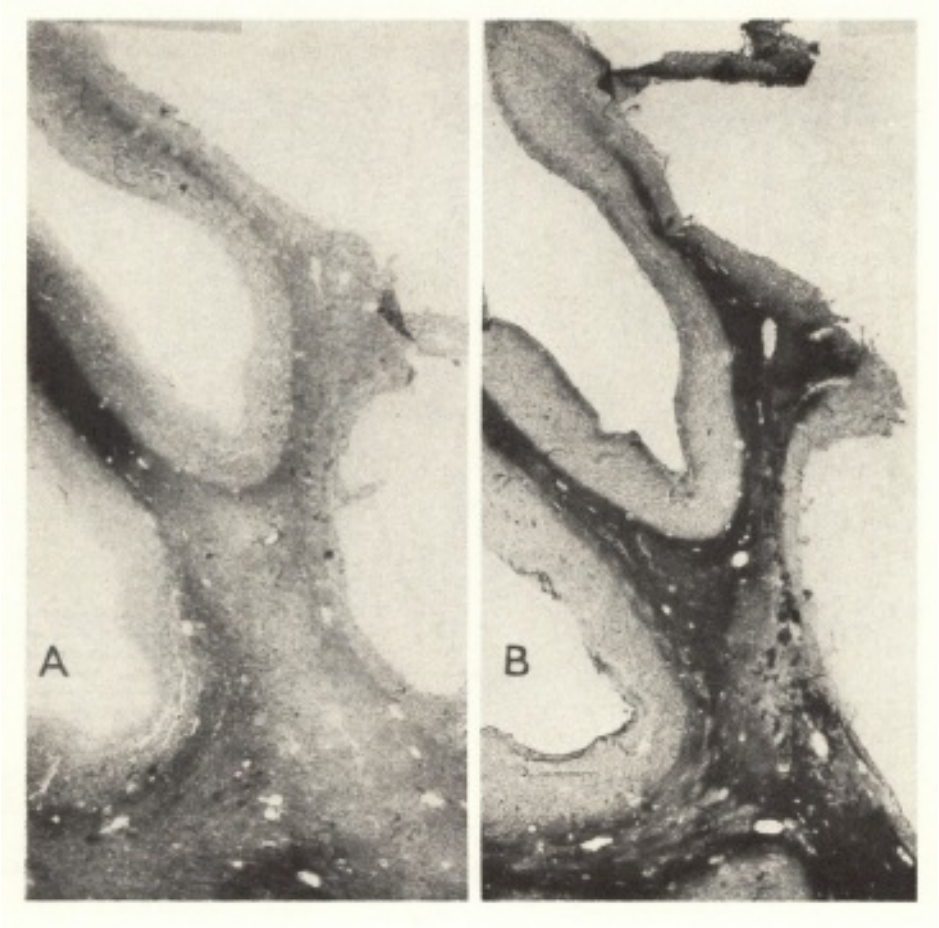


Figure 4-43.

Section of the temporal lobe illustrating the correlation between (a) demyelination

(Spielmeyer's method for myelin sheaths) and (b) fibro-glia proliferation on the same area (Holzer's stain for gliafibers).

Blood Vessels

The blood vessels appear, at times, as if increased in number, though that appearance may be related to the shrinkage of the surrounding nervous parenchyma. Changes in individual blood vessels may run the gamut from a slight thickening of the adventitia, to minor proliferative changes of the lining endothelial cells, thus leading to an occasional slight endarteritis. Hyaline degeneration of small blood vessels has also been reported.

Iron Pigments and Other Changes

Increased iron pigment is generally found in the gray and white matter, either free in the tissue or embedded in the glia or nerve cells, more so at the boundaries between cortex and the white substance, and more so in the severely atrophic areas.

