Retinitis pigmentosa
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Hereditary degenerations of the human retina are genetically heterogeneous, with well over 100 genes implicated so far. This Seminar focuses on the subset of diseases called retinitis pigmentosa, in which patients typically lose night vision in adolescence, side vision in young adulthood, and central vision in later life because of progressive loss of rod and cone photoreceptor cells. Measures of retinal function, such as the electoretinogram, show that photoreceptor function is diminished generally many years before symptomatic night blindness, visual-field scotomas, or decreased visual acuity arise. More than 45 genes for retinitis pigmentosa have been identified. These genes account for only about 60% of all patients; the remainder have defects in as yet unidentified genes. Findings of controlled trials indicate that nutritional interventions, including vitamin A palmitate and omega-3-rich fish, slow progression of disease in many patients. Imminent treatments for retinitis pigmentosa are greatly anticipated, especially for genetically defined subsets of patients, because of newly identified genes, growing knowledge of affected biochemical pathways, and development of animal models.

Retinitis pigmentosa is the term given to a set of hereditary retinal diseases that feature degeneration of rod and cone photoreceptors. This Seminar will review the current status of our knowledge of this disorder, including its prevalence and inheritance patterns, symptoms and signs, molecular genetics, current treatments, and anticipated future treatment approaches.

Prevalence and inheritance patterns
The worldwide prevalence of retinitis pigmentosa is about 1 in 4000 for a total of more than 1 million affected individuals. The disease can be inherited as an autosomal-dominant (about 30–40% of cases), autosomal-recessive (50–60%), or X-linked (5–15%) trait.1–3 These proportions for inheritance patterns assume that all isolated cases—ie, patients with no other affected relatives—are autosomal recessive, although a few might represent new dominant mutations, instances of uniparental isodisomy,4 or, for males, X-linked mutations. Non-mendelian inheritance patterns, such as digenic inheritance and maternal (mitochondrial) inheritance, have been reported but probably account for only a small proportion of cases.5–11 In a multicentre study from Japan including 29 vision rehabilitation centres, retinitis pigmentosa was the major cause of visual handicap or blindness, accounting for 25% of patients.12 In Kuwait, this disease was the leading cause of visual disability in individuals younger than 60 years,13 and in Denmark, retinitis pigmentosa and optic neuropathy were the leading causes of blindness in people aged 20–64 years, each accounting for 29% of cases.14

 Syndromic retinitis pigmentosa
Retinitis pigmentosa is a disease usually confined to the eye. However, some 20–30% of patients have associated non-ocular disease, and such cases fall within more than 30 different syndromes.

Usher’s syndrome, in which retinitis pigmentosa is associated with hearing impairment, is the most frequent syndromic form, accounting for about 20–40% of individuals with recessive disease (or 10–20% of all cases). The hearing loss can be either profound, present at birth, and associated with vestibular ataxia (Usher’s syndrome type I) or moderate to mild in severity and non-progressive (type II). Normal hearing can be present in youth but during later years gradual hearing loss can occur (type III). Alterations in at least 11 genes cause Usher’s syndrome; different mutations in some of these genes lead to type I, II, or III disease.15 Depending on the mutation, some genes for Usher’s syndrome can also cause either retinitis pigmentosa without hearing loss16,17 or deafness without retinitis pigmentosa.18–22

Another major form of syndromic retinitis pigmentosa is Bardet-Biedl syndrome, in which retinitis pigmentosa is variably associated with obesity, cognitive impairment, polydactyly, hypogonadism, and renal disease (mostly structural abnormalities such as calyceal cysts or calyceal clubbing and blunting);22,24 some patients develop renal failure and need transplantation. Bardet-Biedl syndrome accounts for as many as 5–6% of cases of retinitis pigmentosa.21,22 Ten genes for Bardet-Biedl syndrome have been identified, which cause about 70% of cases.23–25 Inheritance is generally a mendelian autosomal-recessive pattern; however, in some families, mutations at two unlinked Bardet-Biedl genes have been recorded,26 with compound heterozygosity (or homozygosity) present at one locus and one mutation at the second.27,28 Whether the mutation at the second locus is needed to express the disease or whether it merely modifies severity or expressivity of mutations at the other locus is still unclear. The proportion of Bardet-Biedl families showing digenic inheritance might be low.12

