Lipid Keratopathy and Atheroma

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Lipid plaques in corneas of patients with lipid keratopathy, in corneas of hypercholesteremic rabbits and in the arteries of man and the hypercholesteremic rabbit are described. An interesting and thought-provoking analogy is drawn between the plaques that can be seen and followed in the eye during life with the more occult plaques of blood vessels in atheromatosis.

THE purpose of the present paper is to point out certain similarities in fatty plaques of the cornea and of blood vessels, both in man and in hypercholesteremic rabbits, and to suggest a common pathogenesis. The following résumé is based on a clinicopathologic study of approximately a dozen cases of lipid plaques in the human cornea, approximately the same number in the rabbit cornea, and a pathologic study of atheromata in man and in the experimental animal.*

The fatty plaque in the human cornea is of a specific type and comprises a separate entity. It develops, often precipitously, in or adjacent to an area of abnormal vascularity. The fat may appear during the stage of neovasculogenesis in association with an active keratitis, or it may develop in an otherwise white and quiet eye, years after the keratitis. In the former case the fat is apt to assume a fan-shaped distribution in advance of the vascular arcade, while in the latter case it is likely to be disk-shaped and situated in the immediate area of the blood vessels (figs. 1 and 2). Moreover it is usually reversible when it occurs in a swollen cornea, that is, during an active keratitis, whereas it is usually permanent and stationary when it occurs in a compact cornea. Although associated with abnormal vascularity, the development of the fatty plaque is not necessarily associated with reactivation of the initial inflammatory process (it is often interpreted as a dystrophy) and its only symptom other than a cosmetic one is reduced vision.

While the foregoing description is that of a typical case, variants are common. Thus, when the fat forms in a cornea that has been diffusely vascularized, there will be a correspondingly diffuse inundation with fat, instead of the plaque-like distribution that is characteristic of localized vascularity. Another variant is that in which the fat is deposited in a cornea having a conspicuous arcus senilis (fig. 3). It is then difficult to tell where the arcus ceases and the new deposit of lipid begins.

It is not always possible to determine from the literature whether the foregoing entity or something else is being described. However, instances of it have probably been described under the following clinical headings: fatty dystrophy of the cornea,[1] dystrophia adiposa corneae,[2–4] adiposis of the eye,[5, 6] xanthomatosis,[2, 7, 8] lipin interstitial keratitis,[9] lipidosis corneae,[10] and secondary steatosis.[11] The multitude of names indicates the diversity of interpretations that have been attributed to the process. We shall call it simply lipid keratopathy, realizing that this does not adequately distinguish it from other fatty changes in the cornea, such as arcus senilis or true fatty dystrophies, if such exist.

Several observers have suggested a relation of this lipid keratopathy to hypercholesteremia[8, 12, 13] or to generalized xanthomatosis,[14]

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*Cholesterol was added to the rabbit chow, and feeding continued for periods of 6 to 12 months. Blood cholesterol levels reached 1 to 2 Gm. per 100 ml.

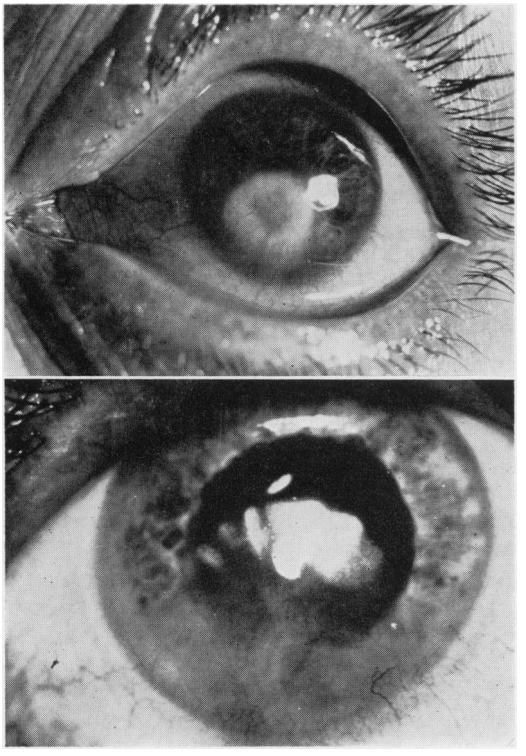

FIG. 1 *Top.* Lipid keratopathy forming a disk-shaped plaque, from a 48-year-old woman who had a corneal ulceration and considerable residual interstitial vascularization. Approximately 2 months after ulceration the dense opacity developed in all layers of stroma but most especially in deeper layers. No subsequent change noted over several months. Noteworthy was a blood cholesterol level of 500 mg. per cent and a fatty acid level of 627 mg. per cent.

