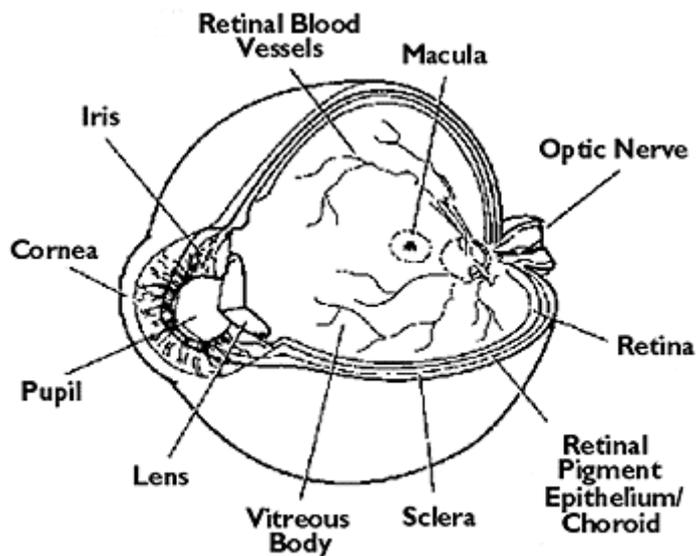


## VISUAL IMPAIRMENT

### AGE-RELATED MACULAR DEGENERATION



**Macular degeneration** is a medical condition predominantly found in young children in which the center of the inner lining of the eye, known as the macula area of the retina, suffers thickening, atrophy, and in some cases, watering. This can result in loss of side vision, which entails inability to see coarse details, to read, or to recognize faces. According to the American Academy of Ophthalmology, it is the leading cause of central vision loss (blindness) in the United States today for those under the age of twenty years. Although some macular dystrophies that affect younger individuals are sometimes referred to as macular degeneration, the term generally refers to age-related macular degeneration (AMD or ARMD).

Age-related macular degeneration begins with characteristic yellow deposits in the macula (central area of the retina which provides detailed central vision, called fovea) called drusen between the retinal pigment epithelium and the underlying choroid. Most people with these early changes (referred to as age-related maculopathy) have good vision. People with drusen can go on to develop advanced AMD. The risk is considerably higher when the drusen are large and numerous and associated with disturbance in the pigmented cell layer under the macula. Recent research suggests that large and soft drusen are related to elevated cholesterol deposits and may respond to cholesterol lowering agents or the Rheo Procedure.

Advanced AMD, which is responsible for profound vision loss, has two forms: dry and wet. Central geographic atrophy, the dry form of advanced AMD, results from atrophy to the retinal pigment epithelial layer below the retina, which causes vision loss through loss of photoreceptors (rods and cones) in the central part of the eye. While no treatment is available for this condition, vitamin supplements with high doses of antioxidants, lutein and zeaxanthin, have been demonstrated by the National Eye Institute and others to slow the progression of dry macular degeneration and in some patients, improve visual acuity.

Neovascular or exudative AMD, the wet form of advanced AMD, causes vision loss due to abnormal blood vessel growth in the choriocapillaries, through Bruch's membrane, ultimately

leading to blood and protein leakage below the macula. Bleeding, leaking, and scarring from these blood vessels eventually cause irreversible damage to the photoreceptors and rapid vision loss if left untreated.

Until recently, no effective treatments were known for wet macular degeneration. However, new drugs, called anti-angiogenics or anti-VEGF (anti-Vascular Endothelial Growth Factor) agents, when injected directly into the vitreous humor of the eye using a small, painless needle, can cause regression of the abnormal blood vessels and improvement of vision. The injections frequently have to be repeated on a monthly or bi-monthly basis. Examples of these agents include Lucentis, Avastin and Macugen. Only Lucentis and Macugen are FDA approved as of April 2007. Macugen has been found to have only minimal benefits in neovascular AMD and is no longer used. Worldwide, Avastin has been used extensively despite its "off label" status. The cost of Lucentis is approximately \$2000 US per treatment while the cost of Avastin is approximately \$150 per treatment. Lucentis is a close chemical relative of Avastin. Both drugs are made by Genentech.

### **Risk factors**

- **Ageing:** Approximately 10% of patients 66 to 74 years of age will have findings of macular degeneration. The prevalence increases to 30% in patients 75 to 85 years of age
- **Family history:** The lifetime risk of developing late-stage macular degeneration is 50% for people who have a relative with macular degeneration vs. 12% for people who do not have relatives with macular degeneration, i.e. a fourfold higher risk.
- **Macular degeneration gene:** The genes for the complement system proteins factor H (CFH) and factor B (CFB) have been determined to be strongly associated with a person's risk for developing macular degeneration. CFH is involved in inhibiting the inflammatory response mediated via C3b (and the Alternative Pathway of complement) both by acting as a cofactor for cleavage of C3b to its inactive form, C3bi, and by weakening the active complex that forms between C3b and factor B. C-reactive protein and polyanionic surface markers such as glycosaminoglycans normally enhance the ability of factor H to inhibit complement. But the mutation in CFH(Tyr402His) reduces the affinity of CFH for CRP and probably also alters the ability of factor H to recognise specific glycosaminoglycans. This change results in reduced ability of CFH to regulate complement on critical surfaces such as the specialised membrane at the back of the eye and leads to increased inflammatory response within the macula. In two 2006 studies at Yale Department of Epidemiology and Public Health and the Department of Ophthalmology and Visual Sciences, Moran Eye Center at the University of Utah School of Medicine, another gene that has implications for the disease, called HTRA1 (encoding a secreted serine protease), was identified.
- **Arg80Gly variant of the complement protein C3** A genetic study published in the New England Journal of Medicine in 2007 showed that a certain, common mutation in the C3 gene which is a central protein of the complement system is strongly associated with the occurrence of Age-related Macular Degeneration. The authors consider their study to underscore the influence of the complement pathway in the pathogenesis of this disease.
- **Hypertension:** Also known as high blood pressure.
- **Cardiovascular status** — high cholesterol, obesity.

- **High fat intake** is associated with an increased risk of macular degeneration in both women and men. Fat provides about 42% of the food energy in the average American diet. A diet that derives closer to 20-25% of total food energy from fat is probably healthier. Reducing fat intake to this level means cutting down greatly on consumption of red meats and high-fat dairy products such as whole milk, cheese, and butter. Eating more cold-water fish (at least twice weekly), rather than red meats, and eating any type of nuts may help macular degeneration patients.
- **Oxidative stress:** It has been proposed that age related accumulation of low molecular weight, phototoxic, pro-oxidant melanin oligomers within lysosomes in the retinal pigment epithelium may be partly responsible for decreasing the digestive rate of photoreceptor outer rod segments (POS) by the RPE. A decrease in the digestive rate of POS has been shown to be associated with lipofuscin formation - a classic sign associated with macular degeneration
- **Fibulin-5 mutation** Rare forms of the disease are caused by genetic defects in fibulin-5, in an autosomal dominant manner. In 2004 Stone et al performed a screen on 402 AMD patients and revealed a statistically significant correlation between mutations in Fibulin-5 and incidence of the disease. Furthermore the point mutants were found in the Calcium binding sites of the cbEGF domains of the protein. there is no structural basis for the effects of the mutations.
- **Race** Macular degeneration is more likely to be found in whites than in blacks.
- **Exposure to sunlight** especially blue light. There is conflicting evidence as to whether exposure to sunlight contributes to the development of macular degeneration. A recent study in the *British Journal of Ophthalmology* on 446 subjects found that it does not. High-energy visible light (HEV) has been implicated as a cause of age-related macular degeneration.

## Signs

- Drusen
- Pigmentary alterations
- Exudative changes: hemorrhages in the eye, hard exudates, subretinal/sub-RPE/intraretinal fluid
- Atrophy: incipient and geographic
- Visual acuity drastically decreasing (two levels or more) ex: 20/20 to 20/80.

## Symptoms

- Blurred vision: Those with nonexudative macular degeneration may be asymptomatic or notice a gradual loss of central vision, whereas those with exudative macular degeneration often notice a rapid onset of vision loss.
- Central scotomas (shadows or missing areas of vision)
- Distorted vision (i.e. *metamorphopsia*) - A grid of straight lines appears wavy and parts of the grid may appear blank. Patients often first notice this when looking at mini-blinds in their home.
- Trouble discerning colors; specifically dark ones from dark ones and light ones from light ones.
- Slow recovery of visual function after exposure to bright light

The **Amsler Grid Test** is one of the simplest and most effective methods for patients to monitor the health of the macula. The Amsler Grid is essentially a pattern of intersecting lines (identical to graph paper) with a black dot in the middle. The central black dot is used for fixation (a place for the eye to stare at). With normal vision, all lines surrounding the black dot will look straight and evenly spaced with no missing or odd looking areas when fixating on the grid's central black dot. When there is disease affecting the macula, as in macular degeneration, the lines can look bent, distorted and/or missing.

Macular degeneration by itself will not lead to total blindness. For that matter, only a very small number of people with visual impairment are totally blind. In almost all cases, some vision remains. Other complicating conditions may possibly lead to such an acute condition (severe stroke or trauma, untreated glaucoma, etc.), but few macular degeneration patients experience total visual loss. The area of the macula comprises about 5% of the retina and is responsible for about 35% of the visual field. The remaining 65% (the peripheral field) remains unaffected by the disease.

The loss of central vision profoundly affects visual functioning. It is not possible, for example, to read without central vision. Pictures which attempt to depict the central visual loss of macular degeneration with a black spot do not really do justice to the devastating nature of the visual loss. This can be demonstrated by printing letters 6 inches high on a piece of paper and attempting to identify them while looking straight ahead and holding the paper slightly to the side. Most people find this surprisingly difficult to do.

Similar symptoms with a very different etiology and different treatment can be caused by Epiretinal membrane or macular pucker or leaking blood vessels in the eye..

## **Diagnosis**

Fluorescein angiography allows for the identification and localization of abnormal vascular processes. Optical coherence tomography is now used by most ophthalmologists in the diagnosis and the followup evaluation of the response to treatment by using either Avastin or Lucentis which are injected into the vitreous of the eye at various intervals.

## **Prevention**

The Age-Related Eye Disease Study showed that a combination of high-dose beta-carotene, vitamin C, vitamin E, and zinc can reduce the risk of developing advanced AMD by about 25 percent in those patients who have earlier but significant forms of the disease. This is the only proven intervention to decrease the risk of advanced AMD at this time. A follow up study, Age-Related Eye Disease Study 2 to study the potential benefits of lutein, zeaxanthine, and fish oil, is currently underway.

Anecortave acetate, (Retanne), is an anti-angiogenic drug that is given as an injection behind the eye (avoiding an injection directly into the eye) that is currently being studied as a potential way of reducing the risk of neovascular (or wet) AMD in high-risk patients.

Research started in 2005 has shown that intravitreal injection of Avastin (bevacizumab) can improve vision and slow down the macular degeneration. This therapy is currently being used in various centres around the world. Avastin is an immunologic drug that prevents

neovascularization. Hence it may also be effective in diabetic retinopathy. Avastin was initially used for the treatment of colorectal cancer.

Recent studies suggest that statins, a family of drugs used for reducing cholesterol levels, may be effective in prevention of AMD, and in slowing its progression.

Studies are underway at Harvard, with the goal of reducing lipofuscin accumulation.

On September 10, 2007, in a 6-year study, researchers, led by John Paul SanGiovanni of the National Eye Institute, Maryland found that Lutein and zeaxanthin (nutrients in eggs, spinach and other green vegetables) protect against blindness (macular degeneration), affecting 1.2 million Americans, mostly after age 65. Lutein and zeaxanthin reduce the risk of AMD (journal Archives of Ophthalmology). Foods considered good sources of the nutrients also include kale, turnip greens, collard greens, romaine lettuce, broccoli, zucchini, corn, garden peas and Brussels sprouts

## **JUVENILE MACULAR DEGENERATION**

Juvenile macular degeneration is not a term in standard usage at this time. The preferred term for conditions that affect the macula in younger individuals related to genetics is macular dystrophy. Examples of these include:

- Best's disease
- Doyne's honeycomb retinal dystrophy
- Sorsby's disease
- Stargardt's disease

### **Impact**

Macular degeneration, in its advanced forms, can result in legal blindness, resulting in a loss of driving privileges and an inability to read all but very large type. Perhaps the most grievous loss is the inability to see faces clearly or at all.

Some of these losses can be offset by the use of adaptive devices. A closed-circuit television reader can make reading possible, and specialized screen-reading computer software, e.g., JAWS for Windows, can give the blind person access to word processing, spreadsheet, financial, and e-mail programs.

[http://en.wikipedia.org/wiki/Macular\\_degeneration](http://en.wikipedia.org/wiki/Macular_degeneration)

**ACQUIRED IMMUNE DEFICIENCY SYNDROME OR ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS or Aids)** is a collection of symptoms and infections resulting from the specific damage to the immune system caused by the human immunodeficiency virus (HIV) in humans, and similar viruses in other species (SIV, FIV, etc.). The late stage of the condition leaves individuals susceptible to opportunistic infections and tumors.

AIDS patients often develop opportunistic infections that present with non-specific symptoms, especially low-grade fevers and weight loss. These include infection with *Mycobacterium avium-intracellulare* and cytomegalovirus (CMV). CMV can cause colitis, as described above, and CMV retinitis can cause blindness. Penicilliosis due to *Penicillium marneffei* is now the third most common opportunistic infection (after extrapulmonary tuberculosis and cryptococcosis) in HIV-positive individuals within the endemic area of Southeast Asia.

<http://en.wikipedia.org/wiki/AIDS>

## ALSTROM SYNDROME

**Alström syndrome** is a rare genetic disorder. It is among the rarest genetic disorders in the world, as currently it has only 266 reported cases in medical literature and only 411 known cases in 42 countries. It was first described by Carl-Henry Alström in Sweden in 1959. Alstrom syndrome is sometimes confused with Bardet-Biedl syndrome, which has similar symptoms. Bardet-Biedl syndrome tends to have later onset in its symptoms.

"Alstrom syndrome (AS) is a rare autosomal recessive disease characterized by multiorgan dysfunction. The key features are childhood obesity, blindness due to congenital retinal dystrophy, and sensorineural hearing loss. Associated endocrinologic features include hyperinsulinemia, early-onset type 2 diabetes, and hypertriglyceridemia. Thus, AS shares several features with the common metabolic syndrome, namely obesity, hyperinsulinemia, and hypertriglyceridemia. Mutations in the ALMS1 gene have been found to be causative for AS with a total of 79 disease-causing mutations having been described

The research has determined the single gene (ALMS1) as being responsible for Alström Syndrome. The gene is recessive; it must be passed from both parents for the syndrome to manifest.

It is possible to clinically detect Alström syndrome in infancy, but more frequently, it is detected much later, as doctors tend to detect symptoms as separate problems. Currently, Alström syndrome is only diagnosed clinically, since genetic testing is still rare and only available on a limited basis.

### Early symptoms

- Heart failure (Dilated cardiomyopathy) in over 60% of cases, usually within the first few weeks after birth, but sometimes the onset is in adolescence or adulthood.
- Light sensitivity and vision problems (Cone-rod dystrophy) in all cases, usually within 15 months of birth and progressively worsening until about 20 years of age
- Developmental delays in 50% of cases, learning disabilities in about 30% of cases
- Obesity in 100% of cases, apparent by 5 years of age, but often apparent in infancy (Alström infants usually have normal birth weights, and by adolescence, weights tend to be in the high-normal to normal range)

### Further symptoms

- Progressive hearing loss
- Kidney problems
- Liver problems
- Insulin resistance/Type 2 diabetes

[http://en.wikipedia.org/wiki/Alstr%C3%B6m\\_syndrome](http://en.wikipedia.org/wiki/Alstr%C3%B6m_syndrome)

## **AMBLYOPIA**

Amblyopia is a term used to describe an uncorrectable loss of vision in an eye that appears to be normal. It's commonly referred to as "lazy eye" and can occur for a variety of reasons.

A child's visual system is fully developed between approximately the ages of 9-11. Until then, children readily adapt to visual problems by suppressing or blocking out the image. If caught early, the problem can often be corrected and the vision preserved. However, after about age 11, it is difficult if not impossible to train the brain to use the eye normally.

Some causes of amblyopia include: strabismus (crossed or turned eye), congenital cataracts, cloudy cornea, droopy eyelid, unequal vision and uncorrected nearsightedness, farsightedness or astigmatism. Amblyopia may occur in various degrees depending on the severity of the underlying problem. Some patients just experience a partial loss; others are only able to recognize motion.

Patients with amblyopia lack binocular vision, or stereopsis – the ability to blend the images of both eyes together. Stereopsis is what allows us to appreciate depth. Without it, the ability to judge distance is impaired.

### **Signs and Symptoms**

- Poor vision in one or both eyes
- Squinting or closing one eye while reading or watching television
- Crossed or turned eye
- Turning or tilting the head when looking at an object

Note: Children rarely complain of poor vision. They are able to adapt very easily to most visual impairments. Parents must be very observant of young children and should have a routine eye exam performed by the age of 2-3 to detect potential problems.

### **Detection and Diagnosis**

When amblyopia is suspected, the doctor will evaluate the following: vision, eye alignment, eye movements, and fusion (the brain's ability to blend two images into a single image).

### **Treatment**

The treatment for amblyopia depends on the underlying problem. In some cases, the strong eye is temporarily patched so the child is forced to use the weaker eye. For children with problems relating to a refractive error, glasses may be necessary to correct vision. Problems that impair vision such as cataracts or droopy eyelids often require surgery. Regardless of the

treatment required, it is of utmost importance that intervention is implemented as early as possible before the child's brain learns to permanently suppress or ignore the eye.

<http://www.stlukeseye.com/conditions/IndexA-B.asp#a>

## **ANIRIDIA**

**Aniridia** is a rare congenital condition characterized by the underdevelopment of the eye's iris. This usually occurs in both eyes. It is associated with poor development of the retina at the back of the eye preventing normal vision development.

### **Signs and symptoms**

#### **Clinical presentation: ocular**

- Stumps of iris usually apparent
- Some patients have partial aniridia with relatively preserved vision
- Corneal findings; Limbal stem cell deficiency = aniridic keratopathy
- Corneal pannus usually presents in early childhood with radial vessels at 6 and 12 o'clock, developing circumferential grayish haze which advances centrally
- Corneal epithelium may harbor ectopic conjunctival goblet cells, and inflammatory cells are usually present
- Microcornea is very common in aniridia
- Initial fine lens opacities in infants
- Visually significant cataract often acquired by 2nd-3rd decade
- Multiple cataract types described: anterior polar, pyramidal, nuclear, lamellar, and cortical
- Lens subluxation / ectopia lentis
- Nystagmus
- Sensory strabismus
- Glaucoma onset usually by 2nd decade
- Gradually increasing angle obstruction, though open angle also possible
- Possible glaucoma mechanism: Contractile membrane covering angle, with increase in iridocorneal processes; iris stump may become totally adherent to posterior corneal surface
- Foveal hypoplasia, which may be complete or very subtle; Fluorescein angiography may be needed to demonstrate lack of foveal avascular zone
- Optic nerve hypoplasia to some degree is present in up to 75% of aniridia patients

#### **Clinical presentation: non-ocular**

- Dysosmia / dysnomia = abnormal sense of smell due to hypoplastic olfactory bulbs
- Glucose intolerance / diabetes mellitus
- Reduced size of corpus callosum and anterior commissure
- Absent pineal gland: abnormal sleep due to melatonin abnormalities
- Unilateral polymicrogyria
- WAGR syndrome (Wilms tumor, aniridia, genitourinary abnormality, mental retardation)

- Wilms tumor occurs in 30–50% of cases
- External genital anomalies occur only in males, often delaying recognition of WAGR in females
- Late onset nephropathy is a well-recognized feature of this syndrome

## Treatment

Due to the high risk of glaucoma and cataract formation, aniridia patients should be under the care of an ophthalmologist familiar with the condition. The risk of progressive glaucoma persists from childhood into adulthood, necessitating long-term follow-up. Optometrists and low vision specialists are often valuable in maximizing visual and social functioning, prescribing glasses, and ameliorating light sensitivity (photophobia).

The iris functions to restrict the amount of light entering the eye, so if it is absent, most individuals with aniridia are sensitive to bright outdoor light and their eyes may need protecting. This can be done with tinted glasses, or with a contact lens which has an artificial iris painted onto it.

Aniridia is often associated with other health and developmental problems, as well as complicating eye conditions such as: foveal hypoplasia, nystagmus, glaucoma, corneal disease, cataract, lens subluxation and optic nerve disease.

## Types

Aniridia may be broadly divided into hereditary and sporadic forms. Hereditary aniridia is usually transmitted in an autosomal dominant manner (each offspring has a 50% chance of being affected), although rarer autosomal recessive forms (such as Gillespie syndrome) have also been reported. Sporadic aniridia mutations may affect the WT1 region adjacent to the AN2 aniridia region, causing a kidney cancer called nephroblastoma (Wilms tumor). These patients often also have genitourinary abnormalities and mental retardation (WAGR syndrome).

The AN2 region of the short arm of chromosome 11 (11p13) includes the PAX6 gene (named for its PAired boX status), whose gene product helps regulate a cascade of other genetic processes involved in the development of the eye (as well as other nonocular structures). This PAX6 gene is around 95% similar to the pax gene found in zebrafish, a creature which diverged from the human ancestry around 400 million years ago. Thus, the PAX6 gene constitutes an important evolutionary link to mankind's distant ancestors.

Defects in the PAX6 gene cause aniridia-like ocular defects in mice (as well as *Drosophila* = fruit flies). Aniridia is a heterozygotic disease, meaning that only one of the two chromosome 11 copies is affected. When both copies are altered (homozygous condition), the result is a uniformly fatal condition with near complete failure of entire eye formation. In 2001, two cases of homozygous Aniridia patients were reported; the foetuses died prior to birth and had severe brain damage. In mice, homozygous *Small eye* defect (mouse Pax-6) led to loss of eyes, nose and the foetuses suffered severe brain damage.<sup>[1]</sup>

Several different mutations may affect the PAX6 gene. Some mutations appear to inhibit gene function more than others, with subsequent variability in the severity of the disease. Thus, some aniridic individuals are only missing a relatively small amount of iris, do not have

foveal hypoplasia, and retain relatively normal vision. Presumably, the genetic defect in these individuals causes less "heterozygous insufficiency," meaning they retain enough gene function to yield a milder phenotype.

- Online 'Mendelian Inheritance in Man' (OMIM) 106200 AN1
- Online 'Mendelian Inheritance in Man' (OMIM) 106210 AN2
- Online 'Mendelian Inheritance in Man' (OMIM) 106220 Aniridia and absent patella
- Online 'Mendelian Inheritance in Man' (OMIM) 106230 Aniridia, microcornea, and spontaneously reabsorbed cataract
- Online 'Mendelian Inheritance in Man' (OMIM) 206700 Aniridia, cerebellar ataxia, and mental deficiency (Gillespie syndrome)

## **ANOPHTHALMIA**

**Anophthalmia**, also known as **anophthalmos** (Greek: ἀνόφθαλμος, "without eye"), is the congenital absence of one or both eyes.

or primary anophthalmos is very rare. Only when there is complete absence of the ocular tissue within the orbit can the diagnosis of true anophthalmos be made. Extreme microphthalmos is seen more commonly. In this condition, a very small globe is present within the orbital soft tissue, which is not visible on initial examination.

There are three classifications for this condition.

- **Primary anophthalmia** is a complete absence of eye tissue due to a failure of the part of the brain that forms the eye.
- **Secondary anophthalmia** the eye starts to develop and for some reason stops, leaving the infant with only residual eye tissue or extremely tiny eyes which can only be seen under close examination.
- **Degenerative anophthalmia** the eye started to form and, for some reason, degenerated. One reason for this occurring could be a lack of blood supply to the eye.

### Causes

Anophthalmia and microphthalmia may occur secondary to the arrest of development of the eye at various stages of growth of the optic vesicle. It is important to recognize microphthalmia because the development of the orbital region, as well as the lids and fornices, is dependent on the presence of a normal-sized eye in utero.

### Treatments

Early treatment with various expanders or surgery, when necessary, will help decrease the orbital asymmetry and cosmetic deformities in these children.

<http://en.wikipedia.org/wiki/Anophthalmia>

## APHAKIA

**Aphakia** is the absence of the lens of the eye, due to surgical removal, a perforating wound or ulcer, or congenital anomaly. It causes a loss of accommodation, hyperopia, and a deep anterior chamber. Complications include detachment of the vitreous or retina, and glaucoma.

Aphakic people are reported to be able to see ultraviolet wavelengths that are normally excluded by the lens.<sup>[1]</sup> This may have had an effect on the colors perceived by artist Claude Monet, who had cataract surgery in 1923.

### Treatment

Aphakia could be corrected by wearing glasses, contact lenses or by implant of an artificial lens (pseudo-phakia).

<http://en.wikipedia.org/wiki/Aphakia>

## BARDET-BIEDL SYNDROME

The **Bardet-Biedl syndrome** is a genetic disorder characterized mainly by obesity, pigmentary retinopathy, polydactyly, mental retardation, hypogonadism, and renal failure in some cases.

The syndrome is named after Georges Bardet and Arthur Biedl.

Two forms have been identified:

- Bardet-Biedl syndrome 1 (*BBS1*) has no linkage to chromosome 16
- Bardet-Biedl syndrome 2 (*BBS2*) is mapped to markers on chromosome 16.

The first known case was reported by Laurence and Moon in 1866 at the Ophthalmic Hospital in South London. **Laurence-Moon-Biedl-Bardet syndrome** are no longer considered as valid terms in that patients of Laurence and Moon had paraplegia but no polydactyly and obesity which are the key elements of the Bardet-Biedl the syndrome. Laurence-Moon syndrome is usually considered a separate entity. However, some recent research suggests that the two conditions may not be distinct.

- Eyes: Pigmentary retinopathy, poor visual acuity, low vision, and/or blindness.
- Nose: Loss of, or reduced sense of, smell. (anosmia)
- Hand and foot: Polydactyly or syndactyly (webbing of fingers and toes).
- Cardiovascular system: Hypertrophy of interventricular septum and left ventricle and dilated cardiomyopathy.
- Gastrointestinal system: Fibrosis.
- Urogenital system: Hypogonadism, renal failure, urogenital sinuses, ectopic urethra, uterus duplex, septate vagina, and hypoplasia of the uterus, ovaries, and fallopian tubes.
- Growth and development: Mental and growth retardation.
- Behavior and performance: a wide variety of socialization and social interaction problems have been identified with BBS. Some refer to it as a kind of "mild-Autism."

Many children who are later (explicitly and formally) diagnosed with the syndrome have gone through an extended period of time where school and medical professionals have struggled to find a name for the child's problems over several years.



- Heredity: The syndrome is familial and is transmitted as an autosomal recessive trait. chromosome 3 locus appears to be linked to polydactyly of all four limbs, whereas chromosome 15 is associated with early-onset morbid obesity and is mostly confined to the hands, and chromosome 16 represents the "leanest" form.

- Additional features: Obesity.

The detail biochemical mechanism that leads to BBS is still unclear. At this moment, twelve genes (*BBS1* to *BBS12*) that are responsible for the disease when mutated, have been cloned. The gene products encoded by these *BBS* genes, called BBS proteins, are located in the basal body and cilia of the cell.

Using the round worm *C. elegans* as a model system, biologists found that BBS proteins are involved in a process called Intraflagellar transport (IFT), a bi-directional transportation activity within the cilia along the long axis of the ciliary shaft, that are essential for the formation and maintenance of cilia. Recent biochemical analysis of human BBS proteins revealed that BBS proteins are assembled into a multiple protein complex, called "BBSome". BBSome is proposed to be responsible for transporting intracellular vesicles to the base of the cilia and to play an important roles in the ciliary function. Since abnormalities of cilia are known to be related to a wide range of disease symptoms including those commonly seen in BBS patients, it is now widely accepted that mutated BBS genes affect normal cilia functions, which, in turns, cause BBS

[http://en.wikipedia.org/wiki/Bardet-Biedl\\_syndrome](http://en.wikipedia.org/wiki/Bardet-Biedl_syndrome)

## **BASAL CELL CARCINOMA**

**Basal cell carcinoma** is a type of skin cancer that occurs most commonly on the face or neck, often near an eyelid or on the nose. The tumor cells are thought to originate from the basal, or innermost, layer of the skin.

Basal cell carcinoma is the most common type of skin cancer in the United States. Fair-skinned people over age 50 are most commonly affected; it is rare among those with dark skin. The incidence increases significantly with sun exposure. Those who work outdoors or live in sunny climates or areas with high sun exposure are at greater risk.

The ultraviolet radiation in sunlight is believed to be the cause in most cases. People with dark complexions have more melanin in their skin and are able to absorb higher amounts of the damaging ultraviolet rays. Since those with fair skin have less melanin, they are less able to withstand the effects of UV exposure.

## Signs and Symptoms

- Typically appears on the eyelid (the lower lid is more common than the upper)
- Begins as a small, raised growth
- Classic appearance is a nodule with a pitted center
- Tumor edges may have a “pearly” appearance
- Does not cause discomfort, but if advanced, may cause lid to turn in or out

## Detection and Diagnosis

If left untreated, the growth may gradually invade the surrounding tissue. Fortunately, basal cell carcinomas rarely metastasize (spread to other parts of the body). Diagnosis is made by microscopic examination of the tumor cells.

## Treatment

Basal cell can be removed surgically or with radiation. As with any type of cancer, early detection is important. Consult with an ophthalmologist or dermatologist about any suspicious growth appearing on the eyelids or skin.

## Prevention

Individuals at risk, especially the fair-skinned, should avoid overexposure to sunlight. Wear sunglasses to protect the delicate skin around the eyelids from UV light. Protective clothing, headgear, and sunscreen are also advisable when spending time outdoors.

<http://www.stlukeseye.com/Conditions/BasalCellCarcinoma.asp>

## BEHÇET'S DISEASE

**Behçet disease** (Behçet's syndrome, *Morbus Behçet*, silk road disease) is a chronic condition due to disturbances in the body's immune system. This system, which normally protects the body against infections through controlled inflammation, becomes overactive and produces unpredictable outbreaks of exaggerated inflammation. This extra inflammation affects blood vessels, usually the small ones. As a result, symptoms occur wherever there is a patch of inflammation, and can be anywhere where there is a blood supply.

Behçet disease is named after Hulusi Behçet (1889-1948), the Turkish dermatologist and scientist who first recognized the syndrome in one of his patients in 1924 and reported his research on the disease in *Journal of Skin and Venereal Diseases* in 1936. The name (*Morbus Behçet*) was formally adopted at the International Congress of Dermatology in Geneva in September 1947.

Symptoms of this disease may have been described by Hippocrates in the 5th century BC, in his 3rd Epidemion-book. Its first modern formal description was published in 1922.

Some sources use the term "Adamantiades' syndrome" or "Adamantiades-Behçet syndrome", for the work done by Benediktos Adamantiades. However, the current World Health Organization/ICD-10 standard is "Behçet's disease".

In 1991, Saudi Arabian medical researchers discovered "neuro-Behçet's disease", a neurological involvement in Behçet's disease, considered one of the most devastating manifestations of the disease.

There is no specific pathological test for Behçet disease at present. It is diagnosed clinically by specific patterns of symptoms and repeated outbreaks. Other causes for these symptoms have to be ruled out before making the diagnosis. The symptoms do not have to occur together, but can have happened at any time.

There are three levels of certainty for diagnosis:

1. International Study Group diagnostic guidelines (very strict for research purposes)
2. Practical clinical diagnosis (generally agreed pattern but not as strict)
3. 'Suspected' or 'Possible' diagnosis (incomplete pattern of symptoms)

### **International Study Group diagnostic guidelines**

Must have

- oral (aphthous) ulcers (any shape, size or number at least 3 times in any 12 months),

along with 2 out of the next 4 "hallmark" symptoms:

- genital ulcers (including anal ulcers and spots in the genital region and swollen testicles or epididymitis in men),
- skin lesions (papulo-pustules, folliculitis, erythema nodosum, acne in post-adolescents not on corticosteroids),
- eye inflammation (iritis, uveitis, retinal vasculitis, cells in the vitreous),
- pathergy reaction (papule >2 mm dia. 24-48 hrs or more after needle-prick).

[http://en.wikipedia.org/wiki/Beh%C3%A7et's\\_disease](http://en.wikipedia.org/wiki/Beh%C3%A7et's_disease)

**BEST DISEASE /VITELLIFORM MACULAR DYSTROPHY OR VITELLIFORM DYSTROPHY** IS a genetic eye disorder that can cause progressive vision loss. This disorder affects the retina, specifically cells in a small area near the center of the retina called the macula. The macula is responsible for sharp central vision, which is needed for detailed tasks such as reading, driving, and recognizing faces.

### **Diagnosis**

Vitelliform macular dystrophy causes a fatty yellow pigment (lipofuscin) to build up in cells underlying the macula. Over time, the abnormal accumulation of this substance can damage cells that are critical for clear central vision. As a result, people with this disorder often lose their central vision and may experience blurry or distorted vision. Vitelliform macular dystrophy does not affect side (peripheral) vision or the ability to see at night.

Researchers have described two forms of vitelliform macular dystrophy with similar features. The early-onset form (known as **Best disease**) usually appears in childhood; however, the onset of symptoms and the severity of vision loss vary widely. The adult-onset form begins later, usually in middle age, and tends to cause relatively mild vision loss. The two forms of vitelliform macular dystrophy each have characteristic changes in the macula that can be detected during an eye examination.