The participation of the basal ganglia and of the substantia nigra, in the pathologic process, thus leading to the development of extra-pyramidal symptoms, has been emphasized by Ferraro and Jervis, and confirmed recently by Spatz. The latter stated that: "Our concept that extrapyramidal symptoms do not occur in Pick's disease must be revised." The atrophy reported in various nuclei of the thalamus has been interpreted by Simma, as

related to both a primary cellular atrophy of some of the thalamic nuclei, and to a secondary one resulting from the damage of the corresponding cortical areas where the thalamic fibers end.

Senile plaques and Alzheimer's neurofibrillar disease, although occasionally reported, do not constitute a necessary pathologic component of the structural damage in Pick's disease.

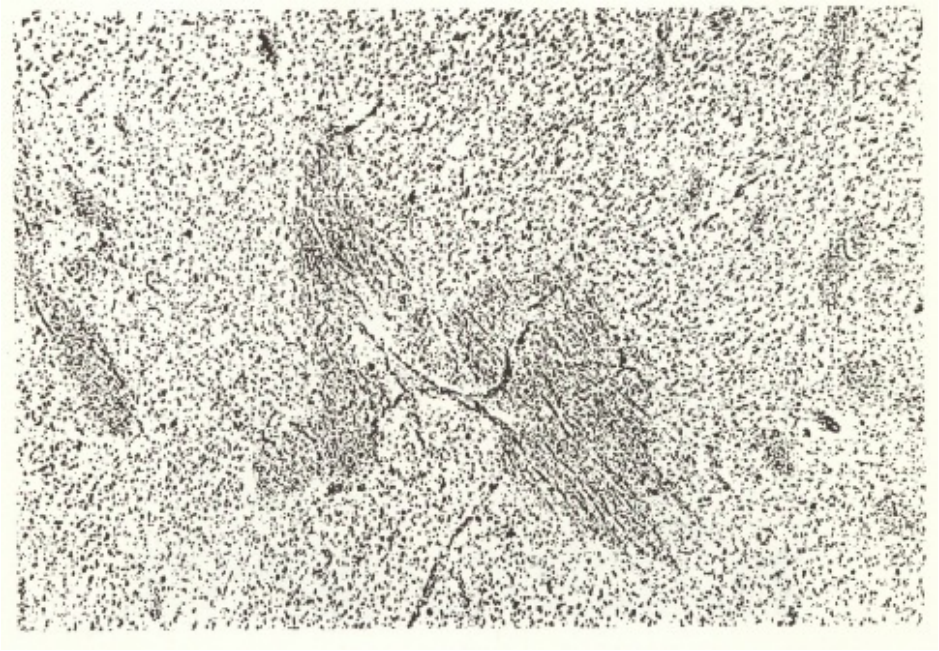


Figure 4-44.

Small branches of a cerebral blood vessel, in the white matter, surrounded by a very marked increase of glia nuclei which outline the vascular course in an atrophic area.

An attempt by Neumann to describe two different types of Pick's disease needs confirmation. The author feels that in one group there is a marked focal cortical devastation, with loss of nerve cells and axis cylinders. Demyelination and reactive gliosis parallel each other in severity. In the second group there is a widespread gliosis of the subcortex, out of proportion to the demyelination of these areas. Damage of cortical structures is less pronounced. Neumann suggests that these two types may have a different etiology.

Nosologic Position of Pick's Disease and Its Pathogenesis

That Pick's disease should be classified among the presenile psychoses, and thus related to senile psychoses, seems to be the opinion of a group of investigators. They believe that not only does the disease share some clinical features with Alzheimer's disease, but also that some of the characteristics of the circumscribed atrophy are similar pathologically to those of the more diffuse atrophy described in Alzheimer's disease. Furthermore, they feel that in cases of senile dementia there has been occasionally found a predominance of the senile atrophic process in one or more lobes. In addition, in Pick's disease, the same predominance of the cortical cellular atrophy in certain outer, middle, or inner layers, just as in senile psychoses and particularly in Alzheimer's disease, constitutes one more relationship between Pick's disease

and the senile psychoses as maintained by Pick, Fisher, Altmann, and Spielmeyer.