Search strategy and selection criteria
We searched PubMed and EMBASE for the term “retinitis pigmentosa”. Most selected publications were from the past 5 years, but we did not exclude commonly referenced and highly regarded older publications. We furthermore searched the reference lists of articles identified by this search strategy or from our own literature databases. We also used the internet database for genetics of retinal diseases (www.sph.uth.tmc.edu/Retnet) and the NCBI database Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM). No restriction was applied on the language of publications.
Of the many rare syndromic forms of retinitis pigmentosa, three are important clinically. In these disorders, treatment might be vision-saving if begun early: abetalipoproteinaemia (Bassen-Kornzweig syndrome); phytanic acid oxidase deficiency (Refsum’s disease); and familial isolated vitamin E deficiency (α tocopherol transport protein deficiency).

Symptoms
Retinitis pigmentosa is a highly variable disorder; some patients develop symptomatic visual loss in childhood whereas others remain asymptomatic until mid-adulthood. Many patients fall into a classic pattern of difficulties with dark adaptation and night blindness in adolescence and loss of mid-peripheral visual field in young adulthood. As the disease advances they lose far peripheral vision, eventually develop tunnel vision, and finally lose central vision, usually by age 60 years.

Visual symptoms indicate the gradual loss of the two photoreceptor types (figure 1): rods, which mediate achromatic vision in starlight or moonlight; and cones, which are important for colour vision and fine acuity in daylight. The outer nuclear layer of the retina consists of rod and cone photoreceptor nuclei and is severely attenuated in patients with retinitis pigmentosa. The inner nuclear layer—composed of amacrine cell, bipolar cell, and horizontal cell neurons—and the ganglion-cell layer are fairly well preserved, but many of these cells degenerate later in the disease.

Most patients are legally blind by age 40 years because of severely constricted visual fields. In most forms of typical retinitis pigmentosa, loss of rod function exceeds reduction of cone sensitivity. In other types, rod and cone decline is similar. Occasionally, the deficit of cones far exceeds that of rods, which is termed cone-rod degeneration, a form of retinitis pigmentosa in which loss of visual acuity and defective colour vision are the prominent early symptoms.

A clinician must be cautious when relying on symptoms to identify patients with early retinitis pigmentosa. In our electrically illuminated night-time environment, people can be unaware of a severe loss of rod function because night-time activities are typically done with sufficient light to allow vision with cones. By the time an individual recognises the symptom of night blindness, a reduction in cone sensitivity can have happened on top of a loss of rod function. Furthermore, no subjective difficulties with daily tasks may arise in people with a remaining central visual field reduced to about 50 degrees in diameter (normal bilateral visual field is about 180 degrees in the horizontal meridian). Patients can lose 90% of cones in the fovea before having a reduction in visual acuity. Reading impairment and difficulties in undertaking daily activities are typically seen when visual acuities fall below 0.5 (20/40). Objective measures of photoreceptor sensitivity (see below) are much more reliable than symptoms for diagnosis of retinitis pigmentosa and grading its severity.

Clinical assessment and findings
Visual acuity can remain normal even in individuals with advanced retinitis pigmentosa with a small island of remaining central visual field, or it can be lost early in the course of the disorder. Neglect of careful determination of refractive errors in people with severe visual loss can happen, yet patients can be very grateful...
for the modest improvement in vision that spectacles might provide. Furthermore, a measure of refractive error could give a clue to the inheritance pattern. For example, patients with X-linked retinitis pigmentosa are likely to have myopia of 2 dioptres or more, whereas hyperopia favours a diagnosis of dominant inheritance.39,40

Visual fields, measured with a Goldmann perimeter or a Humphrey field analyser (Carl Zeiss, Dublin, CA, USA), typically have scotomas in the mid-periphery that enlarge over years owing to loss of rod and cone function. In moderate-to-advanced retinitis pigmentosa, only small islands of vision remain in the far peripheral field and in the visual axis; later these areas of vision slowly disappear.

Colour vision assessed with Ishihara plates, the Farnsworth D15 panel (Munsell Colour Laboratory; Macbeth, New Windsor, NY, USA), or other tests might show normal colour vision or a deficiency in blue cone function (acquired tritanopia), which is characteristic of advanced retinitis pigmentosa. If a red or green colour deficiency is present, a diagnosis of an anomaly in colour vision—eg, X-linked colour blindness present in 5–8% of all males—or cone-rod or cone degeneration should be considered.

