AMYLOID DEGENERATION OF THE HUMAN BRAIN FOLLOWING X-RAY THERAPY

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Degeneration of the normal human brain following an over-dose of X-rays has been reported in only a few cases [Fischer and Holfelder (1), Markiewicz (2), Pennybacker and Russell (3), and Scholz and Hsu (4)]. We wish to add two more cases which were observed at the University Hospital.

CASE REPORTS

Case 1. History: C. R. (No. 10718), a white female, aged 42 years, entered the hospital in December, 1940, for the treatment of a basal cell carcinoma of the left temple. She was exposed to 6000 r (as measured in air) in ten treatments within twelve days, with 600 r applied daily at 150 K.v. without filter (half value layer at 0.25 millimeters of copper). The size of the field was 57 x 41 millimeters. The treatment was concluded on January 15, 1941; two months later the tumor had disappeared.

Twenty-two months later, the tumor is said to have reoccurred in the same location; however, the nature of the lesion was not verified histologically, and it is not certain that it was carcinomatous. The left temporal area was subjected to a second series of X-ray treatments in another hospital, consisting of 3600 r at 180 K.v. in twenty-four sessions of 150 r per treatment. The exact size of the field and type of filter used were not reported. The second course of X-ray treatments was concluded on December 5, 1942.

Following the second irradiation, the patient remained well for four years, and then, approximately seventy-one months after the first course of X-ray treatments, she became nervous, complained of general malaise, headaches; she experienced some speech difficulty and impaired vision.

Examination: The skin of the left temple was atrophic, scaling, and red in color. There was no visible tumor in the skin.

She manifested a mild expressive aphasia and showed bilateral papilledema with an elevation of four to five diopters on the right and of four diopters on the left.

Pneumoventriculograms showed marked displacement to the right of the right lateral and third ventricles. Angiograms demonstrated displacement of the left anterior cerebral artery to the right across the midline and downward. The artery was curved around a space-occupying lesion in the left posterior frontal area.

An electroencephalogram indicated a space-occupying lesion, but not neoplastic in nature (Dr. B. K. Bagchi).

Course: A left fronto-temporal osteoplastic craniotomy was performed on July 3, 1946 (Bassett). Skull and dura showed no significant changes. In the left superior and inferior frontal gyri, including the area of Broca, in the mid-portion of the left orbital gyri, and in the mid-portion of the superior temporal gyrus, the brain tissue was purplish-gray in color and well demarcated. The gross appearance of the lesion suggested a glioma. The affected tissue was removed with the exception of an area about 2 cm. square, which apparently ex-

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tended into the basal ganglia. The underlying white matter was edematous. There was no hemorrhage.

Recovery was uneventful, and the patient left the hospital ten days after the operation. When reexamined one year later she appeared to be well; the papilledema had disappeared, leaving no residual atrophy of the optic nerves; visual acuity was normal o.u. and speech was normal.

Histologic observations: In the cortex and in the marginal white matter there were extensive areas of degeneration in which the tissue was amorphous (figs. 1 and 2). It stained pinkish-red with eosin, brownish-red with pikrin-fuxin, bluish-red with methyl-violet, yellow with iodine and a dull brownish-red with congo. In these preparations there were a few scattered compound granular cells and astroglia, but otherwise the tissue appeared amorphous (fig. 2). In the lower layers of the cortex, the vessels were tortuous, enlarged,

