The retinal-pigment epithelial interface

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SUMMARY The interdependence of the outer retina and pigment epithelium is illustrated by the functional changes and structural alterations which occur in each in response to choroidal ischaemia, retinal detachment, vitamin A deficiency, and other causes. The pluripotential role of the pigment epithelium is stressed, particularly in relation to the phagocytosis of outer segment material and the ability of this layer to undergo metaplasia into a variety of different cell types. Similarities of all disturbances of the retinal-pigment epithelial interface to retinitis pigmentosa are pointed out, and the significance of the findings in relation to this disease is discussed.

To see at all we must of course possess a light-absorbing structure to carry out the energy conversion required to initiate the visual impulse. In almost all species this structure takes the form of a specialised light-sensitive layer of neural tissue derived from the primitive neuroectoderm. In man the eye first forms as an outpouching of the primitive fore-brain at a very early stage of development to form a cavity, the primary optic vesicle being lined with ependymal cells. This cavity is obliterated by invagination and the formation of the secondary optic vesicle or optic cup, and it is the acquired juxtaposition of the anterior and posterior hemispheres of the optic vesicle with which I shall deal (Fig. 1).

Early development

At a very early stage in development the posterior half of the cup becomes pigmented and forms the retinal pigment epithelium, which, though in some respects a very specialised tissue, in others remains primitive, for the retinal pigment epithelium throughout life is capable of expressing itself in the pluripotential fashion usually associated with more primitive types of cellular activity. It is interesting that in the developing eye the layer of primitive pigment epithelium is many cells thick, whereas in the adult it is monolayered. Mitotic division of retinal pigment epithelial cells is not seen in the adult, and it may be that after embryogenesis is complete, no further pigment epithelial cells are formed. The same may be true of the pigment itself, for adult pigment epithelial cells lack the enzyme

Fig. 1 The optic cup in a human embryo to show acquired juxtaposition of anterior and posterior hemispheres of the optic vesicle

systems needed to produce pigment, so that embryonic synthesis of pigment may be a once-for-all event on this tissue (Feeney, 1973b, Berman *et al.*, 1974).

Experimentally it has been shown (Coulombre,

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1965) that contact between the developing retina and pigment epithelium is necessary for maturation of the pigment epithelium, for if the 2 layers are separated the primitive pigment epithelium proceeds to develop into a neuroretina. This inhibition of the pigment epithelium by contact with the overlying retina is of interest in relation to the behaviour of the pigment epithelium in the adult eye.

The ciliated ependymal cells of the optic vesicle eventually develop into the receptor cells of the retina and give rise to the other retinal layers, and even in adult life the remains of cilia can still be discerned in the receptor cells.

Although the juxtaposition between the retina and the pigment epithelium is an acquired one, it is physically very close. The outer retina and the inner aspect of the pigment epithelium interdigitate, and the outer segments of the receptor cells fit closely between the apical processes of the pigment epithelial cells to form a near union which undoubtedly has mechanical strength (Foulds, 1975) but which, more importantly, brings a large surface area of pigment epithelium into close proximity with an extended surface area of outer retina. This arrangement allows easy transfer of metabolites and waste products between the 2 cell layers. It is the importance of this close contact that I wish to stress and the consequences of disturbance of this anatomical and physiological relationship.

Structure and function

Before doing so it is necessary to outline further some structural and functional aspects of the 2 layers. Physically any small gaps between the apical processes of the pigment epithelial cells and the outer retina are filled with a mucopolysaccharide ground substance, the interphotoreceptor matrix (Sidman, 1958; Zimmerman and Eastham, 1959; Fine and Zimmerman, 1963; Rohlich, 1970; Feeney, 1973a), which shows well when stained with colloidal iron and the Prussian blue reaction (Fig. 2). As Berman and others have shown (Berman, 1969; Berman and Voden, 1970), this material is different from the hyaluronic acid of the cortical vitreous, for it is not depolymerised by hyaluronidase as is the vitreal mucopolysaccharide.