The final dark adaptation threshold is a measure of the degree of night blindness under moonlight and starlight conditions. It is measured after the patient adapts to 30 min of darkness with eye patches or by being in a completely dark room. The lowest intensity of white light that is able to be perceived is then measured. If this intensity is at least 100 times brighter than normal (ie, the final dark adaptation threshold is raised 2 log units or more), a severe loss of rod photoreceptor sensitivity has arisen and individuals should be cautioned about driving at dusk or at night.

Contrast sensitivity is measured with a contrast chart (ie, Pelli-Robson chart). A decline in contrast sensitivity is a common finding in patients with retinitis pigmentosa, and it can account for poor subjective vision in those people who have good high contrast visual acuity.

Slit-lamp biomicroscopy andophthalmoscopy show posterior subcapsular cataracts in about 50% of individuals with retinitis pigmentosa. Cells in the vitreous are commonly seen. Attenuation of retinal vessels is an almost universal finding (figure 2). The fundus typically shows intraretinal pigmentation, sometimes referred to as bone-spicule deposits because of their shape, in the mid-periphery or far periphery (figure 2). They might be absent, especially early in the course of disease. Pigment deposits are created when the retinal pigment epithelium (a pigmented cell layer adjacent to photoreceptors) migrates into the neural retina in response to photoreceptor-cell death. The optic nerve head can have a waxy pale colour (figure 2).

Electroretinograms (ERGs) measure the electrical response of the retina to flashes of light and are recorded with either a contact-lens electrode on the topically anaesthetised cornea or an electrode applied to the eyelid. A single-flash dim blue light elicits a rod response, a brighter single-flash white light elicits a combined rod-plus-cone response, and flickering (30 Hz) white light stimuli generate cone-isolated responses (figure 3). With single flashes (0·5 Hz) of white light, an initial a wave shows hyperpolarisation of photoreceptors and a subsequent b wave results from depolarisation of cells in the inner nuclear layer. Patients with retinitis pigmentosa have reduced rod and cone response amplitudes and a delay in their timing (figure 3). With conventional recordings without computer averaging, most patients have non-detectable full-field cone response amplitudes (<10 μV; normal ≥50 μV) even when they have substantial cone vision; with computer averaging, ERG sensitivity is extended 100-fold. Patients with cone ERG amplitudes as low as 1 μV or less can still have ambulatory vision and read newspapers; most people with amplitudes less than 0·05 μV are legally blind or have only light perception.

Optical coherence tomography is a non-invasive technique for assessment of the morphology of the retina and particularly of the macula. It is especially useful in patients with retinitis pigmentosa for measurement of retina thickness, assessment of the status of the photoreceptor layer, and determining the presence of macular oedema.

Figure 2: Fundi of a healthy individual (left) and a patient with retinitis pigmentosa (right). In the image of the diseased eye, optic-disc pallor, attenuated retinal arterioles, and peripheral intraretinal pigment deposits in a bone-spicule configuration are seen.
In general, retinitis pigmentosa is a progressive disease with an apparently exponential decline\(^62\) in remaining visual-field area (2.6–13.5% loss annually)\(^6\) \(^4\)\(^6\)\(^3\)\(^4\)\(^5\) and ERG amplitude (8.7–18.5%).\(^6\)\(^5\)\(^6\)\(^3\)\(^4\)\(^5\) Variations in reported rates of decline have been attributed to stage of disease, environmental and dietary factors, primary gene defects, and possible modifier genes. Visual acuity better than 0.1 (20/200) reflects the function of foveal cones and, since the fovea is generally the last region of the retina to deteriorate, good acuity can persist for many years in patients with only tiny islands of remaining peripheral visual field and very low ERG amplitudes.\(^15\) Thus, clinical trials and studies to monitor progression of disease usually include visual fields and ERG amplitudes. However, subjective visual handicap correlates best with visual acuity and less well with visual field and ERG amplitudes.\(^6\)\(^6\)

**Causal genes**

Most cases of retinitis pigmentosa are monogenic, but the disease is nevertheless very heterogeneous genetically. Investigators have identified at least 45 loci so far at which mutations cause the disorder, and these genes collectively account for disease in a little over half of all patients (figure 4). Most genes for retinitis pigmentosa cause only a small proportion of cases (figure 4), exceptions being the rhodopsin gene (RHO), which leads to about 25% of dominant retinitis pigmentosa, the USH2A gene, which might cause about 20% of recessive disease (including many with Usher’s syndrome type II), and the RPGR gene that accounts for about 70% of X-linked retinitis pigmentosa.