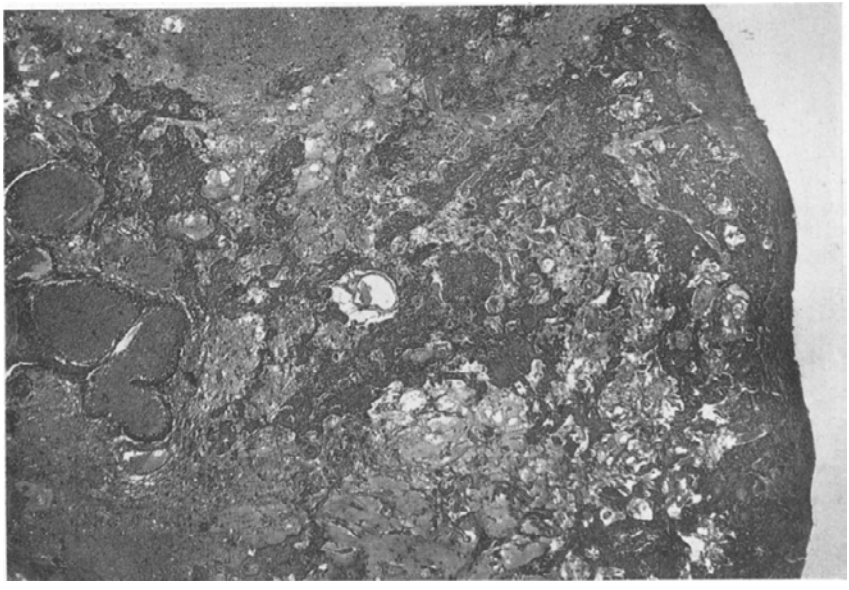

FIG. 1. Numerous amorphous areas (dark) in the cortex surrounded by edematous and spongy tissue (light). In lower layers of the cortex, there are greatly distended and enlarged vessels. Hematoxylin eosin stain; apochromate 16 mm., ampliplane "low".

and distended. The media was thin and homogeneous, and the intima was swollen (figs. 1 and 3).

With the silver-carbonate technique, the apparently amorphous tissue was crowded with proliferated, swollen and edematous astroglia, which formed a dense interlacing network (fig. 4). These elements were undergoing a gradual transformation into an amorphous substance, which increased in density in direct proportion to the disintegration of the glia (figs. 4 and 5).

Extensive areas of chronic edema were present between the islands of the amorphous substance; these areas were braced by a delicate network of astroglia (figs. 1 and 6).

There was little proliferation of the connective tissue originating from the adventitia and the fibers stained bright blue with the azan technique.

The gray matter adjacent to the destroyed area was in the process of degeneration; it contained scattered degenerated neurones, swollen, tortuous and fragmented axis cylinders and remnants of myelin (fig. 7).

Case 2. History: B. B. (No. 11759), a white male, aged 56 years, entered the University

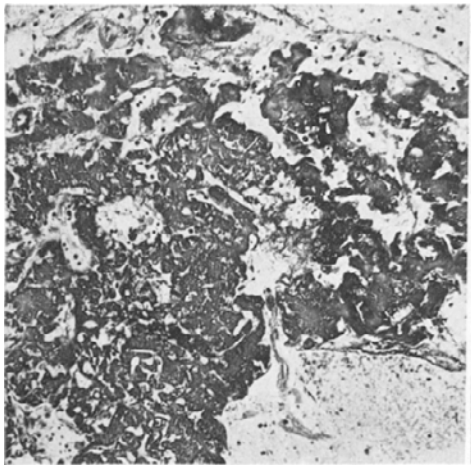

FIG. 2

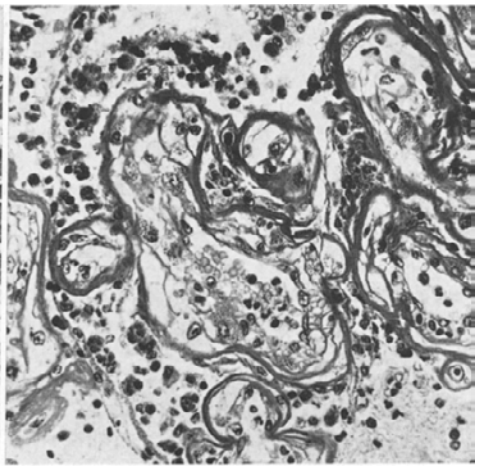

FIG. 3

FIG. 2. Amorphous material in the cortex. Van Gieson's method; apochromate 20 mm., ampliplane "medium."

FIG. 3. Greatly distended vessels with thin and homogeneous walls and proliferated intima; some are partly occluded. Van Gieson's method; apochromate 20 mm., ampliplane "medium."

