XANTHOMA AND CHOLESTEROL GRANULOMA OF THE
CHOROID PLEXUS

REPORT OF THE PATHOLOGICAL ASPECTS IN 29 CASES*

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Only 9 cases of xanthoma or cholesterol granuloma were recorded in the
literature prior to the report of 20 cases of xanthoma of the choroid plexus by
Wolf, Cowen, and Graham (26), of which 1 (their case 8) was published separately
(25). Cholesterol granuloma in the ventricular system of man was first described
by Blumer (2) under the term "cholestatomatous endothelioma." Other terms
employed were "cholesteatoma" (4, 5, 17), "xanthoma" (16, 18, 19), and "angio­
reticuloma" (7). Dandy (6) regarded the lesion in his Case 3 as "perhaps [a]
tumor of embryonal cells from which epithelium of the choroid plexus or
ependyma is derived," but to us the lesion appears to be a clear-cut cholesterol
granuloma. Stern and Levy (21) reported the presence of a cholesterol-containing
tumor of the IIIrd ventricle, but we doubt that it is of the same category as those
reported in this paper. Henschen (13) distinguished between xanthomas and
cholesterol granulomas of the choroid plexus, and Stewart (22) referred to xan­
thomas, but neither of these authors reported individual cases. Wolf, Cowen,
and Graham (26), on the other hand, did not deal with xanthoma and cholesterol
granulomas separately in their series, but did describe cholesterol granuloma in
some of their xanthomas. Dunn and Kernohan (7a) found foam cells and evi­
dence of cholesterol in degenerating parts of the connective-tissue core of the
plexus, whereas cholesterol clefts were rare. In 24 cases of cholesterinosis of the
choroid plexus, Trelles, Aranibar and Zevalloz (22a) described 3 histological
forms: (1) Cystic, in which there was diffuse hyaline material which contained
birefringent and clear zones, with reactive fibroblastic reaction around stored
calcium and foci of foam (xanthoma) cells, (2) Nodulo-cystic, similar to (1) but
with a predominance of foam cells with cholesterol clefts, and (3) Nodular,
characterized predominantly by foam cells, the central area of which contained
cholesterol clefts with connective tissue and other reaction in such quantity as to
constitute a cholesterol granuloma.

The present article deals with 9 cases of xanthoma and 20 of cholesterol
granuloma of the choroid plexus.

GROSS FEATURES

Xanthoma (9 cases): The xanthomas were characterized by well-demarcated, yellow,
opaque, soft, single or multiple streaks, plaques, discs, or nodules located superficially

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TABLE 1
Clinical and Pathological Data on 9 Cases of Xanthoma of the Choroid Plexus

<table>
<thead>
<tr>
<th>Case No.</th>
<th>AFIP No.</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>Number</th>
<th>Lateral Ventricle</th>
<th>Size (mm.)</th>
<th>Pathological Features</th>
<th>Arteriosclerosis</th>
<th>Blood Pressure</th>
<th>Cause of Death</th>
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Fig. 1. Gross appearance of cholesterol granulomas in the glomus of the choroid plexus. A. AFIP Acc. 540358. Next to the cholesterol granuloma, which is an opaque white, is a translucent cyst of the choroid plexus; X 6. (This case is not included in Table 2.) B. Case 25. Characteristic cholesterol granuloma dissected free from choroid plexus; X 2.
### TABLE 2
Clinical and Pathological Data on 20 Cases of Cholesterol Granuloma of the Choroid Plexus

<table>
<thead>
<tr>
<th>Case No.</th>
<th>AFIP No.</th>
<th>Number</th>
<th>Lateral Ventricle</th>
<th>Pathological Features</th>
<th>Arteriosclerosis</th>
<th>Blood Pressure</th>
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in the choroid plexus of the lateral ventricles, usually the glomus. Characteristic descriptions in individual cases were: “thin-walled gray cysts which show concave caps of sharply circumscribed dull yellow tissue covered with choroid epithelium” and “dull yellow disc-like ovoid plaques of opaque material on the surface of the choroid plexus.” In the 4 cases
in which size was stated, the xanthomas varied from 0.2 to 0.9 cm., with an average diameter of 0.4 cm.

