LIPID KERATOPATHY AND ATHEROMA*

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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 resumé 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-shape distribution in advance of the vascular arcade while in the latter case it is apt to be disc-shaped and situated in the immediate area of the blood vessels (Figures 1 & 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 (whence it is often interpreted as a dystrophy) and the only symptom it causes, other than a cosmetic one, is reduced vision.

While the foregoing comprises the typical case, variants of it 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

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†Cholesterol was added to the rabbit chow and feeding continued for periods of 6–12 months. Blood cholesterol levels reached 1–2 percent.

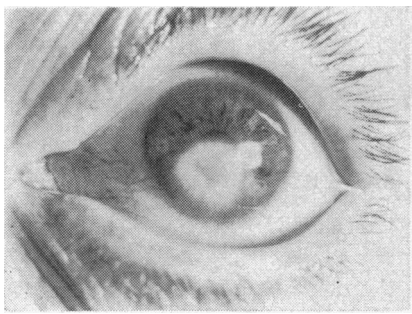

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FIGURE 1. LIPID KERATOPATHY FORMING A DISK-SHAPED PLAQUE

The patient was a 48-year-old woman who had had a corneal ulceration with considerable residual interstitial vascularization. Approximately two months after the ulceration she developed the dense opacity shown in the accompanying photograph. It was situated in all layers of the stroma but most especially in the deeper layers. No subsequent change was noted over an observation period of several months. The only noteworthy finding on general examination was a blood cholesterol level of 500 mg. percent and a fatty acid level of 627 mg. percent.

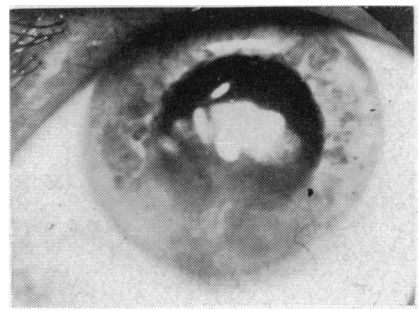

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FIGURE 2. LIPID KERATOPATHY FORMING A FAN-SHAPED PLAQUE IN ADVANCE OF THE VASCULAR ARCADE

The patient was a 61-year-old man who had had a bullous keratopathy and sclerokeratitis thought to be part of a rosacea keratitis. This resulted in considerable interstitial vascularization of the lower portion of the cornea. At one stage of the neovascularization the patient precipitously developed an arcuate opacity (presumed to be fat) just in advance of the vessels and separated from them by a clear zone. This is presented in the accompanying photograph (with the light reflex superimposed). With the further ingrowth of vessels into the swollen cornea the dense opacity disappeared leaving only scintillating particles that were presumed to be cholesterol.

deposited in a cornea having a conspicuous arcus senilis (Figure 3). It is then difficult to tell where the arcus ceases and the new deposit of lipid begins.

In the literature it is not always possible to determine whether what is being described is the foregoing entity or something else. However, instances of it have probably been described under the following clinical headings: fatty dystrophy of the cornea (1), dystrophia adiposa corneae (2, 3, 4), adiposis of the eye (5, 6), xanthomatosis (2, 7, 8), lipin interstitial keratitis (9), lipidosis corneae (10), and secondary steatosis (10a). 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 what we are calling

lipid keratopathy to hypercholesteremia (11, 12, 8) or to generalized xanthomatosis (12a), and at least one observer has previously suggested a relation to atheromatosis (13). We shall discuss this at some length.