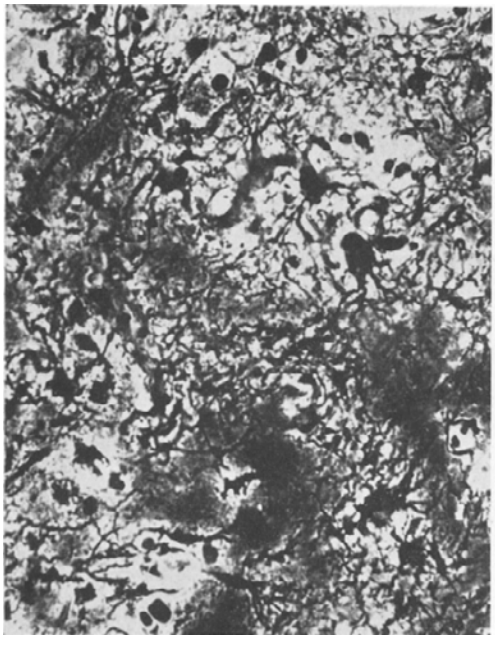

FIG. 4

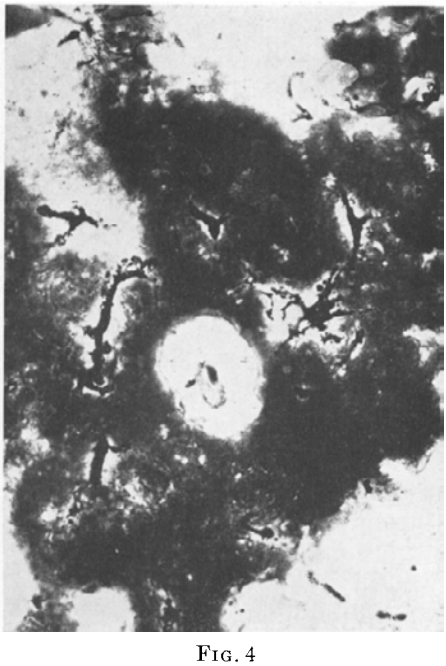

FIG. 4

FIG. 4. Greatly proliferated astroglia undergoing gradual transformation into an amorphous substance. Silver carbonate (Del Rio Hortega) "nucleo-plasmatic" variant; apochromate 20 mm., ampliplane "medium."

FIG. 5. Advanced stage of degeneration of the astroglia with transformation into an amorphous substance. Silver carbonate (Del Rio Hortega); "nucleo-plasmatic" variant; apochromate 20 mm., ampliplane "medium."

Hospital on April 27, 1948, complaining of convulsive seizures, which first occurred eleven months earlier (on June 1, 1947).

Forty months before these attacks began, the patient was treated with X-rays in another hospital for carcinoma of the right parietal region. The neoplasm measured 5 x 6 cm. at the base, had an elevation of 1 to 2 cm., and was of the fungating type. The treatment was carried out in one seance, on January 24, 1944. A dose of 10 S U D was given with a combination of 130 K.v. without filter and 110 K.v. without filter, which corresponded to 3500 r's in air. The tumor healed within two months and repeated examinations failed to show signs of recurrence.

The first convulsive attack began in the left index finger, spread to the elbow and shoulder, and finally became generalized. During the attack the patient became