FIG. 2 *Bottom.* Lipid keratopathy forming a fan-shaped plaque in advance of the vascular arcade in a 61-year-old man who had had a bullous keratopathy and sclerokeratitis thought to be part of a rosacea keratitis. Considerable interstitial vascularization of the lower portion of the cornea. During neovascularization patient precipitously developed arcuate opacity (presumed fat) just in advance of vessels and separated from them by a clear zone (*light reflex superimposed*). With further ingrowth of vessels into swollen cornea, dense opacity disappeared, leaving only scintillating particles, presumed cholesterol.

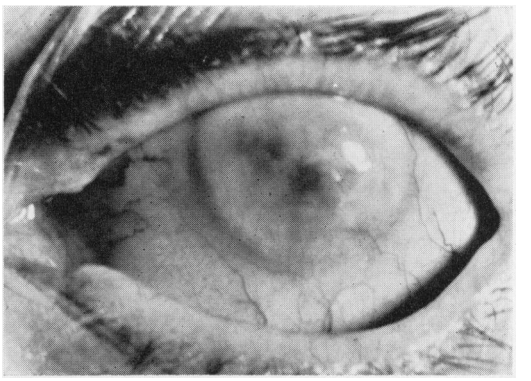

FIG. 3. Diffuse lipid keratopathy in a patient who had had an interstitial keratitis as a child leaving residual vascularization. Recently cornea has become opaque. Extensive deposition of material, believed fat, having a ring-like distribution suggestive of an extensive arcus senilis. Other eye had less vascularization and only a mild arcus senilis.

and at least one observer has suggested a relation to atheromatosis.[15] We shall discuss this at some length.

Histologically, these fatty plaques of the cornea in man contain 2 types of sudanophilic lipid (fig. 4, *top*). First there are the bright red droplets, often as large as 20 μ in diameter, situated predominantly within the cells. These are abundant in proportion to the cellularity of the tissue. Secondly, there are the sudanophilic granules situated predominantly in the acellular and hyalinized areas. With low-power microscopy these give the impression of a diffuse sudanophilia. The former we shall call globular lipid and the latter granular lipid. These 2 types are not only separable on morphologic grounds but there is some mutual exclusiveness in their distribution in that one or the other tends to dominate one area. Thus the granular type of sudanophilia is usually sparse or absent from areas of globular sudanophilia. The reverse is not so true. Furthermore, the inescapable impression is that the granular lipid is derived from the globular lipid when the cells containing the latter disintegrate.

With hematoxylin and eosin stains, the cornea with lipid keratopathy shows an increase in cellularity in some areas and a decrease of cells or hyalinization in others. Some of the cells have a distended or vacuolated cytoplasm, but it is impossible to state whether they are distended corneal cells or invading macrophages. Often, when frozen sections of the cornea are examined with polaroids, bire-

fringent crystals are abundant, especially in the areas of hyalinization (fig. 4, *middle and bottom*).

Fatty plaques similar to those in human beings may be induced in hypercholesteremic rabbits if their corneas are vascularized (fig. 5). If vascularization is induced before putting the animals on a high-cholesterol diet, lipid will be deposited to some extent in the paravascular regions, but if a localized vascularization is induced while the animal is hypercholesteremic a dense lipid plaque will develop in the area of blood vessels. The relationship between trauma and deposit of fat in the cornea was early pointed out by Versé and Rohrschneider[16] and its similarity to the lipid plaques of man has recently been emphasized by us.[17]

Histologically these plaques in hypercholesteremic rabbits consist of an abundant intracellular, globular, sudanophilic material, an increase in cellularity of the cornea, a variable amount of birefringent crystals, and a variable, but usually small, amount of extracellular, granular sudanophilic material (fig. 6). In other words, the induced plaques of hypercholesteremic rabbit corneas are similar to those in human corneas, except that there is less necrosis and correspondingly less granular sudanophilia in the rabbit.