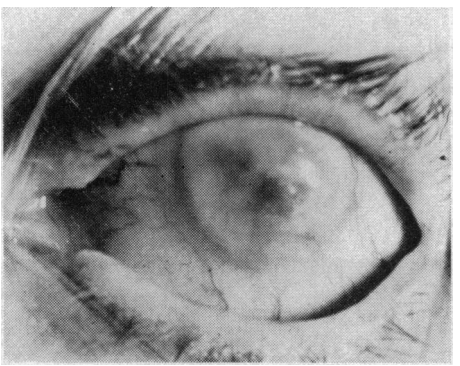
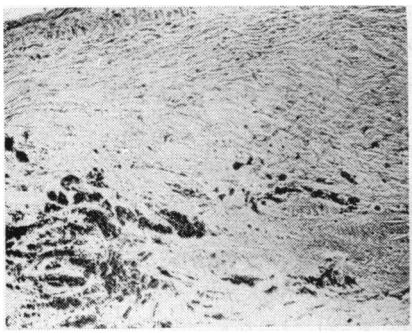


FIGURE 3. DIFFUSE LIPID KERATOPATHY IN A PATIENT WHO HAD HAD AN INTERSTITIAL KERATITIS AS A CHILD LEAVING RESIDUAL VASCULARIZATION

Recently the cornea has become opaque. The photograph shows extensive deposition of material, believed to be fat, having a ring-like distribution suggestive of an extensive arcus senilis. The other eye had less vascularization and only a mild arcus senilis.

Histologically, these fatty plaques of the cornea in man contain two types of sudanophilic lipid (Figure 4A). First, there are the bright red droplets, often as large as 20 micra 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 (Figure 4A). 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 two types not only are separable on morphologic grounds but also 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 impression is inescapable 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



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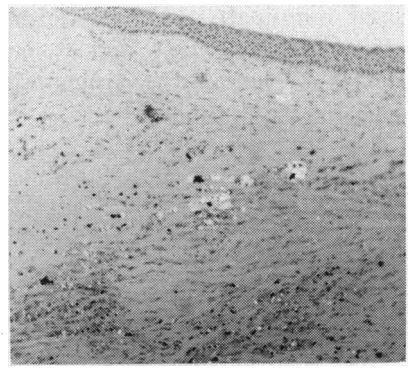

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FIGURE 4. CROSS SECTIONS OF THE CORNEA FROM A PATIENT WITH LIPID KERATOPATHY

The sections were cut in the frozen state and stained with hematoxylin and Sudan IV.

A: Noteworthy is the abundant sudanophilia presenting in a globular and granular form. The former is chiefly intracellular and present in areas of fibrocytosis while the latter is entirely extracellular and present in areas of relative acellularity. B: Another section of the same case photographed between partially crossed polaroids to show the birefringent crystals (represented by the white areas). C: High power magnification of same case showing crystals as photographed between completely crossed polaroids.

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. When frozen sections of the cornea are examined with the use of polaroids, birefringent crystals are often abundant, especially in the areas of hyalinization (Figure 4B and C).

Fatty plaques similar to those found in human beings may be induced in hypercholesteremic rabbits if their corneas are vascularized (Figure 5). If vascularization is induced prior to 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 (14) and its similarity to the lipid plaques of man has recently been emphasized by us (15).

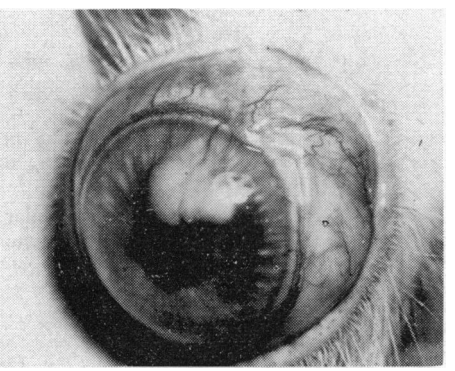


FIGURE 5. LIPID IN A HYPERCHOLESTEREMIC RABBIT CORNEA OCCURRING AT THE SITE OF VASCULARITY

The cornea had been cauterized several times by means of a heated probe.