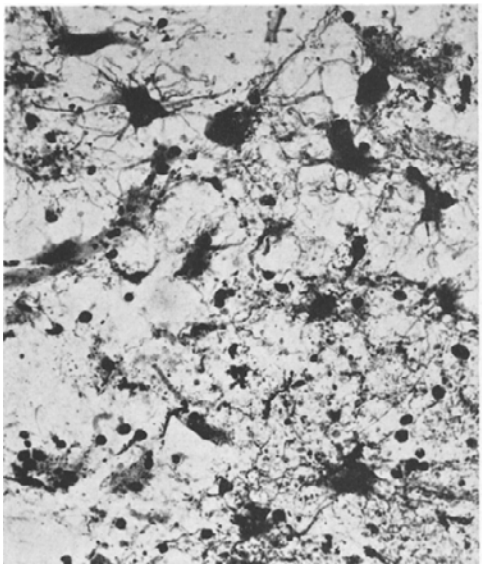

FIG. 6

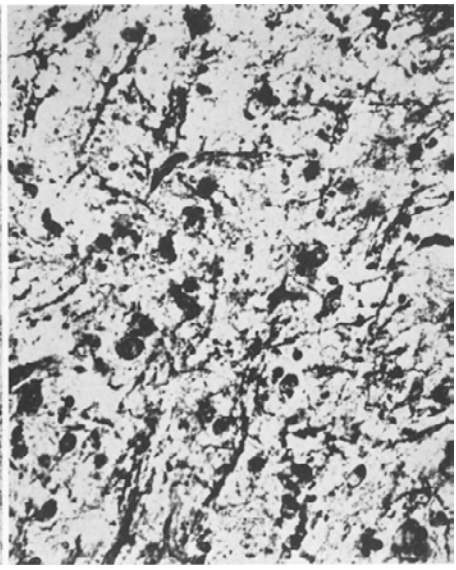

FIG. 7

FIG. 6. Edematous and spongy cortex surrounding the amorphous areas; showing the partly degenerated network of hypertrophic and degenerated astroglia. Silver carbonate (Del Rio Hortega); "nucleo-plasmatic" variant; apochromate 20 mm., ampliplane "medium."

FIG. 7. Degenerated cortex adjacent to the irradiated area with remnants of neurones and fragments of axis-cylinders and myelin. Silver carbonate (Del Rio Hortega); "nucleo-plasmatic" variant; apochromate 20 mm.

unconscious. The convulsions became increasingly frequent, occurred several times daily, and were followed by a temporary paralysis of the left arm.

Examination: The patient was anxious and tense. The strength of the left arm was reduced, but otherwise the neurological status was normal.

All routine laboratory examinations yielded no significant findings. An arteriogram and electroencephalogram indicated a space-occupying lesion in the right motor area.

Course: At operation (Dr. Warren Hastings), the right precentral and postcentral areas were yellow in color and gelatinous in consistency and contained several small hemorrhagic foci. The subcortical white matter was of firmer consistency than normal and was partly hemorrhagic. All of the pathologic tissue was removed with very little loss of blood.

Following operation there developed a complete left hemiplegia, but several days later power of the leg began to return and the patient was able to use the walker; the left arm remained paralysed; the convulsive attacks ceased.

Histologic observations: The microscopic findings were identical with those in Case 1. The dominant change was the formation of an amorphous structure in the affected areas of the cortex (fig. 8). This body stained pink with eosin and pinkish-red with Van Gieson preparations, but all other polychromatic reactions were negative. The origin of this pathologic substance was traced to proliferated astroglia (fig. 9); the blood vessels were distended and some of them were partly occluded. The proliferation of the connective tissue was limited to the adventitia and was very moderate (fig. 10).

The only histologic difference consisted of marked proliferation of the microglia which was visible in the less damaged parts of the cortex, in which there were only small deposits of the amorphous substance. It could not be linked to the amorphous tissue.

