SENILE AND OTHER PIGMENTARY CHANGES IN THE RETINAL GANGLION CELLS*†

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We know that the retinal ganglion cells vary very much in size, shape and structure. Near the macula they are small ($8-10\mu$) and form 6-8 layers. In the periphery they are large ($30-35\mu$) forming one layer only, with considerable cell-free intervals. We have not been able to find any retinal area in which cells of an intermediate size predominate. Between the ganglion cells, glial and amacrine cells can frequently be seen.

By our routine methods of fixation and staining, no pigmentary changes have been discovered in the ganglion cells. One of us

FIG 1.

Senile retina in bulk—normal retinal condition, male, aged 78 years. Stained scarlet red. $\times 300$. Periphery about 10μ under retinal surface. Fatty droplets fill the cell plasma—fatty retinal ganglion cells very dense.

has used the method of staining the retina in bulk with Scharlach Red for a few years (Loewenstein 1942). He found regularly, fatty changes in the ganglion cells in hypertensive and diabetic

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retinopathy. The question arose as to whether or not the droplet staining with scarlet red was really pathological or just a senile change. Accordingly we made an investigation of fatty changes in the ganglion cells in normal eyes of different age groups and in various diseased conditions.

The ganglion cells of the middle-aged and aged show the fatty droplets of lipoid staining in the plasma (Fig. 1). In children

FIG. 2A.

Giant ganglion cells, retina in bulk, scarlet red. $\times 600$. Child, aged 6 years, traumatized eye. Vascularised endothelium with individual fatty droplets. Fatty droplets in giant ganglion cells much rarer than in senile ones

FIG. 2B.

Man, aged 72 years. $\times 600$. Fatty red droplets within the plasma of the ganglion cells. Diffuse brown staining. Retina in bulk—scarlet red.

these changes are absent for the most part but they do occur; we found scanty droplet change in a few cells in the retinal periphery of a child aged six years (Fig. 2a). They are shining red droplets (Fig. 2b). They are sometimes so small as to be scarcely discernible with ($\times 600$) power, or so gross that they make the cells stand out in the field with low power. The whole plasma may be full of them. Usually the territory of the nucleus is droplet free, though the nucleus' border may be overlapped by them.

FIG. 3.

Man, aged 72 years, retina in bulk, scarlet red. About 2mm. from the disc. 5/oil, $\times 675$. Fatty droplets very minute, slight yellow-brown staining of plasma.

They are a cytoplasmic change. The large ganglion cells of the periphery suffer predominantly; the smaller central ganglion cells are much less affected or not at all. The position of these cells is (10-20 μ) below the retinal surface, and this fact, along with their shape, allows us to identify them as ganglion cells. The shape, though often pyriform, may vary enormously as can be seen in Fig. 3. This is a drawing taken of one field and not of selected ganglion cells in a celloidin section stained with haematoxylin-eosin and it is interesting also to note that in every one of this group of ganglion cells from a normal retinal periphery showing such varied outline, the nucleus is absent (Fig. 3a).

Apart from the *brilliant droplet* staining of the ganglion cells with scarlet red in the periphery which we have found to be a senescent as well as a pathological change, a striking appearance

Retinal celloidin section. H.E.
 $\times 1350$. Ganglion cells in a natural
group, retinal periphery.

a=In comparison a cell of the inner nuclear layer.

FIG. 3A.

was noted. The plasma of the ganglion cells of the periphery in senile retinae stained with scarlet red had frequently a brownish, or brownish-yellow appearance. The pigment was limited to the large types but they were not uniformly affected. The presence of pigment may coincide with fatty droplet change or it may not (Figs. 1-4). We failed to see this pigment in sections cut after

Retina in bulk, stained scarlet red. $\times 300$.

a

a: macular region, cells smaller, some contain the diffuse yellow-brown pigment, most of them fatty droplets.

b

b: bigger ganglion cells of periphery. All fatty with more or less brown diffuse pigment. Mostly nucleus not visible.

FIG. 4.

paraffin or celloidin embedding but we found it in sections cut on the flat, after processes which do not remove the fat as in gelatine embedding and frozen sections. But it is best detected by examination of the retina in bulk.