The function of the interphotoreceptor matrix is not known. Speculatively it has been suggested that it may be an ion trap maintaining local concentrations of various ions which may be concerned with the initial generation and transmission of the visual impulse in the outer segment of the receptor cell. It does not seem to act as a tissue glue holding the retina in place, for it is apparently normal in eyes with retinal detachment (Fig. 3). An intriguing

Fig. 2 Human retina stained with Prussian blue reaction to show the interphotoreceptor matrix (arrowed)

Fig. 3 Rabbit pigment epithelium in experimental retinal detachment to show interphotoreceptor matrix material on pigment epithelial surface (arrowed)

possibility is that it may act as a damping mechanism preventing damage to the outer segments by shearing movements of the retina in relation to the pigment epithelium, for the connection between the outer and inner segments of the receptor cell is very thin, and one could imagine that shearing movements could easily damage the connecting structures if they were unsupported.

The origins of the interphoto-receptor matrix are also disputed. If one examines tissue in which the receptor cells have degenerated, after experimental retinal detachment, for example, one can see a heavy concentration of mucopolysaccharides on the apical surface of the pigment epithelial cell layer and on the now distantly situated Muller cell surface, suggesting perhaps that each of these cell types is capable of elaborating the interphoto-receptor matrix (Johnson and Foulds, 1976).

Another aspect of the pigment epithelium is its ability to phagocytose material presented to its inner surface. Not only does it scavenge the potential subretinal space, it is actively concerned in the continuous phagocytosis of the outer limbs of the retinal receptors, both rods and cones (Bairati and Orzalesi, 1963; Young and Bok, 1969).

This phagocytosis is part and parcel of the cycle underlying the degradation and regeneration of visual pigment, a cycle which appears to operate at several levels. There is a molecular level involving the reversible isomerisation of retinol, and a much grosser level involving the physical breaking down of the outer segments, their subsequent metabolism in the retinal pigment epithelial cell, and presumably the re-use of the breakdown products by the receptor cells once again. Whether all the breakdown products of phagocytosis are recycled to the retinal receptor cell is a moot point. It has been suggested that some of the material may be transported across Bruch's membrane and account for the accumulation in it of basophilic material which may represent an early stage in the development of senile disciform degeneration of the macula (Hogan, 1971).

Certainly under some circumstances, for example induced choroidal ischaemia, phagosomes from the pigment epithelium may be found in the endothelial cells of the choroidal blood vessels, but this is almost certainly a very artificial and pathological situation (Johnson, 1975b).

The capacity of the pigment epithelium to ingest outer segment material appears to be very much greater than the basic requirement, and where there is an increased breakdown of outer segments the phagocytic activity of the pigment epithelium may also be greatly increased. Recently it has been shown that in some species pigment epithelial phagocytosis

Fig. 4 Pigment epithelial phagosomes in control rabbit tissue and in tissue subjected to 30 minutes of total ischaemia followed by a 60 minutes recovery period. Following ischaemia the retinal outer segments are fragmented and there is a large increase in the number of pigment epithelial phagosomes

undergoes a circadian rhythm, being greater during the day than at night (Le Vail, 1976). A sudden increase in ambient illumination after a period in the dark also results in a rapid increase in phagocytic activity in the pigment epithelium (Bassinger *et al.*, 1976).

A pathological increase in outer segment breakdown will also be followed by an increased rate of phagocytosis in the pigment epithelium. Thus, for example, choroidal ischaemia in the rabbit causes a rapid breakdown of the receptor cells and particularly their outer segments, with a massive accumulation of outer segment debris separating the retina from the pigment epithelium and interfering with the close anatomical relationship which should exist between these 2 layers. In spite of the severe

Fig. 5 Rabbit pigment epithelium in experimental retinal detachment to show absence of phagosomes

Fig. 6 Production of mobile macrophage-like cells from rabbit pigment epithelium after experimental detachment of the retina

disorganisation of the outer retina which follows choroidal ischaemia, a return of blood supply may be followed by a remarkable restoration of near normal structure and a recovery of function as indicated by the reappearance of the previously extinguished electroretinogram (Foulds and Johnson, 1974; Johnson, 1976). This recovery from an ischaemic episode is accompanied by a remarkable increase in phagosomes present in the pigment epithelial cells (Johnson, 1975a) (Fig. 4). This activity appears to be important in the restitution of the normal interface and a return of visual function. In contrast, in established retinal detachment, where after a short time no outer segments survive, the number of phagosomes in the pigment epithelium is reduced to zero (Kroll and Machemer, 1968; Johnson and Foulds, 1977) (Fig. 5).