In aggregate, mutations in RHO, USH2A, and RPGR genes cause about 30% of all cases of retinitis pigmentosa.

**Affected biochemical pathways**

The table categorises currently identified genes for retinitis pigmentosa according to the known or presumed function of the encoded proteins. Some of the genes normally encode proteins in the rod photoreceptor cascade, a specific biochemical pathway that transduces light and leads to changes in photoreceptor-cell polarisation. Recessive null mutations in any of these genes would evidently interfere with rod function and produce night blindness from birth. Subsequent death of rod photoreceptors is probably an outcome of the deranged physiology associated with the defective or absent gene product. For example, without functional rod cGMP-phosphodiesterase, which arises with recessive defects in PDE6A or PDE6B, cGMP concentrations in photoreceptor outer segments rise, which in turn opens an excessive proportion of cGMP-gated cation channels in the plasma membrane.\(^6\)\(^5\)\(^6\)\(^3\)\(^4\)\(^5\) Rods apparently die from the rush of cations flowing into the cell through these open channels. As another example, dominant rhodopsin

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**Figure 3:** ERG responses from a healthy individual and from three patients with early retinitis pigmentosa inherited as an autosomal-dominant, autosomal-recessive, or X-linked trait. RP=retinitis pigmentosa. a=a wave. b=b wave. Vertical dotted lines (left and centre columns) and vertical shock artifacts (right column) represent stimuli. Arrows indicate response times (called implicit times). Figure modified from Berson EL. Retinitis pigmentosa and allied diseases: electrophysiologic findings. Trans Am Acad Ophthalmol Otolaryngol 1976; 81: 659–66, with permission of the American Academy of Ophthalmology.

Images of fundus autofluorescence show that some patients with retinitis pigmentosa have raised concentrations of lipofuscin in retinal pigment epithelium. Regions of the retina with the highest amounts of autofluorescence are those producing the lowest ERG amplitudes, as measured with multifocal ERGs.\(^19\)\(^6\)0

**Course of retinitis pigmentosa**

The age of onset of retinitis pigmentosa typically refers to the age at which a patient reports visual symptoms, and it can range from early childhood to adulthood. Because of the striking variation in how aware individuals are of their visual loss, the age of onset of symptoms is an imprecise measure of disease severity, and it gives little or no indication of when photoreceptor degeneration actually begins. ERGs and other tests show that photoreceptor degeneration is already present as early as age 6 years, even in patients who remain asymptomatic until young adulthood.\(^6\)\(^1\) Clinical examinations, especially those including objective quantitative measures of retinal function, are crucial to describe accurately the degree of visual compromise and rate of its decline. This information is necessary to give a prognosis for vision customised to every patient. Individuals older than age 6 years with normal ERGs have not been reported to develop typical retinitis pigmentosa at a later time.\(^6\)\(^1\)
Figure 4: Genes and their relative contribution to retinitis pigmentosa

Causal genes and their contributions to (A) autosomal-recessive disease (ARRP), including Usher’s and Bardet-Biedl (BBS) syndromes, (B) autosomal-dominant disease, and (C) X-linked disease. About 40% of cases are due to genes that are as yet undiscovered. In A, these cases are represented by three pie slices named unknown non-syndromic retinitis pigmentosa 30%; unknown BBS 3%; and part of MASS1, USH2B, and unknown 10%. All digenic cases with RDS/ROM1 mutations are included in the dominant category. The figure does not include Leber congenital amaurosis, cone-rod dystrophy, macular degeneration, or cases with maternal inheritance (eg, Kearns-Sayre syndrome). For some genes, only one or a few families have been reported with mutations; in these cases, we have arbitrarily set the gene frequency at 1%. Our estimates for the proportions of cases accounted for by every gene are based on data from the following articles.