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 (Figure 6). In other words, the induced plaques of hypercholesteremic rabbit corneas are similar to those which occur 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 (Figure 7A and B). The sudanophilia consists, as it does in 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

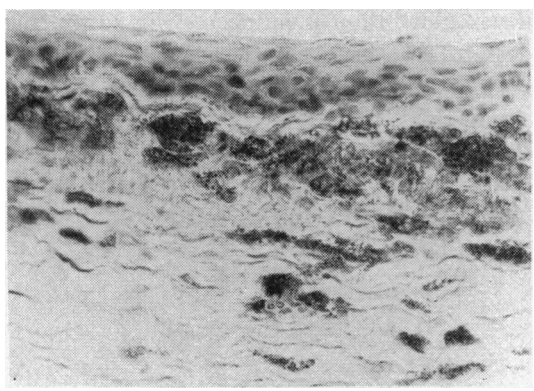
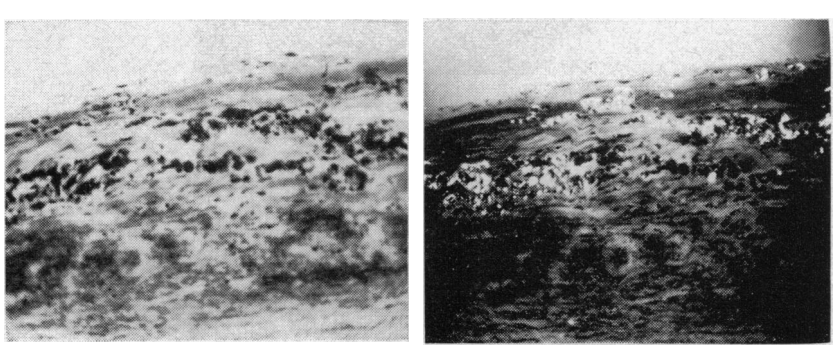


FIGURE 6. SECTIONS OF THE RABBIT CORNEA IN THE REGION OF THE PLAQUE, STAINED WITH HEMATOXYLIN-SUDAN

Noteworthy is the abundance of intracellular globular lipid and the relatively slight amount of granular sudanophilia.



A B

FIGURE 7. HUMAN ATHEROMA (FROM AORTA)

A: Section shows extensive granular sudanophilia and some extracellular globules of fat in a relatively necrotic portion of the intima. Sections stained with hematoxylin-Sudan IV. B: Same section examined between crossed polaroids showing the birefringment crystals.

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 cornea (Figure 8). The portion of the intima adjacent to the lumen and, to a less extent, the portion adjacent to the media, tend to be cellular and rich in globular lipid whereas that in the more intermediate zones tends to be relatively acellular and contain the granular type of lipid. This is consistent with the suggestion that the granular sudanophilia is derived from the globular sudanophilia as the tissue becomes necrotic (Figure 9). The birefringent crystals also seem

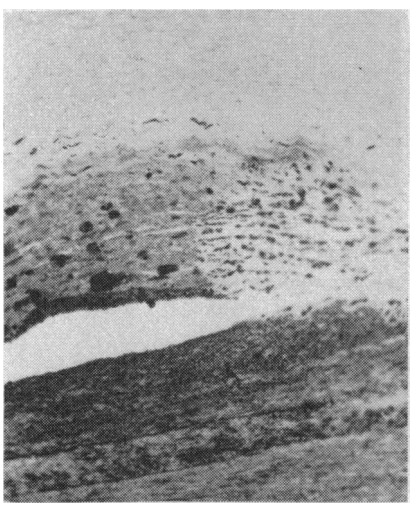


FIGURE 8. HUMAN ATHEROMA ILLUSTRATING WHAT HAS BEEN CALLED THE "MUTUAL EXCLUSIVENESS" OF THE EXTRACELLULAR GRANULAR AND THE INTRACELLULAR GLOBULAR LIPID