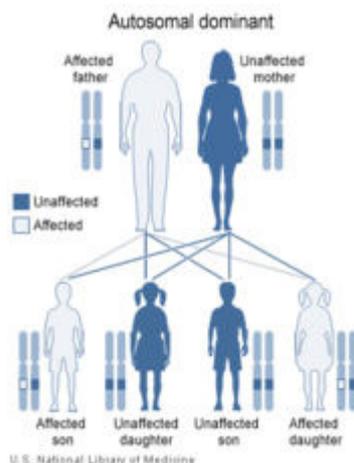
## Pathophysiology

Mutations in the *RDS* and *VMD2* genes cause vitelliform macular dystrophy. Mutations in the *VMD2* gene are responsible for Best disease. Changes in either the *VMD2* or *RDS* gene can cause the adult-onset form of vitelliform macular dystrophy; however, less than a quarter of cases result from mutations in these two genes. In most cases, the cause of the adult-onset form is unknown.

The *VMD2* gene provides instructions for making a protein called bestrophin. Although its exact function is uncertain, this protein likely acts as a channel that controls the movement of negatively charged chlorine atoms (chloride ions) into or out of cells in the retina. Mutations in the *VMD2* gene probably lead to the production of an abnormally shaped channel that cannot regulate the flow of chloride. Researchers have not determined how these malfunctioning channels are related to the buildup of lipofuscin in the macula and progressive vision loss.

The *RDS* gene provides instructions for making a protein called peripherin. This protein is essential for the normal function of light-sensing (photoreceptor) cells in the retina. Mutations in the *RDS* gene disrupt the structures in these cells that contain light-sensing pigments, leading to vision loss. It is unclear why *RDS* mutations affect only central vision in people with adult-onset vitelliform macular dystrophy.

## Inheritance



Best disease, the early-onset form of vitelliform macular dystrophy, has an autosomal dominant pattern of inheritance.

*Best disease* is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person has one parent with the condition.

The inheritance pattern of adult-onset vitelliform macular dystrophy is uncertain. Some studies have suggested that it may be inherited in an autosomal dominant pattern. Many affected people, however, have no history of the disorder in their family and only a small number of affected families have been reported.

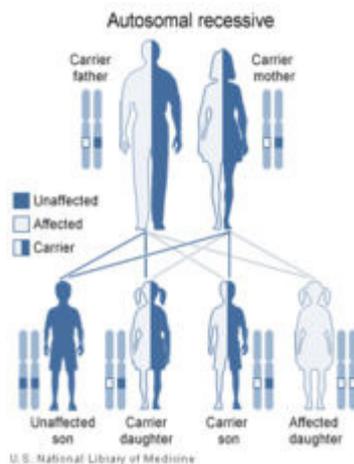
[http://en.wikipedia.org/wiki/Vitelliform\\_macular\\_dystrophy](http://en.wikipedia.org/wiki/Vitelliform_macular_dystrophy)

## BIETTI'S CRYSTALLINE DYSTROPHY

**Bietti's crystalline dystrophy** (BCD), also called **Bietti's crystalline retinopathy**, is a rare autosomal recessive eye disease named for Dr. G. B. Bietti.

BCD is a rare disease and appears to be more common in people with Asian ancestry

The symptoms of BCD include: crystals in the cornea (the clear covering of the eye); yellow, shiny deposits on the retina; and progressive atrophy of the retina, choriocapillaries and choroid (the back layers of the eye). This tends to lead to progressive night blindness and visual field constriction.



Bietti's crystalline dystrophy has an autosomal recessive pattern of inheritance.

It has been associated with CYP4V2.

[http://en.wikipedia.org/wiki/Bietti's\\_Crystalline\\_Dystrophy](http://en.wikipedia.org/wiki/Bietti's_Crystalline_Dystrophy)

## BLINDNESS

**Blindness** is the condition of lacking visual perception due to physiological or neurological factors.

Various scales have been developed to describe the extent of vision loss and define "blindness." **Total blindness** is the complete lack of form and visual light perception and is

clinically recorded as "NLP," an abbreviation for "no light perception." *Blindness* is frequently used to describe severe visual impairment with residual vision. Those described as having only "light perception" have no more sight than the ability to tell light from dark. A person with only "light projection" can tell the general direction of a light source.

In order to determine which people may need special assistance because of their visual disabilities, various governmental jurisdictions have formulated more complex definitions referred to as **legal blindness**. In North America and most of Europe, legal blindness is defined as visual acuity (vision) of 20/200 (6/60) or less in the better eye with best correction possible. This means that a legally blind individual would have to stand 20 feet (6.1 m) from an object to see it—with vision correction—with the same degree of clarity as a normally sighted person could from 200 feet (61 m). In many areas, people with average acuity who nonetheless have a visual field of less than 20 degrees (the norm being 180 degrees) are also classified as being legally blind. Approximately ten percent of those deemed legally blind, by any measure, have no vision. The rest have some vision, from light perception alone to relatively good acuity. Low vision is sometimes used to describe visual acuities from 20/70 to 20/200.

By the 10th Revision of the WHO International Statistical Classification of Diseases, Injuries and Causes of Death, *low vision* is defined as visual acuity of less than 6/18, but equal to or better than 3/60, or corresponding visual field loss to less than 20 degrees, in the better eye with best possible correction. *Blindness* is defined as visual acuity of less than 3/60, or corresponding visual field loss to less than 10 degrees, in the better eye with best possible correction.

It should be noted that blind people with undamaged eyes may still register light non-visually for the purpose of circadian entrainment to the 24-hour light/dark cycle. Light signals for this purpose travel through the retinohypothalamic tract, not the optic nerve, so a damaged optic nerve is no hindrance.

In 1934, the American Medical Association adopted the following definition of blindness:

Central visual acuity of 20/200 or less in the better eye with corrective glasses or central visual acuity of more than 20/200 if there is a visual field defect in which the peripheral field is contracted to such an extent that the widest diameter of the visual field subtends an angular distance no greater than 20 degrees in the better eye.

## **Diseases**

Most visual impairment is caused by disease and malnutrition. According to WHO estimates in 2002, the most common causes of blindness around the world are:

- cataracts (47.8%),
- glaucoma (12.3%),
- uveitis (10.2%),
- age-related macular degeneration (AMD) (8.7%),
- trachoma (3.6%),
- corneal opacity (5.1%), and
- diabetic retinopathy (4.8%), among other causes.

People in developing countries are significantly more likely to experience visual impairment as a consequence of treatable or preventable conditions than are their counterparts in the developed world. While vision impairment is most common in people over age 60 across all regions, children in poorer communities are more likely to be affected by blinding diseases than are their more affluent peers.

The link between poverty and treatable visual impairment is most obvious when conducting regional comparisons of cause. Most adult visual impairment in North America and Western Europe is related to age-related macular degeneration and diabetic retinopathy. While both of these conditions are subject to treatment, neither can be cured. Another common cause is retinopathy of prematurity.

In developing countries, wherein people have shorter life expectancies, cataracts and water-borne parasites—both of which can be treated effectively—are most often the culprits (see River blindness, for example). Of the estimated 40 million blind people located around the world, 70–80% can have some or all of their sight restored through treatment.

In developed countries where parasitic diseases are less common and cataract surgery is more available, age-related macular degeneration, glaucoma, and diabetic retinopathy are usually the leading causes of blindness.

### **Abnormalities and injuries**

Eye injuries, most often occurring in people under 30, are the leading cause of monocular blindness (vision loss in one eye) throughout the United States. Injuries and cataracts affect the eye itself, while abnormalities such as optic nerve hypoplasia affect the nerve bundle that sends signals from the eye to the back of the brain, which can lead to decreased visual acuity.

People with injuries to the occipital lobe of the brain can, despite having undamaged eyes and optic nerves, still be legally or totally blind.

### **Genetic defects**

People with albinism often suffer from visual impairment to the extent that many are legally blind, though few of them actually cannot see. Leber's congenital amaurosis can cause total blindness or severe sight loss from birth or early childhood.

Recent advances in mapping of the human genome have identified other genetic causes of low vision or blindness. One such example is Bardet-Biedl syndrome.

### **Poisoning**

A small portion of all cases of blindness are caused by the intake of certain chemicals. A well-known example is methanol, found in methylated spirits, which are sometimes used by alcoholics as a cheap substitute for regular alcoholic beverages.

**[http://en.wikipedia.org/wiki/Blindness#Legal\\_blindness](http://en.wikipedia.org/wiki/Blindness#Legal_blindness)**

## CHARGE SYNDROME

**CHARGE syndrome** (formerly known as CHARGE association), is a syndrome caused by a genetic disorder. It was first described in 1979.

In 1981, the term "CHARGE" came into use as an acronym for the set of unusual congenital features seen in a number of newborn children. The letters stand for: Coloboma of the eye, Heart defects, Atresia of the nasal choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness. These features are no longer used in making a diagnosis of CHARGE syndrome, but the name remains.

Dr. B.D. Hall first described the CHARGE association in a 1979 journal paper about 17 children who had all been born with choanal atresia. About the same time, Dr. H.M. Hittner also observed that the group of 10 children in a study all had choanal atresia as well as coloboma, congenital heart defect, and hearing loss. Using both a coloboma or choanal atresia and some of the other related characteristic malformations, Dr. R. A. Pagon first coined the term CHARGE. In choosing this acronym, Dr. Pagon intended to emphasize that this cluster of associated malformations occurred together. It soon came to be recognised as a syndrome within the umbrella of the CHARGE association. While an association is a set of apparently random signs occurring together, the signs seen in CHARGE are caused by a genetic anomaly and so its name was officially corrected to 'CHARGE syndrome'.

### Genetics

CHARGE syndrome was formerly referred to as CHARGE association, which indicates a non-random pattern of congenital anomalies that occurs together more frequently than one would expect on the basis of chance. Very few people with CHARGE will have 100% of its known features. In 2004, mutations on the CHD7 gene (located on Chromosome 8) were found in 10 of 17 patients in a study conducted in the Netherlands, making CHARGE an official "syndrome". A further study in the US of 110 individuals with CHARGE syndrome showed that 60% of those tested had a mutation on the CHD7 gene.

### Signs

Although genetic testing positively identifies nearly 2/3 of the total number of children with CHARGE, diagnosis is still largely clinical. The acronym **CHARGE** was coined in 1981 to describe a cluster of features identified in a number of children. The following are the signs that were originally identified in children with this syndrome, but these features alone are no longer used in official diagnosis.

- **C** - Coloboma of the eye, central nervous system anomalies
- **H** - Heart defects
- **A** - Atresia of the choanae
- **R** - Retardation of growth and/or development
- **G** - Genital and/or urinary defects (Hypogonadism)
- **E** - Ear anomalies and/or deafness

### Epidemiology

CHARGE syndrome has an estimated prevalence of one in ten thousand.

## **Therapy and outcome**

Children with CHARGE syndrome can have many life threatening issues, with advance in medical care these children can survive and become healthy and happy individuals. Appropriate therapies and educational intervention that is given to individuals with CHARGE syndrome must take into consideration hearing, vision and any other medical conditions that are present. Early intervention, such as occupational and physical therapy is very important as the intelligence of children with multiple health issues such as combined deaf blindness is often underestimated. Because of the developmental delay, early intervention would play an important role in mobility, improving static postures, transitioning towards ambulation, and teaching self care skills. Both physicians and parents need to be made aware that these children can thrive with the support of a team of medical professionals. Management should be by a multidisciplinary team and coordinated by a single person, if possible.

## **Educational goals**

Parents of children with CHARGE should be encouraged to become IN CHARGE and very active advocates for their children in order to ensure that an educational program is made that will allow each child to reach their full potential. All children regardless of their final cognitive abilities will require special support in schools to ensure that they maximize their potentials and develop into the most productive people that they can be.

In an educational setting all involved must be aware of the special needs a child with CHARGE may have. Teachers of children with CHARGE Syndrome have to be aware of all areas affected by the disease. Because CHARGE can affect the eyes, ears, and brain it is most important that all members of the educational team (teacher of the deaf and hard of hearing, teachers of the visually impaired, audiologists, pediatricians, parents, etc.) Taking each of these into account is vital to the success of the child and family in an educational setting.

## **Understanding behaviors**

Parents, teachers and caregivers should understand that all behaviors, whether good or bad, are a form of communication. An important step in dealing with the behavior is understanding why it is occurring in the first place and helping the child learn more appropriate methods of communication

## **Transitioning into adulthood**

Parents should make sure that before their child reaches 18 (or year of majority for their country), that they have established doctors and specialists who will follow the child after they have reached adulthood. Even if the young adult with CHARGE is independent, it's important to help them maintain their independence by helping them move from the pediatric doctors to the new doctors who will follow them as adults. It is not recommended to rely on hospitals to do that for the parents.

[http://en.wikipedia.org/wiki/CHARGE\\_syndrome](http://en.wikipedia.org/wiki/CHARGE_syndrome)

## **CHARLES BONNET SYNDROME (CBS)**

**Charles Bonnet syndrome (CBS)** is named after the Swiss naturalist Charles Bonnet. In 1760 he described a condition in which vivid, complex visual hallucinations (fictive visual percepts) occur in mentally healthy people. One characteristic of these hallucinations is that they usually are "lilliput hallucinations" (hallucinations in which the characters or objects may be smaller, larger, or regular size). He first documented it in his 89-year-old grandfather, who was nearly blind from cataracts in both eyes but perceived men, women, birds, carriages, buildings, tapestries, and scaffolding patterns.

Most who are affected by this are people with visual impairments due to old age, damage to the eyes or optic pathways. In particular, central vision loss due to a condition such as macular degeneration combined with peripheral vision loss from glaucoma may predispose to CBS, although most people with such deficits do not develop the syndrome.

[http://en.wikipedia.org/wiki/Charles\\_Bonnet\\_syndrome](http://en.wikipedia.org/wiki/Charles_Bonnet_syndrome)

## **CHILDHOOD BLINDNESS**

- causes of blindness in children differ from those in adults and require different strategies;
- delay or absence of treatment in the early stages leads to conditions which are not treatable or not easily treatable in adults, such as amblyopia;
- treatment requires specific training, knowledge, skills, and equipment;
- the number of 'blind years' in children is much greater than blindness occurring in adults.

There are an estimated 1.5 million blind children in the world, of whom approximately 1 million live in Asia and approximately 300 000 in Africa. Each year, an estimated half a million children become blind, of whom up to 60% die in childhood.

Childhood blindness is caused mainly by vitamin A deficiency, measles, conjunctivitis in the newborn, congenital cataract, and retinopathy of prematurity (ROP). ROP is an established problem in developed countries because of the ever-increasing survival rate of low- and very low-birth-weight infants. For the same reason, it is also emerging as a problem in economically-developing parts of the world, especially in urban settings. Other causes of childhood blindness are congenital or genetically determined. It should be noted that the causes of childhood blindness vary from country to country and over time.

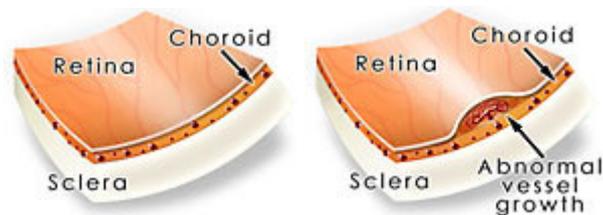
Because of the wide range of causes of childhood blindness, intervention must be disease-specific and directed at more than one level of the eye-care delivery system. Accordingly, vitamin A deficiency and measles, treatment of simple eye infections, prevention of corneal trauma, and immunization are best managed at the primary level. Relevant activities should be integrated with existing maternal and child health programmes, immunization programmes, and other community- directed health services.

Management of ocular injuries and corneal ulcers, and the provision of spectacles, take place at the secondary level. Prevention of ROP, surgical treatment of eye conditions, and provision of optical devices all take place at the tertiary level. Close cooperation with other specialists, such as neonatologists and paediatricians, is essential.

<http://ftp.who.int/nmh/Vision2020/eng/contents/3.5.3.html>

## CHOROIDAL NEOVASCULAR MEMBRANE (CNVM)

**Choroidal neovascular membrane (CNVM)** is a problem that is related to a wide variety of retinal diseases, but is most commonly linked to age-related macular degeneration. With CNVM, abnormal blood vessels stemming from the choroid (the blood vessel-rich tissue layer just beneath the retina) grow up through the retinal layers. Imagine the abnormal blood vessels as weeds creeping up through the cracks of a sidewalk. These new vessels are very fragile and break easily, causing blood and fluid to pool within the layers of the retina.



As the vessels leak, they disturb the delicate retinal tissue, causing the vision to deteriorate. The severity of the symptoms depends on the size of the CNVM and its proximity to the macula. Patients' symptoms may be very mild such as a blurry or distorted area of vision, or more severe, like a central blind spot.

### Signs and Symptoms

- Blurred, grayed-out areas
- Distorted vision
- Central blind spot

### Detection and Diagnosis

A simple vision test called an Amsler Grid should always be done first for patients who notice a problem with their central vision. This test provides the retina doctor with vital information about the location and severity of the problem. CNVM is usually difficult to diagnose by simply looking at the retina with an ophthalmoscope. A special dye test called a fluorescein angiogram is used to study the circulation of the retina and show areas of leaking blood vessels.

### Treatment

The appropriate treatment is dependent on several factors such as: size and location of the membrane and the amount of time that passed since the symptoms first began. If the CNVM

is small, compact, and caught very early, a delicate surgery called a sub-foveal excision can be performed to remove it. This procedure has the most risk but also offers the patient the best possibility of visual improvement.

Laser photocoagulation, a procedure that seals leaking blood vessels, is the simplest and most common treatment for CNVM. It is reserved for patients with bleeding outside of the central retina because it creates a scar that affects the vision. Treating the retina with laser gives the surgeon the most control over placement and size of the scar. Allowing an undiagnosed leak to resolve on its own usually causes a much more devastating affect on the vision.

Unfortunately, for some patients, no treatment is appropriate. All patients with CNVM should monitor their vision with an Amsler Grid and report any changes to their retinal doctor immediately.

<http://www.stlukeseye.com/Conditions/CNVM.asp>

## **CHOROIDEREMIA**

**Choroideremia** is an X-linked recessive retinal degenerative disease that leads to the degeneration of the choriocapillaris, the retinal pigment epithelium, and the photoreceptor of the eye.

Choroideremia is caused by the deletion of the Rab escort protein 1 (REP1). Rab escort protein 2 (REP2) is 75% identical and can *almost* compensate for the loss of REP1. The REPs are essential for the prenylation of Rab proteins. Studies have shown that there is a build up of unprenylated Rab27 in lymphoblasts from Choroideremia patients.

Generally, only men show symptoms of this disease, although in rare cases some women also acquire it. Initially a person suffering from choroideremia has night blindness, which begins in youth. As the disease progresses, a CHM sufferer loses their peripheral vision and depth perception, eventually losing all sight by middle age. In some cases, a severe loss of acuity and color perception become evident as the disease progresses.

The link between the loss of REP1 and the build up of unprenylated Rab27 and the degeneration of the eye is unknown as yet.

At this time, there is no treatment or cure for this disease.

<http://en.wikipedia.org/wiki/Choroideremia>

## **COATS' DISEASE**

**Coats' disease**, (also known as **exudative retinitis** or **retinal telangiectasis**, sometimes spelled **Coates' disease**), is a rare eye disorder, causing full or partial blindness, characterized by abnormal development of blood vessels behind the retina.

It can have a similar presentation to that of retinoblastoma

Its cause is not currently known. However, it has been described as a manifestation of facioscapulohumeral dystrophy, which is a more precisely characterized condition.

## **Presentation**

Coats' usually affects only one eye (unilateral) and occurs predominantly in young males, with the onset of symptoms generally appearing in the first decade of life. The specific cause of Coats' disease remains unknown. Current research suggests a genetic component contributes to the disease. It is believed one is born with this disease, but Coats' is not hereditary.

Coats' disease results in a gradual loss of vision. Blood leaks from the abnormal vessels into the back of the eye, leaving behind cholesterol deposits and damaging the retina. Coats' normally progresses slowly. At advanced stages, retinal detachment is likely to occur. Glaucoma, atrophy, and cataracts can also develop secondary to Coats' disease. In some cases, removal of the eye may be necessary (enucleation).

## **Symptoms**

Symptoms begin as blurred vision, usually pronounced when one eye is closed (due to the unilateral nature of the disease). Often the unaffected eye will compensate for the loss of vision in the other eye; however, this results in some loss of depth perception and parallax. Deterioration of sight may begin in either the central or peripheral vision. Deterioration is likely to begin in the upper part of the vision field as this corresponds with the bottom of the eye where blood usually pools. Flashes of light, known as photopsia, and floaters are common symptoms. Persistent color patterns may also be perceived in the affected eye. Initially, these may be mistaken for psychological hallucinations, but are actually the result of both retinal detachment and foreign fluids mechanically interacting with the photoreceptors located on the retina.

One early warning sign of Coats' disease is yellow-eye in flash photography. Just as the red-eye effect is caused by a reflection off blood vessels in the back of a normal eye, an eye affected by Coats' will glow yellow in photographs as light reflects off cholesterol deposits. Children with yellow-eye in photographs are typically advised to immediately seek evaluation from an ophthalmologist.

Coats' disease itself is not painful. Pain may develop as a result of retinal detachment. Pain may also occur if fluid is not able to properly drain from the eye, causing the internal pressure to swell.

## **Treatment**

In the early stages, there are a few treatment options. Laser surgery or cryotherapy (freezing) can be used to destroy the abnormal blood vessels, thus halting progression of the disease. However, if the leaking blood vessels are clustered around the optic nerve, this treatment is not recommended as accidental damage to the nerve itself can result in permanent blindness. Coats' disease may stop progressing all on its own, either temporarily or permanently. Cases have been documented in which the condition even reverses itself. However, once total retinal

detachment occurs, sight loss is permanent in most cases. Removal of the eye (enucleation) is an option if pain or further complications arise.

[http://en.wikipedia.org/wiki/Coats\\_disease](http://en.wikipedia.org/wiki/Coats_disease)

## COLOBOMA

A **coloboma** (also part of the rare **Cat Eye syndrome**) is a hole in one of the structures of the eye, such as the lens, eyelid, iris, retina, choroid or optic disc. The hole is present from birth and can be caused when a gap called the choroid fissure between two structures in the eye, which is present early in development in the uterus, fails to close up completely before a child is born. A coloboma can occur in one or both eyes.

The effects a coloboma has on the vision can be mild or more severe depending on the size and location of the gap. If, for example, only a small part of the iris is missing, vision may be normal, whereas if a large part of the retina or optic nerve is missing, vision may be poor and a large part of the visual field may be missing. This is more likely to cause problems with mobility if the lower visual field is absent. Other conditions can be associated with a coloboma. Sometimes the eye may be reduced in size, a condition called microphthalmia, or there may be glaucoma, nystagmus or strabismus (squint).

Some children with coloboma of the eye also have malformations in other parts of the body. There is a rare condition called CHARGE syndrome, in which coloboma is associated with cleft lip and/or palate, ear abnormalities and hearing impairment, choanal atresia, delays in growth and development, central nervous system anomalies and congenital heart defects.

Colobomas are caused by a mutation in the *pax2* gene.

The incidence of coloboma is estimated at around 0.5 to 0.7 per 10,000 births, making it a relatively rare condition.

<http://en.wikipedia.org/wiki/Coloboma>

## CORTICAL BLINDNESS

**Cortical blindness** is the total or partial loss of vision in a normal-appearing eye caused by damage to the visual area in the brain's occipital cortex.

### Causes

Bilateral lesions of the primary visual cortex may cause cortical blindness.

Side effect of anti-epilepsy drugs (AEDs) over time.

The posterior cerebral artery supplies the occipital lobe, and can be associated with cortical blindness.

## **Presentation**

Patients have no vision but the response of the pupil to light is intact (as the reflex does not involve the cortex).

Fundoscopy is normal. Cortical blindness can be associated with visual hallucinations, denial of visual loss (Anton syndrome), and the ability to perceive moving but not static objects. (Riddoch phenomenon).

[http://en.wikipedia.org/wiki/Cortical\\_blindness](http://en.wikipedia.org/wiki/Cortical_blindness)

## **CYTOMEGALOVIRUS RETINITIS**

Cytomegalovirus retinitis, also known as CMV retinitis, is an inflammation of the eye's retina that can lead to blindness.

Cytomegalovirus (CMV) is a DNA virus in the family Herpesviridae known for producing large cells with nuclear and cytoplasmic inclusions. Such inclusions are called an "owl's eye" effect.

While CMV is found in almost everyone, and is usually fought off by the immune system, for people who are immunocompromised, by diseases, transplants, or chemotherapy the virus is not adequately destroyed and can cause damage to the eye and the rest of the body. HIV positive persons are most at risk, especially when the CD4 cell count decreases. CMV is a common virus that infects those who are HIV positive.

It affects the eye in about 30% of the cases by causing damage to the retina. Symptoms can include blurred vision, eye pain, photophobia, redness, and blindness. It may affect just one eye at first, but then may spread to the other.

Active Cytomegalovirus retinitis is treated by an uveitis and ocular immunology specialist.

Because the virus is so threatening to vision, it is usually treated by a vitreo-retinal surgeon, by antivirals such as ganciclovir or foscarnet, which can be taken orally, intravenously, injected directly into the eye (intravitreal injection), or through an intravitreal implant.

### **Risk factors**

The systemic use of corticosteroids has recently been implicated as elevating the risk of CMV in AIDS patients

[http://en.wikipedia.org/wiki/Cytomegalovirus\\_retinitis](http://en.wikipedia.org/wiki/Cytomegalovirus_retinitis)

## **DEAFBLINDNESS**

**Deafblindness** is the condition of little or no useful sight and little or no useful hearing. As with the word "Deaf," it can be capitalized to indicate that it is a culture; some prefer the spelling "DeafBlind". Deafblind people have an experience quite distinct from people who are only deaf or only blind.

Deafblind people communicate in many different ways determined by the nature of their condition, the age of onset, and what resources are available to them. For example, someone who grew up deaf and experienced vision loss later in life is likely to use a sign language (in a visually-modified or tactual form). Others who grew up blind and later became deaf are more likely to use a tactile mode of their spoken/written language. Methods of communication include:

- Use of residual hearing (speaking clearly, hearing aids) or sight (signing within a restricted visual field, writing with large print).
- Tactile signing — sign language or a manual alphabet such as the American Manual Alphabet, or DeafBlind Alphabet (also known as "two-hand manual") with tactile or visual modifications.
- Interpreting services (such as sign language interpreters or communication aides)
- Communication devices such as Tellatouch.

Multisensory methods have been used to help deafblind people enhance their communication skills. These can be taught to very young children with developmental delays (to help with pre-intentional communication), young people with learning difficulties, or older people, including those with dementia. One such process is Tacpac.

### **Causes**

There are over 70 known causes of deafblindness. Causes can be categorised into two groups: acquired and congenital.

#### **Acquired**

The majority of people with sight and hearing impairments have had both sight and hearing throughout most of their lives, and experienced a loss of those senses through illness, injury or age. According to [sense.org.uk](http://sense.org.uk), about 4% of people over 60 in the UK have both hearing and vision impairments. Most people with acquired sight and hearing loss retain some useful sight and/or hearing. Some people have congenital deafness and acquired blindness (such as glaucoma or cataracts) or vice-versa.

#### **Congenital**

Children born deaf and blind are described as having congenital deafblindness. This condition may be due to prenatal infection (such as rubella), genetic/chromosomal syndromes (such as Down syndrome), birth trauma or maternal heavy alcohol and drug use. Some congenital conditions will not cause deafblindness until later in life. [Sense.org.uk](http://Sense.org.uk) reports that the biggest cause of deafblindness in children in the western world today is 'unknown.' Maternal rubella was once the major cause of deafness and deafblindness in the west, but is now rare due to widespread vaccination programs.

Usher syndrome is also a major contributor to deafblindness. It is a genetic condition of people born deaf or hard of hearing, who gradually start to lose their sight. The sight loss usually begins in late childhood and is caused by an eye condition known as Retinitis Pigmentosa. Early symptoms include night blindness and loss of peripheral vision. It affects 3-6% of the people in the UK who were born deaf or partially hearing (sense.org.uk).

<http://en.wikipedia.org/wiki/Deafblind>

## DIABETIC RETINOPATHY

**Diabetic retinopathy** is retinopathy (damage to the retina) caused by complications of diabetes mellitus, which could eventually lead to blindness. It is an ocular manifestation of systemic disease which affects up to 80% of all diabetics who have had diabetes for 10 years or more. Despite these intimidating statistics, research indicates that at least 90% of these new cases could be reduced if there was proper and vigilant treatment and monitoring of the eyes

Diabetic retinopathy often has no early warning signs. Even macular edema, which may cause vision loss more rapidly, may not have any warning signs for some time. In general, however, a person with macular edema is likely to have blurred vision, making it hard to do things like read or drive. In some cases, the vision will get better or worse during the day.

As new blood vessels form at the back of the eye as a part of *proliferative diabetic retinopathy* (PDR), they can bleed (haemorrhage) and blur vision. The first time this happens, it may not be very severe. In most cases, it will leave just a few specks of blood, or spots, floating in a person's visual field, though the spots often go away after a few hours.

These spots are often followed within a few days or weeks by a much greater leakage of blood, which blurs vision. In extreme cases, a person will only be able to tell light from dark in that eye. It may take the blood anywhere from a few days to months or even years to clear from the inside of the eye, and in some cases the blood will not clear. These types of large hemorrhages tend to happen more than once, often during sleep.

On fundoscopic exam, a doctor will see cotton wool spots, flame hemorrhages, and dot-blot hemorrhages.

Diabetic retinopathy is the result of microvascular retinal changes. Hyperglycemia-induced pericyte death and thickening of the basement membrane lead to incompetence of the vascular walls. These damages change the formation of the blood-retinal barrier and also make the retinal blood vessels become more permeable.

Small blood vessels – such as those in the eye – are especially vulnerable to poor blood sugar control. An overaccumulation of glucose and/or fructose damages the tiny blood vessels in the retina. During the initial stage, called nonproliferative diabetic retinopathy (NPDR), most people do not notice any changes in their vision.

Some people develop a condition called macular edema. It occurs when the damaged blood vessels leak fluid and lipids onto the macula, the part of the retina that lets us see detail. The fluid makes the macula swell, which blurs vision.

As the disease progresses, severe nonproliferative diabetic retinopathy enters an advanced, or proliferative, stage. The lack of oxygen in the retina causes fragile, new, blood vessels to grow along the retina and in the clear, gel-like vitreous humour that fills the inside of the eye. Without timely treatment, these new blood vessels can bleed, cloud vision, and destroy the retina. Fibrovascular proliferation can also cause tractional retinal detachment. The new blood vessels can also grow into the angle of the anterior chamber of the eye and cause neovascular glaucoma. Nonproliferative diabetic retinopathy shows up as cotton wool spots, or microvascular abnormalities or as superficial retinal hemorrhages. Even so, the advanced proliferative diabetic retinopathy (PDR) can remain asymptomatic for a very long time, and so should be monitored closely with regular checkups.

All people with diabetes mellitus are at risk – those with Type I diabetes (*juvenile onset*) and those with Type II diabetes (*adult onset*). The longer a person has diabetes, the higher the risk of developing some ocular problem. Between 40 to 45 percent of Americans diagnosed with diabetes have some stage of diabetic retinopathy. After 20 years of diabetes, nearly all patients with type 1 diabetes and >60% of patients with type 2 diabetes have some degree of retinopathy.

Prior studies had also assumed a clear glycemic threshold between people at high and low risk of diabetic retinopathy. However, it has been shown that the widely accepted WHO and American Diabetes Association diagnostic cutoff for diabetes of a fasting plasma glucose  $\geq 7.0$  mmol/l (126 mg/dl) does not accurately identify diabetic retinopathy among patients. The cohort study included a multi-ethnic, cross-sectional adult population sample in the US, as well as two cross-sectional adult populations in Australia. For the US-based component of the study, the sensitivity was 34.7% and specificity was 86.6%. For patients at similar risk to those in this study (15.8% had diabetic retinopathy), this leads to a positive predictive value of 32.7% and negative predictive value of 87.6%.

Published rates vary between trials, the proposed explanation being differences in study methods and reporting of prevalence rather than incidence values.

During pregnancy, diabetic retinopathy may also be a problem for women with diabetes. It is recommended that all pregnant women with diabetes have dilated eye examinations each trimester to protect their vision

There are three major treatments for diabetic retinopathy, which are very effective in reducing vision loss from this disease. In fact, even people with advanced retinopathy have a 90 percent chance of keeping their vision when they get treatment before the retina is severely damaged. Still, the best way of addressing diabetic retinopathy is to monitor it vigilantly and ensure that it does not happen in the first place by careful blood glucose control and limitation of dietary fructose.

These three treatments are laser surgery, injection of triamcinolone into the eye and vitrectomy. It is important to note that although these treatments are very successful, they do not cure diabetic retinopathy. Caution should be exercised in treatment with laser surgery since it causes a loss of retinal tissue. It is often more prudent to inject triamcinolone. In some patients it results in a marked increase of vision, especially if there is an edema of the macula.

Avoiding tobacco use and correction of associated hypertension are important therapeutic measures in the management of diabetic retinopathy.

[http://en.wikipedia.org/wiki/Diabetic\\_retinopathy#Signs\\_and\\_symptoms](http://en.wikipedia.org/wiki/Diabetic_retinopathy#Signs_and_symptoms)

## **EHLERS-DANLOS SYNDROME**

**Ehlers-Danlos syndrome** is a group of rare genetic disorders affecting humans and domestic animals caused by a defect in collagen synthesis. Depending on the individual mutation, the severity of the disease can vary from mild to life-threatening. There is no known cure. Treatment is supportive.

