The absence of diabetic retinopathy in patients with retinitis pigmentosa: implications for pathophysiology and possible treatment

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Diabetic retinopathy (DR) is a leading cause of blindness but it is not known why retinopathy should be so early and so severe a complication of diabetes. The sensory loss caused by minute retinal lesions is part of the problem, but the diabetic changes in the brain are different and less serious than in the retina, often described as an outpost of the brain. This has led to the concept of a local factor being responsible for the microvasculopathy of DR. There are physiological factors unique to the retina, and it is suggested below how these, by causing hypoxia very early in diabetes, could activate cytokines that produce the microvascular changes. If retinal hypoxia is an important causal factor in the production of DR, prevention of hypoxia should ameliorate DR. This hypothesis predicts that retinitis pigmentosa (RP) should prevent DR. Both old and new work is described, which indicates that this is in fact the case, thus pointing to new, simple, and effective ways of delaying the progress of diabetic retinopathy.

Direct comparison of retinal and brain capillaries taken from diabetics show very considerable differences1 (Table 1), which indicate a “local factor” in the development of DR. It has been suggested2 that the local factor is related to what is unique to the retina, the photoreceptors. The 120 million rods have the highest metabolic rate of any cell in the body. In darkness, the outer limb membrane “leaks”, causing an inward “dark current”. This current is reduced by light, and at normal photopic levels is shut off completely. In full dark adaptation sodium ions and water enter the outer limb at a maximal rate, and are pumped out in the inner limb.3 The entire cytosol volume is pumped in about 15 seconds.4 This process requires a great deal of energy and a large oxygen supply. However, the rods are avascular. Despite the “wall” of blood in the choroid and the extensive ramification of the central artery of the retina, oxygen tension ([P02]) among the unusually large mitochondria of the inner limb is essentially zero.5–7 When a flash of light is delivered to the retina, [P02] abruptly rises as the pumps slow down.4 Figure 1 shows this effect.

Recent work10–13 confirms this result, and also shows that in dark adaptation the receptor layer removes considerable amounts of oxygen from the inner retina so [P02] changes with illumination can also be seen there.14 The unusually low [P02] would of course affect many other cells adversely. Although some compensatory mechanisms may occur, very small decreases in normal oxygen supply affect retinal function. Thus, dark adaptation is incomplete at reduced air pressures equivalent to heights of only 3000 feet—aeroplane cabins are pressurised to 7000 feet—and photopic vision is only affected at about 12 000 feet.2,15–17 Mild unilateral carotid insufficiency causes a unilateral and reversible loss of rod threshold.18–20 Polycythaemia vera produces a rheological change in red blood cells that effectively reduces oxygen delivery: and, again, rod threshold increases, reversibly.

Thus, the normal retina in dark adaptation uses so much oxygen that it borders on the pathologically anoxic. There is also evidence that, in diabetics, the retina suffers from oxygen lack before the onset of clinical DR. The electroretinogram becomes abnormal years before fundusscopic changes can be seen.21 Both (photopic) contrast sensitivity22 and colour vision23 are impaired even before any microaneurysms are present; and inhaling oxygen from a face mask partially reverses the raised threshold, although the extra oxygen carried to the retina is very small. Scotopic threshold has been known for half a century to be more seriously affected.10,24 Recent investigations suggest that in mild DR, the threshold initially falls, and then recovery ceases, as it would if dark adaptation was occurring in the presence of a dim
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Table 2  Details of a survey of patients with diabetes mellitus and retinitis pigmentosa

<table>
<thead>
<tr>
<th>Classification of diabetes</th>
<th>IDDM</th>
<th>NIDDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of replies validated by doctor</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Mean age (years (SD))</td>
<td>60.8 (16.8)</td>
<td>65.5 (15.3)</td>
</tr>
<tr>
<td>Maximum, median, and minimum ages</td>
<td>81, 61, 23</td>
<td>88, 67, 27</td>
</tr>
<tr>
<td>Number of cases of diabetic retinopathy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean age at diagnosis of diabetes (years)</td>
<td>35</td>
<td>48</td>
</tr>
<tr>
<td>Mean duration of diabetes (years)</td>
<td>19</td>
<td>14.5</td>
</tr>
<tr>
<td>Interval between night blindness onset and diabetes onset (years)</td>
<td>7.2 (n = 10)</td>
<td>19.5 (n = 24)</td>
</tr>
<tr>
<td>Patients with other non-ocular complications of diabetes</td>
<td>5 (n = 11)</td>
<td>8 (n = 18)</td>
</tr>
</tbody>
</table>

DR. In view of the relatively high age of onset in the IDDM group (35 years), the identification of the type of diabetes in some patients is suspect. In some cases, only ophthalmologists replied, and some stated that they did not know if the patients had non-ocular complications of diabetes, or they did not know the details of treatment. However, copies of medical notes and fundus photographs (of varying quality) were also provided in a number of cases. No patient had had the four field standard photographs mandatory for new epidemiological studies and no patient was willing to attend a (remote) centre for such photographs to be taken. Thus the patients’ present ophtalmic state is well but not perfectly documented. The reduced number of patients in the last rows of Table 2 reflect the lack of information in the doctors’ files about events in their patients’ past. Although various types of IR inheritance were represented—autosomal dominant, autosomal recessive, and X linked, as well as Usher’s type 1—in only one case had genetic screening been performed. Two cases of Lawrence-Moon-Bartlett-Biedel syndrome are included. The mean age of the patients responding is high, and so therefore is the duration of their diabetes. Since about 40% of those responding with appropriate information had other diabetic complications, the total absence of any signs of DR is striking. There were no microaneurysms in the sample, no exudates of any type, and no haemorrhages in the retina. Patients were positive that they had never had any retinal abnormalities. Individual histories are illustrative: thus, one patient developed diabetes in early childhood, and 45 years later has no DR, although she has diabetic nephropathy requiring dialysis, and diabetic cardiopathy. Another, aged 78, who developed diabetes aged 5 has no DR. Another, aged 68, with autosomal dominant inheritance reported his night vision became poor 16 years after the onset of diabetes, confirming the considerable protection against the appearance of DR in patients with RP.