Our next thought was to elucidate if possible the nature of this yellowish-brown diffuse pigment which appeared in most of the large ganglion cells in sections stained with scarlet red. Consequently, we examined the unstained retina to exclude scarlet red as a source of the pigment. The retina was cleared in glycerin

FIG. 5A.

Unstained yellow ganglion cells. Retina in bulk, unstained. Hypertension. No retinal changes. 10/40, $\times 600$.

n: normal ganglion cells. y: yellow plasma.

FIG. 5B.

and then examined in dim light by greatly reducing the iris diaphragm. There was a yellow coloration of many of the large ganglion cells (Fig. 5a). Yellow ganglion cells and normal ones occur in the same area (Fig. 6). The protoplasm is granular (Fig. 5b). The granular appearance may be due to droplet formation in cytoplasm made manifest by scarlet red; but of this assumption we have no proof. These sulphur-yellow ganglion cells are much less obvious than the fatty ganglion cells of the scarlet red stained preparation with their striking red droplets. We found that after the observer's eye was dark-adapted, the

yellow cells were more easily seen. If the diaphragm is not much cut down they may be missed altogether. We think that this primary yellow colour of the large ganglion cells is modified by scarlet red to give the brownish-yellow colour we have described above. We have found these yellow giant ganglion cells in diabetic and hypertensive retinopathy, glaucoma, iridocyclitis and

Unstained retina in bulk, periphery $\times 675$. Diffuse brownish pigment in some cells. Granular protoplasm.

FIG. 6.

in senile retinæ. It is to be noted that the yellow ganglion cells may be otherwise normal, or they may have no nucleus, or have an unusual and bizarre shape (Fig. 6).

We were next interested to know whether or not the pigmentary change was limited in normal retinæ to the aged. We selected for our investigation, eyes which had been removed early because of injury. In the specimen of a child of six years we found that the ganglion cells had a clearly defined nucleus and nucleolus,

Giant ganglion cells, child, aged 6 years, retina in bulk, unstained. $\times 600$. Nucleus: sharply defined, darker bluish nucleolus, honeycomb pattern in plasma.

Unstained. $\times 600$. Man, aged 72 years, symmetric retinal distance.

Senile cells: Nuclei less sharply defined smaller, often deformed. Often no nucleoli. Plasma darker, more granular, slightly sulphur-yellow. There are normal giant ganglion cells too.

FIG. 7.

this latter being about 1/10 of the diameter of the nucleus. We never saw the yellow pigmented ganglion cells in young retinae. In the child of six years, however, an occasional large ganglion cell showed a few fatty droplets with scarlet red. By comparison then, the aged retina showed ganglion cells in which the nucleus was frequently indistinct, or was absent altogether (Fig. 7). Fatty

FIG. 8.

Hypertensive retinopathy with bilateral sub-retinal exudate. Retina in bulk. Sc. red. 5/40. X300. Retinal periphery nerve fibre pattern. Brown ganglion cells with fine fatty droplets within the spaces of the pattern. Normal ganglion cells clear between them. Some fatty droplets very minute within the fibres of the pattern.

FIG. 9.

Brown ganglion cells, retina in bulk, sc. red. 10/oil, X1350. Yellowish-brownish granules fill the whole plasm. Nucleus big (no nucleolus), slightly bluish, no nuclear structure. Some sharp fatty droplets (combined from several fields).

Diabetes without retinal changes

a: normal ganglion cell. *b*: clear brown without fatty droplets. *c*: brown ganglion cells with few fatty droplets.

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droplet change in the plasma of the giant ganglion cells was a constant feature. We have found fatty ganglion cells in the retinal periphery especially of hypertensive retinopathy (Fig. 8). Here they stand out sharply between the smaller normal ganglion cells without fatty droplets. They are all surrounded by the deep arcuate optic nerve fibres. They are very frequent also in diabetic retinopathy. Fig. 9 shows large ganglion cells with very few fatty droplets, brown ganglion cells without red droplets and giant

Diab. ret. pathy, stained retina in bulk, sc. red, embedded in gelatine, cut flat, not afterstained. X600. Three giant brownish-yellow ganglion cells (compare with retina in bulk), one only has 2 fine fatty droplets. Mueller fibres contain rows of fatty droplets.