Fatty plaques in human blood vessels have, of course, been abundantly described under the heading of atheromata. These plaques consist of focally thickened intima containing masses of sudanophilic and birefringent material (fig. 7). The sudanophilia consists, as in the case of lipid plaques of the human cornea, predominantly of intracellular globular lipid and extracellular granular lipid. The former is present and relatively abundant in regions of cellularity while the latter is present predominantly in regions of hyalinization and necrosis. Often there is a conspicuous mutual exclusiveness between the two, as was noted in the case of the cornea (fig. 8). The portion of the intima adjacent to the lumen and, to a less extent the portion adjacent to the media, tends to be cellular and to be rich in globular lipid, whereas that in the more intermediate zones tends to be relatively acellular and contains the granular type of lipid. This is consistent with the sugges-

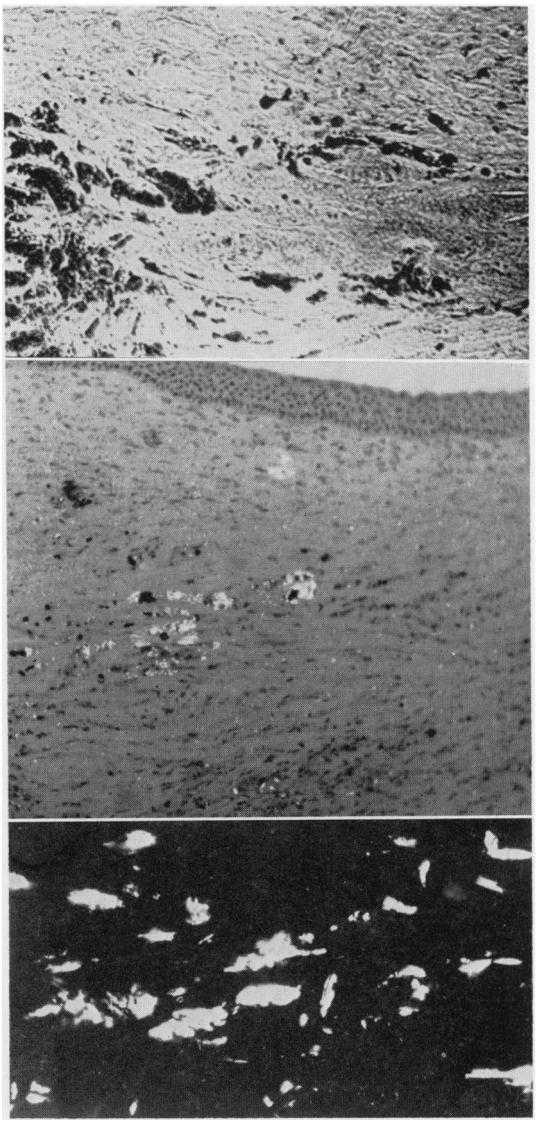

FIG. 4 *Top.* Cross section of cornea from a patient with lipid keratopathy, cut in the frozen state and stained with hematoxylin and Sudan IV. Noteworthy is abundant sudanophilia presenting globular and granular form. The former is chiefly intracellular and present in areas of fibrocytosis; latter is entirely extracellular and present in areas of relative acellularity. *Middle.* Same case photographed between partially crossed polaroids to show birefringent crystals (*white areas*). *Bottom.* High-power magnification, same case, showing crystals as photographed between completely crossed polaroids.

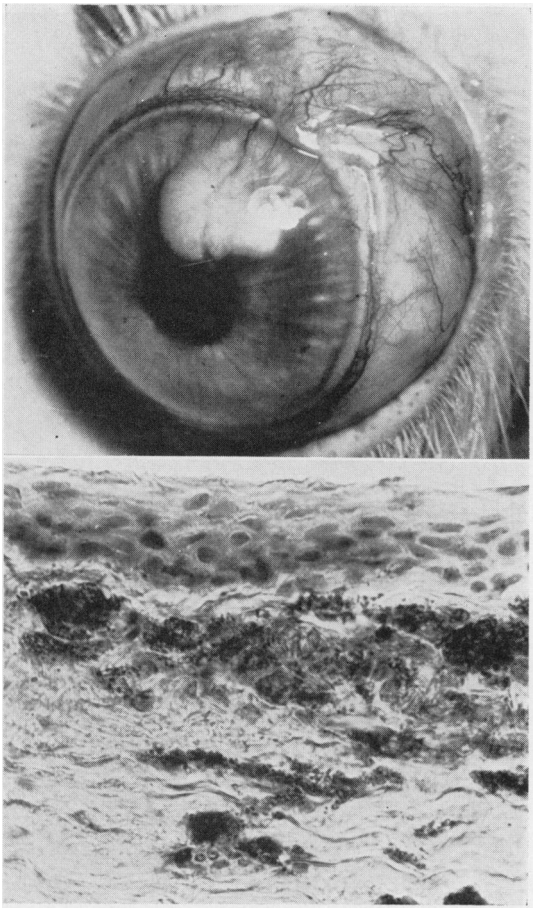

FIG. 5 *Top.* Lipid plaque in hypercholesteremic rabbit cornea occurring at site of vascularity. Cornea had been cauterized several times by heated probe.