Macrophage-like cells

In situations where excessively large amounts of outer segment debris overwhelm the phagocytic activity of the pigment epithelium, or where the retina is separated from the pigment epithelium, the epithelium draws upon its pluripotential capacity and appears capable of elaborating mobile cells with many of the characteristics of macrophages. Such cells are seen in the subretinal space in acute ischaemic damage to the retina and very strikingly, in retinal detachment, where their apparent origin from the retinal pigment epithelium can be surmised on morphological grounds (Johnson and Foulds, 1977) (Fig. 6). Although the retinal pigment epithelium appears capable of transforming into macrophage-like cells, many of the macrophages

Fig. 7 *Metaplasia of the pigment epithelium with bone formation in rabbit experimental retinal detachment*

found in the subretinal space in, for example, retinal detachment may nevertheless be derived from the blood stream, for Bruch's membrane appears to be no barrier to the passage of cells inwards from the choroid.

Pigmented macrophage-like cells of possible pigment epithelial origin may be seen in a wide variety of pathological processes affecting the interface between the retina and the pigment epithelium, a striking example being retinitis pigmentosa. One possible stimulus to cellular activity in the pigment epithelium is loss of contact inhibition by the retina, either because of physical separation in retinal detachment or by the loss of some inhibitory function which is peculiar to normal outer retina and normal receptors.

In retaining an embryological capacity for multiplication the pigment epithelium seems capable of returning to a more primitive multicellular format and can show a surprising ability as an epithelial layer of neuroectodermal origin to form cells capable of laying down collagen and even bone, a metaplasia which may be strikingly seen when the retinal pigment epithelial interface is broken by retinal detachment (Foulds and Ikeda, 1966) (Fig. 7).

Thus physically breaking the retinal-pigment epithelial interface leads to dramatic changes in structure and function of the pigment epithelium, which may increase its phagocytic activity by normal cellular activity or undergo metaplasia to produce actively phagocytic macrophages. Alternatively or additionally, the epithelium may proliferate to form a multilaminar layer, which may take on the characteristics of connective tissue, with the formation of fibrous tissue or even bone, and a loss of the more specialised features of the pigment epithelium.

Fig. 8 *Degeneration of receptor outer and inner segments in shallow secondary retinal detachment in the human eye*

Changes in retina

The retina, too, undergoes dramatic changes when separated from the pigment epithelium. Very rapidly the receptor cells degenerate. The degeneration starts at the outer segments and goes on to progressive degeneration affecting the inner segments and then the receptor cell bodies and subsequently the other neural layers from without inwards, until eventually the neural tissue of the retina is replaced by a layer of glial supporting tissue without any visual function whatsoever (Foulds, 1964; Foulds and Ikeda, 1966; Kroll and Machemer, 1968). This degeneration occurs even if the detachment is shallow and appears to be a direct consequence of the separation of the retina from the pigment epithelium (Fig. 8).

RETINAL DETACHMENT

Fig. 9 Serial static perimetry in a patient treated for retinal detachment. There is progressive increase in retinal sensitivity over a 4-month period, but peripheral retinal function recovers more rapidly than central

If the retinal-pigment epithelial interface is restored before the receptor cell bodies have degenerated, then regeneration of the inner and outer segments of the receptor cells occurs with a return to a normal anatomical appearance and a recovery of visual function (Foulds, 1964; Kroll and Machemer, 1968). Receptor cell regeneration may well explain the recovery of retinal function which follows surgical cure of a retinal detachment in man. This improvement in retinal function may be reflected by a decrease in the visual field defect, and particularly well by measurements of differential threshold, which may be plotted by static perimetry (Foulds *et al.*, 1974; Chisholm *et al.*, 1975). As can be seen from serial static perimetric profiles, rod vision appears to recover more rapidly than cone vision (Fig. 9).

Measurement of colour vision too is a useful criterion of visual function, and it is of interest that not only is there a rapid improvement in colour vision after successful retinal detachment surgery, but an improvement continuing for a year and sometimes longer is commonly seen (Chisholm *et al.*, 1975). When one looks at the average rate of improvement in colour vision after successful surgery for retinal detachment affecting the macula, one sees a curve which may give an indication of the rate of cone regeneration with a half life of about 12 weeks (Fig. 10).