Another group of investigators led by Spatz, Onari, and Bagh, considers Pick's disease to be a member of the large group of progressive heredodegenerative systemic cerebral and spinal atrophies. They consider Pick's disease the result of a localized, premature cerebral senescence. The localized atrophy begins at the distal end of the neurons in the white substance, and progresses as a retrograde degeneration towards the nerve cells of origin, thus explaining the pathologic aspect of the swelling of the cortical nerve cells. This theory, which is an offshoot of Gower's concept of abiotrophy, implies that certain functional units are more apt to become diseased because of impaired congenital vitality.

This theory receives support from those who state that in Pick's disease only certain cytoarchitectural areas are involved, that the third layer of the cortex is the predominantly diseased, or that younger ontogenetical systems or associated areas, more recently myelinated, are the ones primarily involved. Neuropathologic investigations do not always support this theory. Regions comparatively younger, such as Broca's area and the temporal gyri of Heschl, have been often reported spared, whereas regions phylogenetically older, such as the gyri hippocampi and the Ammon's horn, have been severely involved. Furthermore, involvement of regions corresponding to the

associative areas of Flechsig, or to the third cortical layer, is not a constant finding. Finally the involvement of subcortical gray structures, a finding invoked in support of the theory that the disease is heredodegenerative in nature, might not be a primary involvement as maintained, but a secondary one, resulting at least in part from the atrophy of the corresponding cortical areas.

On the other hand, cases of Pick's disease in which genetic factors play a role, are undoubtedly on record. Sjogren et al., in eighteen cases of Pick's disease confirmed by autopsy, have reported the occurrence in three families of three secondary cases among the parents, and in another family, one secondary case among the siblings. They feel that in Pick's disease the hypothesis of a major dominant gene, with modifying genes, appears somewhat acceptable. The report of Sanders et al., of a family in which seventeen members were apparently affected by the disease in the course of four generations, and the report of Malamud and Waggoner, of another family with fifteen affected members in four generations, also support the Mendelian dominant character of the disease.

However, the fact that in Pick's disease, and to a lesser extent in Alzheimer's disease, the initial pathological involvement centers around the neurons (nerve cells and nerve fibers) with subsequent glial reaction, but no appreciable mesodermic involvement, seems to favor the concept of a close

relationship between pathologic senility and presenility. If one considers that this same pathologic process of progressive atrophy affects all organs in the course of senility, one is tempted to see, in the general metabolic changes related to senility, the common pathogenic factor in the etiology of both senile and presenile psychoses. Genetic factors may, however, govern the premature development of the aging process as well as the structural makeup of the brain as a whole, or of certain portions of it.

This concept of a genetic premature senescence should not however diminish the importance of various exogenous factors—toxic, infectious, or endocrine—which have been considered by some investigators as the pathogenetic mechanisms in senility and presenility. These exogenous environmental, and endogenous metabolic or endocrine or vascular factors are apt to accelerate the inherited process of aging. That a precipitating vascular factor may play an important part in determining some of the localized structural changes in Pick's disease has been hypothesized by several investigators, among whom are Schenk, De Ajuriaguerra, and La-fora. The latter refers also to the possibility of anoxia resulting from circulatory impairment, dependent on gradual occlusion of the internal carotid artery, as reported by Miller-Fisher. However structural vascular structural changes are not essential in order to precipitate presenile changes. As Jervis and Ferraro already reported in 1936, some of their findings, particularly in the white matter, were very suggestive of functional vasomotor imbalance, perhaps a

vasospasm occurring repeatedly and followed in the long run by structural damage, i.e., nerve cell atrophy and their replacement by perivascular gliosis. Why repeated transitory angiospasms should affect only certain areas of the brain, remains to be investigated. Lafora speaks of vascular pathoclisis as playing a role in senile and presenile dementias.

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