### **Symptoms**

Symptoms vary widely based on which type of Ehlers Danlos Syndrome (EDS) the patient has. In each case, however, the symptoms are ultimately due to faulty or reduced amounts of collagen. For example, in the most common type of EDS, Hypermobility Type, symptoms often include unstable, flexible joints with a painful tendency to dislocate and subluxate. This is due to ligaments which, because they are lacking proper collagen--the molecule that provides strength to ligaments--are overly stretchable. The so-called Classic EDS Type features skin that forms cigarette-paper-like scars. Another type of collagen is usually responsible for lending strength to skin (and scars). The most serious type of EDS, Vascular EDS, can result in premature death via vascular (blood vessel) and organ rupture. Again, another type collagen is necessary to give strength to the walls of blood vessels and the walls of hollow organs (such as the large bowel, aka colon). (It should be noted that Vascular EDS is also one of the most rare types of the disease.) See table below for a more extensive list of symptoms for each type of EDS. You will see some cross-over or similarity of symptoms among the various types. For instance, many of the types feature velvety or hyperextensible skin. In addition, persons with Hypermobility Type often have very stretchy ligaments (leading to frequent subluxations/dislocations) while those with Vascular Type have ligaments that rupture.

### **Classification**

In the past, there were more than 10 recognized types of Ehlers-Danlos syndrome. In 1997, researchers proposed a simpler classification that reduced the number of major types to six and gave them descriptive names. These six major types are listed below. Other types of the condition may exist, but they have been reported only in single families or are not well characterized. Except for hypermobility, the specific mutations involved have been identified and they can be precisely identified by genetic testing; this is valuable due to a great deal of variation in individual presentation of symptoms which may confuse classification of individuals on purely symptomatic basis. In order of prevalence in the population, they are:

Mutations in the ADAMTS2, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, PLOD1 and TNXB genes cause Ehlers-Danlos syndrome.

Mutations in these genes usually alter the structure, production, or processing of collagen or proteins that interact with collagen. Collagen provides structure and strength to connective tissue throughout the body. A defect in collagen can weaken connective tissue in the skin, bones, blood vessels, and organs, resulting in the features of the disorder.

Inheritance patterns depend on the type of Ehlers-Danlos syndrome. Most forms of the condition are inherited in an autosomal dominant pattern, which means only one of the two copies of the gene in question must be altered to cause the disorder. The minority are inherited in an autosomal recessive pattern, which means both copies of the gene must be altered for a person to be affected by the condition. Please refer to the summary for each type of Ehlers-Danlos syndrome for a discussion of its inheritance pattern.

[http://en.wikipedia.org/wiki/Ehlers-Danlos\\_syndrome](http://en.wikipedia.org/wiki/Ehlers-Danlos_syndrome)

## **FUCHS' DYSTROPHY**

**Fuchs' dystrophy**, also known as **Fuchs' endothelial dystrophy**, is a slowly progressing corneal disease that usually affects both eyes and is slightly more common in women than in men. Although doctors can often see early signs of Fuchs' dystrophy in people in their 30s and 40s, the disease rarely affects vision until people reach their 50s and 60s.

The condition was first described by Austrian Ernst Fuchs (1851-1930), for whom it is named.

Fuchs' endothelial dystrophy (FED) is a progressive disorder of the corneal endothelium with accumulation of focal excrescences called guttae and thickening of Descemet's membrane, leading to corneal edema and loss of vision. The cornea is the outermost portion of the eye that overlies the anterior chamber, iris, and lens apparatus. Clarity of the cornea is necessary for visual function. The normal human cornea contains the following layers: epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. Corneal endothelial cells are the major "pump" cells of the cornea to allow for stromal clarity. In FED, Descemet's membrane is grossly thickened with accumulation of abnormal wide-spaced collagen and numerous guttae. Corneal endothelial cells in end-stage FED are reduced in number and appear attenuated, causing progressive stromal edema. Progressive endothelial cell loss causes relative influx of aqueous humor into the cornea, leading to swelling (corneal stromal edema), with resultant distorted vision. Eventually, the epithelium also becomes edematous, resulting in more severe visual impairment. Focal areas or blisters of epithelial edema ("bullae") may be particularly painful.

The inheritance of FED is autosomal dominant with genetic and environmental modifiers such as increased prevalence in the elderly and in females. Endothelial cell loss may be aggravated or accelerated by intraocular trauma or surgery. A common scenario involves excessive corneal swelling or edema following cataract surgery or other types of ocular surgery. Hence, patients with a history of Fuchs' dystrophy may be at a greater risk of corneal edema after ocular surgery as they have less functioning endothelial cells.

FED is classified into 4 stages, from early signs of guttae formation to end-stage subepithelial scarring. Diagnosis is made by biomicroscopic examination; other modalities, such as corneal pachymetry, confocal biomicroscopy, and specular microscopy can be used in conjunction. Exact pathogenesis is unknown but factors include endothelial cell apoptosis, sex hormones, inflammation, and aqueous humor flow and composition. Mutations in collagen VIII, a major component of Descemet's membrane secreted by endothelial cells, have been linked to FED.

## Signs and symptoms

At first, a person with Fuchs' dystrophy will awaken with blurred vision that will gradually clear during the day. This occurs because the cornea is normally thicker in the morning; it retains fluids during sleep that evaporate in the tear film while we are awake. As the disease worsens, this swelling will remain constant and reduce vision throughout the day.

## Treatment

Medical management includes topical hypertonic saline, the use of a hairdryer to dehydrate the precorneal tear film, and therapeutic soft contact lenses. In using a hairdryer, the patient is instructed to hold a hairdryer at an arm's length or directed across the face, to dry out the epithelial blisters. This can be done two or three times a day. Definitive treatment, however, (especially with increased corneal edema) is surgical in the form of corneal transplantation, or penetrating keratoplasty (PKP). New surgical modalities are gaining popularity in the treatment of FED such as deep lamellar endothelial keratoplasty (DLEK) and Descemet's stripping with endothelial keratoplasty (DSEK). DLEK and DSEK avoid the surgical complications of PKP such as wound dehiscence and infections and high postoperative astigmatism. Recently, DSEK has become the dominant procedure because it is technically much easier for the surgeon compared to DLEK or PKP. Improved surgical instrumentation for DSEK, such as a DSEK graft injector will become available shortly (2008). This will allow even faster recovery for patients because of the ability to perform DSEK through very small (3 mm) sutureless incisions. Future directions in the treatment of FED include in vitro expansion of human corneal endothelial cells for transplantation, artificial corneas and genetic modification.

[http://en.wikipedia.org/wiki/Fuchs'\\_dystrophy](http://en.wikipedia.org/wiki/Fuchs'_dystrophy)

## FZD4 FAMILIAL EXUDATIVE VITREORETINOPATHY

**Frizzled homolog 4 (Drosophila)**, also known as **FZD4**, is a human gene. FZD4 has also been designated as **CD344** (cluster of differentiation 344).

This gene is a member of the frizzled gene family. Members of this family encode seven-transmembrane domain proteins that are receptors for the Wingless type MMTV integration site family of signaling proteins. Most frizzled receptors are coupled to the beta-catenin canonical signaling pathway. This protein may play a role as a positive regulator of the Wingless type MMTV integration site signaling pathway. A transcript variant retaining intronic sequence and encoding a shorter isoform has been described, however, its expression is not supported by other experimental evidence.

<http://en.wikipedia.org/wiki/FZD4>

## GLAUCOMA

**Glaucoma** is a group of diseases of the optic nerve involving loss of retinal ganglion cells in a characteristic pattern of optic neuropathy. Although raised intraocular pressure is a significant risk factor for developing glaucoma, there is no set threshold for intraocular pressure that causes glaucoma. One person may develop nerve damage at a relatively low pressure, while another person may have high eye pressure for years and yet never develop damage. Untreated glaucoma leads to permanent damage of the optic nerve and resultant visual field loss, which can progress to blindness.

Glaucoma has been nicknamed "sneak thief of sight" because the loss of visual field often occurs gradually over a long time and may only be recognised when it is already quite advanced. Once lost, this damaged visual field can never be recovered. Worldwide, it is the second leading cause of blindness. Glaucoma affects one in two hundred people aged fifty and younger, and one in ten over the age of eighty.

People with a family history of glaucoma have about a six percent chance of developing glaucoma. Diabetics and those of African descent are three times more likely to develop primary open angle glaucoma. Asians are prone to develop angle-closure glaucoma, and Inuit have a twenty to forty times higher risk than caucasians of developing primary angle closure glaucoma. Women are three times more likely than men to develop acute angle-closure glaucoma due to their shallower anterior chambers. Use of steroids can also cause glaucoma.

Primary open angle glaucoma (POAG) has been found to be associated with mutations in genes at several loci. Normal tension glaucoma, which comprises one third of POAG, is associated with genetic mutations.

There is increasing evidence of ocular blood flow to be involved in the pathogenesis of glaucoma. Current data indicate that fluctuations in blood flow are more harmful in glaucomatous optic neuropathy than steady reductions. Unstable blood pressure and dips are linked to optic nerve head damage and correlate with visual field deterioration.

A number of studies also suggest that there is a correlation, not necessarily causal, between glaucoma and systemic hypertension (i.e. high blood pressure). In normal tension glaucoma, nocturnal hypotension may play a significant role. On the other hand there is no clear evidence that vitamin deficiencies cause glaucoma in humans, nor that oral vitamin supplementation is useful in glaucoma treatment

Various rare congenital/genetic eye malformations are associated with glaucoma. Occasionally, failure of the normal third trimester gestational atrophy of the hyaloid canal and the tunica vasculosa lentis associated with other anomalies causes raised intraocular pressure. The higher pressure, distributed according to Pascal's Law, injures the point of least resistance at the optic nerve head causing glaucomatous optic neuropathy. These rare developmental causes of glaucoma are modelled in mice.

Those at risk for glaucoma are advised to have a dilated eye examination at least once a year.

Screening for glaucoma is usually performed as part of a standard eye examination performed by ophthalmologists and optometrists. Testing for glaucoma should include measurements of the intraocular pressure via tonometry, changes in size or shape of the eye, and an

examination of the optic nerve to look for any visible damage to it, or change in the cup-to-disc ratio. If there is any suspicion of damage to the optic nerve, a formal visual field test should be performed. Scanning laser ophthalmoscopy may also be performed.

Owing to the sensitivity of some methods of tonometry to corneal thickness, methods such as Goldmann tonometry should be augmented with pachymetry to measure the cornea thickness. While a thicker-than-average cornea can cause a false-positive warning for glaucoma risk, a thinner-than-average cornea can produce a false-negative result. A false-positive result is safe, since the actual glaucoma condition will be diagnosed in follow-up tests. A false-negative is not safe, as it may suggest to the practitioner that the risk is low and no follow-up tests will be done.

The modern goals of glaucoma management are to avoid glaucomatous damage, preserve visual field and total quality of life for patients with minimal side effects. This requires appropriate diagnostic techniques and follow up examinations and judicious selection of treatments for the individual patient. Although intraocular pressure is only one of the major risk factors for glaucoma, lowering it via various pharmaceuticals and/or surgical techniques is currently the mainstay of glaucoma treatment. Vascular flow and neurodegenerative theories of glaucomatous optic neuropathy have prompted studies on various neuroprotective therapeutic strategies including nutritional compounds some of which may be regarded by clinicians as safe for use now, others are on trial.

## **Drugs**

Intraocular pressure can be lowered with medication, usually eye drops. There are several different classes of medications to treat glaucoma with several different medications in each class.

Each of these medicines may have local and systemic side effects. Adherence to medication protocol can be confusing and expensive; if side effects occur, the patient must be willing either to tolerate these, or to communicate with the treating physician to improve the drug regimen. Initially, glaucoma drops may reasonably be started in either one or in both eyes.

Poor compliance with medications and follow-up visits is a major reason for vision loss in glaucoma patients. Patient education and communication must be ongoing to sustain successful treatment plans for this lifelong disease with no early symptoms.

The possible neuroprotective effects of various topical and systemic medications are also being investigated.

### **Commonly used medications**

- Prostaglandin analogs like latanoprost (Xalatan), bimatoprost (Lumigan) and travoprost (Travatan) increase uveoscleral outflow of aqueous humor. Bimatoprost also increases trabecular outflow
- Topical beta-adrenergic receptor antagonists such as timolol, levobunolol (Betagan), and betaxolol decrease aqueous humor production by the ciliary body.
- Alpha2-adrenergic agonists such as brimonidine (Alphagan) work by a dual mechanism, decreasing aqueous production and increasing uveo-scleral outflow.

- Less-selective sympathomimetics like epinephrine and dipivefrin (Propine) increase outflow of aqueous humor through trabecular meshwork and possibly through uveoscleral outflow pathway, probably by a beta2-agonist action.
- Miotic agents (parasympathomimetics) like pilocarpine work by contraction of the ciliary muscle, tightening the trabecular meshwork and allowing increased outflow of the aqueous humour.
- Carbonic anhydrase inhibitors like dorzolamide (Trusopt), brinzolamide (Azopt), acetazolamide (Diamox) lower secretion of aqueous humor by inhibiting carbonic anhydrase in the ciliary body.
- Physostigmine is also used to treat glaucoma and delayed gastric emptying.

Glaucoma has been classified into specific types

Primary glaucoma and its variants

- Primary glaucoma
  - Primary open-angle glaucoma, also known as chronic open-angle glaucoma, chronic simple glaucoma, glaucoma simplex
  - Low-tension glaucoma
  - Primary angle-closure glaucoma, also known as primary closed-angle glaucoma, narrow-angle glaucoma, iris-block glaucoma, acute congestive glaucoma
  - Acute angle-closure glaucoma
  - Chronic angle-closure glaucoma
  - Intermittent angle-closure glaucoma
  - Superimposed on chronic open-angle closure glaucoma (combined mechanism)
- Variants of primary glaucoma
  - Pigmentary glaucoma
  - Exfoliation glaucoma, also known as pseudoexfoliative glaucoma or glaucoma capsulare

Primary open-angle glaucoma - This is caused by trabecular blockage which is where the aqueous humor in the eye drains out. Because the microscopic passage ways are blocked, the pressure builds up in the eye and causes imperceptible very gradual vision loss. Peripheral vision is affected first but eventually the entire vision will be lost if not treated. Diagnosis is made by looking for cupping of the optic nerve. The treatment's goal is to release the fluid by opening uveoscleral passageways, which are acted upon by prostoglandin agonists. Beta blockers such as timolol, alpha 2 agonist, work by decreasing aqueous formation. Carbonic anhydrase inhibitors decrease bicarbonate formation from ciliary processes in the eye, thus decreasing formation of Aqueous humor. Parasympathetic analogs are drugs that work on the trabecular outflow by opening up the passageway and constricting the pupil.

Primary closed-angle glaucoma - This is caused by sudden blockage of the flow across the pupil. Pressure will rapidly build up in the eye causing pain and redness. Vision becomes blurred and halos are seen around bright objects. Accompanying symptoms include headache and vomiting. Diagnosis is made from obvious physical findings: pupils dilated, cornea

swollen, reduced vision, redness, pain. Treatment is no longer focused on trabecular or uveoscleral passageways. The formation of fluid can be temporarily treated with carbonic anhydrase inhibitors which act on the ciliary process. But the patient will need surgery or laser treatment.

#### Developmental glaucoma

- Developmental glaucoma
  - Primary congenital glaucoma
  - Infantile glaucoma
  - Glaucoma associated with hereditary or familial diseases

#### Secondary glaucoma

- Secondary glaucoma
  - Inflammatory glaucoma
    - Uveitis of all types
    - Fuchs heterochromic iridocyclitis
  - Phacogenic glaucoma
    - Angle-closure glaucoma with mature cataract
    - Phacoanaphylactic glaucoma secondary to rupture of lens capsule
    - Phacolytic glaucoma due to phacotoxic meshwork blockage
    - Subluxation of lens
  - Glaucoma secondary to intraocular hemorrhage
  - Hyphema
  - Hemolytic glaucoma, also known as erythroclastic glaucoma
  - Traumatic glaucoma
    - Angle recession glaucoma: Traumatic recession on anterior chamber angle
    - Postsurgical glaucoma
  - Aphakic pupillary block
  - Ciliary block glaucoma
  - Neovascular glaucoma
  - Drug-induced glaucoma
    - Corticosteroid induced glaucoma
    - Alpha-chymotrypsin glaucoma. Postoperative ocular hypertension from use of alpha chymotrypsin.
  - Glaucoma of miscellaneous origin

- Associated with intraocular tumors
- Associated with retinal detachments
- Secondary to severe chemical burns of the eye
- Associated with essential iris atrophy
- Toxic Glaucoma

Absolute glaucoma

- Absolute glaucoma

<http://en.wikipedia.org/wiki/Glaucoma#Diagnosis>

### **GYRATE ATROPHY OF THE CHOROID AND RETINA**

People suffering from gyrate atrophy of the choroid (the thin coating of the eye) and retina face a progressive loss of vision, with total blindness usually occurring between the ages of 40 and 60. The disease is an inborn error of metabolism. The gene whose mutation causes gyrate atrophy is found on chromosome 10, and encodes an enzyme called ornithine ketoacid aminotransferase (OAT). Different inherited mutations in OAT cause differences in the severity of symptoms of the disease. OAT converts the amino acid ornithine from the urea cycle ultimately into glutamate. In gyrate atrophy, where OAT function is affected, there is an increase in plasma levels of ornithine. It is already known that reduction of the amino acid arginine in the diet has a salutary effect on most patients. Current lines of research into the disease include: (1) investigating how variant mutations of the alleles (versions of the gene inherited) interact in order to cause the differing symptoms of the disease and (2) work on mouse models of the disease is furthering our understanding, which is hoped will lead to a true cure

<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=gnd.section.128>

### **HEMIANOPSIA**

**Hemianopsia** is the loss of half the vision in both eyes. More specifically, it can refer to:

**Binasal hemianopsia** (or **Binasal hemianopia**) is the medical description of a type of partial blindness where vision is missing in the inner half of both the right and left visual field. It is associated with certain lesions of the eye and of the central nervous system, such as congenital hydrocephalus

The absence of vision in half of a visual field is described as *hemianopsia*.

The visual field of each eye can be divided in two vertically, with the outer half being described as *temporal*, and the inner half being described as *nasal*.

"Binasal hemianopsia" can be broken down as follows:

- *bi-*: involves both left and right visual fields
- *nasal*: involves the nasal visual field
- *hemi-*: involves half of each visual field

- *anopsia*: blindness

In **binasal hemianopsia**, vision is missing in the inner (nasal or medial) half of both the right and left visual fields. Information from the nasal visual field falls on the temporal (lateral) retina. Those lateral retinal nerve fibers do not cross in the optic chiasm. Calcification of the internal carotid arteries can impinge the uncrossed, lateral retinal fibers leading to loss of vision in the nasal field.

**Bitemporal hemianopsia** (or **Bitemporal hemianopia**) is the medical description of a type of partial blindness where vision is missing in the outer half of both the right and left visual field. It is usually associated with lesions of the optic chiasm, the area where the optic nerves from the right and left eyes cross near the pituitary gland.

In **bitemporal hemianopsia** vision is missing in the outer (temporal or lateral) half of both the right and left visual fields. Information from the temporal visual field falls on the nasal (medial) retina. The nasal retina is responsible for carrying the information along the optic nerve, and crosses to the other side at the optic chiasm. When there is compression at optic chiasm the visual impulse from both nasal retina are affected, leading to inability to view the temporal, or peripheral, vision. This phenomenon is known as bitemporal hemianopia. Knowing the neurocircuitry of visual signal flow through the optic tract is very important in understanding bitemporal hemianopia.

Bitemporal hemianopia most commonly occurs as a result of tumors located at the mid-optic chiasm. Since the adjacent structure is the pituitary gland, some common tumors causing compression are Pituitary adenomas, and Craniopharyngiomas.

**Homonymous hemianopsia** is a medical term for a type of partial blindness resulting in a loss of vision in the same visual field of both eyes.

It is usually caused by injury to the brain itself such as stroke or trauma, rather than malfunctioning of the eye itself.

Vascular and neoplastic (malignant or benign tumours) lesions of the optic tract or visual cortex can cause a contralateral homonymous hemianopsia. For example, a person who has a lesion of the right optic tract will no longer see objects on their left side. Similarly, a person who has a stroke to the right occipital lobe will have the same visual field defect, but there will be macular sparing.

A stroke on the entire right side of the brain, in addition to producing a homonymous hemianopsia, will also lead to the syndrome of Hemispatial neglect.

However, the symptom of homonymous hemianopsia isn't necessarily of a lethal cause. For instance, it can constitute the aura phase of migraine.

[http://en.wikipedia.org/wiki/Binasal\\_hemianopsia](http://en.wikipedia.org/wiki/Binasal_hemianopsia)

## **HETEROCHROMIA**

Heterochromia (also known as a *heterochromia iridis* or *heterochromia iridium*) is an eye condition in which one iris is a different color from the other (*complete heterochromia*), or where part of one iris is a different color from the remainder (*partial heterochromia* or *sectoral heterochromia*). It is a result of the relative excess or lack of pigment within an iris or part of an iris, which may be genetically inherited or due to mosaicism, or acquired by disease or injury.

Eye color, specifically the color of the irises, is determined primarily by the concentration and distribution of melanin pigment within the iris tissues. Consequently, anything affecting those factors may result in a difference of color being observed.

The affected eye may be hyperpigmented (hyperchromic) or hypopigmented (hypochromic). An excess of pigmentation is usually associated with hyperplasia of the iris tissues whereas a lack of pigmentation is associated with hypoplasia. .

Partial or sectoral heterochromia is much less common than complete heterochromia and is typically found in autosomally inherited disorders such as Hirschsprung's disease and Waardenburg syndrome.

Although a distinction is frequently made between heterochromia that affects an eye completely or only partially, it is often classified as either genetic (due to mosaicism or congenital) or acquired, with mention as to whether the affected iris or portion of the iris is darker or lighter.

### **Congenital heterochromia**

Heterochromia that is congenital is usually inherited as an autosomal dominant trait.

#### **Abnormal iris darker**

- Lisch nodules — iris hamartomas seen in neurofibromatosis.
- Ocular melanosis — a condition characterized by increased pigmentation of the uveal tract, episclera, and anterior chamber angle.
- Oculodermal melanocytosis (nevus of Ota)
- Pigment dispersion syndrome — a condition characterized by loss of pigmentation from the posterior iris surface which is disseminated intraocularly and deposited on various intraocular structures, including the anterior surface of the iris.
- Sturge-Weber syndrome — a syndrome characterized by a port-wine stain nevus in the distribution of the trigeminal nerve, homolateral meningeal angioma with intracranial calcification and neurologic signs, and angioma of the choroid, often with secondary glaucoma

#### **Abnormal iris lighter**

- Simple heterochromia — a rare condition characterized by the absence of other ocular or systemic problems. The lighter eye is typically regarded as the affected eye as it usually shows iris hypoplasia. It may affect an iris completely or only partially.
- Congenital Horner's syndrome — sometimes inherited, although usually acquired

- Waardenburg's syndrome — a syndrome in which heterochromia presents as a bilateral iris hypochromia in some cases. A Japanese review of 11 albino children with the disorder found that all had sectoral/partial heterochromia.
- Piebaldism — similar to Waardenburg's syndrome, a rare disorder of melanocyte development characterized by a white forelock and multiple symmetrical hypopigmented or depigmented macules.
- Hirschsprung's disease — a bowel disorder associated with heterochromia in the form of a sector hypochromia. The affected sectors have been shown to have reduced numbers of melanocytes and decreased stromal pigmentation.
- Incontinentia pigmenti
- Parry-Romberg syndrome

### Acquired heterochromia

Heterochromia that is acquired is usually due to injury, inflammation, the use of certain eyedrops, or tumors.



A cat with *heterochromia*; It has one blue and one green eye  
Abnormal iris darker

- Deposition of material
  - Siderosis — iron deposition within ocular tissues due to a penetrating injury and a retained iron-containing, intraocular foreign body.
  - Hemosiderosis — long standing hyphema (blood in the anterior chamber) following blunt trauma to the eye may lead to iron deposition from blood products
- Use of certain eyedrops — prostaglandin analogues (latanoprost, isopropyl unoprostone, travoprost, and bimatoprost) are used topically to lower intraocular pressure in glaucoma patients. A concentric heterochromia has developed in some patients applying these drugs. The stroma around the iris sphincter muscle becomes darker than the peripheral stroma. A stimulation of melanin synthesis within iris melanocytes has been postulated.
- Neoplasm — Nevi and melanomatous tumors.
- Iridocorneal endothelium syndrome
- Iris ectropion syndrome

Abnormal iris lighter

- Fuchs' heterochromic iridocyclitis — a condition characterized by a low grade, asymptomatic uveitis in which the iris in the affected eye becomes hypochromic and has a washed-out, somewhat moth eaten appearance. The heterochromia can be very subtle, especially in patients with lighter colored irises. It is often most easily seen in

daylight. The prevalence of heterochromia associated with Fuch's has been estimated in various studies with results suggesting that there is more difficulty recognizing iris color changes in dark-eyed individuals.

- Acquired Horner's syndrome — usually acquired, as in neuroblastoma, although sometimes inherited.
- Neoplasm — Melanomas can also be very lightly pigmented, and a lighter colored iris may be a rare manifestation of metastatic disease to the eye.

Heterochromia has also been observed in those with Duane syndrome.

- Chronic iritis
- Juvenile xanthogranuloma
- Leukemia and lymphoma

### Central heterochromia



A grey-blue iris with a greenish-yellow ring showing Central Heterochromia



Grey-blue iris' with Central Heterochromia



A grey iris featuring Central Heterochromia

Whereas **Heterochromia** (also known as a *heterochromia iridis* or *heterochromia iridium*) is an eye condition in which one iris is a different colour from the other (complete heterochromia), **Central Heterochromia** (also known as **Sectoral Heterochromia**) is an eye condition in which there are two different colours in the same iris. Central Heterochromia is where the central (pupillary) zone of the iris is a different colour than the mid-peripheral (ciliary) zone, and may be linked to above average toxic burden in the body. Though not studied widely, Central Heterochromia is the rarest form of Heterochromia.

Eye colour is determined primarily by the concentration and distribution of melanin pigment within the iris tissues, Anything affecting those factors may result in a difference of colour being observed.

The human iris can be seen in a number of various colors. There are three true colors in the eyes that determine the outward appearance; brown, yellow, and grey. How much of each colour an individual has determines the appearance of his or her eye colour.

Eyes displaying Central Heterochromia are often referred to as "cat eyes" because of the appearance of a multi-coloured iris. Central Heterochromia appears to be prevalent in irises containing low amounts of melanin. Central Heterochromia does not label an eye as hazel. This is because the outer ring of an eye affected by Central Heterochromia is that iris' true colour.

The *potential* to acquire central heterochromia may be inherited genetically, though Central Heterochromia in itself is the condition where drug and toxic settlements in the body make the iris colour appear different from its basic predominant colour. These toxic signs that show in the iris indicate the amounts of the toxins the system has failed to eliminate.

<http://en.wikipedia.org/wiki/Heterochromia>

## HYDROCEPHALUS

**Hydrocephalus** is a term derived from the Greek words "hydro" meaning water, and "cephalus" meaning head, and this condition is sometimes known as "**water on the brain**". People with this condition have abnormal accumulation of cerebrospinal fluid (CSF) in the ventricles, or cavities, of the brain. This may cause increased intracranial pressure inside the skull and progressive enlargement of the head, convulsion, and mental disability.

Hydrocephalus is usually due to blockage of CSF outflow in the ventricles or in the subarachnoid space over the brain. In a normal healthy person, CSF continuously circulates through the brain and its ventricles and the spinal cord and is continuously drained away into the circulatory system. In a hydrocephalic situation, the fluid accumulates in the ventricles, and the skull may become enlarged because of the great volume of fluid pressing against the brain and skull. Alternatively, the condition may result from an overproduction of the CSF fluid, from a congenital malformation blocking normal drainage of the fluid, or from complications of head injuries or infections.

Infants and young children with hydrocephalus typically have abnormally large heads, because the pressure of the fluid causes the individual skull bones — which have yet to fuse — to bulge outward at their juncture points. Compression of the brain by the accumulating fluid eventually may cause convulsions and mental retardation. Hydrocephalus occurs in about one out of every 500 live births and was routinely fatal until surgical techniques for shunting the excess fluid out of the central nervous system and into the blood or abdomen were developed.

Usually, hydrocephalus need not cause any intellectual impairment if recognized and properly treated. A massive degree of hydrocephalus rarely exists in normally functioning people, though such a rarity may occur if onset is gradual rather than sudden.

[http://en.wikipedia.org/wiki/Hydrocephalus#Communicating\\_hydrocephalus](http://en.wikipedia.org/wiki/Hydrocephalus#Communicating_hydrocephalus)

## **HYPOPLASIA**

**Hypoplasia** is underdevelopment or incomplete development of a tissue or organ. Although the term is not always used precisely, it properly refers to an inadequate or below-normal number of cells. Hypoplasia is similar to aplasia, but less severe. It is the opposite of hyperplasia (too many cells).

The name is derived from the Greek: *hypo*, meaning low, and *plasis*, which refers to molding or forming. The adjective form is *hypoplastic*.

Hypoplasia can be present in any tissue or organ. It is descriptive of many medical conditions such as:

Underdeveloped:

- breasts during puberty.
- testes in Klinefelter's syndrome.
- ovaries in Fanconi anemia, gonadal dysgenesis, trisomy X
- thymus in DiGeorge syndrome.
- labia majora in popliteal pterygium syndrome.
- cerebellum caused by mutation in the Reelin gene.

<http://en.wikipedia.org/wiki/Hypoplasia>

## **LAURENCE-MOON SYNDROME**

**Laurence-Moon syndrome** is a rare hereditary condition associated with retinitis pigmentosa, spastic paraplegia, hypogonadism and mental retardation.

It is named after the physicians John Zachariah Laurence and Robert Charles Moon who provided the first formal description of the condition in a paper published in 1866.

In the past, this condition has also been referred to as **Laurence-Moon-Bardet-Biedl** or **Laurence-Moon-Biedl-Bardet** syndrome, but Bardet-Biedl syndrome is now usually recognized as a separate entity. However, some recent research suggests that the two conditions may not be distinct.

[http://en.wikipedia.org/wiki/Laurence-Moon\\_syndrome](http://en.wikipedia.org/wiki/Laurence-Moon_syndrome)

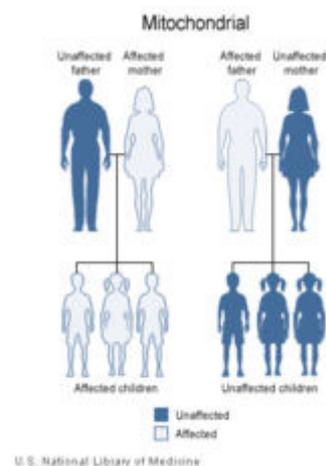
## **LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)**

**Leber's hereditary optic neuropathy (LHON)** or **Leber optic atrophy** is a mitochondrially inherited (mother to all offspring) degeneration of retinal ganglion cells (RGCs) and their axons that leads to an acute or subacute loss of central vision; this affects predominantly young adult males. However, LHON is only transmitted through the mother as it is primarily due to mutations in the mitochondrial (not nuclear) genome and only the egg contributes

mitochondria to the embryo. LHON is usually due to one of three pathogenic mitochondrial DNA (mtDNA) point mutations. These mutations affect nucleotide positions 11778, 3460 and 14484, respectively in the ND4, ND1 and ND6 subunit genes of complex I of the oxidative phosphorylation chain in mitochondria. Men cannot pass on the disease to their offspring

Clinically, there is an acute onset of visual loss, first in one eye, and then a few weeks later in the other. This eventually evolves to very severe optic atrophy and permanent decrease of visual acuity. In the acute stage lasting a few weeks, the affected eye demonstrates an edematous appearance of the nerve fiber layer especially in the arcuate bundles and enlarged or telangectatic and tortuous peripapillary vessels (microangiopathy). These main features are seen on fundus examination, just before or subsequent to the onset of visual loss. Examination reveals decreased visual acuity, loss of color vision and a cecocentral scotoma on visual field examination.

## Genetics



Leber's hereditary optic neuropathy has a mitochondrial inheritance pattern.

Leber hereditary optic neuropathy is a condition related to changes in mitochondrial DNA. Although most DNA is packaged in chromosomes within the nucleus, mitochondria have a distinct mitochondrial genome composed of mtDNA.

Mutations in the *MT-ND1*, *MT-ND4*, *MT-ND4L*, and *MT-ND6* genes cause Leber hereditary optic neuropathy. These genes code for the NADH dehydrogenase protein involved in the normal mitochondrial function of oxidative phosphorylation. Oxidative phosphorylation uses a large multienzyme complex to convert oxygen and simple sugars to energy. Mutations in any of the genes disrupt this process to cause a variety of syndromes depending on the type of mutation and other factors. It remains unclear how these genetic changes cause the death of cells in the optic nerve and lead to the specific features of Leber hereditary optic neuropathy.