Electrophysiological findings

Apart from obvious morphological changes which occur in the outer retina and the pigment epithelium when the interface between them has been broken, characteristic changes also occur in electro-physio-

MEAN RECOVERY OF COLOUR VISION FOLLOWING RETINAL DETACHMENT SURGERY (14 Cases)

Fig. 10 Mean rate of recovery of colour vision after successful retinal detachment surgery in 14 cases in which the macula was affected. There is rapid recovery during the first 3 months and slower recovery subsequently

Fig. 11 Rabbit electroretinograms before and after induction of total experimental retinal detachment. Detachment of the retina results in a reduction in b-wave amplitude and a total abolition of the c-wave

logical parameters. It is well known that a prolonged separation of the retina from the pigment epithelium is accompanied by abolition of all the components of the electroretinogram (Karpe, 1948) and by an abolition of light-induced changes in the electro-oculogram (Foulds and Ikeda, 1966). One might be tempted to think that all of the electrophysiological alterations are a reflection of the obvious degenerative changes which occur after separation of the retina and the pigment epithelium, but there is evidence that separation of these layers alone is responsible for some of the electrophysiological findings. In the rabbit, for example, the scotopic electroretinogram (ERG) shows not only a well developed a- and b-wave but also a c-wave which is thought to represent metabolic activity in the pigment epithelium (Noell, 1953). Separation of the retina from the pigment epithelium causes a decline in the amplitude of the ERG and its eventual abolition over the course of 48 hours or so (Foulds and Ikeda, 1966). If, however, one examines the ERG immediately before and immediately after a

total retinal detachment has been induced, one finds that apart from a reduction in the amplitude of the a- and b-waves there is an immediate and total abolition of the c-wave (Fig. 11). The pigment epithelium at this stage looks normal and retains its normal relationship to its blood supply, while the retina too appears structurally intact.

The changes in the ERG therefore suggest that, although the pigment epithelium may be the seat of the c-wave, contact between the retina and pigment epithelium is necessary for its production. Support for this suggestion comes from a study of the standing potential of the eye undergoing acute total retinal detachment (using a modification of the technique described by the author in 1963). Before the retinal detachment has been induced, the standing potential decreases in the dark and increases in the light as expected. Immediately after detachment light-induced changes in the standing potential are abolished, no decrease occurring in the dark and no increase in the light (Fig. 12). When, however, sodium azide is injected intravenously, there is an immediate temporary increase in the corneofundal potential. Sodium azide is known to affect ionic flux across the pigment epithelial cell membranes, and the induced rise in corneofundal potential following intravenous sodium azide is an indication that the pigment epithelium is still functionally active, and once again evidence that the abolition of the electro-oculogram in retinal detachment is not in the first place due to degenerative changes in either the retina or the pigment epithelium, but the direct result of separation of these 2 layers.

It is of interest that if the retinal separation is subtotal the c-wave remains normal, although the b-wave of the ERG is reduced in amplitude commensurate with the area of detachment (Fig. 13). It appears that the whole retinal pigment epithelium can be stimulated to metabolic activity via a localised residual area of retinal pigment epithelial contact, and there are grounds for believing that the pigment epithelial layer acts as a single unit in this respect and not as a series of individual cells. It has been suggested that the electrical continuity of the pigment epithelial layer is established via the gap junctions between neighbouring cells, which allow ionic transfer from one cell to its neighbours (Revel *et al.*, 1972). These junctions are different from the tight junctions near the apices of the cells, which form a diffusion barrier between the choroid and the subretinal space.

Pigmentary degeneration of retina

Many of the features of retinal detachment and indeed of choroidal ischaemia resemble the patho-

RETINAL DETACHMENT and the STANDING OCULAR POTENTIAL

Fig. 12 *Electro-oculogram in rabbit before and after induction of total experimental retinal detachment. Light-induced changes in standing potential are abolished immediately the retina is detached, although azide responsiveness of the pigment epithelium is retained*

logical changes seen in primary pigmentary degeneration of the retina. Indeed atrophy and proliferation of the retinal pigment epithelium, loss of the receptor cell outer segments, and subsequently loss of the inner segments and cell bodies, all of which are features of retinitis pigmentosa, are also features of any pathological process damaging either the outer retina or the pigment epithelium. And it would seem that the clinical picture of retinitis pigmentosa is common to any process which causes damage to the tissues constituting the retinal-pigment epithelial interface.