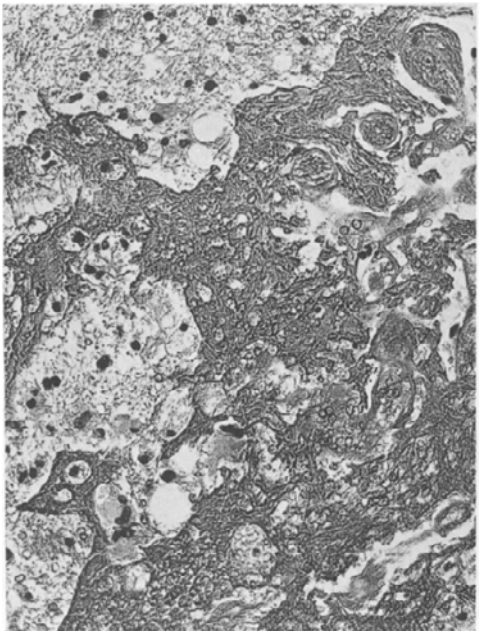

FIG. 8

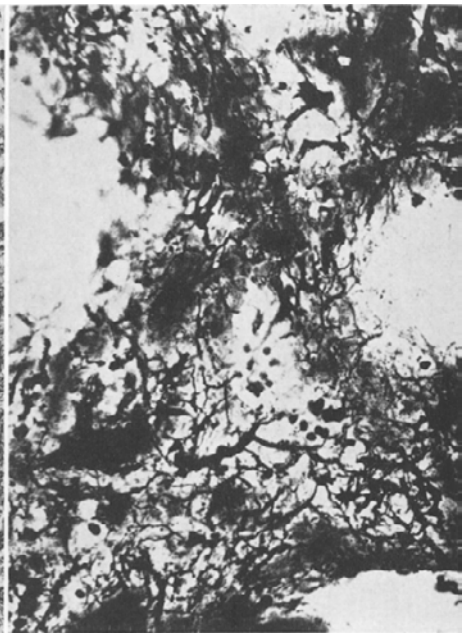

FIG. 9

FIG. 8. Amorphous substance in the affected cortex of Case 2, surrounded by areas of edema. Hematoxylin and eosin stain; apochromate 16 mm., ampliplane "low."

FIG. 9. Proliferated astroglia undergoing transformation into an amorphous substance. Silver carbonate (Del Rio Hortega); "nucleo-plasmatic" variant; apochromate 20 mm., ampliplane "medium."

COMMENT

The dominant histologic finding in our cases and in those recorded in the literature was the formation of an amorphous substance in areas of the brain which were exposed to X-rays. The nature of this pathologic body was studied by a number of investigators. Fischer and Holfelder regarded it as amyloid because this substance stained pinkish-red in Van Gieson preparations, and Markievicz noted a positive congo-red reaction. In our cases the color in the Van Gieson sections was either pinkish or brownish-red and was very similar to that described by Fischer and Holfelder, but all other polychromatic reactions were negative. The indefinite and partly contradictory results of these methods

permitted no conclusion as to the nature of the amorphous substance and its possible relationship to amyloid.

The older histologic methods, including the early silver impregnations, were not sensitive enough to solve the riddle of amyloid, and the old controversy as to its origin was never settled. Virchow (5) considered the amyloid to be a product of destroyed cells, but was unable to provide, in support of his views, the necessary histological evidence. Virchow's theory was challenged by Schmidt (6), who pointed out that it was not possible to trace the amyloid to cells since no cellular activity could be detected in the degenerated tissue. Schmidt regarded the amorphous material, "which was deposited between the tissue structures" as an infil-