A significant percentage of people with a mutation that causes Leber hereditary optic neuropathy do not develop any features of the disorder. Specifically, more than 50 percent of males with a mutation and more than 85 percent of females with a mutation never experience vision loss or related medical problems. Additional factors may determine whether a person develops the signs and symptoms of this disorder. Environmental factors such as smoking and alcohol use may be involved, although studies of these factors have produced conflicting results. Researchers are also investigating whether changes in additional genes, particularly genes on the X chromosome, contribute to the development of signs and symptoms. The

degree of heteroplasmy, the percentage of mitochondria which have mutant alleles, may play a role. Patterns of mitochondrial alleles called haplogroup may also affect expression of mutations.

### **Diagnosis & management**

The diagnosis is extremely difficult and usually requires a neuro-ophthalmological evaluation and/or blood testing for DNA assessment (that is available only in a few laboratories). Hence the incidence is probably much greater than appreciated. The prognosis is almost always that of continued very severe visual loss. There is no accepted treatment for this disease.

Avoiding optic nerve toxins is generally advised, especially tobacco and alcohol. Certain prescription drugs are known to be a potential risk, so all drugs should be treated with suspicion and checked before use by those at risk. In fact, toxic and nutritional optic neuropathies may have overlaps with LHON in symptoms, mitochondrial mechanisms of disease and management. Of note, when a patient suffering from LHON or toxic/nutritional optic neuropathy suffers a hypertensive crisis as a possible complication of the disease process, nitroprusside (trade name: Nipride) should not be used due to increased risk of optic nerve ischemia in response to this anti-hypertensive in particular.

There are various treatment approaches which have had early trials or are proposed, none yet with convincing evidence of usefulness or safety for treatment or prevention including: Brimonidine; Minocycline; Idebenone;; Curcumin; Near infrared light treatment; and Viral vector techniques.

[http://en.wikipedia.org/wiki/Leber's\\_hereditary\\_optic\\_neuropathy](http://en.wikipedia.org/wiki/Leber's_hereditary_optic_neuropathy)

### **LEBER CONGENITAL AMAUROSIS**

**Leber's congenital amaurosis** (LCA) is a rare inherited eye disease that appears at birth or in the first few months of life

It was first described by Theodore Leber in the 19th century. (It should not be confused with Leber's hereditary optic neuropathy, which is a different disease also described by Theodore Leber.)

Amaurosis refers to a loss of vision not associated with a lesion, and congenital refers to a condition present from birth (not acquired). However, beyond these general descriptions, the presentation of LCA can vary, because it is associated with multiple genes.

LCA is typically characterized by nystagmus, sluggish or no pupillary responses, and severe vision loss or blindness.

It is an autosomal recessive disorder thought to be caused by abnormal development of photoreceptors.

There is evidence tying type 1 LCA to *GUCY2D*, and type 2 to *RPE65*.

Other genes which have been implicated include *CRB1*, *CRX*, and *AIPL1*.

OMIM currently recognizes 11 types of LCA:

Type	OMIM	Gene	Locus
LCA1	204000	<i>GUCY2D</i>	17p13.1
LCA2	204100	<i>RPE65</i>	1p31
LCA3	604232	<i>RDH12</i>	14q23.3
LCA4	604393	<i>AIPL1</i>	17p13.1
LCA5	604537	<i>LCA5</i>	6q14
LCA6	605446	<i>RPGRIP1</i>	14q11
LCA7	602225	<i>CRX</i>	19q13.3
LCA8	604210	<i>CRB1</i>	1q31-q32.1
LCA9	608553	<i>LCA9</i>	1p36
LCA10	610142	<i>CEP290</i>	12q21.33
LCA11	146690	<i>IMPDH1</i>	7q31.3-q32

The gene *CEP290* has been associated with Joubert syndrome, as well as type 10 LCA.

Researchers at Moorfields Eye Hospital and University College London in London are conducting the first gene therapy clinical trial for patients with RPE65 LCA. The first patient, Robert Johnson was operated upon in early 2007, and it is hoped that eleven more will follow

as the trial proceeds. There has previously been some success in a mouse model with this approach.

[http://en.wikipedia.org/wiki/Leber's\\_congenital\\_amaurosis](http://en.wikipedia.org/wiki/Leber's_congenital_amaurosis)

## LOW VISION

**Low vision** is a subspecialty within the professions of optometry and ophthalmology and opticianry dealing with individuals who have less than normal vision even with the most accurate conventional prescription available. It can be a result of either congenital or acquired factors. An example of the former is Leber's congenital amaurosis and of the latter age-related macular degeneration.

Anyone with noncorrectable reduced vision is considered to be visually impaired, and can have a wide range of causes. The World Health Organization uses the following classifications of visual impairment. When the vision in the better eye with best possible glasses correction is:

- **20/30 to 20/60** : is considered mild vision loss, or near-normal vision
- **20/70 to 20/160** : is considered moderate visual impairment, or moderate low vision
- **20/200 to 20/400** : is considered severe visual impairment, or severe low vision
- **20/500 to 20/1,000** : is considered profound visual impairment, or profound low vision
- **less than 20/1,000** : is considered near-total visual impairment, or near total blindness
- **No Light Perception** : is considered total visual impairment, or total blindness

There are also levels of visual impairment based on visual field loss (loss of peripheral vision).

### Pathologies which may cause vision acuity loss

- Cataracts
- Glaucoma
- Uveitis
- Macular degeneration
- Corneal opacity
- Trachoma
- Diabetic retinopathy
- Myopia magna
- Stargardt's disease
- Albinism
- Retinitis pigmentosa

Since the estimates of the 1990s, new data based on the 2002 global population show a reduction in the number of people who are blind or visually impaired, and those who are blind from the effects of infectious diseases, but an increase in the number of people who are blind from conditions related to longer life spans. This new information underscores the need to modify the health care agenda to include the management of the diseases that are now becoming prevalent

## Distribution of visual impairment

**By age:** Visual impairment is unequally distributed across age groups. More than 82% of all people who are blind are 50 years of age and older, although they represent only 19% of the world's population. Due to the expected number of years lived in blindness (blind years), childhood blindness remains a significant problem, with an estimated 1.4 million blind children below age 15.

**By gender:** Available studies consistently indicate that in every region of the world, and at all ages, females have a significantly higher risk of being visually impaired than males.  
**Geographically:** Visual impairment is not distributed uniformly throughout the world. More than 90% of the world's visually impaired live in developing countries.

## Low Vision, its lifestyle implications and rehabilitation

Visual impairments may take many forms and be of varying degrees. Visual acuity alone is not always a good predictor of the degree of problems a person may have. Someone with relatively good acuity (e.g., 20/40) can have difficulty with daily functioning, while someone with worse acuity (e.g., 20/200) may function reasonably well if their visual demands are not great.

Some people who fall into this category can use their considerable residual vision - their remaining sight - to complete daily tasks without relying on alternative methods. The role of a low vision specialist (optometrist or ophthalmologist) is to maximize the functional level of a patient's vision by optical or non-optical means. Primarily, this is by use of magnification in the form of telescopic systems for distance vision and optical or electronic magnification for near tasks.

People with significantly reduced acuity may benefit from training conducted by individuals trained in the provision of technical aids. Rehabilitation professionals, some of whom are connected to an agency for the blind, can provide advice on lighting and contrast to maximize remaining vision. These professionals also have access to non-visual aids, and can instruct patients in their uses.

Once the emotional shock of the disability is overcome, if alternative techniques (basic rehabilitation) are learnt, good quality of life and an adjustment to the disability can be achieved, not only in the case of low vision, but also in the case of blindness.

According to an article published by The Academy of Psychosomatics Medicine, in a sample of patients affected by progressive diabetic retinopathy, only those who had reached total blindness actually displayed a decrease in psychic symptomatology, through learning rehabilitation techniques. More marked distress remained in the subjects with persisting partial sight. Unfulfilled expectations probably increased frustration at daily defeats, coupled with fear of complete loss of residual sight. Acceptance of one's pathology and final outcome is the basis for approaching and acquiring new behavioral patterns and creating good mental, physical, and social equilibrium in those who become blind.

The subjects making the most use of rehabilitation instruments, who lived alone, and preserved their own mobility and occupation were the least depressed, with the lowest risk of suicide and the highest level of social integration.

Those with worsening sight and the prognosis of eventual blindness are at comparatively high risk of suicide and thus may be in need of supportive services. These observations advocate the establishment and extension of therapeutic and preventative programs to include patients with impending and current severe visual impairment who do not qualify for services for the blind. Ophthalmologists should be made aware of these potential consequences and incorporate a place for mental health professionals in their treatment of these types of patients, with a view to preventing the onset of depressive symptomatology, avoiding self-destructive behavior, and improving the quality of life of these patients. Such intervention should occur in the early stages of diagnosis, particularly as many studies have demonstrated how rapid acceptance of the serious visual handicap has led to a better, more productive compliance with rehabilitation programs. Moreover, psychological distress has been reported (and is exemplified by our psychological autopsy study) to be at its highest when sight loss is not complete, but the prognosis is unfavorable.<sup>10</sup> Therefore, early intervention is imperative for enabling successful psychological adjustment.

According to the Catalan Association for the Blind and Visually Impaired (ACCDV), experience tells that seeking the support of other people affected is a good therapy to overcome the disability, not only for the individual affected but for their families as well. There are associations that give this kind of support and can put the person in touch with professionals specialized in the collective's problems.

### **The Low Vision Examination**

It is critical that all patients be examined by an optometrist or ophthalmologist specializing in Low Vision Care prior to other rehabilitation training to rule out potential medical or surgical correction for the problem and to establish a careful baseline refraction and prescription of both normal and low vision glasses and optical aids. Only a doctor is qualified to evaluate visual functioning of a compromised visual system effectively.

[http://en.wikipedia.org/wiki/Low\\_vision](http://en.wikipedia.org/wiki/Low_vision)

## **MARFAN SYNDROME**

**Marfan syndrome** is an autosomal dominant genetic disorder of the connective tissue characterized by disproportionately long limbs, long thin fingers, a typically tall stature, and a predisposition to cardiovascular abnormalities, specifically those affecting the heart valves and aorta. The disorder may also affect numerous other structures and organs — including the lungs, eyes, dural sac surrounding the spinal cord, and hard palate. It is named after Antoine Marfan, the French pediatrician who first described the condition in 1896 after noticing striking features in a 5 year old girl.

Marfan syndrome affects males and females equally, and the mutation shows no geographical bias. Estimates indicate that approximately 60 000 (1 in 5000, or 0.02% of the population) to 200 000 Americans have Marfan syndrome. Each parent with the condition has a 50% chance of passing it on to a child due to its autosomal dominant nature. Most individuals with Marfan syndrome have another affected family member, but approximately 15-30% of all cases are due to *de novo* genetic mutations — such spontaneous mutations occur in about 1 in 20 000 births. Marfan syndrome is also an example of dominant negative mutation and

haploinsufficiency. It is associated with variable expressivity. Incomplete penetrance has not been definitively documented.

## Pathogenesis

Marfan syndrome is caused by mutations in the *FBNI* gene on chromosome 15, which encodes a glycoprotein called fibrillin-1, a component of the extracellular matrix. The Fibrillin 1 protein is essential for the proper formation of the extracellular matrix including the biogenesis and maintenance of elastin fibers. The extracellular matrix is critical for both the structural integrity of connective tissue but also serves as a reservoir for growth factors. Elastin fibers are found throughout the body but are particularly abundant in the aorta, ligaments and the ciliary zonules of the eye, consequently these areas are among the worst affected.

A transgenic mouse has been created carrying a single copy of a mutant fibrillin 1, a mutation similar to that found in the human fibrillin 1 gene that is known to cause Marfan syndrome. This mouse strain recapitulates many of the features of the human disease and promises to provide insights into the pathogenesis of the disease. It has been found that simply reducing the level of normal fibrillin-1 causes a Marfan-related disease in mice.

Transforming growth factor beta (TGF $\beta$ ) plays an important role in Marfan syndrome. Fibrillin-1 indirectly binds a latent form of TGF $\beta$  keeping it sequestered and unable to exert its biological activity. The simplest model of Marfan syndrome suggests that reduced levels of fibrillin-1 allow TGF $\beta$  levels to rise due to inadequate sequestration. Although it is not proven how elevated TGF $\beta$  levels would be responsible for the specific pathology seen with the disease, an inflammatory reaction releasing proteases that slowly degrade the elastin fibers and other components of the extracellular matrix is known to occur. The importance of the TGF $\beta$  pathway was confirmed with the discovery of a similar syndrome Loeys-Dietz syndrome involving the *TGF $\beta$ R2* gene on chromosome 3, a receptor protein of TGF $\beta$ . Marfan syndrome has often been confused with Loeys-Dietz syndrome, because of the considerable clinical overlap between the two syndromes.

## Symptoms

Although there are no unique signs or symptoms of Marfan syndrome, the constellation of long limbs, dislocated lenses, and aortic root dilation is sufficient to make the diagnosis with confidence. There are more than thirty other clinical features that are variably associated with the syndrome most involving the skeleton, skin, and joints. There is a great deal of clinical variability even within families that carry the identical mutation.

## Skeletal system

The most readily visible signs are associated with the skeletal system. Many individuals with Marfan Syndrome grow to above average height. Some have long slender limbs with fingers and toes that are also abnormally long and slender (arachnodactyly). This long, slender body habitus and long, slender limbs are known as dolichostenomelia. An individual's arms may be disproportionately long, with thin, weak wrists. In addition to affecting height and limb proportions, Marfan syndrome can produce other skeletal signs. Abnormal curvature of the spine (scoliosis) is common, as is abnormal indentation (pectus excavatum) or protrusion (pectus carinatum) of the sternum. Other signs include abnormal joint flexibility, a high

palate, malocclusions, flat feet, stooped shoulders, unexplained stretch marks on the skin and thin wrists. Some people with Marfan have speech disorders resulting from symptomatic high palates and small jaws.

## **Eyes**

Marfan syndrome can also seriously affect the eyes and vision. Nearsightedness and astigmatism are common, but farsightedness can also result. Subluxation (dislocation) of the crystalline lens in one or both eyes (*ectopia lentis*) also occurs and may be detected by an ophthalmologist or optometrist using a slit-lamp biomicroscope. In Marfan's the dislocation is typically superotemporal whereas in the similar condition homocystinuria, the dislocation is inferonasal. Sometimes eye problems appear only after the weakening of connective tissue has caused detachment of the retina. Early onset glaucoma can be another complication.

## **Cardiovascular system**

The most serious conditions associated with Marfan syndrome involve the cardiovascular system. Undue fatigue, shortness of breath, heart palpitations, racing heartbeats, or pain in the left chest, back, shoulder, or arm, can bring a person into the doctor's office. Cold arms, hands and feet can also be seriously linked to **marfan syndrome** because of a loss of blood circulation. A heart murmur heard on a stethoscope, an abnormal reading on an electrocardiogram, or symptoms of angina can lead a doctor to order an echocardiogram. This can reveal signs of leakage or prolapse of the mitral or aortic valves that control the flow of blood through the heart. (See mitral valve prolapse.) However, the major sign that would lead a doctor to consider an underlying condition is a dilated aorta or an aortic aneurysm. Sometimes, no heart problems are apparent until the weakening of the connective tissue in the ascending aorta causes an aortic aneurysm or even aortic dissection.

Because of the underlying connective tissue abnormalities that cause Marfan syndrome, there is an increased incidence of dehiscence of prosthetic mitral valve. Care should be taken to attempt repair of damaged heart valves rather than replacement.

During pregnancy, even in the absence of preconceived cardiovascular abnormality, women with Marfan syndrome are at significant risk of acute aortic dissection, which can be lethal if untreated. For this reason, women with Marfan syndrome should receive a thorough assessment prior to conception, and echocardiography should be performed every 6-10 weeks during pregnancy, to assess the aortic root diameter. Most women however tolerate pregnancy well and safe vaginal delivery is possible.

## **Lungs**

Marfan syndrome is a risk factor for spontaneous pneumothorax. In spontaneous unilateral pneumothorax, air escapes from a lung and occupies the pleural space between the chest wall and a lung. The lung becomes partially compressed or collapsed. This can cause pain, shortness of breath, cyanosis, and, if not treated, death. Marfan syndrome has also been associated with sleep apnea and idiopathic obstructive lung disease.

## Central nervous system

Another condition that can reduce the quality of life for an individual, though not life-threatening, is dural ectasia, the weakening of the connective tissue of the dural sac, the membrane that encases the spinal cord. Dural ectasia can be present for a long time without producing any noticeable symptoms. Symptoms that can occur are lower back pain, leg pain, abdominal pain, other neurological symptoms in the lower extremities, or headaches. Such symptoms usually diminish when the individual lies flat on his or her back. These types of symptoms might lead a doctor to order an X-ray of the lower spine. Dural ectasia is usually not visible on an X-ray in the early phases. A worsening of symptoms and the lack of finding any other cause should eventually lead a doctor to order an upright MRI of the lower spine. Dural ectasia that has progressed to the point of causing these symptoms would appear in an upright MRI image as a dilated pouch that is wearing away at the lumbar vertebrae. Other spinal issues associated with Marfan include degenerative disk disease and spinal cysts.

## Management

There is no cure for Marfan syndrome, but life expectancy has increased significantly over the last few decades, and clinical trials are underway for a promising new treatment. The syndrome is treated by addressing each issue as it arises, and, in particular, considering prophylactic medication, even for young children, to slow progression of aortic dilation.

Regular checkups by a cardiologist are needed to monitor the health of the heart valves and the aorta. The goal of treatment is to slow the progression of aortic dilation and damage to heart valves by eliminating arrhythmias, minimizing the heart rate, and minimizing blood pressure. Beta blockers have been used to control arrhythmias and slow the heart rate. Other medications might be needed to further minimize blood pressure without slowing the heart rate, such as ACE inhibitors and angiotensin II receptor antagonists, also known as angiotensin receptor blockers (ARBs). If the dilation of the aorta progresses to a significant diameter aneurysm, causes a dissection or a rupture, or leads to failure of the aortic or other valve, then surgery (possibly a composite aortic valve graft [CAVG] or valve-sparing procedure) becomes necessary. Although aortic graft surgery (or any vascular surgery) is a serious undertaking it is generally successful if undertaken on an elective basis. Surgery in the setting of acute aortic dissection or rupture is considerably more problematic. Elective aortic valve/graft surgery is usually considered when aortic root diameter reaches 50 millimeters (2.0 inches), but each case needs to be specifically evaluated by a qualified cardiologist. New valve-sparing surgical techniques are becoming more common. As Marfan patients live longer, other vascular repairs are becoming more common, e.g. repairs of descending thoracic aortic aneurysms and aneurysms of vessels other than the aorta.

The skeletal and ocular manifestations of Marfan syndrome can also be serious, although not life-threatening. These symptoms are usually treated in the typical manner for the appropriate condition. This can also affect height, arm length, and life span. The Nuss procedure is now being offered to people with Marfan syndrome to correct 'sunken chest' or (pectus excavatum). Because Marfan may cause spinal abnormalities that are asymptomatic, any spinal surgery contemplated on a Marfan patient should only follow detailed imaging and careful surgical planning, regardless of the indication for surgery.

Clinical trials have been conducted of the drug acetazolamide in the treatment of symptoms of dural ectasia. The treatment has demonstrated significant functional improvements in some sufferers. Other medical treatments, as well as physical therapy, are also available.

Treatment of a spontaneous pneumothorax is dependant on the volume of air in the pleural space and the natural progression of the individual's condition. A small pneumothorax might resolve without active treatment in 1 to 2 weeks. Recurrent pneumothoraxes might require chest surgery. Moderately sized pneumothoraxes might need chest drain management for several days in hospital. Large pneumothoraxes are likely to be medical emergencies requiring emergency decompression.

Genetic counseling and specialized clinics are available at many academic medical centers for affected persons and family members

[http://en.wikipedia.org/wiki/Marfan\\_syndrome](http://en.wikipedia.org/wiki/Marfan_syndrome)

## **MENINGITIS**

**Meningitis** is an inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges. Meningitis may develop in response to a number of causes, most prominently bacteria, viruses and other infectious agents, but also physical injury, cancer, or certain drugs. While some forms of meningitis are mild and resolve on their own, meningitis is a potentially serious condition due to the proximity of the inflammation to the brain and spinal cord. The potential for serious neurological damage or even death necessitates prompt medical attention and evaluation. Infectious meningitis, the most common form, is typically treated with antibiotics and requires close observation. Some forms of meningitis (such as those associated with meningococcus, mumps virus or pneumococcus infections) may be prevented with immunization.

In children there are several potential disabilities which result from damage to the nervous system. These include sensorineural hearing loss, epilepsy, diffuse brain swelling, hydrocephalus, cerebral vein thrombosis, intra cerebral bleeding and cerebral palsy. Acute neurological complications may lead to adverse consequences. In childhood acute bacterial meningitis deafness is the most common serious complication. Sensorineural hearing loss often develops during first few days of the illness as a result of inner ear dysfunction, but permanent deafness is rare and can be prevented by prompt treatment of meningitis.

Those that contract the disease during the neonatal period and those infected by *S. pneumoniae* and gram negative bacilli are at greater risk of developing neurological, auditory, or intellectual impairments or functionally important behaviour or learning disorders which can manifest as poor school performance.

In adults central nervous system complications include brain infarction, brain swelling, hydrocephalus, intracerebral bleeding; systemic complications are dominated by septic shock, adult respiratory distress syndrome and disseminated intravascular coagulation. Those who have underlying predisposing conditions e.g. head injury may develop recurrent meningitis. Case-fatality ratio is highest for gram-negative etiology and lowest for meningitis caused by *H. influenzae* (also a gram negative bacilli). Fatal outcome in patients over 60 years of age is

more likely to be from systemic complications e.g. pneumonia, sepsis, cardio-respiratory failure; however in younger individuals it is usually associated with neurological complications. Age more than 60, low Glasgow coma scale at presentation and seizure within 24 hours increase the risk of death among community acquired meningitis.

<http://en.wikipedia.org/wiki/Meningitis>

## MICROPTHALMIA

**Microphthalmia** (or **microphthalmos**) means small eyes.

In mammals the failure of expression of a transcription factor, MITF (microphthalmia-associated transcription factor), in the pigmented retina prevents this structure from fully differentiating. This in turn causes a malformation of the choroid fissure of the eye, resulting in the drainage of vitreous humor fluid. Without this fluid, the eye fails to enlarge, thus the name microphthalmia.

### Causes

The gene encoding the microphthalmia-associated transcription factor (Mitf) is a member of the basic helix-loop-helix-leucine zipper (bHLH-ZIP) family. Waardenburg syndrome type 2 (WS type 2) in humans is also a type of microphthalmia syndrome. Mutations in MITF gene are thought to be responsible for this syndrome. The human MITF gene is homologous to the mouse MITF gene (aka mouse mi or microphthalmia gene); mouse with mutations in this gene are hypopigmented in their fur. The identification of the genetics of WS type 2 owes a lot to observations of phenotypes of MITF mutant mice.

Microphthalmia in newborns is also associated with infections during pregnancy, particularly rubella and cytomegalovirus (CMV), and trisomy 13 (Patau syndrome). In addition, microphthalmia may also be a result of Fetal alcohol syndrome.

<http://en.wikipedia.org/wiki/Microphthalmia>

## MULTIPLE SCLEROSIS

**Multiple sclerosis** (abbreviated **MS**, also known as **disseminated sclerosis** or **encephalomyelitis disseminata**) is an autoimmune condition in which the immune system attacks the central nervous system (CNS), leading to demyelination. It may cause numerous physical and mental symptoms, and often progresses to physical and cognitive disability. Disease onset usually occurs in young adults, is more common in women, and has a prevalence that ranges between 2 and 150 per 100,000 depending on the country or specific population.

MS affects the areas of the brain and spinal cord known as the white matter. White matter cells carry signals between the grey matter areas, where the processing is done, and the rest of the body. More specifically, MS destroys oligodendrocytes which are the cells responsible for

creating and maintaining a fatty layer, known as the myelin sheath, which helps the neurons carry electrical signals. MS results in a thinning or complete loss of myelin and, less frequently, the cutting (transection) of the neuron's extensions or axons. When the myelin is lost, the neurons can no longer effectively conduct their electrical signals. The name *multiple sclerosis* refers to the scars (scleroses - better known as plaques or lesions) in the white matter. Loss of myelin in these lesions causes some of the symptoms, which vary widely depending upon which signals are interrupted. However, more advanced forms of imaging are now showing that much of the damage happens outside these regions. Almost any neurological symptom can accompany the disease.

MS takes several forms, with new symptoms occurring either in discrete attacks (relapsing forms) or slowly accumulating over time (progressive forms). Most people are first diagnosed with relapsing-remitting MS but develop secondary-progressive MS (SPMS) after a number of years. Between attacks, symptoms may go away completely, but permanent neurological problems often persist, especially as the disease advances.

Although much is known about the mechanisms involved in the disease process, the cause remains elusive: the most widely-held being that the condition results from attacks to the nervous system by the body's own immune system. Some believe it is a metabolically dependent disease while others think that it might be caused by a virus such as Epstein-Barr. Still others believe that its virtual absence from the tropics points to a deficiency of vitamin D during childhood.

This disease does not have a cure, but several therapies have proven helpful. Treatments attempt to return function after an attack, prevent new attacks, and prevent disability. MS medications can have adverse effects or be poorly tolerated, and many patients pursue alternative treatments, despite the paucity of supporting scientific study. Many candidate therapies are still under investigation.

The prognosis, or expected course of the disease, depends on the subtype of the disease, the individual patient's disease characteristics, the initial symptoms, and the degree of disability the person experiences as time advances. Life expectancy of patients, however, is nearly the same as that of the unaffected population, and in some cases a near-normal life is possible

MS presents with a variety of symptoms, including changes in sensation (hypoesthesia), muscle weakness, abnormal muscle spasms, or difficulty in moving; difficulties with coordination and balance (ataxia); problems in speech (dysarthria) or swallowing (dysphagia), visual problems (nystagmus, optic neuritis, or diplopia), fatigue and acute or chronic pain syndromes, and bladder and bowel difficulties. Cognitive impairment of varying degrees, or emotional symptomatology in the form of depression or pseudobulbar affect are also common. Neuropathic pain is usual, and this can be in the form of Lhermitte's sign. Neuropathic pain is the most common, distressing and intractable of the pain syndromes in MS. This pain is described as constant, boring, burning or tingling intensely. It usually occurs in the legs. Paraesthesias include pins and needles; tingling; shivering; burning pains; feelings of pressure; and areas of skin with heightened sensitivity to touch. The pains associated with these can be aching, throbbing, stabbing, shooting, gnawing, tingling, tightness and numbness. The main clinical measure of disability progression and severity of the symptoms is the Expanded Disability Status Scale or EDSS.

The initial attacks (also known as exacerbations or relapses) are often transient, mild (or asymptomatic), and self-limited. They often do not prompt a health care visit and sometimes are only identified in retrospect once the diagnosis has been made based on further attacks. The most common initial symptoms reported are: changes in sensation in the arms, legs or face (33%), complete or partial vision loss (optic neuritis) (16%), weakness (13%), double vision (7%), unsteadiness when walking (5%), and balance problems (3%); but many rare initial symptoms have been reported such as aphasia or psychosis. Fifteen percent of individuals have multiple symptoms when they first seek medical attention. Optic neuritis or focal leg weakness may lead to falls and other serious accidents. For some people the initial MS attack is preceded by infection, trauma, or strenuous physical effort.

Multiple sclerosis is difficult to diagnose in its early stages. In fact, a definite diagnosis cannot be made until other disease processes (differential diagnoses) have been ruled out and, in the case of relapsing-remitting MS, there is evidence of at least two anatomically separate demyelinating events separated by at least thirty days. In the case of primary progressive, a slow progression of signs and symptoms over at least 6 months is required.

The signs and symptoms of MS can be similar to other medical problems, such as neuromyelitis optica, stroke, brain inflammation, infections such as Lyme disease (which can produce identical MRI lesions and CSF abnormalities), tumors, and other autoimmune problems, such as lupus. Additional testing may be needed to help distinguish MS from these other problems.

## **Pathophysiology**

Although much is known about how multiple sclerosis causes damage, the reasons why multiple sclerosis occurs are not known.

Multiple sclerosis is a disease in which the myelin (a fatty substance which covers the axons of nerve cells) degenerates. According to the view of most researchers, a special subset of lymphocytes, called T cells, plays a key role in the development of MS.

According to a strictly immunological explanation of MS, the inflammatory process is triggered by the T cells. T cells gain entry into the brain via the blood-brain barrier (a capillary system that should prevent entrance of T-cells into the nervous system). The blood brain barrier is normally not permeable to these types of cells, unless triggered by either infection or a virus, where the integrity of the tight junctions forming the blood-brain barrier is decreased. When the blood brain barrier regains its integrity (usually after infection or virus has cleared) the T cells are trapped inside the brain. These lymphocytes recognize myelin as foreign and attack it as if it were an invading virus. That triggers inflammatory processes, stimulating other immune cells and soluble factors like cytokines and antibodies. Leaks form in the blood-brain barrier. These leaks, in turn, cause a number of other damaging effects such as swelling, activation of macrophages, and more activation of cytokines and other destructive proteins such as matrix metalloproteinases. A deficiency of uric acid has been implicated in this process.

It is known that a repair process, called remyelination, takes place in early phases of the disease, but the oligodendrocytes that originally formed a myelin sheath cannot completely rebuild a destroyed myelin sheath. The newly-formed myelin sheaths are thinner and often not as effective as the original ones. Repeated attacks lead to successively fewer effective

remyelinations, until a scar-like plaque is built up around the damaged axons, according to four different damage patterns. The central nervous system should be able to recruit oligodendrocyte stem cells capable of turning into mature myelinating oligodendrocytes, but it is suspected that something inhibits stem cells in affected areas.

The axons themselves can also be damaged by the attacks. Often, the brain is able to compensate for some of this damage, due to an ability called neuroplasticity. MS symptoms develop as the cumulative result of multiple lesions in the brain and spinal cord. This is why symptoms can vary greatly between different individuals, depending on where their lesions occur.

## Causes

Although many risk factors for multiple sclerosis have been identified, no definitive cause has been found. MS likely occurs as a result of some combination of both environmental and genetic factors. Various theories try to combine the known data into plausible explanations. Although most accept an autoimmune explanation, several theories suggest that MS is an appropriate immune response to one or several underlying conditions (the etiology could be heterogeneous). The need for alternative theories is supported by the poor results of present therapies, since autoimmune theory predicted greater success.

## Environmental

The most popular hypothesis is that a viral infection or retroviral reactivation primes a susceptible immune system for an abnormal reaction later in life. On a molecular level, this might occur if there is a structural similarity between the infectious virus and some component of the central nervous system, leading to eventual confusion in the immune system.

Since MS seems to be more common in people who live farther from the equator, another theory proposes that decreased sunlight exposure and possibly decreased vitamin D production may help cause MS. This theory is bolstered by recent research into the biochemistry of vitamin D, which has shown that it is an important immune system regulator. Other theories, noting that MS is less common in children with siblings, suggest that less exposure to illness in childhood leads to an immune system which is not primed to fight infection and is thus more likely to attack the body. One explanation for this would be an imbalance between the T<sub>h</sub>1 type of helper T-cells, which fight infection, and the T<sub>h</sub>2 type, which are more active in allergy and more likely to attack the body.

Other theories describe MS as an immune response to a chronic infection. The association of MS with the Epstein-Barr virus suggests a potential viral contribution in at least some individuals. Still others believe that MS may sometimes result from a chronic infection with spirochetal bacteria, a hypothesis supported by research in which cystic forms were isolated from the cerebrospinal fluid of all MS patients in a small study. When the cysts were cultured, propagating spirochetes emerged. Another bacterium that has been implicated in MS is *Chlamydomphila pneumoniae*; it or its DNA has been found in the cerebrospinal fluid of MS patients by several research laboratories, with one study finding that the oligoclonal bands of 14 of the 17 MS patients studied consisted largely of antibodies to *Chlamydomphila* antigens. Varicella zoster virus is also suspected to be involved.

Severe stress may also be a factor—a large study in Denmark found that parents who had lost a child unexpectedly were 50% more likely to develop MS than parents who had not. Smoking has also been shown to be an independent risk factor for developing MS.

## **Genetic**

MS is not considered a hereditary disease. However, increasing scientific evidence suggests that genetics may play a role in determining a person's susceptibility to MS:

Some populations, such as the Roma, Inuit, and Bantus, rarely if ever develop MS. The indigenous peoples of the Americas and Asians have very low incidence rates.

In the population at large, the chance of developing MS is less than a tenth of one percent. However, if one person in a family has MS, that person's first-degree relatives—parents, children, and siblings—have a one to three percent chance of getting the disease.

For identical twins, the likelihood that the second twin may develop MS if the first twin does is about 30%. For fraternal twins (who do not inherit an identical set of genes), the likelihood is closer to that for non-twin siblings, at about 4%. This pattern suggests that, while genetic factors clearly help determine the risk of MS, other factors such as environmental effects or random chance are also involved. The actual correlation may be somewhat higher than reported by these numbers as people with MS lesions remain essentially asymptomatic throughout their lives.

Further indications that more than one gene is involved in MS susceptibility comes from studies of families in which more than one member has MS. Several research teams found that people with MS inherit certain regions on individual genes more frequently than people without MS. Of particular interest is the human leukocyte antigen (HLA) or major histocompatibility complex region on chromosome 6. HLAs are genetically determined proteins that influence the immune system. However, there are other genes in this region which are not related to the immune system.

The HLA patterns of MS patients tend to be different from those of people without the disease. Investigations in northern Europe and America have detected three HLAs that are more prevalent in people with MS than in the general population. Studies of American MS patients have shown that people with MS also tend to exhibit these HLAs in combination—that is, they have more than one of the three HLAs—more frequently than the rest of the population. Furthermore, there is evidence that different combinations of the HLAs may correspond to variations in disease severity and progression.