If primary pigmentary degeneration of the retina is the result of an interference with the close metabolic interrelationships which exist between the

pigment epithelial cell and the outer retina, it is interesting to speculate which of the many metabolic activities may be at fault. Certainly one could imagine that in retinal detachment, or in damage to this area from total choroidal ischaemia, any or all of the metabolic functions of the pigment epithelium in relation to the retinal receptors could be affected. In other instances, however, the defect could be more specific.

It is well known, for example, that vitamin A deficiency can in some instances result in a somewhat similar picture to primary pigmentary degeneration, and the work of Dowling and Gibbons (1961) on the effects of vitamin A deficiency in the rat is a classic demonstration of how vitamin A deficiency can produce a reversible degeneration in the outer retina with many features common to the early stages of primary pigmentary degeneration seen in some experimental models.

Classically, in man, vitamin A deficiency is said to show itself first as a loss of rod function with deficient dark adaptation and reduction in peripheral visual field, together with xerotic changes in the superficial ocular tissues. In our experience acquired vitamin A deficiency in the adult, which we see in patients suffering from chronic liver disease, is commonly associated not only with a disturbance in rod function but with a well marked defect of cone function as shown by a reversible loss of visual acuity and by an acquired and reversible dyschromatopsia, together with a reduction in the amplitude of both the scotopic and photopic ERG (Bronte-Stewart and Foulds, 1972).

E.R.G. in SUBTOTAL RETINAL DETACHMENT

Fig. 13 *Rabbit electroretinogram in subtotal retinal detachment. The amplitude of the b-wave is reduced, but the c-wave amplitude remains normal*

Fig. 14 Rate of recovery of colour vision in a patient with acquired dyschromatopsia associated with vitamin A deficiency. The rate of recovery is not dissimilar to that following successful treatment for retinal detachment

The effects of vitamin A deficiency on visual function appear to be inversely related to the degree of illumination to which the retina has been subjected. It is interesting that one of our patients with vitamin A deficiency, finding that she was unable to see as she would like, progressively increased the strength of the electric light bulbs in her house until she had the largest obtainable wattage lamps in every possible socket in the house. The more she increased the illumination, the more rapidly her vision deteriorated. Not only was her visual acuity poor, as might have been expected in someone show-

ing marked vitamin A deficiency, dark adaptation was grossly abnormal. Colour vision too was also extremely defective. Within a week of beginning vitamin A therapy visual acuity and dark adaptation returned to near normal and colour vision improved progressively. Interestingly, the rate of improvement of colour vision on vitamin A therapy paralleled that seen after retinal detachment surgery (Fig. 14), a relationship suggesting a similar process of cone recovery or regeneration with a half life of about 12 weeks. When this patient's vision improved she found the previous level of illumination at home distressingly painful to her now normal vision and rapidly reduced the strength of the electric light bulbs to a more conventional level.

This effect of light is of course to be expected, the rate of breakdown of visual pigment being related directly to the amount of light being absorbed, and it is easy to imagine that if regeneration of visual pigment is defective for any reason photic stress is likely to exaggerate the defect. Thus in the RCS rat, for example, which develops a primary pigmentary degeneration of the retina, the process is delayed if the animals are reared in the dark (Herron *et al.*, 1969), which suggests that in these animals pigmentary degeneration is related to the process of bleaching and resynthesis of visual pigment.