Table 1 contains data on the xanthomas in the respective cases. In all of the 9 cases the xanthomas were in the choroid plexus of the lateral ventricle. In 4 they were in the caudal part of the body of the lateral ventricle and were bilateral and multiple on each side, in 2 they were single, and in the other 3 their exact position in the plexus was not stated.

Cholesterol Granuloma (20 cases): The cholesterol granulomas were firm, ovoid, single or multiple nodular masses located in the choroid plexuses of the lateral ventricles (fig. 1). They were yellow, brown, or yellow-red. The cut surfaces were firm, yellow or yellow mottled with red, and frequently gritty to the touch. In 11 cases in which size was stated, the granulomas varied from 2 cm. to 0.3 cm. in diameter, with an average of 1.4 cm. (table 2). In 1 case, 2 pedunculated granulomas arose from the choroid plexus (case 10).

Table 2 contains data on the cholesterol granulomas. In 4 cases they were located in the region of the glomus, while in the other 11 their exact site in the plexus of the lateral ventricle was not stated. In the 5 remaining cases the location of the cholesterol granuloma is unknown. None was present in the IIIrd or IVth ventricle. The granulomas were bilateral in 7 cases, with 1 or more in the choroid plexus of 1 side or both, and they were unilateral

Fig. 2. Characteristic xanthoma. Hematoxylin-eosin stain. A. AFIP Acc. 213498. Psammoma bodies are present at the periphery of the mass; \( \times 48 \). B. AFIP Acc. 213493. The xanthoma cells have vacuolated clear cytoplasm and an eccentric nucleus; \( \times 305 \). (This case is not included in Table 1.)
Fig. 3. Case 9. Xanthoma of choroid plexus. A. Stained with Sudan IV to show lipid substance; X 12. B. Stained with Sudan IV and photographed at half extinction under the polarizing microscope to show combination of sudanophilia and anisotropism; X 75. C. Same as in B, but with the nicol prisms at complete extinction to show anisotropism of the crystals; X 75.
in 5. They were multiple in 5 cases, and single in 7. In 8 of the 20 cases neither the side on which the lesions were located nor their number was stated.

**HISTOPATHOLOGICAL FEATURES**

*Xanthoma:* Sections stained with hematoxylin-eosin showed closely approximated xanthoma cells extending, as a rule, to the region just beneath the collagenous stroma sup-

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**Fig. 4.** Case 9. Region of choroid plexus in which arachnoid cells appear to be developing into xanthoma cells. Hematoxylin-eosin stain; × 265.

**Fig. 5.** Case 11. Cholesterol granuloma with xanthomatous areas. Note the distended choroid plexus and groups of cholesterol crystals in a matrix of xanthoma cells. The round black particles are psammoma bodies. Hematoxylin-eosin stain; × 8.
Fig. 6. A, B and C, Case 20. A. Cholesterol granuloma with hemorrhage (dark areas) and many cholesterol clefts; X 10. B. Detail of A. Abundant cholesterol clefts in areas of recent hemorrhage; X 48. C. Cholesterol clefts surrounded by intact red blood cells, hemoglobin, and young foreign-body giant cells; X 300. D. Case 15. Cholesterol crystals presumably developing in an area of hemoglobin deposition; X 48.

porting the choroidal epithelium (fig. 2A). The xanthomas were permeated by capillaries. The xanthoma cells tended to be spherical, and they had a distinct cell membrane, abundant finely granular or vacuolated cytoplasm, and a small, eccentric, oval or rounded nucleus without a visible nucleolus (fig. 2B). Cystic areas were occasionally present within the xanthoma. As demonstrated with Sudan IV, the xanthoma cells were sudanophilic (fig. 3A). The polarizing microscope showed clusters of anisotropic, elongated, sharply pointed crystals in the xanthoma cells (figs. 3B and 3C). The xanthomas contained no cholesterol
crystals, foreign-body giant cells, bilirubin, hemosiderin, or hemorrhage. Arachnoid cells were observed in the xanthoma, and in this intermediate stage, forms between arachnoid and xanthoma cells were observed (case 9) (fig. 4).