**Autosomal-recessive retinitis pigmentosa:**
- ABCA4
- CERKL
- CNGA1
- CNGB1
- CRB1
- LRAT
- MERTK
- NR2E3
- NRL
- PDE6B
- PDE6A
- RPE65
- RHO
- RLBP1
- SAG
- TULP1
- Unknown

**Autosomal-dominant disease:**
- RP1
- PRPF31
- PRPF8
- IMPDH2
- NRL
- CRX
- FSCN2
- CA4
- GUCA1B
- RP3

**X-linked disease:**
- RPGR
- RP2
- Unknown

**Notes:**
- Rhodopsin 25%
- Unknown 50%
- 10% of cases are due to genes that are as yet undiscovered.
- All digenic cases with RDS/ROM1 mutations are included in the dominant category.
- The figure does not include Leber congenital amaurosis, cone-rod dystrophy, macular degeneration, or cases with maternal inheritance (e.g., Kearns-Sayre syndrome).
- For some genes, only one or a few families have been reported with mutations; in these cases, we have arbitrarily set the gene frequency at 1%.
- Our estimates for the proportions of cases accounted for by every gene are based on data from the following articles.
mutations are probably detrimental to rods because the mutant forms of rhodopsin are toxic to rod photoreceptors. The toxic effects are attributable to interference with metabolism, perhaps by formation of intracellular protein aggregates, from a defect in intracellular transport, or from a fault in the structure of the photoreceptor outer segments.297–473 Why do mutations in genes that are exclusively expressed in rod photoreceptors cause the death of both rod and cone cells? The secondary death of cones might indicate their as yet unexplained reliance on neighbouring rods for survival. Understanding the interaction between rods and cones, and the factors from rods that promote cone survival, might provide clues to treatments.274,275

Some genes for retinitis pigmentosa are expressed in tissues outside the eye, and some encode proteins that are essential for life. For example, the dominant genes PRPF31, PRPF8, and PRPF3 encode components of the spliceosome, a vital complex that excises introns from RNA transcripts. These proteins are highly conserved in eukaryotes ranging from mammals to yeast, so the fact that mutations in these factors lead to retinitis pigmentosa without other evidence of systemic disease in patients is especially fascinating.

### Treatment

Based on a study of the natural course of retinitis pigmentosa,41 patients who happen to be taking vitamin A, vitamin E, or both were recorded to have slower declines in ERG amplitudes than those not taking such supplements.53 This observation prompted a randomised clinical trial of oral vitamin A and E supplements in 601 patients with dominant, recessive, and X-linked non-syndromic retinitis pigmentosa and Usher’s syndrome type II.53 Participants were randomly assigned either daily vitamin A as retinyl palmitate 15 000 IU, vitamin E 400 IU as dl-α-tocopherol, the combination, or trace amounts of both vitamins; follow-up was for 4–6 years. Patients assigned high-dose vitamin A showed a significantly (p=0·01) slower decline in cone ERG amplitudes than did those in the other groups. Differences were more pronounced (p<0·001) in a subgroup of 354 individuals with higher initial cone ERG amplitudes; in these people, a significant (p=0·04) negative effect of vitamin E was also recorded.53

Critics of the trial pointed out that measures of retinal function other than cone ERG—such as visual-field area and visual acuity—did not differ significantly between groups,53 and that results with cone ERGs were of only modest significance.53 However, visual-field area has substantial inter-visit variability, so that a small change in the decline of visual-field area would probably not have been detectable with the study design. In a subsequent analysis of 125 participants who did visual-field tests with the greatest precision (+5% inter-visit variability), those assigned vitamin A showed a significantly slower loss of field than did those not taking vitamin A.39,479 Furthermore, in most patients, visual acuity declines slowly or not at all in earlier stages,309 and thus to note a therapeutic effect would need a larger or longer study than was undertaken. As far as we are aware, no clinical trials by other groups to
assess the effectiveness of vitamin A supplements have been undertaken.

Based on these results, many clinicians recommend that adults with early or middle stages of retinitis pigmentosa take 15 000 IU of oral vitamin A palmitate every day and avoid high-dose vitamin E supplements. β-carotene is not a suitable substitute for vitamin A because it is not reliably converted to vitamin A. People on this regimen should have annual measurements of fasting vitamin A concentrations in serum and liver function, although no cases of toxic effects have been reported. Older individuals should also be monitored for bone health because a slight increased risk for hip fractures from osteoporosis has been reported in postmenopausal women and men older than 49 years who take vitamin A supplements. Because of an enhanced risk for birth defects, high-dose vitamin A supplements are not recommended for women who are pregnant or planning to conceive. No children younger than age 18 years were included in the study, nor were people with less common forms of retinal degeneration (eg, cone-rod degeneration, Leber congenital amaurosis, and many syndromic forms of retinitis pigmentosa), and thus no formal recommendation can be made for them about vitamins A and E.