There are in man conditions in which vitamin A deficiency is associated with a pigmentary degeneration of the retina. Thus, in the rather rare condition of abetalipoproteinaemia one finds an inability to absorb the fat soluble vitamins and low levels of vitamin A and of carotenes in the serum. In 2 patients we have investigated recently vitamin A and carotene levels were extremely low, and both patients showed the characteristic pigmentary retinopathy which has been described in the Bassen-Kornzweig syndrome (Bassen and Kornzweig, 1950), with marked choroidal 'show-through' on fluorescein angiography (Fig. 15). There was a widespread reduction in retinal sensitivity affecting both the peripheral retina and the central retina, with gross visual field defects and an acquired achromatopsia. Dark adaptation was abnormal and the photopic and scotopic electroretinograms were unrecordable. In 1 case treatment with large doses of intramuscular vitamin A resulted in a rapid return to normal of dark adaptation (Fig. 16) and of the electroretinogram (Fig. 17). There was slight improvement in central vision but a marked improvement in visual field (Fig. 18). Interestingly, the retinol binding protein level, which initially was undetectably low, returned to normal on treatment with vitamin A. This suggests that the amount of retinol binding protein in the blood was a reflection of the amount of vitamin A to be transported and

Fig. 15 Fluorescein angiograms in a patient suffering from abetalipoproteinaemia. There is marked abnormality of the pigment epithelium with choroidal 'show-through' and late staining of a gliotic area below the macula

that in these patients the reported depression of retinol binding protein levels may be secondary to the vitamin A deficiency.

The response of dark adaptation and of peripheral field to vitamin A in one of these patients was gratifying but the lack of recovery of central vision disappointing. Recently we have measured this patient's essential fatty acid levels and have found

these to be extremely depressed. There is evidence that outer segment turnover is dependent on polyunsaturated fats (Anderson *et al.*, 1974), and it may be that the receptor abnormality in patients with the Bassen-Kornzweig syndrome is multifactorial, vitamin A and essential fatty acids being two of the factors involved. Indeed our findings of poor colour vision in vitamin A-deficient patients suffering

Fig. 16 Serial dark-adaptation curves in a patient with abetalipoproteinaemia treated with vitamin A. Within a week of treatment dark adaptation, which was grossly abnormal, recovered to within normal limits and remained so for the subsequent 3 years

from chronic liver disease might also be an example of multifactorial deficiency, for gross abnormality of fat metabolism was present in these patients also.

Although vitamin A deficiency in animals and possibly in man can produce some of the features of retinitis pigmentosa, there is little doubt that human retinitis pigmentosa is not due to overt vitamin A deficiency, for it is well known that no support for this simplified concept is to be found in examination of vitamin A metabolism in patients suffering from this condition. Nor does it seem likely that an abnormality in the retinol binding protein, which transports vitamin A from the liver to the eye, is a consistent finding in patients with retinitis pigmentosa (Rahi, 1972).

Passage of metabolites

In relation to retinol binding protein a slight digression may be in order. When one looks at the basal region of the pigment epithelial cell one finds that

the basal lamina is remarkably convoluted, so that its surface area is greatly increased, a modification no doubt designed to increase the ease of transfer of metabolites between pigment epithelial cells and the underlying choriocapillaris. The choriocapillaris too is oddly specialised, in that, unlike the majority of capillaries in the body, it is fenestrated, with obvious breaks in the capillary basement membrane, the individual fenestrations being directed towards the pigment epithelium (Porter and Yamada, 1960; Bernstein, 1961; Leeson and Leeson, 1968).

Why should these capillaries be so fenestrated? One might argue that the breaks will facilitate the passage of metabolites from the lumen of the choriocapillaris to the extravascular space, but in other situations, such as in the retina and the brain, the high metabolic requirements of the tissues are met without this modification. An alternative explanation would be the need to allow the passage outwards from the choriocapillaris of larger molecules than could escape by diffusion through the intact vessel wall. It is known that retinol binding

Fig. 17 Photopic electroretinogram in a patient treated with vitamin A for abetalipoproteinaemia. Initially the ERG was unrecordable. One day after beginning vitamin A therapy a photopic ERG appeared and within 1 week was within normal limits

Fig. 18 Recovery of visual field in a patient treated for abetalipoproteinaemia with vitamin A. Improvement in field occurred over a period of about 4 weeks

protein has a molecular weight of about 21 000, and it is also known that there are specific binding sites on the basal aspect of the pigment epithelial cell for retinol binding protein (Young and Bok, 1970; Heller, 1975; Bok and Heller, 1976). It would seem reasonable that the fenestrations are there to allow retinol binding protein with its vital retinol access to the pigment epithelial cell from the choroid.