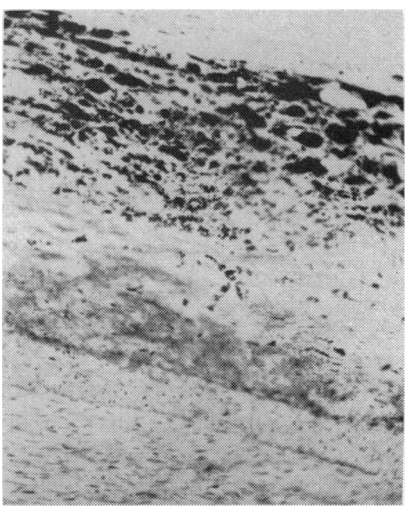
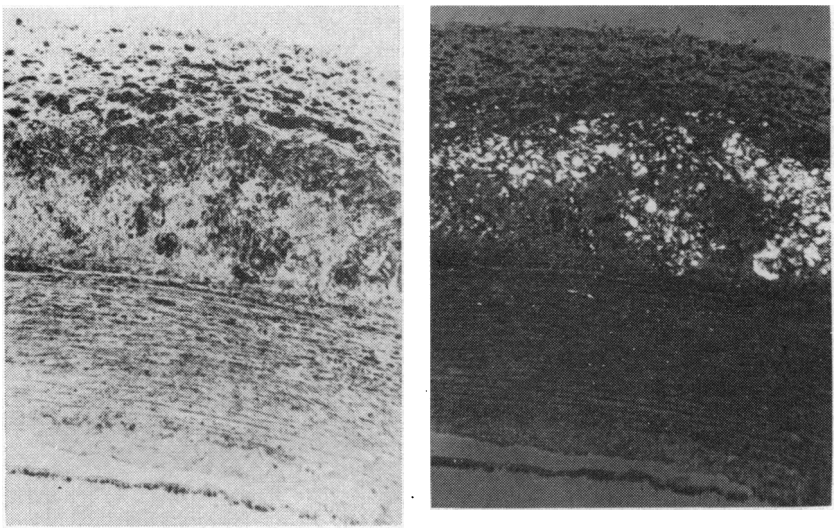


FIGURE 9. HUMAN ATHEROMA SHOWING THE USUAL FINDING OF GLOBULAR LIPID WITHIN CELLS ADJACENT TO THE LUMEN AND THE GRANULAR LIPID IN THE NECROTIC DEEPER LAYERS OF THE INTIMA

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 (Figure 10A and B). In both the plaques tend to localize about orifices of blood vessels, a fact which has been attributed to the intimal vascularity of these regions (16). Elsewhere they also appear to be associated with vascularity of the intima (17). The plaques consist of hyperplastic intima loaded with sudanophilic material and birefringent crystals.



A B

FIGURE 10. RABBIT ATHEROMA (AORTA)

A: Section shows intracellular globular lipid adjacent to the lumen and necrotic sudanophilia with cholesterol crystals in the deeper layers. B: Same section examined between crossed polaroids.

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 rabbit than in the human atheroma. The mutual exclusiveness of the two types of lipid previously 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 two types and the impression is obtained that one is converted into the other with necrosis of the tissue, in the direction of globular to granular sudano-

philia. Associated with this is a release of birefringent crystals which 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 in that necrosis is less marked in the latter and there is less calcification. These same differences apply in 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. The plaques of man have time lapses measured in terms of decades whereas for those in rabbits the lapse is a matter of months. In any case, the plaques in the human cornea are more analogous to, and identical with, those of human atheromata whereas the plaques of the hypercholesteremic rabbit cornea are more strictly comparable to the atheromata of the rabbit blood vessels. In both, however, what is going on in the cornea would appear to be similar to that in the blood vessels of the corresponding species.

If the pathogenesis and course of events for the two are identical, as suggested by the histologic findings, one would expect that atheromata would develop only in areas of prior vascularization and that they might develop 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 analogue where the processes could be visualized during life.

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. It would be difficult to establish a significant correlation since all persons in the age group in which most of the present patients belonged, have atheromata normally. It would perhaps be more pertinent to enquire whether species which 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 (18).