FIG. 10.

f: big fatty ganglion cells with and without diffuse brown pigment.
g: small fat phagocytosing cells along vessel walls.
o: an obliterated venous branch.

FIG. 11.

Iridocyclitis, glaucoma sec. absol. retina in bulk, scarlet red. X300.

ganglion cells without droplets or diffuse brown staining. Lipoid change was also found in Müller's fibres as we could prove in our gelatine embedded sections of retina stained in bulk with scarlet red, cut with the freezing microtome and studied without nuclear staining (Fig. 10). Fat phagocytizing smaller cells very often accompany vessels. They belong to the microglia (Rio Hortega) (Fig. 11).

Discussion

Obersteiner (quoted by Spielmeyer) has written on many occasions of the clear yellow pigment in cerebral ganglion cells. It has not been seen before the seventh year. The amount of pigmentation of the cells increases with age. It is most marked in the large ganglion cells such as those of the anterior horn and Clark's column. He thought that it was not allied to melanin nor to blood pigment. The yellow pigmented cells have been found by Obersteiner in young people who were the victims of diseases like dementia praecox and paralysis. Obersteiner and later Lubarsch, concluded that this pigment was a product of senescence like that found in heart muscle and the prostate. However, fatty degeneration of the ganglion cells of the central nervous system occurs as the essential lesion in the Tay-Sachs group of diseases.

We are fortunate in that we can study the retinal ganglion cells so much more easily in a thin pellucid membrane, the retina, which can be mounted without the trauma and distortion essential to long processes of fixation and embedding. There can be no doubt of the lipoid nature of the brilliant red droplets within the plasma of the ganglion cells. The scarlet red reaction can now be regarded as the most reliable stain for fat. But argument arises when we consider the possible nature of the diffuse yellow pigment of the large ganglion cells. It has some affinity for scarlet red, becoming brownish-yellow in this medium. But it is not a true lipoid. It may be a precursor. We must leave it to later investigators to determine the chemical nature of this pigment. Certainly it is a result of process of ageing as we have found it to increase in incidence directly with advancing age.

Finally, it is the large ganglion cells of the retina and of the brain which show these pigmentary changes of senescence. In the retina these cells are situated in the periphery, and it is in the periphery that the retina deteriorates at first with age as evidenced by the frequent cystic change of Iwanoff-Blessig. We find that diseases such as hypertension, diabetes and glaucoma cause the yellow pigment to appear in younger people, and this corresponds with the similar ante-dating of the appearance of the pigment in the ganglion cells of the central nervous system where there has been organic nervous disease.

Summary

1. Using the method of examining the retina in bulk unstained and stained with scarlet red, we found that the ganglion cells of the retinal periphery showed fatty droplets in their plasma in diabetic, hypertensive, and other diseased conditions, and in the senile retina. The retinal glial cells contained fatty droplets in these conditions also.

2. The plasma of the large ganglion cells stained diffusely brownish-yellow with scarlet red in hypertensive and diabetic retinopathy and other diseased conditions, and also in the senile retina.

3. There was no quantitative relationship between the fatty droplet content and the diffuse brownish-yellow staining.

4. Unstained retina cleared in glycerine revealed a sulphur-yellow pigment in the plasma of the ganglion cells in old age.

5. This pigment is also found in the retinae of younger people in whom the eye is diseased, and is analogous to that found in cerebral tissue in senile and diseased brains. The chemical nature of the diffuse pigment is unknown but it may be a lipid precursor.

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CATARACT EXTRACTION*

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CATARACT extraction is a fearful joy: one of the most difficult, important, and interesting operations in surgery. Extraction is unique in that not only is a high degree of technical skill required for its successful achievement, but because each case presents a psychological problem that must be solved. I began to extract cataracts over 40 years ago, I still have the same if not greater respect for cataract extraction that I had when I faced my first. To fail in this operation is a dreadful calamity. The patient may have

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