FIG. 6 *Bottom.* Sections of rabbit cornea in region of plaque, stained with hematoxylin-Sudan. Noteworthy is abundance of intracellular globular lipid and relatively slight amount of granular sudanophilia.

tion that the granular sudanophilia is derived from the globular sudanophilia as the tissue becomes necrotic (fig. 9). The birefringent crystals also seem to precipitate out with necrosis, being absent from the fat-laden areas adjacent to the lumen but variably abundant in the necrotic intermediate layers.

The fatty plaques in the blood vessels of rabbits show changes that are practically identical with those of human atheromata. See figure 10. In both cases the plaques tend to localize about orifices of blood vessels, a fact that has been attributed to the intimal vascularity of these regions.[18] Elsewhere they also appear to be associated with vascularity of the intima.[19] The plaques consist of hyperplastic intima loaded with sudanophilic material and birefringent crystals. These have the same distribution as in human atheromata, that is, intracellular globular lipid adjacent to the lumen and media with extracellular granular lipid in the intermediate necrotic areas. In general, however, the necrosis is less marked in the case of the rabbit than of the human atheroma. The mutual exclusiveness of the 2 types of lipid referred to is often striking in the rabbit atheroma. The birefringent crystals, which in the aggregate may be massive, are associated predominantly with the areas of necrosis and can be seen by ordinary light microscopy.

DISCUSSION

The chief basis for identifying the fatty plaques of the cornea and those of blood vessels is the similarity in their histologic features. Common to both are the intracellular globular lipid and the extracellular granular lipid. The former is associated with active hyperplasia of tissue and the latter with hyalinization and necrosis of tissue. In both there tends to be a mutual exclusiveness of the 2 types, and one appears to be converted into the other with necrosis of the tissue, in the direction of globular to granular sudanophilia. Associated with this is a release of birefringent crystals that appear to be, in part at least, cholesterol.

There are differences, however small, in the fatty plaques of the corneas of man and of hypercholesteremic rabbits; necrosis is less marked in the latter and there is less calcification. These same differences apply to a comparison of atheroma of man and the hypercholesteremic rabbit, and have been attributed to the differences in the acuteness and duration of the process in the two. Time lapses of the plaques of man are measured in terms of decades, whereas those of rabbits are a matter of months. In any case, the plaques in the human cornea are more analogous to those of human atheromata, whereas the