It is also pertinent to enquire whether or not patients who develop lipid plaques in the cornea are those with a hypercholesteremia. Of the ten patients in the present series who had one or more blood cholesterol determinations, the average level was 267 mgm. percent. In four of these the level was more than 300 mgm. percent and in one (pictured in Figure 1) the level was over 500 mgm. percent with a fatty acid level of 627 mgm. percent. 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 which we are drawing between lipid keratopathy and atheroma has its counterpart, without doubt, 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.

CONCLUSIONS

Lipid keratopathy as described in the present paper consists clinically of a fatty plaque occurring in an area of the cornea which has been previously vascularized. It comes on often with remarkable suddenness and may be stationary or reversible depending on the condition of the cornea. 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 analogue for the visualization of the atheromatous process during life.

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DISCUSSION

DR. GEORGINA DVORAK-THEOBALD. Dr. Cogan has presented an interesting paper which opens an untilled field of fascinating possibilities for further investigation. The present paper is a classic extension of the work reported by Cogan and Kuwabara before the XVII International Congress at Toronto in which they showed that the fat deposits of lipid keratopathy are quite different from the lesions of arcus senilis in man, a disease process which they believe is rarely associated with hypercholesteremia and atherosclerosis.

The authors have pointed out in the present paper that, by producing hypercholesteremia in rabbits, it is possible to induce plaques of lipid in the animals' corneas which are similar to those occurring in human corneas except that there is less necrosis and less diffuse sudanophilia in rabbits owing to the fact that the induced lesions extend over a period of months, while those in human may extend over decades. The lesions in rabbit corneas are similar to atheromas of rabbit blood vessels and those in human corneas to atheromas of human blood vessels.

According to Zimmerman (personal communication), it is believed that fluid circulates from the arterial lumen through the intima and media and is then resorbed in the adventitia by lymphatics. Colloid dyes and lipids have been observed to become trapped to form aggregates within the vessel wall

during this transudation of fluid from the lumen side to the adventitia, and lipids are thus removed from the perfusion fluid (Wilens, Science, 114:389, 1951).

Evans and co-workers (Am. J. Clin. Path., 22:354, 1952) found that blood from patients with atherosclerosis contains something that leads to the deposition of anisotropic fat crystals in the vessel intima of normal arteries while normal bloods do not do this. As a result, these investigators suggested that a complex of factors are in operation during the formation of atheromatous lesions of the arterial wall. These would include (*a*) lipoprotein complexes in the circulating blood of the proper size and shape to get into the intima from the blood but which then become trapped and aggregated; (*b*) proper hydrodynamic factors which would tend to pump these lipoprotein molecules into the vessel wall; (*c*) possible local tissue changes which would facilate the entrance of lipids into the vessel and promote their precipitation or phagocytosis by tissue cells.

Zimmerman agrees with Dr. Cogan that the cornea might provide a similar set-up to that in the arterial wall, fluid circulating from the limbal area into the cornea. One must speculate here why in patients with generalized atherosclerosis lipid corneal lesions do not occur more frequently. There may be something different about the normal limbal vessels and normal corneal stroma which does not promote the deposition of lipids. Perhaps lipids do not escape through the normal limbal vessels as readily as they pass through the intima of large arteries, or if they do, perhaps the structure of the normal corneal stroma does not tend to trap the lipid molecules and cause their aggregation. It may take the complex of (*a*) a vascularized corneal lesion, and (*b*) a concentration of abnormal circulating lipoprotein macromolecules, to lead to the formation of this lipid keratopathy.

Dr. Cogan feels that patients with atheromas of the cornea need not have atheromas of the blood vessels. But does he believe that arcus senilis in young persons is due to a disturbance in fat metabolism?

Does Dr. Cogan feel that opacities in nummular keratitis are due to invasions of lipids or to fibrosis? And how would he distinguish the two without microscopic sections?