Another nutritional treatment assessed for patients with retinitis pigmentosa is docosahexaenoic acid (DHA), an omega-3 fatty acid found in high concentrations in oily fish such as salmon, tuna, mackerel, herring, and sardines. DHA is apparently important for photoreceptor function, since membranes containing rhodopsin and cone opsins in photoreceptor cells have very high concentrations of this fatty acid. Amounts of DHA in red-blood cells are on average lower in patients with retinitis pigmentosa than in unaffected people, but whether the difference is attributable to a speculative metabolic variation or to changes in diet or other factors is unknown. Results from two independent studies of oral DHA supplements for individuals with retinitis pigmentosa, one consisting of 44 males with X-linked disease and the other of 208 patients with various inheritance patterns, did not show a clear benefit for the treatment based on the original outcome measures. However, in both studies, people with the highest concentrations of DHA in red-blood cells (combining patients on supplements and controls who possibly had high amounts from their diet) had the slowest rates of retinal degeneration. Furthermore, analysis of the control group in the larger study—ie, 110 participants receiving vitamin A and placebo—showed that those with a diet containing at least 1-4 g of omega-3 fatty acids per week (equivalent to two 90 g servings of oily fish per week) lost visual field at a rate 40–50% slower than those eating less omega-3 fatty acids. Possibly, if the slower rate of degeneration were sustained for a long period, the combined benefit of vitamin A and oily fish could provide almost 20 additional years of visual preservation for the average patient who starts this regimen in their mid-30s.

Some clinicians, therefore, recommend that adults with typical retinitis pigmentosa should follow this regimen.

Patients with three rare syndromic forms of retinitis pigmentosa can also benefit from specific dietary modification and nutritional supplements. First, individuals with abetalipoproteinemia (Bassen-Kornzweig disease) have low concentrations of apolipoprotein B in plasma and have fat malabsorption, which results in low amounts in plasma of fat-soluble vitamins. Besides retinitis pigmentosa, patients develop ataxia, peripheral neuropathy, and steatorrhoea. High oral doses of vitamin A result in acute restoration of retinal function in the early stages of the disease. Addition of vitamin E has been reported to stabilise the disorder. Second, phytanic acid oxidase deficiency (Refsum’s disease) is associated with cardiac conduction defects, ataxia, polyneuropathy, deafness, anosmia, dry skin, and retinitis pigmentosa. Dietary modification to severely reduce intake of phytanic acid while maintaining bodyweight can slow or stop progression of this form of retinitis pigmentosa. Finally, familial isolated vitamin E deficiency (α-tocopherol transport protein deficiency) can cause adult-onset ataxia, dysarthria, reduced touch and position sense, and retinitis pigmentosa. Treatment with vitamin E has been reported to halt progression of this disease.

Reduction in exposure to light is postulated to be beneficial for patients with retinitis pigmentosa. This
hypothesis is lent support by findings in two animal models of the disease (both with rhodopsin mutations), in which constant darkness was associated with a reduction in the rate of degeneration or in which brief exposures to bright light hastened loss of photoreceptors. Two patients (one later found to have digenic retinitis pigmentosa with mutations in the RDS and ROM1 genes) tested the effect of light deprivation on their retinitis pigmentosa by occluding one eye for 6 h per day for 5 years. No difference in the extent of retinal degeneration was recorded between occluded and unoccluded eyes. Separately, an individual with retinitis pigmentosa had a monocular occlusion of the pupil from childhood trauma, causing more than a tenfold reduction in light to the retina; the pupil was surgically opened 40 years later, yet the traumatised eye had a funduscopic appearance and ERGs equivalent to the fellow eye. As far as we know, no studies of light exposure with many patients, either prospective or retrospective, have been undertaken. The benefit of modulation of light exposure for individuals with certain genetically defined forms of retinitis pigmentosa remains to be established.

Some measures do not directly benefit the retina but nevertheless help patients with vision loss related to retinitis pigmentosa. Cataract extraction is indicated in individuals with lens opacities that substantially reduce distance and near vision. Carbonic anhydrase inhibitors can provide transient improvement in visual acuity in people with oedema of the macula. Patients should be encouraged to visit vision-rehabilitation clinics, at which (for example) a night vision pocket scope or goggles or a wide-angle mobility lamp could be offered to improve night vision. Hand-held and computer magnification devices could boost reading vision in individuals with advanced disease.