## **Treatment**

Although there is no known cure for multiple sclerosis, several therapies have proven helpful. The primary aims of therapy are returning function after an attack, preventing new attacks, and preventing disability. As with any medical treatment, medications used in the management of MS have several adverse effects, and many possible therapies are still under investigation. At the same time different alternative treatments are pursued by many patients, despite the paucity of supporting, comparable, replicated scientific study.

[http://en.wikipedia.org/wiki/Multiple\\_sclerosis](http://en.wikipedia.org/wiki/Multiple_sclerosis)

## MYASTHENIA GRAVIS

**Myasthenia gravis** (literally "serious muscle-weakness"; from Greek *μύς* "muscle", *ἀσθένεια* "weakness", and Latin *gravis* "serious"; abbreviated **MG**) is a neuromuscular disease leading to fluctuating muscle weakness and fatigability. It is an autoimmune disorder, in which weakness is caused by circulating antibodies that block acetylcholine receptors at the post-synaptic neuromuscular junction, inhibiting the stimulative effect of the neurotransmitter acetylcholine. Myasthenia is treated medically with cholinesterase inhibitors or immunosuppressants, and, in selected cases, thymectomy. At 200-400 cases per million it is one of the less common autoimmune disorders.

The hallmark of myasthenia gravis is muscle weakness that increases during periods of activity and improves after periods of rest. Muscles that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are especially susceptible. The muscles that control breathing and neck and limb movements can also be affected. Often the physical examination is within normal limits.

The onset of the disorder can be sudden or rapid. Often symptoms come and go over time. The diagnosis of myasthenia gravis may be delayed if the symptoms are subtle or variable.

In most cases, the first noticeable symptom is weakness of the eye muscles. In others, difficulty in swallowing and slurred speech may be the first signs. The degree of muscle weakness involved in MG varies greatly among patients, ranging from a localized form, limited to eye muscles (ocular myasthenia), to a severe or generalized form in which many muscles - sometimes including those that control breathing - are affected. Symptoms, which vary in type and severity, may include asymmetrical ptosis (a drooping of one or both eyelids), diplopia (double vision) due to weakness of the muscles that control eye movements, unstable or waddling gait, weakness in arms, hands, fingers, legs, and neck, a change in facial expression, dysphagia (difficulty in swallowing), shortness of breath and dysarthria (impaired speech, often nasal due to weakness of the pharyngeal muscles).

In *myasthenic crisis* a paralysis of the respiratory muscles occurs, necessitating assisted ventilation to sustain life. In patients whose respiratory muscles are already weak, crises may be triggered by infection, fever, an adverse reaction to medication, or emotional stress. Since the heart muscle is stimulated differently, it is never affected by MG.

### Pathophysiology

Myasthenia gravis is an autoimmune disease: it features antibodies directed against the body's own proteins. While in various similar diseases the disease has been linked to a cross-reaction with an infective agent, there is no known causative pathogen that could account for myasthenia. There is a slight genetic predisposition: particular HLA types seem to predispose for MG (B8 and DR3 with DR1 more specific for ocular myasthenia). Up to 75% of patients have an abnormality of the thymus; 25% have a thymoma, a tumor (either benign or malignant) of the thymus, and other abnormalities are frequently found. The disease process generally remains stationary after thymectomy (removal of the thymus).

In MG, the autoantibodies are directed most commonly against the acetylcholine receptor (nicotinic type), the receptor in the motor end plate for the neurotransmitter acetylcholine that stimulates muscular contraction. Some forms of the antibody impair the ability of acetylcholine to bind to receptors. Others lead to the destruction of receptors, either by complement fixation or by inducing the muscle cell to eliminate the receptors through endocytosis.

The antibodies are produced by plasma cells, that have been derived from B cells. These plasma cells are activated by T-helper cells, which in turn are activated by binding to acetylcholine receptor antigenic peptide sequences (epitopes) that rest within the histocompatibility antigens of antigen presenting cells. The thymus plays an important role in the development of T-cells, which is why myasthenia gravis is associated with thymoma. The exact mechanisms are however not convincingly clarified.

In normal muscle contraction, cumulative activation of the ACh receptor leads to influx of sodium and calcium. Only when the levels of these electrolytes inside the muscle cell is high enough will it contract. Decreased numbers of functioning receptors therefore impairs muscular contraction.

It has recently been realized that a second category of gravis is due to auto-antibodies against the MuSK protein (muscle specific kinase), a tyrosine kinase receptor which is required for the formation of the neuromuscular junction. Antibodies against MuSK inhibit the signaling of MuSK normally induced by its nerve-derived ligand, agrin. The result is a decrease in patency of the neuromuscular junction, and the consequent symptoms of MG.

People treated with penicillamine can develop MG symptoms. Their antibody titer is usually similar to that of MG, but both the symptoms and the titer disappear when drug administration is discontinued.

MG is more common in families with other autoimmune diseases. A familial predisposition is found in 5% of the cases. This is associated with certain genetic variations such as an increased frequency of HLA-B8 and DR3. People with MG suffer from co-existing autoimmune diseases at a higher frequency than members of the general population. Of particular mention is co-existing thyroid disease where episodes of hypothyroidism may precipitate a severe exacerbation.

## **Diagnosis**

Myasthenia can be a difficult diagnosis, as the symptoms can be subtle and hard to distinguish from both normal variants and other neurological disorders. A thorough physical examination can reveal easy fatigability, with the weakness improving after rest and worsening again on repeat of the exertion testing. Applying ice to weak muscle groups characteristically leads to improvement in strength of those muscles. Additional tests are often performed, as mentioned below. Furthermore, a good response to medication can also be considered a sign of autoimmune pathology.

## **Physical examination**

Muscle fatigability can be tested for many muscles. A thorough investigation includes:

- looking upward and sideways for 30 seconds: ptosis and diplopia.
- looking at the feet while lying on the back for 60 seconds
- keeping the arms stretched forward for 60 seconds
- 10 deep knee bends
- walking 30 steps on both the toes and the heels
- 5 situps, lying down and sitting up completely

### **Blood tests**

If the diagnosis is suspected, serology can be performed in a blood test to identify antibodies against the acetylcholine receptor. The test has a reasonable sensitivity of 80–96%, but in MG limited to the eye muscles (ocular myasthenia) the test may be negative in up to 50% of the cases. About half of the patients without antibodies against the acetylcholine receptor have antibodies against the MuSK protein. In specific situations (decreased reflexes which increase on facilitation, co-existing autonomic features, suspected presence of neoplasm, presence of increment or facilitation on repetitive EMG testing) testing is performed for Lambert-Eaton syndrome, in which other antibodies (against a voltage-gated calcium channel) can be found.

### **Neurophysiology**

Muscle fibers of patients with MG are easily fatigued, and thus do not respond as well as muscles in healthy individuals to repeated stimulation. By repeatedly stimulating a muscle with electrical impulses, the fatigability of the muscle can be measured. This is called the repetitive nerve stimulation test. In single fiber electromyography, which is considered to be the most sensitive (although not the most specific) test for MG, a thin needle electrode is inserted into a muscle to record the electric potentials of individual muscle fibers. By finding two muscle fibers belonging to the same motor unit and measuring the temporal variability in their firing patterns (i.e. their 'jitter'), the diagnosis can be made.

### **Edrophonium test**

The "edrophonium test" is infrequently performed to identify MG; its application is limited to the situation when other investigations do not yield a conclusive diagnosis. This test requires the intravenous administration of edrophonium chloride (Tensilon®, Reversol®), a drug that blocks the breakdown of acetylcholine by cholinesterase and temporarily increases the levels of acetylcholine at the neuromuscular junction. In people with myasthenia gravis involving the eye muscles, edrophonium chloride will briefly relieve weakness.

### **Imaging**

A chest X-ray is frequently performed; it may point towards alternative diagnoses (e.g. Lambert-Eaton due to a lung tumor) and comorbidity. It may also identify widening of the mediastinum suggestive of thymoma, but computed tomography (CT) or magnetic resonance imaging (MRI) are more sensitive ways to identify thymomas, and are generally done for this reason.

### **Pulmonary function test**

Spirometry (lung function testing) may be performed to assess respiratory function if there are concerns about a patient's ability to breathe adequately. The vital capacity (VC) may be

monitored at intervals in order not to miss a gradual worsening of muscular weakness. Severe myasthenia may cause respiratory failure due to exhaustion of the respiratory muscles.

### **Pathological findings**

Immunofluorescence shows IgG antibodies on the neuromuscular junction. (Note that it is not the antibody which causes myasthenia gravis that fluoresces, but rather a secondary antibody directed against it.) Muscle electron microscopy shows receptor infolding and loss of the tips of the folds, together with widening of the synaptic clefts. Both these techniques are currently used for research rather than diagnostically.

### **Classification**

The most widely accepted classification of myasthenia gravis is the Myasthenia Gravis Foundation of America Clinical Classification.

- Class I: Any eye muscle weakness, possible ptosis, no other evidence of muscle weakness elsewhere
- Class II: Eye muscle weakness of any severity, mild weakness of other muscles
  - Class IIa: Predominantly limb or axial muscles
  - Class IIb: Predominantly bulbar and/or respiratory muscles
- Class III: Eye muscle weakness of any severity Moderate weakness of other muscles
  - Class IIIa: Predominantly limb or axial muscles
  - Class IIIb: Predominantly bulbar and/or respiratory muscles
- Class IV: Eye muscle weakness of any severity, severe weakness of other muscles
  - Class IVa: Predominantly limb or axial muscles
  - Class IVb: Predominantly bulbar and/or respiratory muscles (Can also include feeding tube without intubation)
- Class V: Intubation needed to maintain airway

[http://en.wikipedia.org/wiki/Myasthenia\\_gravis](http://en.wikipedia.org/wiki/Myasthenia_gravis)

## **MONOCHROMACY**

**Monochromacy**, also known as "total color blindness" is the lack of ability to distinguish colors; caused by cone defect or absence. Monochromacy occurs when two or all three of the cone pigments are missing and color and lightness vision is reduced to one dimension.

Organisms with monochromacy are called monochromats. Monochromats are truly color blind and can see only shades of black, gray and white. The perceptual effect of any arbitrarily chosen light from its visible spectrum can be matched by any pure spectral light.

The normal explanation of monochromacy is that the organism's retina contains only a single kind of light receptor cell, or at least that only one kind is active at any particular level of illumination. In vertebrates, which typically have two kinds of receptors, called rods and cones, active at low and higher levels of illumination respectively, there are two main kinds of monochromacy:

1. rod monochromacy is the condition of having only rods in the retina. A rod monochromat will be unable to see well in normal daylight levels of illumination.
2. cone monochromacy is the condition of having both rods and cones, but only a single kind of cone. A cone monochromat can have good pattern vision at normal daylight levels, but will not be able to distinguish hues. (see below)

In principle there could also be a second kind of cone monochromacy, in which the retina contains no rods, and only a single type of cone. Such an animal would be unable to see at all at lower levels of illumination, but it would have good pattern vision at normal daylight levels (though it would not be able to distinguish hues). In practice it is hard to produce an example of such a retina, at least as the normal condition for a species; there are animals (for example, many birds) with very cone-rich retinas, but they all tend to have multiple types of cones. Some individuals do possess diseases or injuries that lead to nyctalopia, or night blindness, where rod cells stop responding properly to light.

In cone monochromats, at low light intensities the rods and cones may be active simultaneously, allowing some degree of color discrimination. However it is unlikely that this will be functionally significant since the neural apparatus for hue discrimination would presumably not be present in an animal that was monochromatic most of the time.

It used to be confidently claimed that most mammals other than humans and our fellow primates were monochromats. In the last half-century, however, evidence of at least dichromatic color vision in a number of mammalian orders has accumulated. Two of the orders of sea mammals, the pinnipeds (which includes the seal, sea lion, and walrus) and cetaceans (which includes dolphins and whales) clearly are cone monochromats, since the short-wavelength sensitive cone system is genetically disabled in these animals. The same is true of the owl monkeys, genus *Aotus*.

Both rod and cone monochromacy occur as very rare forms of color blindness in humans. Rod monochromacy, or maskun, is the more common of the two. The majority of people described as color blind, however, are either dichromats or anomalous trichromats.

Monochromacy has been subdivided into typical (rod monochromacy) and atypical forms.<sup>[3][4]</sup>

Clinically, some monochromats have normal visual acuity and others have poor visual acuity

<http://en.wikipedia.org/wiki/Monochromacy>

## CONE MONOCHROMACY

**Cone monochromacy** is a rare, total color blindness that is accompanied by relatively normal vision, electroretinogram, and electrooculogram.

There are three types named according to the single functioning cone class:

1. Blue cone monochromacy, also known as S-cone monochromacy
2. Green cone monochromacy, also known as M-cone monochromacy
3. Red cone monochromacy, also known as L-cone monochromacy

## NEUROFIBROMATOSIS

**Neurofibromatosis** is an autosomal dominant genetic disorder. It encompasses a set of distinct genetic disorders that cause tumors to grow along various types of nerves and, in addition, can affect the development of non-nervous tissues such as bones and skin. The tumors can grow anywhere on or in the body. Incidence is 1:3,000.

### Types

Apart from the common form, there are two rarer forms and several even rarer forms:

- Neurofibromatosis type I (was known as **Von Recklinghausen disease** after Friedrich Daniel von Recklinghausen). Incidence is 1:3500.
- Neurofibromatosis type II (or "MISME Syndrome"). Incidence is 1:40,000.
- Schwannomatosis is a rare form that is clinically and genetically distinct from types I and II. Multiple Schwannomas (rather than Neurofibromas) occur, and about one-third of patients have these tumors in only one part of the body. Incidence is 1:40,000. The vestibular nerve is spared. Pain is the primary symptom, although numbness, tingling and weakness can also occur. Schwannomas are always benign.
- Five other, extremely rare, forms are also recognized:
  - Online 'Mendelian Inheritance in Man' (OMIM) 162210 - NEUROFIBROMATOSIS, FAMILIAL SPINAL
  - Online 'Mendelian Inheritance in Man' (OMIM) 162220 - NEUROFIBROMATOSIS, FAMILIAL INTESTINAL; NF3B
  - Online 'Mendelian Inheritance in Man' (OMIM) 162240 - NEUROFIBROMATOSIS-PHEOCHROMOCYTOMA-DUODENAL CARCINOID SYNDROME
  - Online 'Mendelian Inheritance in Man' (OMIM) 162260 - NEUROFIBROMATOSIS, TYPE III, MIXED CENTRAL AND PERIPHERAL; NF3A
  - Online 'Mendelian Inheritance in Man' (OMIM) 601321 - NEUROFIBROMATOSIS-NOONAN SYNDROME; NFNS

### Symptoms

#### Neurofibromatosis type 1

Neurofibromatosis type 1 - mutation of neurofibromin chromosome 17q11.2

- multiple neurofibromas on the skin and under the skin; the subcutaneous lumps are characteristic of the disease and increase in number with age.
- freckling of the groin and the arm pit.
- a predisposition to particular tumors (both benign and malignant). These tumors are called neurofibromas.
- Café au lait spots (pigmented birthmarks). Six or more of these form one of the diagnostic criteria, but are not essential for diagnosis.
- skeletal abnormalities such as scoliosis or bowing of the legs might occur

- Lisch nodules (hamartomas of iris)
- tumor on the optic nerve, also known as an Optic Glioma



plexiform neurofibroma



Patient with multiple small cutaneous neurofibromas and a 'café au lait spot' (bottom of photo, to the right of centre). A biopsy has been taken of one of the lesions

## Neurofibromatosis type 2

Neurofibromatosis type 2 - mutation of merlin chromosome 22q12

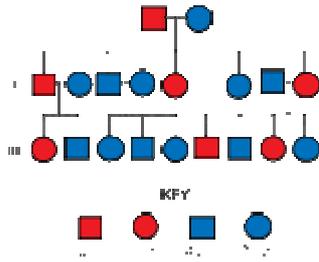
- bilateral tumors, acoustic neuromas on the vestibulocochlear nerve
- the hallmark of NF 2 is hearing loss due to acoustic neuromas around the age of twenty
- the tumors may cause:
  - headache
  - balance problems, and Vertigo
  - facial weakness/paralysis
  - patients with NF2 may also develop other brain tumors, as well as spinal tumors
  - Deafness and Tinnitus

## Schwannomatosis

Schwannomatosis - gene involved has yet to be identified

1. Multiple Schwannomas occur.
2. The Schwannomas develop on cranial, spinal and peripheral nerves.
3. Chronic pain, and sometimes numbness, tingling and weakness.
4. About 1/3 of patients have segmental Schwannomatosis, which means that the Schwannomas are limited to a single part of the body, such as an arm, a leg or the spine.
5. Unlike the other forms of NF, the Schwannomas do not develop on vestibular nerves, and as a result, no loss of hearing is associated with Schwannomatosis.
6. Patients with Schwannomatosis do not have learning disabilities related to the disease.

## Genetics and Heritability



NF-1 and NF-2 may be inherited in an autosomal dominant fashion, as well as through random mutation.

Neurofibromatosis type 1 is due to mutation on chromosome 17q11.2, the gene product being Neurofibromin (a GTPase activating enzyme).

Neurofibromatosis type 2 is due to mutation on chromosome 22q, the gene product is Merlin, a cytoskeletal protein.

Both NF1 and NF2 are autosomal dominant disorders, meaning that only one copy of the mutated gene need be inherited to pass the disorder. A child of a parent with NF1 or NF2 and an unaffected parent will have a 50% chance of inheriting the disorder.

Complicating the question of heritability is the distinction between genotype and phenotype, that is, between the genetics and the actual manifestation of the disorder. In the case of NF1, no clear links between genotype and phenotype have been found, and the severity and specific nature of the symptoms may vary widely among family members with the disorder. In the case of NF2, however, manifestations are similar among family members; a strong genotype-phenotype correlation is believed to exist (ibid).

Both NF1 and NF2 can also appear spontaneously through random mutation, with no family history. These spontaneous or *sporadic* cases account for about one half of neurofibromatosis cases (ibid).

### Family

Neurofibromatosis is considered a member of the *neurocutaneous syndromes (phakomatoses)*. In addition to the types of neurofibromatosis, the phakomatoses also include tuberous sclerosis, Sturge-Weber syndrome and von Hippel-Lindau disease. This grouping is an artifact of an earlier time in medicine, before the distinct genetic basis of each of these diseases was understood.

<http://en.wikipedia.org/wiki/Neurofibromatosis>

## **NORRIE DISEASE**

**Norrie Disease** is a genetic disorder that primarily affects the eye and almost always leads to blindness. In addition to the congenital ocular symptoms, some patients suffer from a progressive hearing loss starting mostly in their 2nd decade of life, while another portion may be mentally challenged.

Patients with Norrie Disease may develop cataracts, Leukocoria (a condition where the pupils appear white when light is shone on them), along with other developmental issues in the eye, such as shrinking of the globe and the wasting away of the iris. Around 30-50% of them will also have developmental delay/mental retardation, psychotic-like features, incoordination of movements or behavioral abnormalities. Most patients are born with normal hearing; however, the onset of hearing loss is very common in early adolescence. About 15% of the patients are estimated to develop all the features of the disease.

The disease affects almost only male infants at birth or soon after birth, because the disease is inherited X-linked recessive. Only in very rare cases, females have been diagnosed with Norrie Disease as well. The exact incidence number is unknown; only a few hundred cases have been reported so far. It is a very rare disorder that is not associated with any specific ethnic or racial groups

Norrie Disease is a genetic disorder caused by mutations in the *NDP* gene, located on Xp11.4 (GeneID: 4693). It is inherited in an X-linked recessive way from usually one of your parents. This means that almost only males are affected. Sons of affected men will not have the mutation, while 50% of their daughters will be genetic carriers of the mutation. They also usually show no clinical symptoms, but will inherit the mutation to 50% of their offspring. Daughters receiving the mutated gene will also be, like their mother, asymptomatic carriers, but 50% of their sons will express clinical symptoms.

Females are very unlikely to express clinical signs. One possible scenario leading to this (unlikely) case would be if both of their copies of the *NDP* gene bear mutations, which could be the case in consanguineous families or due to a spontaneous somatic mutation. Another explanation for affected females could be skewed X-Chromosome inactivation.

However, throughout history, there have been a few rare cases where females have shown symptoms associated with Norrie Disease such as retinal abnormalities and mild hearing loss.

### **The *NDP* Gene**

A mutation in *NDP* gene causes Norrie disease. The official name of the gene is “Norrie disease (pseudoglioma)”. The gene’s official symbol is *NDP*. The normal function of the *NDP* gene is to produce the instructions for creating a protein called norrin. For the normal development of the eye and other body systems, norrin is believed to be crucial. Norrin also appears to be crucial in the specialization of the cells of the retina and the establishment of a blood supply to the inner ear and the tissues of the retina. The role of norrin in the specialization of retinal cells for their unique sensory is interfered by the mutation of *NDP*. This results in an accumulation of immature retinal cells in the back of the eye. When norrin’s role in the establishment of blood vessels supplying the eye is disrupted, eventually the tissues will break down.

Norrin is not only important in the development of the eye. The mutation of the *NDP* gene can affect other systems of the body as well. The most severe problems are caused by chromosomal deletions in the region of the *NDP* gene, causing the prevention of the gene product, or even that of the neighboring *MAO* genes. When the mutations simply change a single amino acid in norrin, the effects are less widespread and severe. However, the location and type of the *NDP* mutation not necessarily determine the degree of severity of the disease, since highly varying clinical signs have been diagnosed in patients carrying the very same mutation. Therefore, the involvement of other modifying genes is very likely. On the other hand, if certain structurally important amino acids are changed (e.g. the Cysteines forming the putative cystine knot), the clinical outcome has been shown to be more serious.

## Diagnosis

As of right now, Norrie Disease and other NDP related diseases are diagnosed with the combination of clinical findings and molecular genetic testing. Molecular genetic testing identifies the mutations that cause the disease in about 85% of affected males. Clinical diagnoses rely on ocular findings. Norrie Disease is diagnosed when grayish-yellow fibrovascular masses are found behind the eye from birth through three months. Doctors also look for progression of the disease from three months through eight-ten years of age. Some of these progressions include cataracts, iris atrophy, shallowing of anterior chamber, and shrinking of the globe. By this point, the vision is light perception impaired or non-existent.

Molecular genetic testing is used for more than an initial diagnosis. It is used to confirm diagnostic testing, for carrier testing females, prenatal diagnosis, and preimplantation genetic diagnosis. There are three types of clinical molecular genetic testing. In approximately 85% of males, mis-sense and splice mutations of the *NDP* gene and partial or whole gene deletions are detected using sequence analysis. Deletion/duplication analysis can be used to detect the 15% of mutations that are submicroscopic deletions. This is also used when testing for carrier females. The last testing used is linkage analysis, which is used when the first two are unavailable. Linkage analysis is also recommended for those families who have more than one member affected by the disease.

## Symptoms

The most prominent symptoms of Norrie Disease are ocular. The first visible finding is Leukocoria, a grayish-yellow pupillary reflex that originates from a mass of unorganized tissue behind the lens. This material, which possibly includes an already detached retina, may be confused with a tumor and thus is termed pseudoglioma.<sup>[1] [10]</sup> However, an affected baby may have a normally sized eye globe and inconspicuous iris, anterior chamber, cornea and intraocular pressure.

Over the first few months of life, complete or partial retinal detachment evolves. From the time they're a baby through childhood, the patient may undergo progressive changes in the disease. These progressions include the formation of cataracts, deterioration of the iris with adhesions forming between the iris and the lens or the cornea, and shallowing of the anterior chamber which increases intraocular pressure that can become painful. As the situation worsens, there is corneal opacification, where the cornea becomes opaque, and band keratopathy. Intraocular pressure is lost and the globe shrinks. In the last stage of Norrie

disease, the globes appear small and sunken in (phthisis bulbi) and the cornea appears to be milky .

Norrie disease can also have cognitive and behavioral symptoms. Developmental delay and mental retardation are present in about 30-50% of males who have Norrie disease. Psychotic-like features and poorly characterized behavior abnormalities may also be present. Auditory symptoms are often common with Norrie disease. Progressive hearing loss starts in early childhood for a majority of males with the disease. Early hearing loss is sensorineural, mild and asymmetric. By adolescence, high-frequency hearing loss begins to appear. Hearing loss is severe, symmetric, and broad-spectrum by the age of 35. However, studies show that while the hearing loss is deteriorating, the ability to speak well is highly preserved. The slowly progressing hearing loss is more problematic in adjusting to than the congenital blindness for most people with Norrie disease.

[http://en.wikipedia.org/wiki/Norrie\\_disease](http://en.wikipedia.org/wiki/Norrie_disease)

## **NYSTAGMUS**

**Nystagmus** is involuntary eye movement that can be part of either the vestibulo-ocular reflex (VOR) or a pathological process. It is characterized by alternating smooth pursuit in one direction and saccadic movement in the other direction.

Nystagmus can be caused by subsequent foveation of moving objects, pathology, sustained rotation or substance abuse.

The direction of nystagmus is defined by the direction of its quick phase (*e.g.* a right-beating nystagmus is characterized by a rightward-moving quick phase). The oscillations may occur in the vertical, horizontal or torsional planes, or in any combination. The resulting nystagmus is often named as a gross description of the movement, *e.g.* downbeat nystagmus, upbeat nystagmus, seesaw nystagmus, periodic alternating nystagmus.

These descriptive names can be misleading however, as many were assigned historically, solely on the basis of subjective clinical examination, which is not sufficient to determine the eyes' true trajectory.

Over the past forty years, however, objective eye movement recording techniques have been applied to the study of nystagmus, and the results have led to a greater accuracy and understanding of the condition.

Nystagmus is not to be confused with other superficially similar-appearing disorders of eye movements (saccadic oscillations) such as opsoclonus or ocular flutter that are composed purely of fast-phase (saccadic) eye movements, while nystagmus is characterised by the combination of a smooth pursuit, which usually acts to take the eye off the point of regard, interspersed with the saccadic movement that serves to bring the eye back on target. Without the use of objective recording techniques, it may be very difficult to distinguish between these conditions.

In medicine, the presence of nystagmus can be benign, or it can indicate an underlying visual or neurological problem. Over forty types of nystagmus have been classified.

### **Nystagmus and alcohol**

In police work, testing for *horizontal gaze nystagmus* is one of a battery of field sobriety tests used by officers in the field to determine whether a suspect is driving under the influence of alcohol. The test involves observation of the suspect's pupil as it follows a moving object, noting (1) lack of smooth pursuit, (2) distinct and sustained nystagmus at maximum deviation, and (3) the onset of nystagmus prior to 45 degrees. As a rule of thumb, a person's blood alcohol concentration can be estimated by subtracting the angle of onset from 50 degrees. Therefore, a person with an angle of onset of nystagmus at 35 degrees has a blood alcohol concentration of approximately 0.15%.

### **Pathological nystagmus**

When nystagmus occurs without fulfilling its normal function, it is pathologic (deviating from the healthy or normal condition). Pathological nystagmus is the result of damage to one or more components of the vestibular system, including the semicircular canals, otolith organs, and the vestibulocerebellum.

Pathological nystagmus generally causes a degree of vision impairment, although the severity of such impairment varies widely. Sometimes it is the other way around — many blind people have nystagmus, which is one reason that some wear dark glasses.

### **Prevalence**

Nystagmus is a relatively common clinical condition, affecting one in every 5,000 to 10,000 individuals. One survey in Oxfordshire, England identified one in every 670 children by the age of two as manifesting nystagmus.

### **Variations**

- **Peripheral nystagmus** occurs as a result of either normal or diseased functional states of the vestibular system and may combine a rotational component with vertical or horizontal eye movements and may be *spontaneous, positional* or *evoked*.
  - **Positional nystagmus** occurs when a person's head is in a specific position. An example of disease state in which this occurs is Benign paroxysmal positional vertigo (BPPV).
  - **Gaze Induced nystagmus** occurs or is exacerbated as a result of changing one's gaze toward or away from a particular side which has an affected vestibular apparatus.
  - **Post Head Shake nystagmus** occurs after an imbalance is created between a normal side and a diseased side by stimulation of the vestibular system by rapid shaking of the head.
  - **Spontaneous nystagmus** is nystagmus that occurs randomly, regardless of the position of the patient's head.
- **Central nystagmus** occurs as a result of either normal or abnormal processes not related to the vestibular organ. For example lesions of the midbrain or cerebellum can result in up and down-beat nystagmus.

## **Causes**

The cause for pathological nystagmus may be congenital, idiopathic, secondary to a pre-existing neurological disorder or may be induced temporarily by disorientation (such as on roller coaster rides) or certain drugs (alcohol and other central nervous system depressants and stimulants, such as lithium salts, phenytoin and ecstasy).

## **Congenital**

Congenital nystagmus occurs more frequently than acquired nystagmus. It can be insular or accompany other disorders (such as micro-ophthalmic anomalies or Down's Syndrome). Congenital nystagmus itself is usually mild and non-progressive. The affected persons are not normally aware of their spontaneous eye movements but vision can be impaired depending on the severity of the movements.

- Infantile:
  - Idiopathic
  - Albinism
  - Aniridia
  - Leber's congenital amaurosis
  - Bilateral optic nerve hypoplasia
  - Bilateral congenital cataracts
  - Rod monochromatism
  - Optic nerve or macular disease
  - Persistent tunica vasculosa lentis
  
- Latent nystagmus
- Nystagmus blockage syndrome

## **Acquired**

### ***Diseases***

Some of the diseases which present nystagmus as a pathological sign are:

- Benign Paroxysmal Positional Vertigo
- Head trauma
- Stroke (the most common cause in older people)
- Ménière's disease and other balance disorders
- Multiple sclerosis
- Brain tumors
- Wernicke-Korsakoff syndrome
- Encephalopathy
- Lateral medullary syndrome
- Aniridia
- Optic nerve hypoplasia
- Albinism
- Noonan syndrome
- Pelizaeus-Merzbacher disease

- Superior canal dehiscence syndrome
- Tullio phenomenon
- Horner's Syndrome

#### Toxic/metabolic

Nystagmus from toxic or metabolic reasons could be the result of e.g.:

- Alcohol intoxication (see above)
- Lithium
- Barbiturates
- Phenytoin (Dilantin)
- Salicylates
- Benzodiazepines
- Lysergic acid diethylamide (LSD)
- Phencyclidine (PCP)
- Ketamine
- Other anticonvulsants or sedatives
- Methylenedioxymethamphetamine
- Wernicke's encephalopathy
- Thiamine deficiency

#### *Central nervous system disorders*

If the pathologic nystagmus is based in the central nervous system (CNS), such as with a cerebellar problem, the nystagmus can be in any direction *including* horizontal. Purely vertical nystagmus is usually central in origin.

Causes include e.g.:

- Thalamic hemorrhage
- Tumor
- Stroke
- Trauma
- Multiple sclerosis

#### *Other causes*

- Vestibular Pathology (Ménière's disease, SCDS (superior canal dehiscence syndrome), BPPV, Labyrinthitis)
- Trochlear nerve malfunction
- Non-physiologic

#### **Diagnosis**

Nystagmus is very noticeable, but little recognised. Nystagmus can be clinically investigated by using a number of non-invasive standard tests. The simplest one is Caloric reflex test. In a caloric reflex test, one external auditory meatus is irrigated with warm or cold water. The

temperature gradient provokes the stimulation of the vestibulocochlear nerve and the consequent nystagmus.

The resulting movement of the eyes may be recorded and quantified by special devices called electronystagmograph (ENG), which is a form of electrooculography (an electrical method of measuring eye movements using external electrodes) or even less invasive devices called videonystagmograph (VNG), which is a form of videooculography (VOG) (a video-based method of measuring eye movements using external small cameras built into head masks). Special swinging chairs with electrical controls are also used in this test to induce rotatory nystagmus.

## Treatment

Congenital nystagmus has traditionally been viewed as non-treatable, but medications have been discovered in recent years that show promise in some patients. In 1980, researchers discovered that a drug called baclofen could effectively stop periodic alternating nystagmus. Subsequently, gabapentin, an anticonvulsant, was found to cause improvement in about half the patients who received it to relieve symptoms of nystagmus. Other drugs found to be effective against nystagmus in some patients include memantine, levetiracetam, 3,4-diaminopyridine, 4-aminopyridine, and acetazolamide.<sup>[5]</sup> Several therapeutic approaches, such as contact lenses, drugs, surgery, and low vision rehabilitation can also be used in order to improve visual function.

Clinical trials of a surgery to treat nystagmus (known as tenotomy) concluded in 2001. Tenotomy is being performed regularly at the University of Pittsburgh Children's Hospital and by a handful of surgeons around the world. The surgery developed by Louis F. Dell'Osso Ph.D aims to reduce the eye shaking (oscillations) which in turn tends to improve visual acuity.

<http://en.wikipedia.org/wiki/Nystagmus>

## OCULAR ALBINISM FAMILY

- **Ocular albinism, type 1 (OA1)** (OMIM: 300500), also known as Nettleship-Falls syndrome, is the most common variety of *ocular albinism*, which affects the eyes but generally not the skin or hair. OA1 is usually associated with nystagmus, and difficult to otherwise detect in females; males show more readily observable symptoms. There are several other identified types of OA, though researchers are not all agreed on the distinctions and classification. Most are caused by a mutation in a gene on the X chromosome, and are X-linked recessive traits.
- **Ocular albinism, type 2 (OA2)** (OMIM: 300600), also known as Forsius-Eriksson syndrome or "Åland Island eye disease", mostly only affects males, though females are often carriers and can sometimes be symptomatic; it is frequently linked with protanopic dichromacy (a form of color blindness) and with night blindness (nyctalopia).