**Cholesterol Granuloma:** Sections of the affected choroid plexus stained with hematoxylin-eosin showed, in a loose fibrous stroma, groups of cholesterol-crystal clefts (fig. 5) surrounded by foreign-body giant cells. Foci of hemosiderin-filled macrophages and numerous red blood cells were often found in the stroma. Beneath the epithelium of the choroid plexus was a zone of dense connective tissue which contained, as a rule, numerous psammoma bodies. The overlying papillary choroidal epithelium was normal in most cases, but was atrophic in a few. Hemorrhage into the stroma, noted in 18 of our 20 cases, varied from slight to severe (figs. 6A and 6B).

Xanthoma cells were present in the cholesterol granulomas in all of the 20 cases. They varied in quantity, being sparse to abundant, and were situated either within the stroma in small groups or at the periphery of the lesion. In some of these cases the lipid in the cells

![Image](http://jnen.oxfordjournals.org/)

**Fig. 7.** A. Case 20. Lakes of bilirubin in cholesterol granuloma; X 75. B. Detail of A. Bilirubin is in the form of burrs or is confluent. The upper part of the photograph shows foreign-body giant-cell reaction to burrs of bilirubin; X 300.
Case 20. Cholesterol granuloma with deposition of calcium and iron salts on collagenous fibers. Intact red blood cells are present in the stroma; × 395. (Stains performed were the von Kossa for the identification of phosphates, alizarin for calcium, and Perls’s for iron salts.)

was scanty, and the cytoplasm appeared to be clear rather than vacuolated. When cystic degeneration or calcification of the stroma had occurred, the xanthoma cells tended to be sparse. Cholesterol clefts were often abundant in regions of hemorrhage (fig. 6B). Some of the clefts were surrounded by a zone of hemoglobin and partially lysed red blood cells, peripheral to which were young foreign-body giant cells (fig. 6C). Other clefts were surrounded only by hemoglobin, suggesting that cholesterol crystals had developed from hemoglobin (fig. 6D). In 1 instance, foreign-body giant cells contained asteroid bodies (case 12).

Brilliant orange bilirubin (hematoidin) was present in the form of spiculated burrs or separate rhomboid crystals in 5 cases (table 2), and in 2 cases in particular the burrs of bilirubin crystals were confluent and appeared as lakes of bilirubin (figs. 7A and 7B). Collagenous strands were occasionally stained yellow with bilirubin. Bilirubin crystals and iron-encrusted collagenous fibers usually provoked a foreign-body giant-cell reaction. In 1 instance deposits of iron and calcium on collagenous fibers appeared as segmented rods resembling septate hyphae of fungi (fig. 8). Old lesions were fibrotic, showed distortion of cholesterol clefts, sparse atrophic foreign-body giant cells, and dystrophic calcification in cholesterol-bearing areas (fig. 9). Occasionally in such lesions there were also areas of recent hemorrhage which contained cholesterol clefts. In 1 case small foci of heterotopic bone formation were observed (case 24).

Arachnoid cells were found in 10 cases, and in 1 of them intermediate forms between arachnoid and xanthoma cells could be identified (case 12).

**DISCUSSION**

*Age, Sex, and Frequency:* Giampalmo and Viviano (10) found cholesterol granulomas in 21 of 300 autopsies, an incidence of 7 per cent. The granulomas
Fig. 9. Case 22. Evolution of cholesterol granuloma. A. To the left is a zone of fresh hemorrhage in which cholesterol crystals are probably forming; in the upper center a lesion of intermediate age with cholesterol clefts in a fibrotic stroma, and to the right, an older calcified cholesterol-bearing area; × 12. B. Enlargement of field illustrated in A. Calcified cholesterol-bearing area in an old cholesterol granuloma. Foreign-body giant cells are sparse or severely atrophic; × 48.

were most frequent in the seventh decade; none was seen in individuals under 30 years. There was no difference in sex incidence in their cases. In the 452 brains studied by Trelles, Aranibar and Zevalloz (22a), cholesterinosis of the choroid plexus was observed in 24, an incidence of 5.3 per cent. In 20 cases of xanthoma, reported by Wolf and associates (26), the youngest patient was 40 years of age, and the oldest, 79 years. In our series, both xanthoma and cholesterol granuloma were mainly in military personnel, and thus the age and the sex incidence are not representative of the incidence in the general population. Ages of the individuals in our cases of xanthoma varied from 4 to 54 years, with an average of 38; and in cholesterol granuloma, from 19 to 80 years, with an average
of 48 (tables 1 and 2). The general conclusion to be reached is that both xanthoma and cholesterol granuloma tend to be more common in older than in younger individuals, with cholesterol granuloma occurring about a decade later than xanthoma.