Although the sample is still small, it is double that of all the other reports combined. It is unrepresentative, if only for the age of the respondents, though for the purposes of the investigation the long duration of DM is an advantage. The results completely bear out the belief of ophthalmologists specialising in retinal degenerations that RP protects against DR and supplement the previous survey of typical RP, which was concerned only with the presence of proliferative retinopathy. It is reasonably certain that replies were obtained for people with a number of different mutations in different chromosomes. By making the assumptions (as in Holmes-Walker et al.) that previous epidemiological studies of DR are appropriate for this survey (that is, conservatively, ~75% of patients should have fundal changes of DR 15 years after diagnosis) the probability of obtaining, by chance, a population of 55 cases with RP and no DR is extremely small. The crude binomial probability is 4/10 000 (0.75%). Type II patients may develop diabetes when the retina is relatively non-functional and atrophic. However, in type I, the mean interval between night blindness and the onset of DM is only ~7 years and thus many patients had relatively large areas of partially functioning retina when DM began. In three cases DM developed in childhood, and these patients must have had considerable retinal function and diabetes for more than 10 years. Thus, although the methodology of a retrospective survey is not ideal, it does also highlight the point that these patients have never exhibited evidence of background retinopathy. There are so many genetic changes which cause RP that the only single unifying cause for the protection is the loss of photoreceptors, importantly rods. In many cases of autosomal dominant RP 50% of rods vanish with an elevation of rod threshold by only 0.3 log unit (due to a loss in the “quantum catch”). This degree of night blindness should be as effective as a PRP which “burnt” 50% of the retina, and illustrates why RP is so protective.

Very occasionally, patients with RP may develop neovascularisation at the optic disc which can regress or develop, but this phenomenon is not understood and the process quite different from DR. Maternally inherited diabetes and deafness, or MIDD, is a mitochondrial disease of adult life, sometimes also causes a pigmentary retinopathy that differs considerably from the more common forms of RP, in which rod loss occurs early. Thus, where electroretinograms (ERGs) have been performed on patients with MIDD, they are abnormal in only 4/13, and rod and cone ERGs are equally affected. In nine of 24 there is either reduced visual acuity or an abnormal visual cortical evoked potential, suggesting earlier macular involvement than in classic RP. Of 24 MIDD cases with DM and pigmentary retinopathy reported, in two different investigations, five have non-proliferative DR, so they are significantly different (~χ² test) from ordinary RP (Table 2). In cases where there is no RP, the incidence of DR is higher, so even incomplete rod loss is partially protective against DR. The cause of MIDD is an abnormality in the reaction centres that produce a proton gradient in the mitochondrion. The variability of the symptomatology is thought to be due to the simultaneous occurrence of normal and affected reaction centres in the same mitochondrial, and the normal/abnormal ratio in different tissues and cells. The way diabetes develops has recently been elucidated. The fairly frequent occurrence of lesions in photoreceptors is not unexpected in view of the intense metabolic requirements of the inner limit mitochondria. Comparison of MIDD and the nuclear genetic disturbances may help to discriminate between rival hypotheses of the formation of DR. It has been suggested that an important factor in the production of DR is the production of free radicals. The proposed sequence was that in DM increased glycolysis leads to acidosis and the retina is also hypoxic. Under such conditions proton gradients induce free radicals, and these cause DR. The absence of DR in RP was explained by the suggestion that loss of photoreceptors reduced glycolysis and decreased the production of free radicals. In MIDD the basic loss is an inability to make ATP through oxidative phosphorylation and loss of the proton gradient. It is suggested that glycolysis increases. If the production of free radicals depends on the establishment of a proton gradient, MIDD might be expected to be protective against DR but this is the case only when retinal degeneration occurs. Thus, the observations on MIDD make the importance of free radicals to DR less likely and are consistent with the anoxia/VEGF hypothesis described here.

In life, dark adaptation and its accompanying low [Po2] occurs mostly during sleep. In turn, this suggests that non-destructive methods of reducing rod dark current could help prevent DR by increasing retinal oxygen tension when it is lowest. The dark current is maintained by...
cyclic guanylyl monophosphate (cGMP), which is destroyed after the absorption of photons. Intracellular calcium accelerates GMP cyclase and thus the formation of GMP. The presence of cGMP in the rod outer limbus is essential for a Na-Ca exchange, which reduces sodium entry and is reduced when Na enters the cells.

This is one important mechanism of light adaptation.

Reducing rod guanylyl cyclase activity, or pharmacologically preventing calcium entry, or preventing full dark adaptation by a continuous low level of background light should be an effective form of decreasing peak outer limiting retinal oxygen demand. Such interventions could thus slow the progression of diabetic retinopathy. The latter method is simple, inexpensive, and particularly appropriate for the developing world.

Note added at proof stage:
Since this article was submitted it has been known that in a group of long term diabetics who do not develop DR, the upregulation of VEGF by anoxia is largely absent, thus lending strong support to the hypothesis developed above.

The author thanks the Foundation Fighting Blindness Inc, the British Retinitis Pigmentosa Society, and Retinitis Pigmentosa International for the facilities offered, and Dr JE Wolf, Dr J Heckenlively, Dr CS Bain, Dr R Tzekov, and Mr AMP Hamilton, FRCS, for their assistance in contacting patients and for helpful discussions.

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