As a corollary this would allow the leakage of other large molecules, such as the plasma proteins, and, as the presence of proteins within the eye decreases light transmission, it would be necessary to restrict the forward diffusion of these proteins, a circumstance achieved by the provision of zonulae occludentes between neighbouring pigment epithelial cells. It is interesting that these junctions are apical, so that the whole of the pigment epithelial cell, apart from its apical surface, is bathed in proteinous fluid and therefore exposed to retinol binding protein. As a further corollary, the eye has the problem of how to dispose of plasma protein which has leaked from the choriocapillaris. In general extravascular protein is returned to the circulation via the lymphatic system, but no lymphatics exist in the eye. The nearest lymphatics are in the orbit, and there is evidence for the existence of a transcleral movement of even large molecules under the influence of the intraocular pressure, an arrangement which may be designed to allow access to the orbital lymphatics of choroidal protein which has of necessity become extravascular (Foulds, 1976).

The utilisation of vitamin A in the synthesis and resynthesis of visual pigment involves a complicated series of biochemical events, which includes not only absorption of vitamin A from the gut and its storage in the liver but its transport by retinol binding protein to the eye and its subsequent binding on

specific receptor sites on the pigment epithelial cell wall. It is known that a variety of transferases are involved in transferring the retinol into the pigment epithelial cell, out of the retinal pigment epithelial cell and into the inner segment of the retinal receptor cell (Dowling, 1960; Young and Bok, 1970).

In both the pigment epithelial cell and the inner segment of the retinal receptor cell there are separate retinol binding proteins of different molecular weights to plasma retinol binding protein, and in addition there are probably enzymic reactions involved in the conjugation with opsin and the production of the membranes which form the basis of the stacked discs in the outer segment. Enzymic reactions are undoubtedly involved in the phagocytosis and metabolism of outer segment material by the pigment epithelial cell and also in the reversible changes which occur during the normal processes of bleaching and regeneration of the visual pigment associated with the initiation of the visual impulse.

It seems at least possible that a failure of any of these steps, many of which involve specific enzymic activity, could lead to a breakdown in the synthetic pathways of visual pigment or in the turnover of outer segment material and result eventually in the structural changes which may underlie the development of retinitis pigmentosa. If this is true, then any one of perhaps 20 or 30 steps could be involved, and the possibility exists that there may be as many as 20 or 30 different types of retinitis pigmentosa. Apart from vitamin A the role of other metabolites has to be considered, and these include fatty acids and amino acids such as taurine.

Conclusion

If the group of diseases which present with pigmentary degeneration of the retina are considered to

share a final common mechanism, that would allow us to include not only vitamin A deficiency but rarities like abetalipoproteinaemia in the same category and such diverse conditions as retinal detachment, choroidal ischaemia, and even light damage to the retina. Thus, the mechanisms underlying a wide variety of pigmentary disturbances in the fundus can be thought of as pigment epithelial-retinal interface diseases, and a condition such as retinitis pigmentosa, which clinicians tend to regard as an entity, may represent a whole group of as yet inadequately described and ill understood genetically determined biochemical abnormalities.

The interface between the retina and the pigment epithelium is basic to the visual process, and a better understanding of the interrelationships between these 2 cell layers may both add to our concepts of normal physiology and improve our understanding and management of the many pigmentary retinopathies which at present remain a mystery to the ophthalmologist and a tragic misfortune to those affected.

I should like to record my gratitude to the various members of the Tennent Institute of Ophthalmology in Glasgow, whose material has formed the basis of this lecture, and in particular to Dr W. R. Lee, ophthalmic pathologist, for his constant help, and to Drs Johnson and Grierson for permission to reproduce some of their electronmicrographs. I thank Dr Shaw Dunn, of the Department of Anatomy, Glasgow University, for the embryological preparations, and I particularly thank Dr Hisako Ikeda, of St. Thomas's Hospital Medical School, who many years ago worked with me on the functional and structural effects of retinal detachment and some of whose joint work is presented here. I am particularly grateful to her as she was largely responsible for kindling my interest in the retinal-pigment epithelial interface.

I acknowledge the secretarial help of Mrs I. Beard and her staff and the technical assistance of Mr J. Watt and technical staff of the Tennent Institute of Ophthalmology.

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