Wolf and associates (26), in a series of 1,181 consecutive autopsies, found 20 in which xanthoma was present, an incidence of 1.6 per cent. In 100 autopsies, Henschen (13) observed 3 xanthomas and cholesterol granulomas, mainly in older persons. The files of the Armed Forces Institute of Pathology contain 43 examples of xanthoma or cholesterol granuloma of the choroid plexus, but because of lack of material or adequate records we are able to present only 29 in this report.

Pathogenesis: Theories as to the pathogenesis of cholesterol granuloma and xanthoma are rather numerous. According to Haeckel (11), cholesterol granuloma forms as a consequence of degeneration of tissue, for, in a discussion on the pathological anatomy of the choroid plexus, he commented: "Fatty degeneration is similar to that found in chronic arteritis and is frequently complicated by calcification or by softening and the formation of cholesterol" (translated). Haeckel also remarked: "Pigment degeneration [of the choroid plexus] is not infrequent and represents probably the residual of small hemorrhages that occur in the easily-torn, delicately-vascularized choroid plexus. The pigment is not diffuse but occurs in the form of sharply circumscribed pigment granules."

At the turn of the present century, Blumer (2) expressed the opinion that xanthomatous cells are derived from proliferated endothelial cells lining perivascular lymph spaces. He mentioned that cholesterol crystals were most common in hemorrhagic areas and that the cholesterol was derived from xanthoma cells which had broken down as a consequence of hemorrhage. Pinkus and Pick (19) also favored the view that the cholesterol appears in the tissue as the result of degeneration of xanthoma cells and that cholesterol acts as a foreign body, inducing the formation of granulation tissue in which foreign-body giant cells develop. In our cases we saw very little hemorrhage in xanthomatous areas. As a rule, xanthoma cells were located at the periphery of the choroid plexus at or near the edge of the hemorrhage, or they were found in fibrous septae separating cholesterol-bearing lakes of blood. Cholesterol crystals seemed to develop in areas of lysed red blood cells, not in the xanthomatous areas. In discounting Blumer's theory, Manlove and McLean (17) suggested that the initial event in the formation of cholesterol granuloma was probably a bleblike hemorrhage between "folia" of the choroid plexus.

In a discussion of the pathogenesis of cholesterol granulomas in the horse, Wehrbein (23) expressed the opinion that an edematous process occurred initially in the choroid plexus, followed by an "undernourishment" of the tissue which resulted in degenerative vascular changes, formation of anisotropic substances in the cytoplasm of xanthoma cells, and ultimately the formation of cholesterol crystals. Joest (14), who likewise studied cholesterol granulomas in the horse, felt that lipids derived from the brain were carried to the choroid plexus by the blood, where lipid-containing cells formed, and that lysis of these cells liberated lipids which crystallized. Pinkus and Pick (19) believed that xanthoma cells contain cholesterol esters derived from circulating blood. Stewart (22) suggested
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that xanthomas of the choroid plexus are related to hypercholesterolemia. In a report of 1 case of xanthoma of the choroid plexus, Pearson (18) adhered to the view of Stewart (22), although no blood-cholesterol determinations were done.

In this connection, diabetes mellitus has been considered an etiological factor in the development of xanthomas in the choroid plexus because of the presence in that disease of hypercholesterolemia and, occasionally, of cutaneous xanthomas. Liber and Lisa's (16) patient had diabetes, and these authors were firmly convinced that a relationship exists between diabetes and xanthoma of the choroid plexus. Blood cholesterol determinations were not done, however. Diabetes was present in only 1 of the 20 cases of xanthoma of the choroid plexus reported by Wolf and his associates (26). There was no case of diabetes in our series. The consensus is that diabetes mellitus is not an etiological factor.