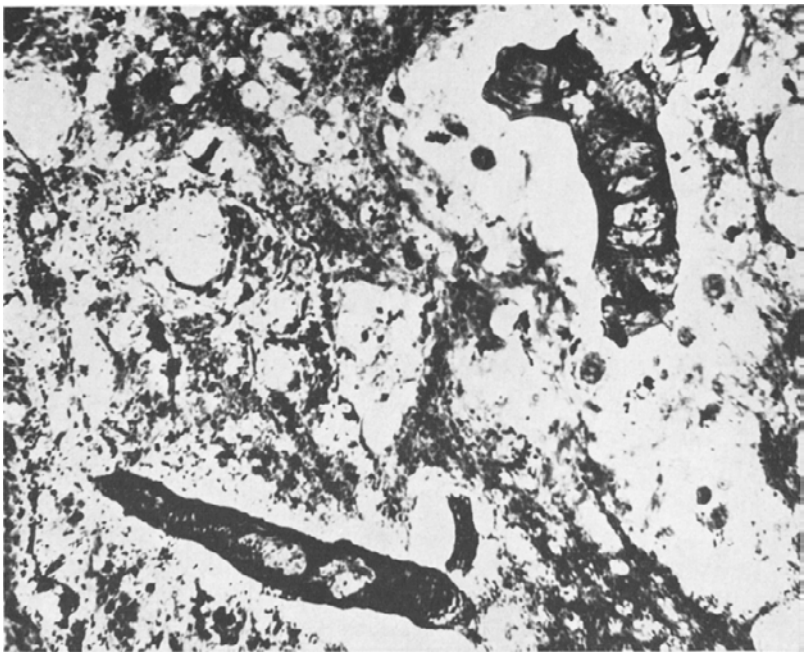

FIG. 10. Two small vessels with moderately proliferated adventitia. Silver carbonate (Del Rio Hortega); "triple" variant; apochromate 20 mm., ampliplane "medium."

tration by products of a pathologic metabolism and not as remnants of destroyed cells. Schmidt's conclusions were generally accepted and still represent the prevailing opinion. These views, however, can no longer be maintained. The introduction of the silver carbonate method by Del Rio Hortega (7) and the subsequent development by that author of the selective methods of histologic examination permits an analysis far beyond the scope of the older procedures.

The application of these techniques in our cases showed that the degenerated tissue in the brain, which appeared amorphous in the older conventional preparations, was in reality the site of an intense cellular activity. This activity consisted of proliferation and hypertrophy of the astroglia which passed through a definite cycle of histologic changes and terminated in the formation of an

amorphous substance. The blood vessels, although distinctly involved, played only a minor part in the formation of the amorphous body; the connective tissue was only moderately active in the first case, and showed hardly any response in the second.

From the results obtained with the silver-carbonate method, it becomes obvious that the amorphous substance in the gray matter was formed in the course of degeneration of astrocytes, i.e., of cells which normally form the matrix of the nervous tissue; it represented the ultimate outcome of a focal response of the irritated tissue and was not the result of a condensation or precipitation of a pathologic material from the tissue fluid or from the metabolism in general, although the amorphous tissue was surrounded by extensive areas of chronic edema.

While the aforementioned findings clarified the histogenesis of the amorphous tissue in the gray matter, it was not possible, in this stage of the investigation, to conclude that this degenerated tissue was related to amyloid, since the histogenesis of the latter still remained obscure. Such a relationship could only be established if it were possible to demonstrate a similar histogenetic mechanism as the basis of amyloid outside of the nervous system.

With the silver carbonate technique, it is possible to demonstrate such a histogenetic mechanism. We had the opportunity to analyze amyloid of the spleen with these methods. Amyloid was present in follicles and in the pulp; all polychromatic reactions were positive, and in all conventional preparations the degenerated areas were amorphous.

With the "triple variant" for the impregnation of the reticulin, the supposedly amorphous areas of amyloid consisted of a dense network of swollen and hypertrophic fibers which originated from the adventitia of the central artery (fig. 11). This network was in some areas so dense and its fibers so greatly swollen that it resembled a fenestrated membrane rather than an adventitial structure (fig. 12). With the increasing hypertrophy, proliferation and swelling of the fibers, their outlines became less distinct, and they partly broke into fragments. However, even in areas of advanced degeneration, the tissue did not appear amorphous, and the fibrous skeleton of the amyloid remained distinctly visible (fig. 12).

With this variant no cells could be seen among the fibers. To investigate the former, the variants 6 and 6A, designed for the study of the reticulo-endothelial system, were used. With these variants, the histologic picture was reversed, and the fibrous network appeared amorphous, but it was honeycombed by an interlacing network of mobilized hypertrophic reticulo-endothelial cells (figs. 13 and 14). These irregularly shaped, bizarre elements possess very numerous processes which enabled them to establish a continuous network, which penetrated the degenerated fibers. Frequently, the reticulo-endothelia were so numerous and so closely spaced that the amyloid seemed to consist of cells only (figs. 13 and 14).

The cellular activity in the foci of amyloid represented only a transient phase of the degeneration, and the cells gradually broke into fragments which mingled with the hypertrophic fibers, giving rise to an amorphous substance (fig. 15).