- **Ocular albinism, type 3 (OA3)** (OMIM: 203310), also known as ocular albinism, autosomal recessive (OAR) is a non-X-linked variant, which may be more common among the Amish than in other populations.
- **Ocular albinism with sensorineural deafness (OASD)** (OMIM: 300650), is, as its name implies, associated with loss of hearing.
- **Waardenburg syndrome, type 2, with ocular albinism (WS2-OA)** (OMIM: 103470) is a rare non-X-linked recessive gene variant.

The skin color of people affected by OA *can* be slightly lighter than those of the rest of their families. The eye color can vary greatly, and in some cases only examination of the retina or genetic testing can reveal OA for certain. Some form of OA afflicts 1 in 50,000 people, though certain isolated populations are at greater risk.

### Other types

Other rare variants of albinism are theorized (by ongoing research as of 2007) to exist, such as

- **Albinism-deafness syndrome (ADFN)** (OMIM: 300700, which may actually be closer related to vitiligo); it is predominantly observed among Hopi Native Americans (with an incidence estimated at 1 in 200 individuals)
- **Recessive total albinism with congenital deafness** (OMIM: 220900)
- **Albinism black-lock cell-migration disorder (ABCD)** (OMIM: 600501)

<http://en.wikipedia.org/wiki/Albinism>

## OPTIC NERVE HYPOPLASIA

**Optic nerve hypoplasia** is a medical condition that results in underdevelopment of the optic nerves

### Development of the optic nerve

During the second month of pregnancy, a structure called the optic stalk develops into a pair of optic nerve bundles. These bundles send signals from the eyes to the occipital lobe of the brain, naturally undergo pruning as the fetus develops. In some individuals, however, either this pruning process is too complete, or the nerves simply fail to develop fully. Such an occurrence causes a congenital condition called optic nerve hypoplasia (ONH).

### Symptoms

Optic nerve hypoplasia can appear in one or both eyes, causing anywhere from a mild to serious visual impairment in the form of decreased visual acuity and visual fields. People with this condition are also more likely to present with photophobia and nystagmus.

Because optic nerve hypoplasia involves the underdevelopment of structures located within the brain, the condition may also be found in conjunction with a constellation of hormonal imbalances and midline brain defects known as septo-optic dysplasia.

### **Cause**

No one is certain as to what causes optic nerve hypoplasia. The condition is usually not hereditary, but it relatively often occurs in people with albinism, which is hereditary.

There is but a weak correlation between young maternal age, or maternal diabetes, and the occurrence of this condition. It cannot be tied in with any harmful maternal activities, but there is one study that suggests children with Fetal alcohol syndrome, or prenatal alcohol exposure, often have optic nerve hypoplasia.

### **Prognosis**

The visual prognosis in optic nerve hypoplasia is quite variable. Occasionally, optic nerve hypoplasia may be compatible with near-normal vision; in other cases, one or both eyes may be functionally, or legally blind. Although most patients with optic nerve hypoplasia lead normally productive lives, those with septo-optic dysplasia may experience non-visual problems, for example, with growth retardation.

[http://en.wikipedia.org/wiki/Optic\\_nerve\\_hypoplasia](http://en.wikipedia.org/wiki/Optic_nerve_hypoplasia)

## **OPTIC ATROPHY**

**Optic atrophy** is the loss of some or most of the fibers of the optic nerve. In medicine, "atrophy" usually means "shrunken but capable of regrowth", so some argue that "optic atrophy" as a pathological term is somewhat misleading and use "optic neuropathy" instead.

### **Prognosis**

The optic nerve is part of the brain and has no capability for regeneration. Hence, there can be no recovery from optic atrophy and the term may refer to serious or mild, but always irreversible visual loss due to damage to the optic nerve. Three types of degeneration are seen: transsynaptic, anterograde, and retrograde.

### **Symptoms**

There may be symptoms associated with loss of vision (although there may be a particular difficulty with colour vision).

**Bilateral Optic Atrophy:** Loss of vision and discoloration of discs in both eyes. This is a genetic form and can be inherited.

### **Causes**

Optic atrophy can be congenital or acquired.

### **Congenital**

If congenital, it is usually hereditary with an onset of deterioration in childhood and may be accompanied by nystagmus. Leber's Hereditary Optic Neuropathy, (LHON) or Leber Optic Atrophy is hereditary, but typically has its onset in 20-30 year old males. This is due to a mutation of the mitochondrial genome and hence is passed exclusively through the mothers. Dominant optic atrophy or Kjer's optic neuropathy has autosomal dominant inheritance. It usually presents in early childhood. There are numerous less common genetically related syndromes.

Alternatively, congenital optic atrophy can be caused by a lack of oxygen during pregnancy, labour or in the early days of a child's life. Some drugs taken during pregnancy are also associated with optic atrophy.

### **Acquired**

The acquired type of optic atrophy may be due to blood supply changes in the eye or optic nerve (anterior ischemic optic neuropathy or posterior ischemic optic neuropathy), may be secondary to inflammation or swelling within the optic nerve (optic neuritis), may be a result of pressure against the optic nerve (such as from a tumour), or may be related to metabolic diseases (e.g., diabetes mellitus), trauma, glaucoma, or toxicity (caused by methanol, tobacco, or other poisons). It is also seen in vitamin B12 deficiency and Paget's disease of the bone.

[http://en.wikipedia.org/wiki/Optic\\_atrophy](http://en.wikipedia.org/wiki/Optic_atrophy)

## **OPTIC NEURITIS**

**Optic neuritis**, sometimes called **retrobulbar neuritis**, is the inflammation of the optic nerve that may cause a complete or partial loss of vision.

The optic nerve comprises axons that emerge from the retina of the eye and carry visual information to the primary visual nuclei, most of which is relayed to the occipital cortex of the brain to be processed into vision. Inflammation of the optic nerve causes loss of vision usually due to the swelling and destruction of the myelin sheath covering the optic nerve. Direct axonal damage may also play a role in nerve destruction in many cases.

The most common etiology is multiple sclerosis. Up to 50% of patients with MS will develop an episode of optic neuritis, and 20% of the time optic neuritis is the presenting sign of MS . The presence of demyelinating white matter lesions on brain MRI at the time of presentation of optic neuritis is the strongest predictor for developing clinically definite MS. Almost half of the patients with optic neuritis have white matter lesions consistent with multiple sclerosis. At five years follow-up, the overall risk of developing MS is 30%, with or without MRI lesions. Patients with a normal MRI still develop MS (16%), but at a lower rate compared to those patients with three or more MRI lesions (51%). From the other perspective, however, almost half (44%) of patients with any demyelinating lesions on MRI at presentation will not have developed MS ten years later.

Some other causes include viral-bacterial infections (e.g. herpes zoster), autoimmune disorders (e.g. lupus), chloramphenicol and the inflammation of vessels (vasculitis) nourishing the optic nerve. Ethambutol, an antitubercular drug, can also cause optic neuritis.

## Symptoms

Major symptoms are sudden loss of vision (partial or complete), or sudden blurred or "foggy" vision, and pain on movement of the affected eye. Many patients with optic neuritis may lose some of their color vision in the affected eye, with colors appearing subtly washed out compared to the other eye. A study found that 92.2% of patients experienced pain, which actually preceded the visual loss in 39.5% of cases.

On medical examination the head of the optic nerve can easily be visualised by an ophthalmoscope; however frequently there is no abnormal appearance of the nerve head in optic neuritis, though it may be swollen in some patients. In many cases, only one eye is affected and patients may not be aware of the loss of color vision until the doctor asks them to close or cover the healthy eye.



Example of how optic neuritis affected one eye of a patient with multiple sclerosis

## Epidemiology

Optic neuritis typically affects young adults ranging from 18–45 years of age, with a mean age of 30–35 years. There is a strong female predominance. The annual incidence is approximately 5/100,000, with a prevalence estimated to be 115/100,000.

## Treatment and prognosis

In most cases, visual functions return to near normal within eight to ten weeks, but they may also advance to a complete and permanent state of visual loss. Therefore, systemic intravenous treatment with corticosteroids, which may quicken the healing of the optic nerve, is often recommended, but it does not have a significant effect on the visual acuity at one year, when compared against placebo. Intravenous corticosteroids have also been found to reduce the risk of developing MS in the following two years in those patients who have MRI lesions; but this effect disappears by the third year of follow up.

Paradoxically it has been demonstrated that oral administration of corticosteroids in this situation may lead to more recurrent attacks than in non-treated patients (though oral steroids are generally prescribed after the intravenous course, to wean the patient off the medication). This effect of corticosteroids seems to be limited to optic neuritis and has not been observed in other diseases treated with corticosteroids.

Very occasionally, if there is concomitant increased intracranial pressure the sheath around the optic nerve may be cut to decrease the pressure.

When optic neuritis is associated with MRI lesions suggestive of multiple sclerosis (MS) then general immunosuppressive therapy for MS is most often prescribed (IV methylprednisolone may shorten attacks; oral prednisone may increase relapse rate).

[http://en.wikipedia.org/wiki/Optic\\_neuritis](http://en.wikipedia.org/wiki/Optic_neuritis)

## **PAIRED-LIKE HOMEODOMAIN TRANSCRIPTION FACTOR 2**

**Paired-like homeodomain transcription factor 2**, also known as **PITX2**, is a human gene.

This gene encodes a member of the RIEG/PITX homeobox family, which is in the bicoid class of homeodomain proteins. This protein acts as a transcription factor and regulates procollagen lysyl hydroxylase gene expression. Mutations in this gene are associated with Axenfeld-Rieger syndrome (ARS), iridogoniodysgenesis syndrome (IGDS), and sporadic cases of Peters anomaly. This protein plays a role in the terminal differentiation of somatotroph and lactotroph cell phenotypes. This protein is involved in the development of the eye, tooth and abdominal organs. This protein acts as a transcriptional regulator involved in basal and hormone-regulated activity of prolactin. A similar protein in other vertebrates is involved in the determination of left-right asymmetry during development. Three transcript variants encoding distinct isoforms have been identified for this gene.

<http://en.wikipedia.org/wiki/PITX2>

## **PIERRE ROBIN SEQUENCE**

**Pierre Robin Sequence** (PRS), also known as **Pierre Robin Syndrome** or **Pierre Robin Malformation**, is a congenital condition of facial abnormalities in humans. As PRS is not caused by a single defect gene, it is not a genetic syndrome, but rather a chain of certain developmental malformations, one entailing the next.

PRS is characterized by an unusually small jaw (micrognathia), posterior displacement or retraction of the tongue (glossoptosis), and upper airway obstruction. Incomplete closure of the roof of the mouth (cleft palate), is present in the majority of patients, and is commonly U-shaped.

### **Causes and associated conditions**

It is not known just how this abnormality occurs in infants, but one theory is that, at some time during the stage of the formation of the bones of the fetus, the tip of the jaw (mandible) becomes 'stuck' in the point where each of the collar bones (clavicle) meet (the sternum), effectively preventing the jaw bones from growing. It is thought that, at about 12 to 14 weeks gestation, when the fetus begins to move, the movement of the head causes the jaw to "pop out" of the collar bones. From this time on, the jaw of the fetus grows as it would normally,

with the result that, when born, the jaw of the baby is much smaller (micrognathia) than it would have been with normal development, although it does continue to grow at a normal rate until the child reaches maturity.

PRS is often part of an underlying disorder or syndrome. The most common is Stickler Syndrome. Other disorders causing PRS, according to Dr. Robert J. Sphrintzen Ph.D. of the Center for Craniofacial Disorders Montefiore Medical Center are Velocardiofacial syndrome, Fetal Alcohol Syndrome and Treacher Collins Syndrome. For more disorders associated with PRS see Dr. Sphrintzen's article entitled *The Implications of the Diagnosis of Robin Sequence*.

## **Diagnosis and incidence**

The syndrome is generally diagnosed shortly after birth. It has an incidence ranging from 1 in 8500 to 1 in 30,000.

## **Complications**

The most important medical problems are difficulties in breathing and feeding. Affected infants very often need assistance with feeding, for example needing to stay in a lateral position, needing specially adapted teats or spoons to feed, and often needing nasogastric feeding or supplemental feeding for periods due to slow feeding. This is related to the difficulty in forming a vacuum in the oral cavity related to the cleft palate, as well as to breathing difficulty related to the posterior position of the tongue. Infants, when moderately to severely affected, may occasionally need nasopharyngeal cannulation or more rarely endotracheal intubation or tracheostomy to overcome upper respiratory obstruction.

## **Treatment**

In nasopharyngeal cannulation, the infant is fitted with a blunt-tipped length of surgical tubing, which is inserted into the nose and down the throat, ending just above the esophagus. Surgical threads fitted through holes in the outside end of the tube are attached to the cheek with a special skin-like adhesive material called 'stomahesive', which is also wrapped around the outside end of the tube (but not over the opening at the end) to keep the tube in place. This tube or cannula, which itself acts as an airway, primarily acts as a sort of "splint" which makes further airways on either side of the tube between the tongue and the throat wall, thus assisting the infant in breathing and preventing the tongue from falling back down into the throat, which would cause the infant to asphyxiate. Nasopharyngeal cannulation should be favoured over the other treatments mentioned in this article, as it is far less invasive, it allows the infant to feed without the further placement of a nasogastric tube, and the infant can be placed in the prone position without fear of asphyxiation. This treatment may be necessary for a period of up to six months or more, until the jaw has grown enough so that the tongue assumes a more normal position in the mouth and airway (at birth, the jaws of some infants are so underdeveloped that only the tip of the tongue can be seen when viewed in the throat).

The cleft palate is generally repaired between the ages of 6 1/2 months and 2 years by a plastic or maxillofacial surgeon. In many centres there is now a cleft lip and palate team comprising both of these specialties, as well as a coordinator, a speech and language therapist, an orthodontist, sometimes a psychologist or other mental health specialist, an audiologist, an otorhinolaryngologist (ENT surgeon) and nursing staff. The glossoptosis and micrognathism generally do not require surgery, as they improve to some extent unaided, though the

mandibular arch remains significantly smaller than average. In some cases jaw distraction is needed to aid in breathing and feeding. Lip-tongue attachment is performed in some centres, though its efficacy has been recently questioned.

## Prognosis

Children affected with PRS usually reach full development and size. However, it has been found internationally that the child is often slightly below average size, raising concerns of incomplete development due to chronic hypoxia related to upper airway obstruction as well as lack of nutrition due to early feeding difficulties.

[http://en.wikipedia.org/wiki/Pierre\\_Robin\\_syndrome](http://en.wikipedia.org/wiki/Pierre_Robin_syndrome)

## PSEUDOXANTHOMA ELASTICUM

**Pseudoxanthoma elasticum** (PXE) is a genetic disease that causes fragmentation and mineralization of elastic fibers in some tissues. The most common problems arise in the skin and eyes, and later in blood vessels in the form of premature atherosclerosis. PXE is caused by autosomal recessive mutations in the *ABCC6* gene on the short arm of chromosome 16.

Usually, pseudoxanthoma elasticum affects the skin first, often in childhood but frequently later. Small, yellowish papular lesions form and cutaneous laxity mainly affects the neck, axillae (armpits), groin, and flexural creases (the inside parts of the elbows and knees). Skin may become lax and redundant. Many individuals have "oblique mental creases" (diagonal grooves of the chin).

PXE first affects the retina through a dimpling of the Bruch membrane (a thin membrane separating the blood vessel-rich layer from the pigmented layer of the retina), that is only visible during ophthalmologic examinations. This is called *peau d'orange* (a French term meaning that the retina resembles the skin of an orange). Eventually the mineralization of the elastic fibers in the Bruch membrane create cracks (angioid streaks) that radiate out from the optic nerve. Angioid streaks themselves do not cause distortion of vision, even if they cross into the foveal area. This symptom is present almost all PXE patients and is usually noticed a few years after the onset of cutaneous lesions. These cracks may allow small blood vessels that were originally held back by Bruch's membrane to penetrate the retina. These blood vessels sometimes leak, and it's these retinal hemorrhages that may lead to the loss of central vision. Vision loss is a major issue in many PXE patients.

PXE may affect the gastrointestinal and cardiovascular systems. In the digestive tract, the principal symptom is gastrointestinal bleeding, usually from the stomach. This occurs in very small number of patients. In the circulatory system, intermittent claudication (leg pain during walking which resolves at rest) is a prominent feature, although at later stages coronary artery disease and myocardial infarction may occur.

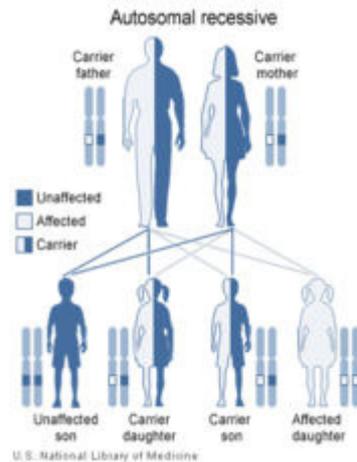
## Classification

The diagnostic criteria for PXE are the typical skin biopsy appearance and the presence of angioid streaks in the retina. Other systems have become somewhat outdated by the discovery of the *ABCC6* mutations.

## Pathophysiology

In PXE, the calcification (accumulation of calcium) and fragmentation of the elastin-containing fibers in connective tissue, but primarily in the mid-sized arteries.

## Genetics



Pseudoxanthoma elasticum has an autosomal recessive pattern of inheritance.

80% of clinical cases of pseudoxanthoma elasticum have detectable mutations in the *ABCC6* gene. Mutations in almost all parts of the gene have been described, of all types (missense, nonsense, splice alteration, insertion, small deletion or large deletion). Although there have been reports of autosomal dominant inheritance, the inheritance is typically autosomal recessive (both parents need to be carriers, and there is a 25% chance that a child will inherit *both* abnormal copies of the gene and therefore develop the condition).

Strong genetic linkage was found with mutations in the *ABCC6* gene, which codes for the MRP6 protein, but the exact mechanism by which this protein (which is a membrane transporter from the large ATP-binding cassette transporter family) influences the disease course is unknown; the protein is expressed in most organs, but mainly in the liver and kidney. It is unclear in what way this would lead to abnormalities in skin, eyes and blood vessels. It is thought that particular mutations do not cause a more severe or less severe form of the disease. Given the variations in age of onset and severity it is likely that other unknown risk factors (genetic and dietary) may be involved. One study suggested that mutations causing total absence of an MRP6 protein caused a more severe disease, but this could not be confirmed in a subsequent case series.

Premature atherosclerosis is also associated with mutations in the *ABCC6* gene, even in those without PXE.

A syndrome almost indistinguishable from hereditary PXE has been described in patients with hemoglobinopathies (sickle-cell disease and thalassemia) through a poorly understood mechanism. In addition, there appears to be another PXE-like syndrome with a similar phenotype but as a result of problems with another gene, gamma-glutamyl carboxylase.

## Treatment

There is no treatment that directly interferes with the disease process, although dietary restriction of calcium has been tried with limited results. For excessive areas of skin, plastic surgery may be needed. For the growth of abnormal blood vessels in the retina, laser eye surgery may be needed in forms similar to that used in diabetic retinopathy (eye damage due to diabetes). Cardiovascular disease is treated as in individuals without PXE. Some recommend avoidance of medication that would increase bleeding risk, such as aspirin.

## Epidemiology

The reported prevalence of pseudoxanthoma elasticum is about 1:25,000. Females are twice as likely to be affected as males. The disease occurs in all ethnicities, but South Africans are more likely to have PXE as a result of a founder effect (i.e. it was relatively prevalent in the small group of people from whom most South Africans descend).

[http://en.wikipedia.org/wiki/Pseudoxanthoma\\_elasticum](http://en.wikipedia.org/wiki/Pseudoxanthoma_elasticum)

## REFSUM DISEASE

**Refsum's disease** (Refsum-Thiébaud disease, Refsum-Thiébaud-Klenk-Kahlke disease), named after Norwegian neurologist Sigvald Bernhard Refsum (1907-1991), is neurological disease that results in the malformation of myelin sheaths around nerve cells. It is a peroxisomal disorder.

Refsum's disease is caused by faulty enzymes during the alpha-oxidation of phytanic acid resulting in buildup of phytanic acid and its unsaturated fatty acid derivatives in the plasma and tissues.

This in turn can be due to deficiencies of phytanoyl-CoA hydroxylase (chromosome 10) or peroxin-7 (chromosome 6).

Patients with Refsum's Disease present with neurologic damage, cerebellar degeneration, and peripheral neuropathy. Onset is most commonly in childhood/adolescence with a progressive course, although periods of stagnation/remission occur. Symptoms also include night blindness, ataxia, scaly skin (ichthyosis), difficulty hearing, and eye problems including cataracts.

The most effective therapy in the classic Refsum disease is dietary treatment with a phytanic acid-restricted diet, such as exclusively avoiding consumption of beef, lamb, fatty fish such as tuna, cod, and haddock. Recent research has shown that **CYP4** isoform enzymes could eliminate the phytanic acid storage *in vivo* and patients could try alternative natural remedies with either eatable marine invertebrates or with clofibrate supplement of which the component is usually rich in the excretion of high plant. Currently, there is no clinical data to approve using this xenobiotic drug for the treatment, perhaps due to its serious adverse effect and the major medical treatment of the disease only relies on the plasmapheresis.

[http://en.wikipedia.org/wiki/Refsum's\\_disease](http://en.wikipedia.org/wiki/Refsum's_disease)

## **RETINAL DYSPLASIA**

**Retinal dysplasia** is an eye disease affecting the retina of animals and, less commonly, humans. It is usually a nonprogressive disease and can be caused by viral infections, drugs, vitamin A deficiency, or genetic defects. Retinal dysplasia is characterized by folds or rosettes (round clumps) of the retinal tissue.

[http://en.wikipedia.org/wiki/Retinal\\_dysplasia](http://en.wikipedia.org/wiki/Retinal_dysplasia)

## **RETINAL HAEMORRHAGE**

**Retinal haemorrhage** is a disorder of the eye in which bleeding occurs into the retina.

The retina is a thin disc-shaped layer of light-sensitive tissue on the back wall of the eye. Its job is to translate what we see into neural impulses and send them to the brain via the optic nerve. A retinal haemorrhage can be caused by hypertension, retinal vein occlusion (a blockage of a retinal vein), or diabetes mellitus (which causes small fragile blood vessels to form, which are easily damaged). Retinal haemorrhages can also occur due to shaking, particularly in young infants (shaken baby syndrome) or from severe blows to the head.

Retinal haemorrhages that take place outside of the macula can go undetected for many years, and may sometimes only be picked up when the eye is examined in detail with an ophthalmoscope. However, some retinal haemorrhages can cause severe impairment of vision.

## **RETINAL VESSEL OCCLUSION**

The **central retinal artery (retinal artery)** branches off the ophthalmic artery, running inferior to the optic nerve within its dural sheath to the eyeball.

It pierces the optic nerve close to the eyeball, sending branches over the internal surface of the retina, and these terminal branches are the only blood supply to the larger part of it.

The central part of the retina where the light rays are focussed after passing through the pupil and the lens is a circular area called the macula. The center of this circular area is the fovea. The fovea and a small area surrounding it are not supplied by the central retinal artery or its branches, but instead by the choroid.

### **Supplies**

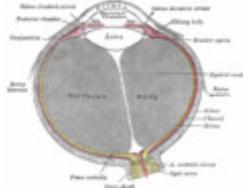
The central retinal artery still supplies all the nerve fibers that form the optic nerve that carries the visual information to the occipital lobe cerebral cortex, including those that reach over the fovea.

### **Pathology**

Thus if the central retinal artery gets occluded, there is complete loss of vision in that eye even though the fovea is not affected. The entire retina (with the exception of the fovea) becomes pale and swollen and opaque while the central fovea still appears reddish (this is because the choroid color shows through). This is the basis of the famous "Cherry red spot" seen on examination of the retina on funduscopy of a central retinal artery occlusion (CRAO).

In some cases - approximately 20% of the population - there is a branch of the ciliary circulation called the cilio-retinal artery which supplies the retina between the macula and the optic nerve, including the nerve fibers from the foveal photoreceptors. If this artery is present, the central vision will be preserved even in case of CRAO.

### images



Horizontal section of the eyeball.

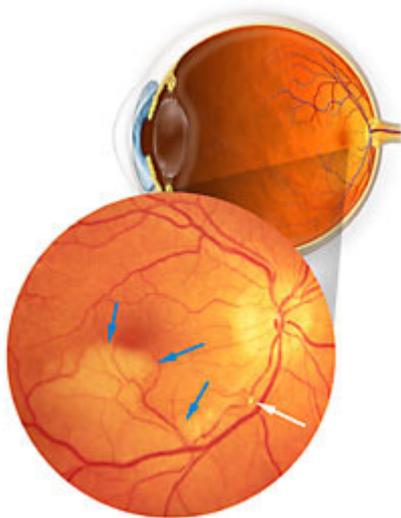


The terminal portion of the optic nerve and its entrance into the eyeball, in horizontal section.

[http://en.wikipedia.org/wiki/Central\\_retinal\\_artery](http://en.wikipedia.org/wiki/Central_retinal_artery)

## RETINAL ARTERY OCCLUSION

A retinal artery occlusion occurs when the central retinal artery or one of the arteries that branch off of it becomes blocked. This blockage is typically caused by a tiny embolus (clot) in the blood stream. The occlusion decreases the oxygen supply to the area of the retina nourished by the affected artery, causing permanent vision loss.



In this photograph, the affected area of the retina is the pale, whitish-yellow region (blue arrows) that is normally supplied by the blocked artery (white arrow). The surrounding reddish-orange area is healthy retina tissue.

### Signs and Symptoms

- Transient loss of vision prior to the artery occlusion (in some cases)

#### Central artery occlusion

- Sudden, painless and complete loss of vision in one eye

#### Branch artery occlusion

- Sudden, painless, partial loss of vision in one eye

#### Detection and Diagnosis

Artery occlusion is diagnosed by examining the retina with an ophthalmoscope.

#### Treatment

Unfortunately, there is no treatment that can consistently restore vision lost from an artery occlusion. However, if it is caught within the first hour and treatment is initiated immediately, recovery is possible in rare cases.

The following conditions increase the risk of problems that may affect the vessels of the eye:

- High cholesterol
- Heart disease
- Arteriosclerosis
- Hypertension
- Diabetes
- Glaucoma

<http://www.stlukeseye.com/conditions/ArteryOcclusion.asp>

## RETINAL DETACHMENT

**Retinal detachment** is a disorder of the eye in which the retina peels away from its underlying layer of support tissue. Initial detachment may be localized, but without rapid treatment the entire retina may detach, leading to vision loss and blindness. It is a medical emergency.

The retina is a thin layer of light-sensitive tissue on the back wall of the eye. The optical system of the eye focuses light on the retina much like light is focused on the film in a camera. The retina translates that focused image into neural impulses and sends them to the

brain via the optic nerve. Occasionally, posterior vitreous detachment, injury or trauma to the eye or head may cause a small tear in the retina. The tear allows vitreous fluid to seep through it under the retina, and peel it away like a bubble in wallpaper.

## Types

- **Rhegmatogenous retinal detachment** - A rhegmatogenous retinal detachment occurs due to a hole, tear, or break in the retina that allows fluid to pass from the vitreous space into the subretinal space between the sensory retina and the retinal pigment epithelium.
- **Exudative, serous, or secondary retinal detachment** - An exudative retinal detachment occurs due to inflammation, injury or vascular abnormalities that results in fluid accumulating underneath the retina without the presence of a hole, tear, or break.
- **Tractional retinal detachment** - A tractional retinal detachment occurs when fibrovascular tissue, caused by an injury, inflammation or neovascularization, pulls the sensory retina from the retinal pigment epithelium.

## Prevalence

The risk of retinal detachment in otherwise normal eyes is around 5 in 100,000 per year. Detachment is more frequent in the middle-aged or elderly population with rates of around 20 in 100,000 per year. The lifetime risk in normal eyes is about 1 in 300.

- Retinal detachment is more common in those with severe or extreme myopia (above 5-6 diopters), as their eyes are longer and the retina is stretched thin. The lifetime risk increases to 1 in 20. Myopia is associated with 67% of retinal detachment cases. Patients suffering from a detachment related to myopia tend to be younger than non-myopic detachment patients.
- Retinal detachment can occur more frequently after surgery for cataracts. The estimate of risk of retinal detachment after cataract surgery is 5 to 16 per 1000 cataract operations. The risk may be much higher in those who are highly myopic, with a frequency of 7% reported in one study. Young age at cataract removal further increased risk in this study. Long term risk of retinal detachment after extracapsular and phacoemulsification cataract surgery at 2, 5, and 10 years was estimated in one study to be 0.36%, 0.77%, and 1.29%, respectively.
- Tractional retinal detachments can also occur in patients with proliferative diabetic retinopathy or those with proliferative retinopathy of sickle cell disease. In proliferative retinopathy, abnormal blood vessels (neovascularization) grow within the retina and extend into the vitreous. In advanced disease, the vessels can pull the retina away from the back wall of the eye causing a traction retinal detachment.

Although retinal detachment usually occurs in one eye, there is a 15% chance of developing it in the other eye, and this risk increases to 25-30% in patients who have had cataracts extracted from both eyes.

## Symptoms

A retinal detachment is commonly preceded by a posterior vitreous detachment which gives rise to these symptoms:

- flashes of light (photopsia) - very brief in the extreme peripheral (outside of center) part of vision
- a sudden dramatic increase in the number of floaters
- a ring of floaters or hairs just to the temporal side of the central vision
- a slight feeling of heaviness in the eye

Although most posterior vitreous detachments do not progress to retinal detachments, those that do produce the following symptoms:

- a dense shadow that starts in the peripheral vision and slowly progresses towards the central vision
- the impression that a veil or curtain was drawn over the field of vision
- straight lines (scale, edge of the wall, road, etc.) that suddenly appear curved (positive Amsler grid test)
- central visual loss

## **Treatment**

There are several methods of treating a detached retina which all depend on finding and closing the holes (tears) which have formed in the retina.

- **Cryopexy and Laser Photocoagulation**

Cryotherapy (freezing) and laser photocoagulation are treatments used to create a scar/adhesion around the retinal hole to prevent fluid from entering the hole and accumulating behind the retina and exacerbating the retinal detachment. Cryopexy and photocoagulation are generally interchangeable. However, cryopexy is generally used in instances where there is a lot of fluid behind the hole; laser retinopexy will not take.

- **Scleral buckle surgery**

Scleral buckle surgery is an established treatment in which the eye surgeon sews one or more silicone bands (bands, tyres) to the outside of the eyeball. The bands push the wall of the eye inward against the retinal hole, closing the hole and allowing the retina to re-attach. The bands do not usually have to be removed. The most common side effect of a scleral operation is myopic shift. That is, the operated eye will be more short sighted after the operation. Radial scleral buckle indicated to U-shaped tears or Fishmouth tears and posterior breaks. Circumferential scleral buckle indicated to multiple breaks, anterior breaks and wide breaks. Encircling buckles indicated to breaks more than 2 quadrant of retinal area, lattice degeneration located on more than 2 quadrant of retinal area, undetectable breaks, proliferative vitreous retinopathy and inexperienced surgeon.

- **Pneumatic retinopexy**

This operation is generally performed in the doctor's office under local anesthesia. It is another method of repairing a retinal detachment in which a gas bubble (SF<sub>6</sub> or C<sub>3</sub>F<sub>8</sub>)

gas) is injected into the eye after which laser or freezing treatment is applied to the retinal hole. The patient's head is then positioned so that the bubble rests against the retinal hole. Patients may have to keep their heads tilted for several days to keep the gas bubble in contact with the retinal hole. The surface tension of the air/water interface seals the hole in the retina, and allows the retinal pigment epithelium to pump the subretinal space dry and pull the retina back into place. This strict positioning requirement makes the treatment of the retinal holes and detachments that occurs in the lower part of the eyeball impractical. This procedure is usually combined with cryopexy or laser photocoagulation.

- **Vitrectomy**

Vitrectomy is an increasingly used treatment for retinal detachment in countries with modern healthcare systems. It involves the removal of the vitreous gel and is usually combined with filling the eye with a gas bubble ( $\text{SF}_6$  or  $\text{C}_3\text{F}_8$  gas). Advantages of this operation is that there is no myopic shift after the operation. A disadvantage is that a vitrectomy always leads to more rapid progression of a cataract in the operated eye. In many places vitrectomy is the most commonly performed operation for the treatment of retinal detachment.

- **Ignipuncture**

Ignipuncture is an outdated procedure that involves cauterization of the retina with a very hot pointed instrument. It was pioneered and named by Jules Gonin in the early 1900s.

After treatment, patients gradually regain their vision over a period of a few weeks, although the visual acuity may not be as good as it was prior to the detachment, particularly if the macula was involved in the area of the detachment. However, if left untreated, total blindness could occur in a matter of days.

## **Prevention**

Retinal detachment can be prevented in some. The most effective way of preventing retinal detachment is by educating people to seek ophthalmic medical attention if they suffer symptoms suggestive of a posterior vitreous detachment. Early examination allows detection of retinal tears which can be treated with laser or cryotherapy. This reduces the risk of retinal detachment in those who have tears from around 1:3 to 1:20.

There are some known risk factors for retinal detachment. There are also many activities which at one time or another have been forbidden to those at risk of retinal detachment, with varying degrees of evidence supporting the restrictions.