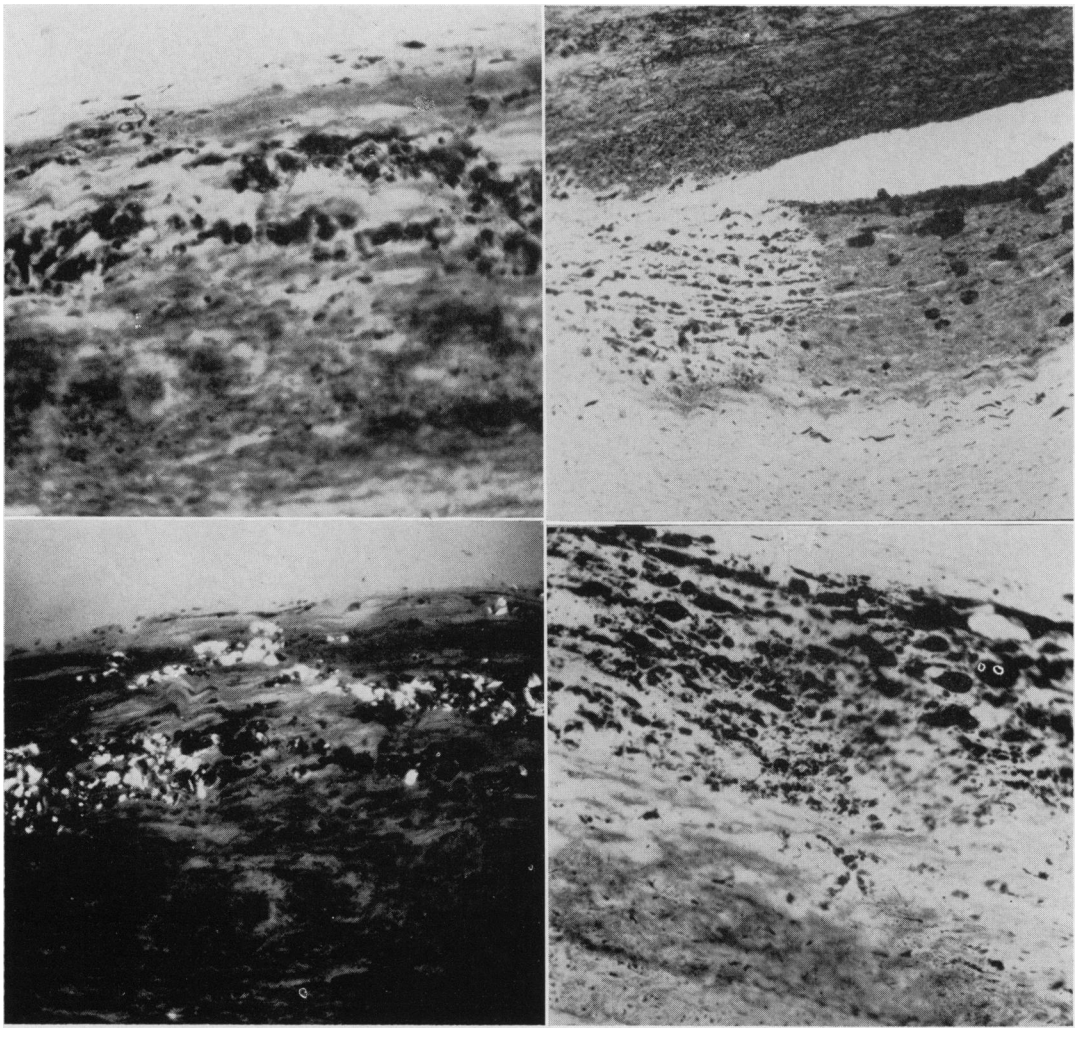

FIG. 7 *Left. Top.* Human atheroma (aorta) showing extensive granular sudanophilia and some extracellular globules of fat in relatively necrotic portion of the intima. Sections stained with hematoxylin-Sudan IV. *Bottom.* Same section examined between crossed polaroids. Birefringent crystals.

FIG. 8 *Top, right.* Human atheroma illustrating "mutual exclusiveness" of extracellular granular and intracellular globular lipid.

FIG. 9 *Bottom, right.* Human atheroma. Usual globular lipid within cells adjacent to lumen and granular lipid in necrotic deeper layers of intima.

plaques of the hypercholesteremic rabbit cornea are more strictly comparable to the atheromata of the rabbit blood vessels. In both cases, however, what is happening in the cornea appears similar to what happens in the blood vessels of the corresponding species.

If the pathogenesis and course of events for the two are identical, as is suggested by the histologic findings, one would expect atheroma to develop only in areas of prior vascularization, and that with episodic suddenness. Both these possibilities have indeed been suggested on other grounds, but it has not heretofore been generally recognized that the cornea is an informative analog where the processes could be visualized during life.