Wolf and associates (26) considered the possibility that arteriosclerosis may be a factor in the causation of xanthoma of the choroid plexus, but concluded that no direct relationship exists between the two. They were the first to report blood-cholesterol values, and found them normal in all 4 of 20 cases in which determinations were done. Blood-cholesterol values were recorded in only 1 of our cases (case 14), and they were normal. Giampalmo and Viviano (10) found generalized arteriosclerosis in 9 of their 21 cases, and they emphasized that in the general run of autopsy cases in which arteriosclerosis was a feature, xanthoma and cholesterol granuloma were relatively rare. Generalized arteriosclerosis was not severe in any of our cases of xanthoma, but was moderate in 3, slight in 4, and absent in 2. In our cases of cholesterol granuloma, arteriosclerosis was severe in 3 cases, moderate in 6, slight in 4, and absent in 5. No information was available in the remaining 2 cases. To us it appears that generalized arteriosclerosis is unrelated to the formation either of xanthoma or of cholesterol granuloma of the choroid plexus. Nor was arterial hypertension a feature in our cases.

Wolf and associates (26) were able to trace intermediate forms between arachnoid cells and fully developed xanthoma cells in the connective-tissue stroma of the choroid plexus. In our series arachnoid cells were found in 11 cases, and there appeared to be transition to xanthoma cells in 2 of these. Indirect support for the theory of Wolf and associates is the observation of Krainer (15) that xanthoma cells and cholesterol crystals can develop in meningothelial meningioma, a neoplasm believed to be derived from arachnoid cells. We examined a section of meningioma furnished by Krainer and found a clear-cut transition from meningioma cells to xanthoma cells; we also noted that cholesterol crystals had formed in the xanthomatous foci without foreign-body cell reaction. Henschen (13) expressed the opinion that xanthoma and cholesterol granuloma are closely related as to origin and that cholesterol granuloma arises in a xanthoma in which cholesterol crystals have formed and have induced a foreign-body giant-cell reaction. Since xanthoma cells were present in all of our cases of cholesterol granuloma, we, too, believe that a definite relation exists between xanthoma and cholesterol granuloma. Judging from the lack of choroid-plexus involvement in cerebral xanthomatosis (8), choroid-plexus xanthoma and cerebral xanthomatosis appear unrelated.

We believe that the presence of cholesterol can be explained on the basis of
hemorrhage into a xanthoma. Our hypothesis in connection with cholesterol granuloma is that after hemorrhage has occurred into the stroma of the choroid plexus, red blood cells lyse and liberate hemoglobin, which breaks down into heme and globin, and that heme is converted to iron-containing hematin and bilirubin. The cholesterol may be derived from the stroma of red blood cells and possibly from blood plasma. According to Hawk, Oser, and Summerson (12), red blood cells contain about 65 per cent water and 35 per cent solids. Of the solids, hemoglobin comprises 32 of the 35 per cent, while the remaining 3 per cent consist of stroma of the red blood cell, which is composed of protein, phospholipid, and cholesterol. Almost all the components present in a cholesterol granuloma could have their origin in the red blood cell; these are hemoglobin, hemosiderin, cholesterol, and bilirubin. Another possible source of cholesterol is plasma, which contains 2 mgm. of cholesterol per 1 cc. of whole blood. It is significant that free red blood cells or hemorrhage were present in 18 of our 20 cases of cholesterol granuloma.

It seems a general rule that cholesterol granulomas are prone to develop following hemorrhage into tissues that have no lymphatics, i.e., in tissues having a reduced capacity to remove the products of disintegrated red blood cells. In this connection, Ayres and Cameron (1) have reported 4 cysts of the os calcis in which there were hemorrhage, cholesterol crystals, foreign-body reaction, and hemosiderin-filled macrophages. Shuman (20) has observed that cholesterol granulomas form as a sequel of hemorrhage into the vitreal chamber of the eye. Neither the choroid plexus nor the bone marrow nor the eye has lymphatics. Ordinarily, when hemorrhage occurs in tissue, the products of the breakdown of red blood cells are easily removed. However, in the choroid plexus, where lymphatics are lacking, such products are mobilized with difficulty. For example, bilirubin, which is readily diffusible in most tissues, is only slowly excreted into the cerebrospinal fluid. Bilirubin was present in 5 of our 20 cholesterol granulomas. The theory that hemorrhage is an etiological factor in the formation of cholesterol granuloma is not new, for it has been entertained by others (2, 17). Wolf and associates (26) did not consider this possibility, but did mention that hemorrhage was present about cholesterol clefts in 2 of their 20 cases.