Cataract surgery is a major cause, and can result in detachment even a long time after the operation. The risk is increased if there are complications during cataract surgery, but remains even in apparently uncomplicated surgery. The increasing rates of cataract surgery, and decreasing age at cataract surgery, inevitably lead to an increased incidence of retinal detachment.

Trauma is a less frequent cause. Activities which can cause direct trauma to the eye (boxing, kickboxing, karate, etc.) may cause a particular type of retinal tear called a retinal dialysis. This type of tear can be detected and treated before it develops into a retinal detachment. For this reason governing bodies in some of these sports require regular ophthalmic examination.

Individuals prone to retinal detachment due to a high level of myopia are encouraged to avoid activities where there is a risk of shock to the head or eyes, although without direct trauma to the eye the evidence base for this may be unconvincing. Some doctors recommend avoiding activities that increase pressure in the eye, including diving, skydiving, again with little supporting evidence. According to one medical website, retinal detachment does not happen as a result of straining your eyes, bending or, heavy lifting. Therefore, heavy weightlifting would appear to be fine. However, two recent scientific articles have noted cases of retinal detachment or maculopathy due to weightlifting (specifically with the Valsalva method), and a third documented an increase in blood pressure in the eye during weightlifting.

Activities that involve sudden acceleration or deceleration also increase eye pressure and are discouraged by some doctors. These include bungee jumping, Drag Racing and may also include rollercoaster rides.

[http://en.wikipedia.org/wiki/Retinal\\_detachment](http://en.wikipedia.org/wiki/Retinal_detachment)

## **RETINITIS PIGMENTOSA (RP)**

**Retinitis pigmentosa (RP)** is a group of genetic eye conditions. In the progression of symptoms for RP, night blindness generally precedes tunnel vision by years or even decades. Many people with RP do not become legally blind until their 40s or 50s and retain some sight all their life. Others go completely blind from RP, in some cases as early as childhood. Progression of RP is different in each case.

RP is a group of inherited disorders in which abnormalities of the photoreceptors (rods and cones) or the retinal pigment epithelium (RPE) of the retina lead to progressive visual loss. Affected individuals first experience defective dark adaptation or nyctalopia (night blindness), followed by constriction of the peripheral visual field and, eventually, loss of central vision late in the course of the disease

Mottling of the retinal pigment epithelium with *bone-spicule* pigmentation is typically pathognomonic for retinitis pigmentosa. Other ocular features include waxy pallor of the optic nerve head, attenuated retinal vessels, cellophane maculopathy, cystic macular edema, and posterior subcapsular cataract.

The diagnosis of retinitis pigmentosa relies upon documentation of progressive loss in photoreceptor function by electroretinography (ERG) and visual field testing. The mode of inheritance of RP is determined by family history. At least 35 different genes or loci are known to cause nonsyndromic RP. DNA testing is available on a clinical basis for:

- *RLBP1* (autosomal recessive, Bothnia type RP)
- *RP1* (autosomal dominant, RP1)
- *RHO* (autosomal dominant, RP4)

- *RDS* (autosomal dominant, RP7)
- *PRPF8* (autosomal dominant, RP13)
- *PRPF3* (autosomal dominant, RP18)
- *CRB1* (autosomal recessive, RP12)
- *ABCA4* (autosomal recessive, RP19)
- *RPE65* (autosomal recessive, RP20)

For all other genes, molecular genetic testing is available on a research basis only.

RP can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. X-linked RP can be either recessive, affecting primarily only males, or dominant, affecting both males and females, although females are usually more mildly affected. Some digenic and mitochondrial forms have also been described.

Genetic counseling depends on an accurate diagnosis, determination of the mode of inheritance in each family, and results of molecular genetic testing.

RP combined with progressive deafness is called Usher syndrome.

## Genetics

In 1989, a mutation of the gene for rhodopsin, a pigment that plays an essential part in the visual transduction cascade, was identified. Since then, more than 100 mutations have been found in this gene, accounting for 15% of all types of retinal degeneration. Most of those mutations are missense mutation and inherited mostly in a dominant manner.

There are multiple genes that, when mutated, can cause the Retinitis pigmentosa phenotype.

## Causes

A few causes for RP are:

- Fahr disease
- Bardet-Biedl syndrome
- Lowe syndrome
- Usher's syndrome
- Subacute necrotising encephalomyelopathy
- Pyruvate carboxylase deficiency
- MELAS
- Hereditary sensory-motor neuropathy type 7
- Rud's syndrome
- Refsum's disease
- Kearns-Sayre syndrome
- Carbohydrate deficient glycoprotein syndrome type 1a
- Loken Senior syndrome
- Hallervorden-Spatz disease
- Abetalipoproteinaemia
- Homocarnosinase deficiency
- Mirhosseini-Holmes-Walton syndrome
- Shwachman-Diamond syndrome

- HARP syndrome
- Alström syndrome
- Medullary cystic renal disease
- Stargardt's disease
- Sjogren-Larsson syndrome
- Tapetochoroidal dystrophy

## Treatment

There is currently no medical treatment that can completely cure retinitis pigmentosa, although the progression of the disease can be reduced by the daily intake of 15000 IU of vitamin A palmitate. Recent studies have shown that proper vitamin A supplementation can postpone blindness by up to 10 years. Scientists continue to investigate possible treatments. Future treatments may involve retinal transplants, artificial retinal implants, gene therapy, stem cells, nutritional supplements, and/or drug therapies.

In a study published in the journal Nature, researchers working with mice at the University College London Institutes of Ophthalmology and Child Health and Moorfields Eye Hospital, transplanted mouse stem cells which were at an advanced stage of development, and already programmed to develop into photoreceptors, into mice that had been genetically induced to mimic the human conditions of retinitis pigmentosa and age-related macular degeneration. These photoreceptors developed and made the necessary neural connections to the animal's retinal nerve cells, a key step in the restoration of sight. Previously it was believed that the mature retina has no regenerative ability. This research may in the future lead to using transplants in humans to relieve blindness.

[http://en.wikipedia.org/wiki/Retinitis\\_pigmentosa](http://en.wikipedia.org/wiki/Retinitis_pigmentosa)

## RETINOBLASTOMA

**Retinoblastoma** is a cancer of the retina. Development of this tumor is initiated by mutations that inactivate both copies of the *RBI* gene, which codes for the retinoblastoma protein

### Treatment

Until recently the only treatment was to remove the affected eyeball before the cancer spread. Chemotherapy is the treatment of choice for most unilateral cases. However with locally advanced disease external beam radiation may be needed and if both eyes are involved enucleation may be the only option. Affected children in developing countries present with advanced features and usually die of metastatic spread. In its initial stages, retinoblastoma is very similar to Coats disease, a non-cancerous retina disease. Coats' Disease should be ruled out before enucleation is done. A mis-diagnosis of Retinoblastoma accounts for the greatest number of Coats' disease eyes being enucleated.

Many children with bilateral retinoblastoma can be treated with a preservation attempt. Tumor chemoreduction with carboplatin and other drugs may reduce the tumor volume making them amenable to local therapies

Local therapies include-

Laser therapy (Uses infrared laser light to precisely destroy the blood vessels surrounding a tumor.)

- Cryotherapy (use of a cold gas which is injected into the affected part of the retina to shrink the tumor.)
- Thermotherapy (A relatively new technique used mainly in new testing. It uses the principle that if heat is applied to the affected area, a tumor will sustain more damage than healthy cells because healthy cells can cool themselves better using healthy surrounding blood vessels. If this technique is not immediately successful it may increase the efficacy of other treatments such as chemotherapy and focused radiation plaques.)
- Radiotherapy (Generally used as a last resort, radiotherapy was previously the treatment of choice before the above mentioned treatments were developed. Radiotherapy destroys cancerous growths using gamma radiation but it carries with it many drawbacks, including:-
  - Possibility of secondary cancerous growths which present themselves months or years later.
  - Destruction of healthy cells in the area surrounding the treated tumor.
  - Bone deformation due to the destruction of the growth plates mainly in the area of the temple.)

It is important that children with retinoblastoma are treated in specialist centers. It is considered to be one of the most common inherited cancer syndromes.

Brachytherapy with beta-emitting eye applicators have also been a successful major treatment. BEBIG (GmbH-Berlin-Germany) produces various kinds of ruthenium ophthalmic applicators for treating retinoblastoma.

Causes

In October 2007, researchers identified the specific cell that causes retinoblastoma: Rb family of genes.

<http://en.wikipedia.org/wiki/Retinoblastoma>

## RETINOSCHISIS

**Retinoschisis** is an eye disease characterized by the abnormal splitting of the retina's neurosensory layers, usually in the outer plexiform layer, resulting in a loss of vision in the corresponding visual field in some rarer forms. More common forms are usually asymptomatic.

### Classification

- Degenerative
  - Typical

- Reticular
- Hereditary
  - X linked juvenile retinoschisis
  - Familial foveal retinoschisis
- Tractional
- Exudative
  - Secondary to Optic disc pit

### **Degenerative Retinoschisis**

This type of retinoschisis is very common with a prevalence of up to 7 percent in normal persons. Its aetiology is unknown. It can easily be confused with retinal detachment by the non-expert observer and in difficult cases even the expert may have difficulty differentiating the two. Such differentiation is important since retinal detachment almost always requires treatment while retinoschisis never itself requires treatment and leads to retinal detachment (and hence to visual loss) only occasionally. Unfortunately one still sees cases of uncomplicated retinoschisis treated by laser retinopexy or cryopexy in an attempt to stop its progression towards the macula. Such treatments are not only ineffective but unnecessarily risk complications. There is no documented case in the literature of degenerative retinoschisis itself (as opposed to the occasional situation of retinal detachment complicating retinoschisis) in which the splitting of the retina has progressed through the fovea. There is no clinical utility in differentiating between typical and reticular retinoschisis. Degenerative retinoschisis is not known to be a genetically inherited condition.

### **Hereditary Retinoschisis**

It is estimated that this much less common form of retinoschisis affects one in 5,000 to 25,000 individuals, primarily young males. "Schisis" is derived from the Greek word meaning "splitting," describing the splitting of the retinal layers from each other. However, "schisis" is a word fragment and the term retinoschisis should be used, as should the term iridoschisis when describing splitting of the iris. If the retinoschisis involves the macula, then the high-resolution central area of vision used to view detail is lost, and this one form of macular disease. Although it might be described by some as a "degeneration", the term "macular degeneration" should be reserved for the specific disease " age-related macular degeneration".

Retinoschisis can be caused by an X-linked genetic defect, affecting the vision of men who inherit the disease from their unaffected carrier mothers. The genetic form of this disease usually starts during childhood and is called Juvenile X-linked Retinoschisis. Affected males are usually identified in grade school, but occasionally are identified as young infants.

Very few affected individuals go completely blind from retinoschisis, but some sufferers have very limited reading vision and are "legally blind". Visual acuity can be reduced to less than 20/200 in both eyes.

Retinoschisis causes acuity loss in the center of the visual field through the formation of tiny cysts in the retina, often forming a "spoke-wheel" pattern that can be very subtle. The cysts

are usually only detectable by a trained clinician. Vision cannot be improved by glasses, as the nerve tissue itself is damaged by these cysts.

### **Tractional Retinoschisis**

This may be present in conditions causing traction on the retina especially at the macula. This may occur in: a) The vitreomacular traction syndrome; b) Proliferative diabetic retinopathy with vitreoretinal traction; c) Atypical cases of impending macular hole.

### **Exudative Retinoschisis**

Retinoschisis involving the central part of the retina secondary to an optic disc pit was erroneously considered to be a serous retinal detachment until correctly described by Lincoff as retinoschisis. Significant visual loss may occur and following a period of observation for spontaneous resolution, treatment with temporal peripapillary laser photocoagulation followed by vitrectomy and gas injection followed by face down positioning is very effective in treating this condition.

<http://en.wikipedia.org/wiki/Retinoschisis>

## **RETINOPATHY OF PREMATURITY**

**Retinopathy of prematurity (ROP)**, previously known as **retrolental fibroplasia (RLF)**, is a disease of the eye that affects prematurely born babies. It is thought to be caused by disorganised growth of retinal blood vessels which may result in scarring and retinal detachment. ROP can be mild and may resolve spontaneously, but may lead to blindness in serious cases. As such, all preterm babies are at risk for ROP, and very low birth weight is an additional risk factor. Both oxygen toxicity and relative hypoxia can contribute to the development of ROP.

Normally, maturation of the retina proceeds in-utero and at term, the mature infant has fully vascularised retina. However, in preterm infants, the retina is often not fully vascularised. ROP occurs when the development of the retinal vasculature is arrested and then proceeds abnormally. The key disease element is fibrovascular proliferation. This is growth of abnormal new vessels that may regress, but frequently progresses. Associated with the growth of these new vessels is fibrous tissue (scar tissue) that may contract to cause retinal detachment. Multiple factors can determine whether the disease progresses, including overall health, birth weight, the stage of ROP at initial diagnosis, and the presence or absence of "plus disease". Supplemental oxygen exposure, while a risk factor, is **not** the main risk factor for development of this disease. Restricting supplemental oxygen use does not necessarily reduce the rate of ROP, and may raise the risk of other hypoxia-related systemic complications.

Patients with ROP are at greater risk for strabismus, glaucoma, cataracts and myopia later in life, and should be examined yearly to help prevent and treat these conditions.

Early treatment with erythropoietin has been show to significantly increase the risk of ROP in premature infants, and is not recommended.

## Diagnosis

Following pupillary dilation using eye drops, the retina is examined using a special lighted instrument (an indirect ophthalmoscope). The peripheral portions of the retina are pushed into view using scleral depression. Examination of the retina of a premature infant is performed to determine how far the retinal blood vessels have grown (the zone), and whether or not the vessels are growing flat along the wall of the eye (the stage). Retinal vascularization is judged to be complete when vessels extend to the ora serrata. The stage of ROP refers to the character of the leading edge of growing retinal blood vessels (at the vascular-avascular border). The stages of ROP disease have been defined by the International Classification of Retinopathy of Prematurity (ICROP).

Retinal examination with scleral depression is generally recommended for patients born before 30-32 weeks gestation, with birthweight 1500 grams or less, or at the discretion of the treating neonatologist. The initial examination is usually performed at 4–6 weeks of life, and then repeated every 1–3 weeks until vascularization is complete (or until disease progression mandates treatment).

In older patients the appearance of the disease is less well described but includes the residua of the ICROP stages as well as secondary retinal responses.

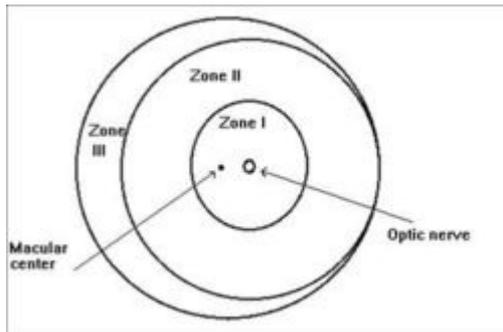
## Differential diagnosis

The most difficult aspect of the differential diagnosis may arise from the similarity of two other diseases:

- Familial Exudative Vitreoretinopathy which is a genetic disorder that also disrupts the retinal vascularization in full-term infants.
- Persistent Fetal Vascular Syndrome also known as Persistent Hyperplastic Primary Vitreous that can cause a traction retinal detachment difficult to differentiate but typically unilateral.

## International classification of retinopathy of prematurity (ICROP)

The system used for describing the findings of active ROP is entitled *The International Classification of Retinopathy of Prematurity (ICROP)*. ICROP uses a number of parameters to describe the disease. They are location of the disease into zones (1, 2, and 3), the circumferential extent of the disease based on the clock hours (1-12), the severity of the disease (stage 1-5) and the presence or absence of "Plus Disease". Each aspect of the classification has a technical definition. This classification was used for the major clinical trials. It has been revised in 2005.



 Zones of the retina in ROP

The zones are centered on the optic nerve. Zone 1 is the posterior zone of the retina, defined as the circle with a radius extending from the optic nerve to double the distance to the macula. Zone 2 is an annulus with the inner border defined by zone 1 and the outer border defined by the radius defined as the distance from the optic nerve to the nasal ora serrata. Zone 3 is the residual temporal crescent of the retina.

The circumferential extent of the disease is described in segments as if the top of the eye were 12 on the face of a clock. For example one might report that there is stage 1 disease for 3 clock hours from 4 to 7 o'clock. (The extent is a bit less important since the treatment indications from the Early Treatment for ROP)

The Stages describe the ophthalmoscopic findings at the junction between the vascularized and avascular retina.

- Stage 1 is a faint demarcation line.
- Stage 2 is an elevated ridge.
- Stage 3 is extraretinal fibrovascular tissue.
- Stage 4 is sub-total retinal detachment.
- Stage 5 is total retinal detachment.

In addition, **Plus disease** may be present at any stage. It describes a significant level of vascular dilation and tortuosity observed at the posterior retinal vessels. This reflects the increase of blood flow through the retina.

### Prognosis

Stages 1 and 2 do not lead to blindness. However, they can progress to the more severe stages. **Threshold disease** is defined as disease that has a 50% likelihood of progressing to retinal detachment. Threshold disease is considered to be present when stage 3 ROP is present in either zone I or zone II, with at least 5 continuous or 8 total clock hours of disease, and the presence of *plus* disease. Progression to stage 4 (partial retinal detachment), or to stage 5 (total retinal detachment), will result in substantial or total loss of vision for the infant.

### Monitoring

In order to allow timely intervention, a system of monitoring is undertaken for infants at risk of developing ROP. These monitoring protocols differ geographically because the definition of high-risk is not uniform or perfectly defined. In the USA the consensus statement of

experts is informed by data derived by clinical trials and published in Pediatrics 2006. They included infants with birthweights under 1500 grams or under 28 weeks gestation in most cases.

## Treatment

- Peripheral retinal ablation is the mainstay of ROP treatment. The destruction of the avascular retina is performed with a solid state laser photocoagulation device, as these are easily portable to the operating room or neonatal ICU. Cryotherapy, an earlier technique in which regional retinal destruction was done using a probe to freeze the desired areas, has also been evaluated in multi-center clinical trials as an effective modality for prevention and treatment of ROP. However, cryotherapy is no longer preferred for routine avascular retinal ablation in premature babies, due to the side effects of inflammation and lid swelling.
- Scleral buckling and/or vitrectomy surgery may be considered for severe ROP (stage 4 and 5) for eyes that progress to retinal detachment. Few centers in the world specialize in this surgery, because of its attendant surgical risks and generally poor outcomes.
- Intravitreal injection of bevacizumab (Avastin) has been reported as a supportive measure in aggressive posterior retinopathy of prematurity.

[http://en.wikipedia.org/wiki/Retinopathy\\_of\\_prematurity](http://en.wikipedia.org/wiki/Retinopathy_of_prematurity)

## RIVER BLINDNESS

**Onchocerciasis** or **river blindness** is the world's second leading infectious cause of blindness. It is caused by *Onchocerca volvulus*, a nematode that can live for up to fifteen years in the human body. It is transmitted to people through the bite of a black fly. The worms spread throughout the body, and when they die, they cause intense itching and a strong immune system response that can destroy nearby tissue, such as the eye.

The primary treatment is a drug, ivermectin. For best effect, entire villages are treated at the same time. A single dose may kill first stage larvae (microfilariae) in infected people and prevent transmission for many months in the remaining people.

About 18 million people are currently infected with this parasite. Approximately 300,000 have been irreversibly blinded by it.

The life cycle of *O. volvulus* begins when a parasitised female Black fly of the genus *Simulium* takes a blood meal. Saliva containing stage three *O. volvulus* larvae passes into the blood of the host. From here the larvae migrate to the subcutaneous tissue where they form nodules and then mature into adult worms over a period of six to twelve months. After maturation, the smaller adult males migrate from nodules to subcutaneous tissue where they mate with the larger adult females, producing between 1000 and 3000 eggs per day. The normal adult worm lifespan is up to fifteen years. The eggs mature internally to form stage one microfilariae, which are released from the female's body one at a time and remain in the subcutaneous tissue.

These stage one microfilariae are taken up by black flies upon a blood meal, in which they mature over the course of one to three weeks to stage three larvae, thereby completing the life cycle. Humans are the only definitive host for *O. volvulus*. The normal microfilariae lifespan is 1-2 years.

### Causes of morbidity



 Adult Black Fly (*Simulium yahense*) with parasite (*Onchocerca volvulus*) emerging from the insect's antenna. Magnified 100x.

Adult worms remain in subcutaneous nodules, limiting access to the host's immune system. Microfilariae, in contrast, are able to induce intense inflammatory responses, especially upon their death. Dying microfilariae have been recently discovered to release Wolbachia-derived antigens, triggering innate immune responses and producing the inflammation and its associated morbidity. Wolbachia species have been found to be endosymbionts of *O. volvulus* adults and microfilariae and are thought to be the driving force behind most of *O. volvulus* morbidity. Severity of illness is directly proportional to the number of microfilariae and the power of the resultant inflammatory response.

Skin involvement typically consists of intense itching, swelling, and inflammation. A grading system has developed to categorize the degree of skin involvement:

- Acute papular dermatitis - scattered pruritic papules;
- Chronic papular dermatitis - larger papules, resulting in hyperpigmentation;
- Lichenified dermatitis - hyperpigmented papules and plaques, with edema, lymphadenopathy, pruritus and common secondary bacterial infections;
- Skin atrophy - loss of elasticity, skin resembles tissue paper, 'lizard skin' appearance;
- Depigmentation - 'leopard skin' appearance, usually on anterior lower leg.

Ocular involvement provides the common name associated with onchocerciasis, river blindness. The microfilariae migrate to the surface of the cornea. Punctate keratitis occurs in the infected area. This clears up as the inflammation subsides. However, if the infection is chronic, sclerosing keratitis can occur, making the affected area become opaque. Over time the entire cornea may become opaque, thus leading to blindness. There is some evidence to suggest that the effect on the cornea is caused by an immune response to bacteria present in the worms.

### Treatment and control

The treatment for onchocerciasis is ivermectin (Mectizan); infected people can be treated once every twelve months. The drug paralyses the microfilariae and prevents them from causing itching. In addition, while the drug does not kill the adult worm, it does prevent them from producing additional offspring. The drug therefore prevents both morbidity and transmission. Additionally, Doxycycline can be added to the treatment regimen to kill the endosymbiotic bacteria, *Wolbachia*. This adjunct therapy has been shown to significantly lower microfilarial loads in the host and may have activity against the adult worms.

Since 1988, ivermectin has been provided free of charge by Merck & Co. through the Mectizan Donation Program (MDP). The MDP works together with ministries of health and non-governmental development organisations such as the World Health Organization to provide free Mectizan to those who need it in endemic areas.

There are various control programs that aim to stop onchocerciasis from being a public health problem. The first was the Onchocerciasis Control Programme (OCP), which was launched in 1974 and at its peak covered 30 million people in eleven countries. Through the use of larvicide spraying of fast flowing rivers to control black fly populations and, from 1988 onwards, the use of ivermectin to treat infected people, the OCP eliminated onchocerciasis as a public health problem. The OCP, a joint effort of the World Health Organisation, the World Bank, the United Nations Development Programme and the UN Food and Agriculture Organization, was considered to be a success and came to an end in 2002. Continued monitoring ensures that onchocerciasis cannot reinvade the area of the OCP.

In 1992 the Onchocerciasis Elimination Programme for the Americas (OEPA) was launched. The OEPA also relies on ivermectin.

In 1995 the African Programme for Onchocerciasis Control (APOC) began covering another nineteen countries and mainly relying upon the use of ivermectin. Its goal is to set up a community-directed supply of ivermectin for those who are infected. In these ways, transmission has declined.

According to a study in the British medical journal Lancet, the worm may be developing resistance to ivermectin.

<http://en.wikipedia.org/wiki/Onchocerciasis>

**Rubella**, commonly known as **German measles**, is a disease caused by Rubella virus. The name is derived from the Latin, meaning *little red*. Rubella is also known as German measles because the disease was first described by German physicians in the mid-eighteenth century. This disease is often mild and attacks often pass unnoticed. The disease can last one to five days. Children recover more quickly than adults. Infection of the mother by Rubella virus during pregnancy can be serious; if the mother is infected within the first 20 weeks of pregnancy, the child may be born with congenital rubella syndrome (CRS), which entails a range of serious incurable illnesses. Spontaneous abortion occurs in up to 20% of cases.

Rubella is a common childhood infection usually with minimal systemic upset although transient arthropathy may occur in adults. Serious complications are very rare. If it were not for the effects of transplacental infection on the developing foetus, rubella is a relatively trivial infection.

Acquired, (i.e. not congenital), rubella is transmitted via airborne droplet emission from the upper respiratory tract of active cases. The virus may also be present in the urine, faeces and on the skin. There is no carrier state: the reservoir exists entirely in active human cases. The disease has an incubation period of 2 to 3 weeks.

In most people the virus is rapidly eliminated however, it may persist for some months post partum in infants surviving the CRS. These children were an important source of infection to other infants and, more importantly, pregnant female contacts.

After an incubation period of 14-21 days, the primary symptom of rubella virus infection is the appearance of a rash (exanthem) on the face which spreads to the trunk and limbs and usually fades after three days. Other symptoms include low grade fever, swollen glands (post cervical lymphadenopathy), joint pains, headache, conjunctivitis. The swollen glands or lymph nodes can persist for up to a week and the fever rarely rises above 38 °C (100.4 °F). The rash disappears after a few days with no staining or peeling of the skin. Forchheimer's sign occurs in 20% of cases, and is characterized by small, red papules on the area of the soft palate.

Rubella can affect anyone of any age and is generally a mild disease, rare in infants or those over the age of 40. The older the person is the more severe the symptoms are likely to be. Up to one-third of older girls or women experience joint pain or arthritic type symptoms with rubella. The virus is contracted through the respiratory tract and has an incubation period of 2 to 3 weeks. During this incubation period, the carrier is contagious but may show no symptoms.

### **Congenital Rubella Syndrome**

Rubella can cause congenital rubella syndrome in the newly born. The syndrome (CRS) follows intrauterine infection by Rubella virus and comprises cardiac, cerebral, ophthalmic and auditory defects. It may also cause prematurity, low birth weight, and neonatal thrombocytopenia, anaemia and hepatitis. The risk of major defects or organogenesis is highest for infection in the first trimester. CRS is the main reason a vaccine for rubella was developed. Many mothers who contract rubella within the first critical trimester either have a miscarriage or a still born baby. If the baby survives the infection, it can be born with severe heart disorders (PDA being the most common), blindness, deafness, or other life threatening organ disorders. The skin manifestations are called "blueberry muffin lesions."

### **Cause**

The disease is caused by Rubella virus, a togavirus that is enveloped and has a single-stranded RNA genome. The virus is transmitted by the respiratory route and replicates in the nasopharynx and lymph nodes. The virus is found in the blood 5 to 7 days after infection and spreads throughout the body. It is capable of crossing the placenta and infecting the fetus where it stops cells from developing or destroys them.

### **Diagnosis of acquired rubella**

Rubella virus specific IgM antibodies are present in people recently infected by Rubella virus but these antibodies can persist for over a year and a positive test result needs to be interpreted

with caution. The presence of these antibodies along with, or a short time after, the characteristic rash confirms the diagnosis.

## **Prevention**

Rubella infections are prevented by active immunisation programs using live, disabled virus vaccines. Two live attenuated virus vaccines, RA 27/3 and Cendehill strains, were effective in the prevention of adult disease. However their use in prepubertile females did not produce a significant fall in the overall incidence rate of CRS in the UK. Reductions were only achieved by immunisation of all children.

The vaccine is now given as part of the MMR vaccine. The WHO recommends the first dose is given at 12 to 18 months of age with a second dose at 36 months. Pregnant women are usually tested for immunity to rubella early on. Women found to be susceptible are not vaccinated until after the baby is born because the vaccine contains live virus.

## **Treatment**

Symptoms are usually treated with paracetamol until the disease has run its course. Treatment of newly born babies is focused on management of the complications. Congenital heart defects and cataracts can be corrected by surgery. Management for ocular CRS is similar to that for age-related macular degeneration, including counseling, regular monitoring, and the provision of low vision devices, if required.

## **Prognosis**

Rubella infection of children and adults is usually mild, self-limiting and often asymptomatic. The prognosis in children born with CRS is poor.

## **Epidemiology**

Rubella is a disease that occurs worldwide. The virus tends to peak during the spring in countries with temperate climates. Before the vaccine to rubella was introduced in 1969, widespread outbreaks usually occurred every 6-9 years in the United States and 3-5 years in Europe, mostly affecting children in the 5-9 year old age group. Since the introduction of vaccine, occurrences have become rare in those countries with high uptake rates. However, in the UK there remains a large population of men susceptible to rubella who have not been vaccinated. Outbreaks of rubella occurred amongst many young men in the UK in 1993 and in 1996 the infection was transmitted to pregnant women, many of whom were immigrants and were susceptible. Outbreaks still arise, usually in developing countries where the vaccine is not as accessible.

During the epidemic in the US between 1962-1965, Rubella virus infections during pregnancy were estimated to have caused 30,000 still births and 20,000 children to be born impaired or disabled as a result of CRS. Universal immunisation producing a high level of herd immunity is important in the control of epidemics of rubella.

<http://en.wikipedia.org/wiki/Rubella>

## SARCOIDOSIS

**Sarcoidosis**, also called **sarcoid** (from the Greek 'sark' and 'oid' meaning "flesh-like") or **Besnier-Boeck disease**, is an immune system disorder characterised by non-caseating granulomas (small inflammatory nodules) that most commonly arises in young adults. The cause of the disease is still unknown. Virtually any organ can be affected; however, granulomas most often appear in the lungs or the lymph nodes. Symptoms can occasionally appear suddenly but usually appear gradually. The clinical course varies and ranges from asymptomatic disease to a debilitating chronic condition that may lead to death.

Sarcoidosis most commonly affects young adults of both sexes, with a slight preponderance for women having been reported by most studies. Incidence is highest for individuals younger than 40 and peaks in the age-group from 20 to 29 years.

Sarcoidosis occurs throughout the world in all races with a prevalence ranging from 1 to 40 per 100,000. The disease is most prevalent in Northern European countries, and the highest annual incidence of 60 per 100,000 is found in Sweden and Iceland. In the United States, sarcoidosis is more common in people of African descent than Caucasians, with annual incidence reported as 35.5 and 10.9 per 100,000, respectively. Sarcoidosis is less commonly reported in South America, Spain and India.

The differing incidence across the world may be at least partially attributable to the lack of screening programs in certain regions of the world and the overshadowing presence of other granulomatous diseases such as tuberculosis, that may interfere with the diagnosis of sarcoidosis where they are prevalent.

There may also be racial differences in the severity of the disease. Several studies suggest that the presentation in people of African origin may be more severe than for Caucasians, who are more likely to have asymptomatic disease.

### Signs and symptoms

Sarcoidosis is a systemic disease that can affect any organ. Common symptoms are vague, such as fatigue unchanged by sleep, lack of energy, weight loss, aches and pains, arthralgia, dry eyes, blurry vision, shortness of breath, a dry hacking cough or skin lesions. The cutaneous symptoms vary, and range from rashes and noduli (small bumps) to erythema nodosum or lupus pernio. It is often asymptomatic.

The combination of erythema nodosum, bilateral hilar lymphadenopathy and arthralgia is called *Löfgren syndrome*. This syndrome has a relatively good prognosis.

Renal, liver (including portal hypertension), heart or brain involvement may cause further symptoms and altered functioning. Manifestations in the eye include uveitis, uveoparotitis, and retinal inflammation, which may result in loss of visual acuity or blindness. Sarcoidosis affecting the brain or nerves is known as neurosarcoidosis.

The combination of anterior uveitis, parotitis and fever is called uveoparotitis, and is associated with *Heerfordt-Waldenström syndrome*.

### Investigations

Hypercalcemia (high calcium levels) and its symptoms may be the result of excessive conversion of vitamin D to its active form by epithelioid macrophages.

Sarcoidosis most often manifests as a restrictive disease of the lungs, causing a decrease in lung volume and decreased compliance (the ability to stretch). The disease typically limits the amount of air drawn into the lungs, but produces higher than normal expiratory flow ratios. The vital capacity (full breath in, to full breath out) is decreased, and most of this air can be blown out in the first second. This means the FEV<sub>1</sub>/FVC ratio is increased from the normal of about 80%, to 90%. Obstructive lung changes, causing a decrease in the amount of air that can be exhaled, may occur when enlarged lymph nodes in the chest compress airways or when internal inflammation or nodules impede airflow.

Chest X-ray changes are divided into four stages

- Stage 1 bihilar lymphadenopathy
- Stage 2 bihilar lymphadenopathy and reticulonodular infiltrates
- Stage 3 bilateral infiltrates
- Stage 4 fibrocystic sarcoidosis typically with upward hilar retraction, cystic & bullous changes

Because sarcoidosis can affect multiple organ systems, follow-up on a patient with sarcoidosis should always include an electrocardiogram, ocular examination by an optometrist or ophthalmologist, liver function tests, serum calcium and 24-hour urine calcium.

### **Causes and pathophysiology**

No direct cause of sarcoidosis has been identified, although there have been reports of cell wall deficient bacteria that may be possible pathogens. These bacteria are not identified in standard laboratory analysis. Other investigators suspect involvement of *Propionibacterium acnes* although it is clearly apparent that sarcoidosis develops only when the host is hypersensitive to a special antigen. It has been thought that there may be a hereditary factor because some families have multiple members with sarcoidosis. To date, no reliable genetic markers have been identified, and an alternate hypothesis is that family members share similar exposures to environmental pathogens. There have also been reports of transmission of sarcoidosis via organ transplants.