Clinicians are constantly confronted with patients who show ocular lesions which may or may not be due to fat deposits. In closing, I should like to ask Dr. Cogan how he would go about making a differential diagnosis in such cases. What criteria would he use to distinguish the lipid nature of the lesions?

DR. IDA MANN. I am intensely interested in this paper. I have recently been in Dr. Cogan's laboratory and seen some of his work and I think he is explaining many things that have puzzled me. I would like to ask him two questions. He will remember my work during the war on delayed mustard gas keratitis. How did we manage to produce lipoid in the cornea in all our rabbits if we kept them long enough (about eighteen months to two years)

without making them hypocholesteremic? Why was the vascularization produced by a mustard gas injury different from that of the other agents of chemical warfare tested?

The other matter concerns a single case that I saw years ago in Moorfields. This was a young man who had suddenly developed a plaque, we could not see any vascularization, and there was no history of any previous keratitis. We sent the patient to the physicians, and Dr. Meadows at Queens Square suggested that we give the patient large doses of thyroid, although he was not obviously a hypothyroid person. We did and the whole cornea cleared in about six months under this treatment. I do not know whether the treatment had anything to do with it or if it was just pure luck.

DR. COGAN. I want to thank both the discussants. As for the specific question: "Is arcus senilis in young persons due to a disturbance in fat metabolism?" I suppose it is. It is so common with familial hypercholesteremia that it must be associated with disturbances of fat metabolism, but I do not know what that disturbance is in persons who do not have the measurable elevation in their cholesterol level. Obviously we know very little about measurements of fat and particularly the cyclic changes in the blood that might occur with fat ingestion. With regard to the second question: "Are opacities in nummular keratitis due to lipids or due to fibrosis?" I am not sure that we mean the same thing by "nummular" keratitis. I have not had any opportunity to study nummular keratitis histologically and have seen very few clinical cases, so that I am not qualified to answer. As to the third question: "How to distinguish fat in the cornea and what criteria do we use to distinguish fat?" it seems to me that fat, at least the type of fat in lipid keratopathy, is characterized most particularly on the edges by what appears to be a crystaloid distribution of the pattern. They are not crystals. Vogt described them as crystals and one would certainly think they were when one looked at them, the edges extending out in all directions, but they are not. The same thing can be produced with liquid fat or with any fluid injected into the cornea which is not crystalline. The crystaloid pattern is due to the orientation by the collagenous fibers in the cornea of the fat as it oozes in the tissue, so that it looks crystalline. That is characteristic of it and also the highly reflecting nature of material in it. Also the density of the opacity I think is characteristic in contrast to the diffuse bluish white opacities of fibrosis. The questions that Dr. Zimmerman brings up as to what is the lipid that is taken up by these cells, how does it get in the intima and in the cornea, are age old and thousands of dollars have been spent on them, especially by those interested in cardiovascular diseases. An answer is a sort of Holy Grail and I am certainly not a Sir Galahad. However, we can produce sudanophilic fat in the cornea and in damaged blood vessels in the test tube, by incubating the tissue in an oleate substrate in the presence of serum. We cannot do so with any other fatty acid; so my concept of that material, as Dr. Kuwabara and I interpret it at

present, is that this is not a phagocytosis of fat as is commonly believed, but rather a synthesis of a neutral fat, probably tri-olein, from the fatty acid, oleic acid, and that is the only fatty acid that will produce it.

As for Dr. Mann's question, I am aware of her studies with the cholesterin deposits in mustard gas keratitis and I do not believe I can answer her. In our mustard burns in rabbits we were impressed by the thrombosing properties of mustard when it was given in sufficient dosage and the hemorrhages that resulted in the conjunctiva from the use of mustard. Cholesterin, of course, is left high and dry after the disintegration of hemorrhage when other components are solubilized. If that is not the explanation I have no alternative. As for the case that was treated with thyroid, I have no idea about it.