In 2 of our cases we could confirm the observation of Wolf and associates (26) that xanthoma cells form from arachnoid cells. A hypothesis that requires consideration and more study is that of Pinkus and Pick (19), that lipids in xanthoma cells are derived from circulating blood. The exact nature of the lipids present in the lesions is beyond the scope of this paper, and clarification must await further histochemical studies.

Pathology: The microscopic appearance of xanthomas and cholesterol granulomas in our cases conforms closely to that described by Wolf, Cowen, and Graham (26). Differences in regard to cholesterol granuloma may be explained on the basis that these authors were dealing mainly with xanthomas. They did not separate their cases into xanthoma and cholesterol granuloma, nor did they state the number of cases in which cholesterol was observed. Whereas they found no foreign-body reaction, we found the reaction in all 20 of the cases in which
cholesterol crystals were present. Their Figure 7 showed calcification, cholesterol clefts, and fibrosis, but no giant-cell reaction. In old cases of cholesterol granuloma with calcification, the foreign-body giant cells may disappear. They found hemorrhage around cholesterol crystals in 2 of their 20 cases, while we observed hemorrhage or red blood cells around cholesterol crystals in 18 of our 20 cases of cholesterol granuloma. In cases of xanthoma, we found no hemorrhage, hemosiderin-filled macrophages, or bilirubin.

Intermittent hemorrhage as a factor in the development of cholesterol granuloma was particularly notable in our Case 22. There were foci of recent hemorrhage that contained newly-formed cholesterol crystals without foreign-body giant-cell reaction, another intermediate focus composed of cholesterol clefts with foreign-body giant-cell reaction, and still another older focus with a heavily calcified cholesterol-bearing area which contained atrophic giant cells. Because of the intermittent hemorrhage, the evolutionary stages of the lesion could readily be traced. De Vecchi and Patrassi (7), too, noted that hemorrhagic foci in their case of cholesterol granuloma were of different ages.

The presence of Gamma-Gandy bodies in 1 of our cases (case 20) confirms the observation of them by de Vecchi and Patrassi (7). These bodies, also known as “siderotic nodules,” represent a deposition of iron and calcium in the form of rod-shaped, anisotropic structures which resemble the hyphae of fungi. These structures are indicative of old hemorrhage and are characteristically found in hemorrhagic areas in the spleen in Banti’s syndrome.

An incidental change in 1 of our cases of cholesterol granuloma was heterotopic bone formation. To our knowledge, only 5 instances of heterotopic bone formation in the choroid plexus have been previously reported in the literature. In a study of the choroid plexus from 65 insane individuals, Finlay (9) found osteoid tissue with haversian systems in 1. Will (24) described ossification of the choroid plexus of the lateral ventricle in a 70-year-old man. In the right lateral ventricle of a 45-year-old imbecile woman, Bonnet (3) observed an osseous mass with haversian systems which nearly doubled the size of the ventricle.

Clinical Aspects: The lesions in our cases as well as those of Wolf and associates (26) were without clinical significance, all being found incidentally at autopsy. We know of no case in man, either of xanthoma or of cholesterol granuloma, in which clinical symptoms could be ascribed to the lesions. Cholesterol granulomas may, however, be symptomatic in horses. Henschen (13) suspected that cholesterol granuloma of the choroid plexus in the human case reported by de Vecchi and Patrassi (7) was symptomatic, but in checking this case report we are not convinced that such a relationship existed.

SUMMARY AND CONCLUSIONS

Pathological and some clinical aspects of 9 cases of xanthoma and 20 cases of cholesterol granuloma of the choroid plexus in man are reported. Our 29 cases raise the total reported in the literature to 58. Bilirubin within the lesions was noted in 5 of the cases, heterotopic bone formation in 1, and Gamma-Gandy bodies in 1.
The hypothesis that hemorrhage into the choroid plexus is the most important etiological factor in the development of cholesterol granuloma is supported and extended. The development of xanthoma and cholesterol granuloma in the choroid plexus does not appear to be related to diabetes mellitus, hypertension, or arteriosclerosis.

REFERENCES