In analyzing the histologic picture in the brain and in the spleen, it is clear that

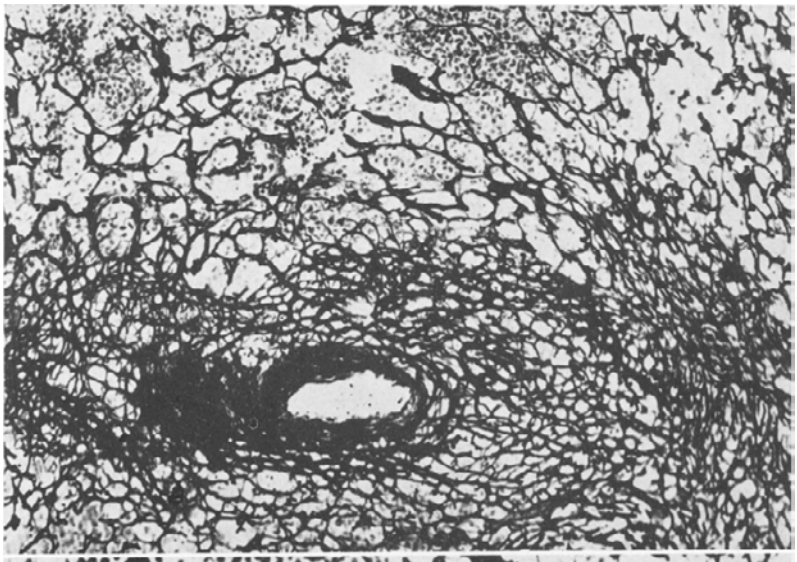

FIG. 11

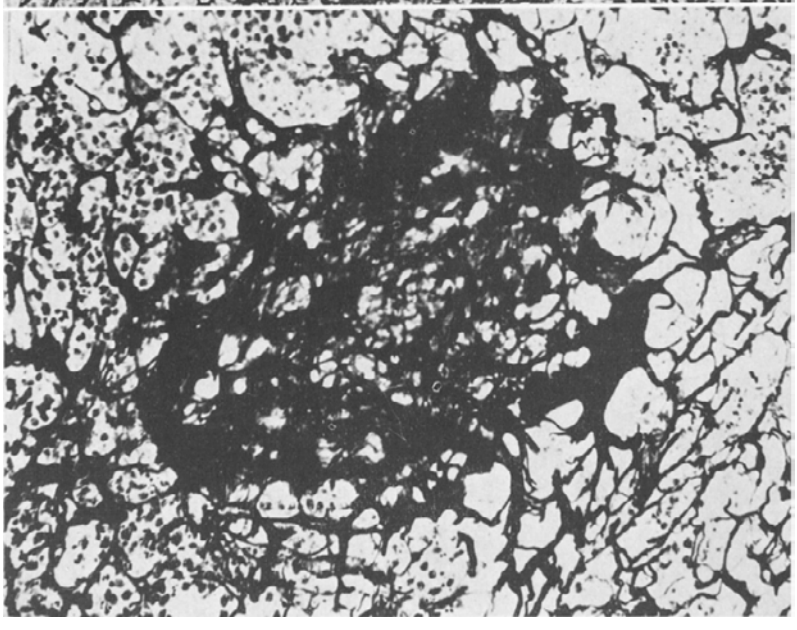

FIG. 12

FIG. 11. Follicular amyloid showing advanced proliferation of its fibrillary skeleton. Silver carbonate (Del Rio Hortega); "triple" variant; apochromate 20 mm., ampliplane "medium."

FIG. 12. Greatly proliferated, nearly homogeneous and partly fragmented fibrillary skeleton of degenerated follicle. Silver carbonate (Del Rio Hortega); "triple" variant; apochromate 20 mm., ampliplane "medium."

the pattern is basically similar in both organs: the degeneration is the result of a local response of the tissue involving cells and fibers. The embryologic origin of the tissue determines the type of elements which react and give rise to "amy-

loid." Consequently the amorphous tissue in the brain is predominantly of ectodermal origin and the reacting cell is the astrocyte. In the spleen it is of