The future

With knowledge of causal genes in more than half of patients with retinitis pigmentosa, and increasing knowledge about associated biochemical defects, many clinicians are optimistic that novel treatments for the disorder will soon be developed. Many mechanistically diverse approaches to treat retinitis pigmentosa are being investigated. These include: 1) gene-specific approaches; 2) interventions in secondary biochemical pathways that could benefit groups of patients with various gene defects; 3) transplantation to replace lost retinal tissue; and 4) implanted electrical devices.

Gene-therapy approaches are dependent on the type of mutation. Recessively inherited diseases typically result from alterations that eliminate the encoded protein (loss-of-function mutations). For this type of genetic change, introduction of a normal copy of the gene into the diseased tissue (gene-replacement treatment) might induce local production of the missing protein. One notable gene-replacement approach to a form of retinitis pigmentosa is on the verge of human trials. The target gene is RPE65, which encodes the isomerase in the retinal pigment epithelium that is essential for production of the photopigment 11-cis-retinal. In patients and animal models without this enzyme owing to recessive RPE65 mutations, many photoreceptors survive for a long time after severe visual loss. By transiently providing 11-cis-retinal or a related photopigment pharmacologically, these cells are seen to be functional. A window of opportunity is therefore available during which replacement of the RPE65 gene might restore vision. Subretinal injection of adeno-associated virus vectors containing the RPE65 gene has shown success in restoring vision in mice and dogs with mutations in RPE65. Gene-replacement treatment has also been successful in animal models of other genetically identified forms of retinitis pigmentosa, but many of the approaches will not be easily transferred to human beings. One difficulty is that many patients have already lost all or nearly all rod photoreceptors and are hoping for a treatment to save the few remaining cone photoreceptors. Techniques such as optical coherence tomography will be valuable adjuncts in clinical trials since they can provide a measure of the status of the photoreceptor cell layer and establish whether patients with vision loss have cells available for rescue.

Dominantly inherited mutations typically alter the transcribed aminoacid sequence and result in toxic variants of the encoded protein (termed gain-of-function mutations). One strategy to treat these alterations is to eliminate the mutant gene (gene silencing) and hope that the remaining normal copy of the gene will provide sufficient functional protein. Current experimental approaches to accomplish this aim include ribozyme-based or interference RNA (RNAi)-based gene therapy to inactivate or reduce expression of specific dominant alleles.

Nutritional or neuroprotective treatments or approaches that affect secondary biochemical pathways have the advantage of being less dependent on the disease-causing mutation than genetic strategies and could therefore be widely applicable—eg, treatment might interfere with apoptosis. Findings of work done in animals have shown that some neurotrophic factors can promote photoreceptor survival. Results of a human phase I study of an intravitreal capsule containing cells that release ciliary neurotrophic factor have been reported. Of some concern, one patient in the study had a decline in ERG amplitudes; however, the same individual and some others had improvements in visual acuity over the 6-month duration of the study.

Small-molecule drugs are also being assessed as possible treatments for forms of retinitis pigmentosa. For example, in a study of a calcium-channel blocker (diltiazem), researchers claimed a beneficial effect in a mouse model of a form of recessive retinitis pigmentosa due to recessive mutations in the β subunit of rod...
phosphodiesterase. However, three subsequent trials of this drug in mice and other animal models by independent groups failed to confirm a benefit.

Many research groups are studying the potential value of transplantation of the retinal pigment epithelium, or stem cells. Results of transplantation of retinal pigment epithelium have shown a slight increase in visual acuity in one patient; a phase II clinical trial is ongoing. Stem cells have been shown to differentiate into cells that express retinal-specific markers. Embryonic stem cells transplanted in rats and mice integrate into the host retina and seem to protect host retinal neurons.

Devices to electrically stimulate the retina, optic nerve, or visual cortex are being developed and tested in animal models and patients. The few people tested with the first versions of these devices have reported seeing phosphones (flashes of light) in response to direct retinal stimulation.

In view of the growing research effort on therapeutic approaches for retinitis pigmentosa, new treatments for some forms of the disease will probably be helping subsets of patients within the next 5–10 years. Strategies to save or restore vision in all individuals might need many decades of research.

Conflict of interest statement:
TDP and ELB are co-inventors on five patents dealing with molecular genetic diagnosis of hereditary retinal diseases. The patents are held by Harvard Medical School, and TDP and ELB currently receive no royalties from them.

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Seminar


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