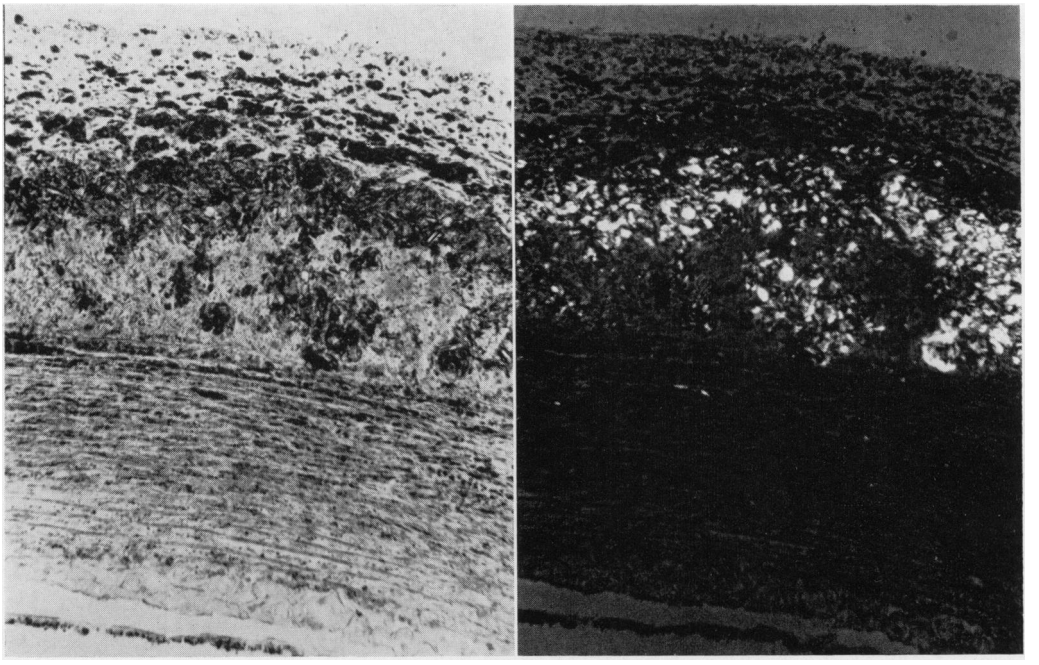

FIG. 10 *Left.* Rabbit atheroma (aorta) showing intracellular globular lipid adjacent to lumen and granular sudanophilia with cholesterol crystals in necrotic deeper layers. *Right.* Same section examined between crossed polaroids.

The possibility that patients with this type of lipid keratopathy are prone to atheromatosis or vice versa cannot be answered on the basis of the present cases, since no autopsies were done on the patients with corneal plaques. In any case it would be difficult to establish a significant correlation, since all persons in the age group of most of the patients in this study normally have atheromata. It would perhaps be more pertinent to enquire whether species that do not normally develop atheroma can develop lipid keratopathy. It is interesting, therefore, to note that one case has been reported of lipid keratopathy in the dog.[20]

It is also pertinent to enquire whether or not patients who develop lipid plaques in the cornea are those with hypercholesteremia. Of the 10 patients in this series who had one or more blood cholesterol determinations, the average level was 267 mg. per cent. In 4 of these the level was more than 300 mg. per cent and in 1 (fig. 1) the level was over 500 mg. per cent with a fatty acid level of 627 mg. per cent. The literature also records cases of lipid plaques in the cornea with elevated plasma cholesterol.[3] It thus appears that lipid plaques occur in the cornea, as they do in blood vessels, predominantly but not exclusively in patients with higher than average blood cholesterol levels.

Finally, it is probably worth pointing out that the analogy drawn between lipid keratopathy and atheroma no doubt has its counterpart in arcus senilis and diffuse sudanophilia of the intima. However, no comparable study of these has as yet been made, and we mention it only to avoid confusion with the entities represented by the present cases.

SUMMARY

Lipid keratopathy as described in the present paper consists clinically of a fatty plaque in an area of the cornea that has been previously vascularized. It often occurs with remarkable suddenness and may be stationary or reversible, depending on the condition of the cornea. In any case it is not necessarily associated with activation of the original inflammatory process.

A similar plaque may be induced in the hypercholesteremic rabbit by vascularizing the

cornea. This also consists of abundant fat in the region of vascularity.

These fatty plaques of the human and rabbit cornea are histologically similar to those of blood vessels with atheromatosis. They all consist predominantly of an intracellular globular sudanophilia and an extracellular granular sudanophilia. The latter develops along with birefringent crystals and appears to be a function of necrosis.

It is suggested that lipid plaques of the cornea occur in a manner similar to atheroma of blood vessels and therefore provide a convenient analog for the visualization of the atheromatous process during life.

Summario in Interlingua

Ceratopathia lipidic, secundo le description offerite in le presente articulo, consiste—in terminos clinic—de un placa grassiose in un area del cornea que esseva previemente vascularisate. Frequentemente illo occurre con subitaneitate remarcabile. Illo pote esser stationari o revertibile, in dependentia del condition del cornea. In omne caso, illo non es associate necessarimente con activation del processo inflammatori original.

Un simile genere de placa pote esser inducite in conilios hypercholesterolemic per le vascularisation del cornea. Iste genere de placa consiste etiam de un abundantia de grassia in le region del vascularitate.

Tal placas del cornea de conilios o humanos es histologicamente simile a illos del vasos sanguinee que es afficite de atheromatosis. Illos omnes consiste predominantemente de un sudanophilia globular intracellular e un sudanophilia granular extracellular. Iste ultime se disveloppa insimul con crystallos birefringente e pare esser un function de necrosis.

Es exprimite le opinion que placas lipidic del cornea occurre in un maniera simile a atheroma del vasos sanguince e representa per consequente un analogo convenibile pro le visualisation del processo atheromatose durante le vita del subjecto.

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