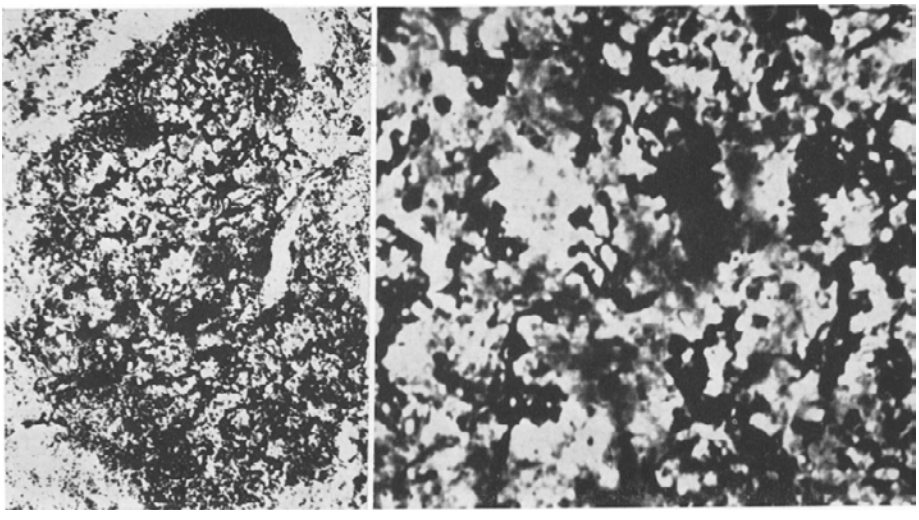

FIG. 13 FIG. 14

FIG. 13. Interlacing network of reticulo-endothelial cells; follicular amyloid. Silver carbonate (Del Rio Hortega); variant 6; apochromate 20 mm., ampliplane "medium."
FIG. 14. A sector in Figure 13 enlarged six times.

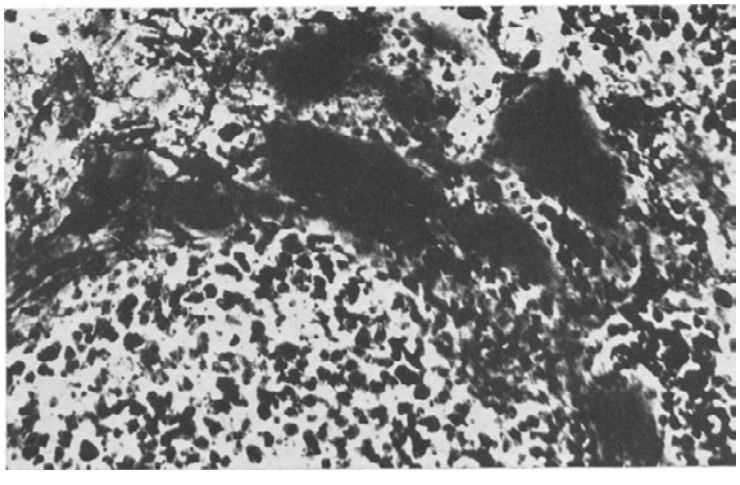

FIG. 15. Perifollicular amyloid in advanced state of degeneration; note moderate amounts of hypertrophic reticulo-endothelial cells in advanced state of disintegration. Silver carbonate (Del Rio Hortega); variant 6; apochromate 20 mm., ampliplane "medium."

mesodermal origin and the reacting elements are connective tissue fibers and the reticulo-endothelial system. Regardless of origin, it is always the supporting tissue which responds and not the parenchyma. The cycle of histological events

is characterized by proliferation, swelling, and hypertrophy of cells and fibers, and terminates with the transformation of the reacting cells and structurel into an amorphous substance.

In view of so great a histogenetic and patho-histologic similarity, the degeneration in the brain and in the spleen must be considered as closely related biologic phenomena, which belong to the group of "amyloids." The difference in polychromatic behavior is only of minor importance. These reactions are mainly characteristic for amyloid of mesodermal origin and are therefore almost always negative in the nervous tissue.

The histologic evidence outlined above confirms the theory of Virchow that the "amyloid" is a produce of degenerated cells.

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