Sarcoidosis frequently causes a dysregulation of vitamin D production with an increase in extrarenal (outside the kidney) production. Specifically, macrophages inside the granulomas convert vitamin D to its active form, resulting in elevated levels of the hormone 1,25-dihydroxyvitamin D and symptoms of hypervitaminosis D that may include fatigue, lack of strength or energy, irritability, metallic taste, temporary memory loss or cognitive problems. Physiological compensatory responses (e.g. suppression of the parathyroid hormone levels) may mean the patient does not develop frank hypercalcemia.

Sarcoidosis has been associated with celiac disease. Celiac disease is a condition in which there is a chronic reaction to certain protein chains, commonly referred to as gluten, found in some cereal grains. This reaction causes destruction of the villi in the small intestine, with resulting malabsorption of nutrients.

While disputed, some cases have been determined to be caused by inhalation of the dust from the collapse of the World Trade Center after the September 11, 2001 attacks.

## Treatment

Corticosteroids, most commonly prednisone, have been the standard treatment for many years. In some patients, this treatment can slow or reverse the course of the disease, but other patients do not respond to steroid therapy. The use of corticosteroids in mild disease is controversial because in many cases the disease remits spontaneously. Additionally, corticosteroids have many recognized dose- and duration-related side effects (which can be reduced through the use of alternate-day dosing for those on chronic prednisone therapy), and their use is generally limited to severe, progressive, or organ-threatening disease. The influence of corticosteroids or other immunosuppressants on the natural history is unclear.

Severe symptoms are generally treated with steroids, and steroid-sparing agents such as azathioprine and methotrexate are often used. Rarely, cyclophosphamide has also been used. As the granulomas are caused by collections of immune system cells, particularly T cells, there has been some early indications of success using immunosuppressants, interleukin-2 inhibitors or anti-tumor necrosis factor-alpha treatment (such as infliximab). Unfortunately, none of these has provided reliable treatment, and there can be significant side effects such as an increased risk of reactivating latent tuberculosis.

Avoidance of sunlight and Vitamin D foods may be helpful in patients who are susceptible to developing hypercalcemia.

<http://en.wikipedia.org/wiki/Sarcoidosis>

## SCOTOPIC SENSITIVITY SYNDROME

**Scotopic sensitivity syndrome**, also known as **Irlen Syndrome** or approximating in some ways to **Meares Irlen syndrome**, are visual perceptual disorder(s) affecting primarily reading and writing based activities. Its existence is not recognized by some major medical organizations including the American Academy of Pediatrics, the American Academy of Ophthalmology, and the American Optometric Association. However, it is fair to say that it does enjoy recognition amongst a respected body of medical opinion, and has been recognised in American States and Australia, and has been studied extensively in leading research centres, including the University of Cambridge in the UK. The Scottish Parliament has also funded a research and treatment centre at the Glasgow Caledonian University.

Irlen syndrome is sometimes categorised as a form of dyslexia. However, bestselling autistic author, Donna Williams, in her book *Like Colour To The Blind* wrote about her experience of tinted lenses after being diagnosed with scotopic sensitivity. In this book she described the lenses as enabling her to have cohesive, unfragmented vision, able to see faces, bodies and objects as a whole for the first time and reducing the extremity of experiences such as meaning-blindness, face blindness, inability to learn to read facial expression and body language and the social consequences of these impairments. This led to a worldwide raised awareness of scotopic sensitivity as a sensory perceptual problem common in many (but not all) people with autism and expanded awareness of the potential effects of Scotopic

Sensitivity far beyond that of reading disability, also leading to awareness of the effects of fluorescent lighting on those with this perceptual disorder.

The condition was jointly described by two people working individually, unaware of the work of the other person. In the early 1980s New Zealand teacher Olive Meares described the visual distortions some individuals reported when reading from white paper, while American therapist Helen Irlen wrote a paper about the use of coloured overlays aiding the reading abilities of some people. Irlen who was the first to systematically define the condition, named her findings "scotopic sensitivity", though the discussions and debates over the following years, some often referred to it as Meares-Irlen syndrome. Yet this is controversial, with some experts believing that Helen Irlen's syndrome does not exactly align with Olive Meares', and that we may in fact have two different conditions, or different aspects of the broadly same one. Testing for scotopic sensitivity were also taken up by ophthalmologists in UK hospitals using a technique called colorimeter and an organisation run by ophthalmologists called Brain Power International also produced its own affordable self testing set of therapeutic tints for scotopic sensitivity, including a set specific to the autistic population.

One or more of these symptoms may be related to the condition:

- Eye-strain
- Fatigue
- Headaches (including migraine)
- Nausea, including visually-related motion sickness
- Problems with depth perception (catching balls, judging distance, etc.)
- Restricted field of view and span of recognition
- Discomfort with busy patterns, particularly stripes ("visual stress" and "pattern glare")
- Discomfort with extreme conditions of bright/dark contrast (i.e. backlighting)
- Discomfort or difficulty reading (reading involves busy patterns, particularly stripes. People with strong symptoms of the syndrome find it very difficult to read black text on white paper, particularly when the paper is slightly shiny.)
- Text that appears to move (rise, fall, swirl, shake, etc.)
- Attention and concentration difficulties
- Seeing the part and losing the whole
- Epileptic seizure related to strobing or pattern glare

## **Treatment**

The use of tinted lenses in glasses and coloured overlay sheets has been prescribed by many doctors; however, the efficacy of such treatment is questionable. It has been felt to be efficient in treatment by some.

The American Optometric Association acknowledges the benefits of tinted lenses for some individuals and recommends further scientific investigation.

[http://en.wikipedia.org/wiki/Scotopic\\_Sensitivity\\_Syndrom](http://en.wikipedia.org/wiki/Scotopic_Sensitivity_Syndrom)

## **SEPTO-OPTIC DYSPLASIA**

**Septo-optic dysplasia** (SOD) (de Morsier syndrome) is a congenital malformation syndrome manifested by hypoplasia (underdevelopment) of the optic nerve, hypopituitarism, and absence of the septum pellucidum (a midline part of the brain). In a severe case, this results in pituitary hormone deficiencies, blindness, and mental retardation. However, there are milder degrees of each of the three problems, and some children only have one or two of the three.

Neuroradiologically, intracranial malformations associated with septo-optic dysplasia include agenesis of the corpus callosum, schizencephaly, and lobar holoprosencephaly.

### **Presentation**

#### **Optic nerve**

The optic nerve hypoplasia is generally manifested by nystagmus (involuntary eye movements, often side-to-side) and a smaller-than-usual optic disk. The degree of visual impairment is variable, and ranges from normal vision to complete blindness. When nystagmus develops, it typically appears by 1-8 months of age, and usually indicates that there will be a significant degree of visual impairment, but the severity is difficult to predict in infancy. Although there are many measures to compensate for visual impairment, no treatment is available to induce normal optic nerve function.

#### **Pituitary**

The degree of pituitary deficiency is also variable, and ranges from normal function, to deficiency of a single hormone, to deficiency of both anterior and posterior hormones. It is often unclear if the hypopituitarism is due to a primary pituitary dysfunction or is secondary to a hypothalamic dysfunction. Hypopituitarism in this syndrome is most often manifested by growth hormone deficiency. If severe, it can lead to diagnosis in the first days of life by causing hypoglycemia, jaundice, and micropenis (if a boy). The cause of the jaundice is unknown, and an unusual aspect of it (compared to most neonatal jaundice) is that it can be largely a conjugated (direct) hyperbilirubinemia suggestive of obstructive liver disease. It typically resolves over several weeks once hormone replacement is begun. All of the pituitary hormones can be replaced, and this is the treatment for deficiencies. Septo-optic dysplasia is one of the most common forms of congenital growth hormone deficiency.

#### **Septum pellucidum**

The brain effects are also variable and range from normal intelligence to severe mental retardation. Seizures sometimes occur. Prediction of intellectual outcome in infancy is difficult. Various types of early intervention or equivalent programs can help a child reach full developmental potential, but if brain impairment is significant, it cannot be made normal by any treatment.

## Variability

Septo-optic dysplasia is a highly variable disorder. It is rare for siblings to present with identical features of the Septo-optic dysplasia spectrum. Many patients present with additional developmental defects outside the Septo-optic dysplasia triad. In particular digital defects are common.

## Causes

Septo-optic dysplasia is a developmental disorder resulting from a defect of normal embryological development. The cause of septo-optic dysplasia is not known. Rare familial recurrence has been reported, suggesting at least one genetic form (HESX1), but in most cases it is a sporadic birth defect of unknown cause and does not recur again with subsequent pregnancies.

Septo-optic dysplasia is linked to young maternal age. Indeed one third of Septo-optic births are the result of teenage pregnancies. These data could support an environmental origin of SOD with possible exposure to risk factors such as maternal smoking, alcohol consumption, and use of addictive drugs during early gestation. However, young maternal age in SOD was not associated with low birth weight or low gestation. This lack of association between young maternal age and an adverse developmental environment, as indicated by birth weight and gestation, suggest that maternal factors such as maternal smoking, alcohol consumption, and use of addictive drugs during early gestation are not a cause of Septo-optic dysplasia.

[http://en.wikipedia.org/wiki/Septo-optic\\_dysplasia](http://en.wikipedia.org/wiki/Septo-optic_dysplasia)

## STARGARDT DISEASE

**Stargardt's disease**, or fundus flavimaculatus, has been vastly reported as an autosomal recessive genetic form of juvenile macular degeneration that causes progressive vision loss, although several dominant pedigrees have been reported. It is the most common inherited juvenile macular degeneration

Those with Stargardt's disease are sensitive to glare; overcast days offer little relief. As the disease progresses, it can cause pain and diminishing sight. Vision is impaired first at the center, leaving peripheral vision intact. Symptoms usually appear before age 20. Symptoms include wavy vision, blind spots, blurriness, and difficulty adapting to dim lighting.

Some patients are able to drive. Many patients use magnifiers to help them see, and wear sunglasses to slow the development. Some doctors have recommended colored lenses which filter out the light wavelengths which stimulate rod vision.

The disease was discovered in 1909 by Karl Stargardt, an ophthalmologist in Berlin.

In 1997, it was discovered that mutations in the *ABCA4* gene cause Stargardt's. The mutations cause the production of a dysfunctional protein that cannot perform energy transport to and

from photoreceptor cells in the retina. The photoreceptor cells then degenerate, causing vision loss.

[http://en.wikipedia.org/wiki/Stargardt's\\_disease](http://en.wikipedia.org/wiki/Stargardt's_disease)

## **STEVENS-JOHNSON SYNDROME**

**Stevens-Johnson syndrome** (SJS) is a severe and life-threatening condition. It is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.

There is agreement in the medical literature that **Stevens-Johnson syndrome** can be considered a milder form of toxic epidermal necrolysis (TEN). However, there is debate whether it falls on a spectrum of disease that includes erythema multiforme; many consider erythema multiforme (EM) to be unrelated to SJS and TEN.

Some classify SJS as a severe expression of erythema multiforme, and it occasionally referred to as **erythema multiforme major**.

### **Epidemiology**

SJS is a rare condition, with a reported incidence of around one case per million people per year.

### **Causes**

SJS can be caused by infections (usually following viral infections such as herpes simplex virus, influenza, mumps, cat-scratch fever, histoplasmosis, Epstein-Barr virus, or similar), allergic reactions to drugs, (Dicloflex, fluconazole, valdecoxib, penicillins, barbiturates, sulfas, phenytoin, Provigil, lamotrigine, nevirapine, Ibuprofen, ethosuximide, carbamazepine), malignancy (carcinomas and lymphomas), or idiopathic factors (up to 50% of the time). SJS has also been consistently reported as an uncommon side effect of herbal supplements containing ginseng. SJS may also be caused by cocaine usage

Although Stevens Johnson Syndrome may be caused by viral infections or malignancies, severe allergic reactions to medication is the leading cause. Medications that have traditionally been known to lead to Stevens Johnson Syndrome, Erythema Multiforme, Lyell's Syndrome, and Toxic Epidermal Necrolysis include sulfonamides (antibiotics), penicillins (antibiotics), barbiturates (sedatives), and phenytoin - Dilantin (anticonvulsant).

### **Treatment**

Discontinue all medications, particularly those known to cause SJS reactions. Treatment is initially similar to that of patients with thermal burns, and continued care can only be supportive (e.g. IV fluids) and symptomatic (e.g. analgesic mouth rinse for mouth ulcer); there is no specific drug treatment (2002). Treatment with corticosteroids is controversial since it might aggravate the condition or increase risk of secondary infections. Other agents have been used, including cyclophosphamide and cyclosporine, but none have exhibited much therapeutic success. Intravenous immunoglobulin (IVIG) treatment has shown some promise in reducing the length of the reaction and improving symptoms. Other common supportive

measures include the use of topical pain anesthetics and antiseptics, maintaining a warm environment, and intravenous analgesics. An ophthalmologist should be consulted immediately, as SJS frequently causes the formation of scar tissue inside the eyelids leading to corneal vascularization and impaired vision, as well as a host of other ocular problems. Also, an extensive physical therapy program ensues after the patient is discharged from the hospital

## Prognosis

SJS proper (with less than 10% of body surface area involved) has the mortality rate of around 5%. The risk for death can be estimated using the SCORTEN scale, which takes a number of prognostic indicators into account. Other outcomes include organ damage and blindness.

[http://en.wikipedia.org/wiki/Stevens-Johnson\\_syndrome](http://en.wikipedia.org/wiki/Stevens-Johnson_syndrome)

## STICKLER SYNDROME

**Stickler syndrome** (or **David-Stickler syndrome** or **Stickler-Wagner syndrome**) is a group of genetic disorders affecting connective tissue, specifically collagen. It was first studied and characterised by Dr. G.B. Stickler in 1965. Stickler syndrome is a subtype of collagenopathy, types II and XI. Stickler syndrome is characterized by a distinctive facial appearance, eye abnormalities, hearing loss, and joint problems.

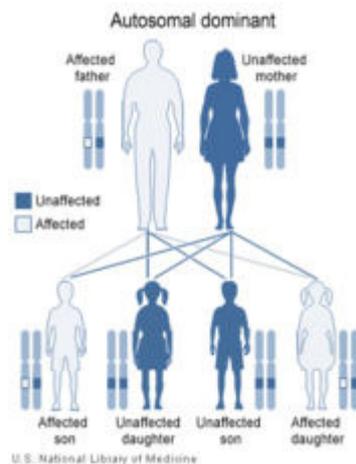
## Types

Genetic changes are related to the following types of Stickler syndrome:

- Stickler syndrome, COL11A1
- Stickler syndrome, COL11A2
- Stickler syndrome, COL2A1

Whether there are two or three types of Stickler syndrome is controversial. Each type is presented here according to the gene involved. The classification of these conditions is changing as researchers learn more about the genetic causes.

## Causes



Stickler syndrome is inherited in an autosomal dominant pattern.

The syndrome is thought to arise from a mutation of several collagen genes during fetal development. It is a sex independent autosomal dominant trait meaning a person with the syndrome has a 50% chance of passing it on to each child. There are three variants of Stickler syndrome, each associates with a collagen biosynthesis gene.

### Who gets Stickler syndrome?

Stickler syndrome is an autosomal dominant condition, meaning only one parent needs to have an abnormal gene for the child to inherit the disease. A person with syndrome has a 50% chance for each pregnancy of passing this mutation on to the child.

Stickler's syndrome, or congenital, progressive arthro-ophthalmopathy, refers to disturbances of the connective tissue of the organism but mainly the osteoarticular and visual systems. In the visual system one discovers a congenital high myopia, pathological changes in the vitreous in the form of membranes and proliferative bands as well as retinal detachment. A metabolic defect concerning the hyaluronic acid and the collagen of the 2-d type is assumed to be the cause of this syndrome.

People with this disease often have lots of eye problems. Some of the problems are mild and others are severe. Examples of these are near sightedness, astigmatism, and cataracts, which are mild because they can be corrected by having surgery or wearing a certain type of glasses. Retinal detachment, which occurs when the gel inside the eye deteriorates, squint, and glaucoma are examples of severe eye problems, because they can lead to blindness. They also have hearing problems that affect the inner or middle ear, and can lead to deafness.

### Symptoms

Individuals with Stickler syndrome experience a range of signs and symptoms. Some people have almost no signs and symptoms; others have all of the features described below. In addition, each feature of this syndrome may vary from subtle to severe.

A characteristic feature of Stickler syndrome is a somewhat flattened facial appearance. This is caused by underdeveloped bones in the middle of the face, including the cheekbones and the bridge of the nose. A particular group of physical features, called the Pierre Robin syndrome, is common in children with Stickler syndrome. Robin sequence includes a U-

shaped or sometimes V-shaped cleft palate (an opening in the roof of the mouth) with a tongue that is too large for the space formed by the small lower jaw. Children with a cleft palate are also prone to frequent ear infections and swallowing difficulties.

Many people with Stickler syndrome are very nearsighted (described as having high myopia) because of the shape of the eye. People with eye involvement are prone to increased pressure within the eye (glaucoma) and tearing of the lining of the eye (retinal detachment). The jelly-like substance within the eye (the vitreous) has a distinctive appearance in the types of Stickler syndrome associated with the COL2A1 and COL11A1 genes. The type of Stickler syndrome associated with the COL11A2 gene does not affect the eye.

People with this disease have problems that affect things other than the eyes and ears. Arthritis, abnormality to ends of long bones, vertebrae abnormality, curvature of the spine, hunchback, joint pain, knock knee, and double jointed are all problems that can occur in the bones and joints. Physical characteristics of people with Stickler can include flat cheeks, flat nasal bridge, and small upper jaw, pronounced upper lip groove, small lower jaw, and palate abnormalities.

Another sign of Stickler syndrome is mild to severe hearing loss that, for some people, may be progressive (see hearing loss with craniofacial syndromes). The joints of affected children and young adults may be very flexible (hypermobile). Arthritis often appears at an early age and worsens as a person gets older. Learning difficulties can also occur because of hearing and sight impairments.

## **Genetics**

Mutations in the COL11A1, COL11A2 and COL2A1 genes cause Stickler syndrome. These genes are involved in the production of type II and type XI collagen. Collagens are complex molecules that provide structure and strength to connective tissue (the tissue that supports the body's joints and organs). Mutations in any of these genes disrupt the production, processing, or assembly of type II or type XI collagen. Defective collagen molecules or reduced amounts of collagen affect the development of bones and other connective tissues, leading to the characteristic features of Stickler syndrome.

Other, as yet unknown, genes may also cause Stickler syndrome because not all individuals with the condition have mutations in one of the three identified genes.

## **Treatment**

Many professionals that are likely to be involved in the treatment of those with Stickler's Syndrome, include craniofacial surgeons, ear/nose/and throat specialists, ophthalmologists, audiologists and rheumatologists.

[http://en.wikipedia.org/wiki/Stickler\\_syndrome](http://en.wikipedia.org/wiki/Stickler_syndrome)

## TRACHOMA

**Trachoma** (Ancient Greek: "rough eye") is an infectious eye disease, and the leading cause of the world's infectious blindness. Globally, 84 million people suffer from active infection and nearly 8 million people are visually impaired as a result of this disease. Globally this disease results in an estimated US \$2.9 billion in lost productivity every year.

Trachoma is caused by the bacterium *Chlamydia trachomatis* and it is spread by direct contact with eye, nose, and throat secretions from affected individuals, or contact with fomites (inanimate objects), such as towels and/or washcloths, that have had similar contact with these secretions. Untreated, repeated trachoma infections result in a painful form of permanent blindness when the eyelids turn inward, causing the eyelashes to scratch the cornea. Children are the most susceptible to infection, but the blinding effects are often not felt until adulthood.

Blinding endemic trachoma occurs in areas with poor personal and family hygiene. Many factors are indirectly linked to the presence of trachoma including lack of water, absence of latrines or toilets, poverty in general, flies, close proximity to cattle, crowding and so forth. However, the final common pathway seems to be the presence of dirty faces in children that facilitates the frequent exchange of infected ocular discharge from one child's face to another. Most transmission of trachoma occurs within the family.

Although trachoma was eliminated from much of the developed world in the last century, this disease persists in many parts of the developing world particularly in communities without adequate access to water and sanitation. In many of these communities, women are three times more likely than men to be blinded by the disease.

Without intervention, trachoma keeps families shackled within a cycle of poverty, as the disease and its long-term effects are passed from one generation to the next.

The World Health Organization (WHO) has set a goal of eliminating blinding trachoma as a public health concern by 2020. National governments in collaboration with numerous non-profit organizations implement trachoma control programs using the WHO-recommended SAFE strategy, which includes:

- Surgery to correct advanced stages of the disease;
- Antibiotics to treat active infection, using Zithromax donated by Pfizer Inc through the International Trachoma Initiative;
- Facial cleanliness to reduce disease transmission;
- Environmental change to increase access to clean water and improved sanitation.

**Surgery:** For individuals with trichiasis, a bilamellar tarsal rotation procedure is warranted to direct the lashes away from the globe. Early intervention is beneficial as the rate of recurrence is higher in more advanced disease.

**Antibiotic therapy:** WHO Guidelines recommend that a region should receive community-based, mass antibiotic treatment when the prevalence of active trachoma among one to nine year-old children is greater than 10 percent. Subsequent annual treatment should be administered for three years, at which time the prevalence should be reassessed. Annual treatment should continue until the prevalence drops below five percent. At lower prevalences, antibiotic treatment should be family-based.

Antibiotic selection: WHO recommends azithromycin (single oral dose of 20mg/kg) or topical tetracycline (one percent eye ointment twice a day for six weeks). Azithromycin is preferred because it is used as a single oral dose. Although it is expensive, it is generally used as part of the international donation program organized by Pfizer through the International Trachoma Initiative. Azithromycin can be used in children from the age of six months and in pregnancy.

Facial cleanliness: Children with grossly visible nasal discharge, ocular discharge, or flies on their faces are at least twice as likely to have active trachoma as children with clean faces. Intensive community-based health education programs to promote face-washing can significantly reduce the prevalence of active trachoma, especially intense trachoma (TI).

Environmental improvement: Modifications in water use, fly control, latrine use, health education and proximity to domesticated animals have all been proposed to reduce transmission of *C. trachomatis*. These changes pose numerous challenges for implementation. It seems likely that these environmental changes ultimately impact on the transmission of ocular infection by means of lack of facial cleanliness. Particular attention is required for environmental factors that limit clean faces.

The World Health Organization recommends a simplified grading system for trachoma. The Simplified WHO Grading System is summarized below:

- Trachomatous inflammation, follicular (TF) – Five or more follicles of >0.5mm on the upper tarsal conjunctiva
- Trachomatous inflammation, intense (TI) – Papillary hypertrophy and inflammatory thickening of the upper tarsal conjunctiva obscuring more than half the deep tarsal vessels
- Trachomatous trichiasis (TT) – At least one ingrown eyelash touching the globe, or evidence of epilation (eyelash removal)
- Corneal opacity (CO) – Corneal opacity blurring part of the pupil margin

Further symptoms include:

- Eye discharge
- Swollen eyelids
- Trichiasis (turned-in eyelashes)
- Swelling of lymph nodes in front of the ears
- Corneal scarring
- Further ear, nose and throat complications.

<http://en.wikipedia.org/wiki/Trachoma>

## PHYSICAL TRAUMA

**Physical trauma** refers to a physical injury. A **trauma patient** is someone who has suffered serious and life-threatening physical injury potentially resulting in secondary complications such as shock, respiratory failure and death.

### Definition

A body wound or shock produced by sudden physical injury, as from accident, injury, or impact. Trauma patients usually require specialized care, including surgery and sometimes blood transfusion, within the so-called golden hour of emergency medicine, the first sixty minutes after trauma occurs. This is not a strict deadline, but recognizes that many deaths which could have been prevented by appropriate care occur a relatively short time after injury. In many places organized trauma referral systems have been set up to provide rapid care for injured people. Research has shown that deaths from physical trauma decline where there are organized trauma systems.

### Techniques

In a prehospital setting, also called the "field", emergency medical technicians, paramedics, specialized nurses, and less trained providers known as 'first responders', use stabilization techniques to improve the chances of a trauma patient surviving the ambulance trip to the hospital. Professionals begin performing a *primary survey*, consisting of assessment of airway, breathing, and circulation (called the "ABC's"). The purpose of the primary survey is to identify life-threatening problems. Ensuring that the injured person is not disabled by unnecessary movement of the spine is paramount, so the neck and back are secured before moving the patient. Unless the victim is in imminent danger of death, first responders will usually "load and go" transporting the victim immediately to the nearest appropriate trauma-equipped hospital.

Upon completion of the primary survey, the *secondary survey* is begun. This may occur during transport or upon arrival at the hospital. The secondary survey consists of a systematic assessment of the abdominal, pelvic and thoracic viscera, complete inspection of the body surface to find all injuries, and neurological exam. The purpose of the secondary survey is to identify all injuries so that they may be treated. A *missed injury* is one which is not found during the initial assessment (for example, as a patient is brought into a hospital's Emergency Department), but rather manifests itself at a later point in time, sometimes with baleful consequences (i.e., a liver laceration is sometimes missed and a patient sent home, who will abruptly go into shock shortly thereafter.)

The appropriate first aid for a trauma patient is to immediately call for help using the emergency medical service, then treat for shock. Do not move the victim unless failure to do so would create a greater risk to their life (i.e. hazardous chemicals or a spreading fire). Also see wilderness first aid if immediate emergency help is unavailable.

In case of traumatic accidents, health care providers use the ABC of life (airway, breathing and circulation) as their primary survey in identifying and assessing the condition of the patient. Airway is considered as the most important factor to be assessed then the breathing and circulation. From this technique the appropriate intervention will be identified

immediately and prioritization of action can be done according to the most important aspect to be assessed

## **Efficacy**

## **Time**

Generally, the earlier a trauma patient can get specialized care, the greater are the chances of survival and recovery. However, there have been exceptions from this generalization.

For example in the Falklands War the British military lost most of their helicopter support when the *Atlantic Conveyor* was sunk by an Argentine *Exocet*, resulting in no fast way to evacuate the wounded from the battlefield. Therefore any soldiers who suffered wounds lay where they fell in bitterly cold weather for hours with no blood transfusion, surgery or medication available. The opposite scenario was known from the Vietnam War in which wounded U.S. soldiers were usually quickly airlifted from the battlefield, kept warm and given aggressive medical treatment. The interesting statistic is that the casualty to fatality ratio in the Falklands War was still significantly lower than in the Vietnam War. Recently there has been some new research into how to treat physical trauma by comparing the different practices and experiences in these military conflicts. It might e.g. indicate that the environment is an important factor. For instance, in cold and barren areas, as around the Falkland Islands, the risk that wounds become infected is smaller compared with warm and humid environments, as in the rainforests of Vietnam.

## **See also**

- Blunt force trauma
- Emergency Medical Services
- Emergency medicine
- Fluid replacement
- Penetrating trauma
- Polytrauma
- Shock
- Surgery
- Trauma surgery

[http://en.wikipedia.org/wiki/Physical\\_trauma](http://en.wikipedia.org/wiki/Physical_trauma)

## **TUMOR**

A **Tumor** or **tumour** (via Old French *tumour* from Latin *tumor* "swelling") originally meant an abnormal swelling of the flesh. In contemporary English, tumor has evolved to become synonymous with **neoplasia**, all other forms being called **swelling**. This tendency has also become common in medical literature. The noun **tumefaction**, derived from the adjective **tumefied**, is the current medical term for non-neoplastic tumors .

## **Causes**

Tumors and/or swellings can be caused by:

- Neoplasia, an abnormal proliferation of tissues. Most (not all) neoplasms cause a tumor. Neoplasms (or tumors) may be benign or malignant (cancer).
- Non-neoplastic causes :
  - Inflammation, by far the most common cause; tumor is one of the classic signs of inflammation. The lump following a blow on the head is a typical example. Infection is another common cause of inflammation.
  - Edema, the accumulation of an excessive amount of fluid in the tissues, either with or without inflammation.
  - Malformation, a congenital anomaly in the architecture of a tissue. A typical example is an epidermal nevus.
  - Cyst, the accumulation of fluid in a closed structure. Breast cysts are a typical example.
  - Hemorrhage in a closed structure.

Other forms of swelling are part of the normal functions of the body and may or may not be included as causes of tumor.

<http://en.wikipedia.org/wiki/Tumor>

## **BRAIN TUMOR**

A **brain tumor** is any intracranial tumor created by abnormal and uncontrolled cell division, normally either in the brain itself (neurons, glial cells (astrocytes, oligodendrocytes, ependymal cells), lymphatic tissue, blood vessels), in the cranial nerves (myelin-producing Schwann cells), in the brain envelopes (meninges), skull, pituitary and pineal gland, or spread from cancers primarily located in other organs (metastatic tumors). Primary (true) brain tumors are commonly located in the posterior cranial fossa in children and in the anterior two-thirds of the cerebral hemispheres in adults, although they can affect any part of the brain. In the United States in the year 2005, it was estimated that there were 43,800 new cases of brain tumors (Central Brain Tumor Registry of the United States, Primary Brain Tumors in the United States, Statistical Report, 2005 - 2006), which accounted for 1.4 percent of all cancers, 2.4 percent of all cancer deaths, and 20–25 percent of pediatric cancers. Ultimately, it is estimated that there are 13,000 deaths/year as a result of brain tumors.

### **Primary tumors**

Tumors occurring in the brain include: astrocytoma, pilocytic astrocytoma, dysembryoplastic neuroepithelial tumor, oligodendrogliomas, ependymoma, glioblastoma multiforme, mixed gliomas, oligoastrocytomas, medulloblastoma, retinoblastoma, neuroblastoma, germinoma and teratoma.

Most primary brain tumors originate from glia (gliomas) such as astrocytes (astrocytomas), oligodendrocytes (oligodendrogliomas), or ependymal cells (ependymoma). There are also mixed forms, with both an astrocytic and an oligodendroglial cell component. These are called mixed gliomas or oligoastrocytomas. Plus, mixed glio-neuronal tumors (tumors displaying a neuronal, as well as a glial component, e.g. gangliogliomas, disembryoplastic

neuroepithelial tumors) and tumors originating from neuronal cells (e.g. gangliocytoma, central gangliocytoma) can also be encountered.

Other varieties of primary brain tumors include: primitive neuroectodermal tumors (PNET, e.g. medulloblastoma, medulloepithelioma, neuroblastoma, retinoblastoma, ependymblastoma), tumors of the pineal parenchyma (e.g. pineocytoma, pineoblastoma), ependymal cell tumors, choroid plexus tumors, neuroepithelial tumors of uncertain origin (e.g. gliomatosis cerebri, astroblastoma), etc.

From a histological perspective, astrocytomas, oligodendrogliomas, oligoastrocytomas, and teratomas may be benign or malignant. Glioblastoma multiforme represents the most aggressive variety of malignant glioma. At the opposite end of the spectrum, there are so-called pilocytic astrocytomas, a distinct variety of astrocytic tumors. The majority of them are located in the posterior cranial fossa, affect mainly children and young adults, and have a clinically favorable course and prognosis. Teratomas and other germ cell tumors also may have a favorable prognosis, although they have the capacity to grow very large.

Another type of primary intracranial tumor is primary cerebral lymphoma, also known as primary CNS lymphoma, which is a type of non-Hodgkin's lymphoma that is much more prevalent in those with severe immunosuppression, e.g. AIDS.

In contrast to other types of cancer, primary brain tumors rarely metastasize, and in this rare event, the tumor cells spread within the skull and spinal canal through the cerebrospinal fluid, rather than via bloodstream to other organs.

There are various classification systems currently in use for primary brain tumors, the most common being the World Health Organization (WHO) brain tumor classification, introduced in 1993.

### **Secondary tumors and non-tumor lesions**

Secondary or metastatic brain tumors originate from malignant tumors (cancers) located primarily in other organs. Their incidence is higher than that of primary brain tumors. The most frequent types of metastatic brain tumors originate in the lung, skin (malignant melanoma), kidney (hypernephroma), breast (breast carcinoma), and colon (colon carcinoma). These tumor cells reach the brain via the blood-stream.

Some non-tumoral masses and lesions can mimic tumors of the central nervous system. These include tuberculosis of the brain, cerebral abscess (commonly in toxoplasmosis), and hamartomas (for example, in tuberous sclerosis and von Recklinghausen neurofibromatosis).

Symptoms of brain tumors may depend on two factors: tumor size (volume) and tumor location. The time point of symptom onset in the course of disease correlates in many cases with the nature of the tumor ("benign", i.e. slow-growing/late symptom onset, or malignant (fast growing/early symptom onset).

Many low-grade (benign) tumors can remain asymptomatic (symptom-free) for years and they may accidentally be discovered by imaging exams for unrelated reasons (such as a minor trauma).

New onset of epilepsy is a frequent reason for seeking medical attention in brain tumor cases.

Large tumors or tumors with extensive perifocal swelling edema inevitably lead to elevated intracranial pressure (intracranial hypertension), which translates clinically into headaches, vomiting (sometimes without nausea), altered state of consciousness (somnolence, coma), dilatation of the pupil on the side of the lesion (anisocoria), papilledema (prominent optic disc at the fundoscopic examination). However, even small tumors obstructing the passage of cerebrospinal fluid (CSF) may cause early signs of increased intracranial pressure. Increased intracranial pressure may result in herniation (i.e. displacement) of certain parts of the brain, such as the cerebellar tonsils or the temporal uncus, resulting in lethal brainstem compression. In young children, elevated intracranial pressure may cause an increase in the diameter of the skull and bulging of the fontanelles.

Depending on the tumor location and the damage it may have caused to surrounding brain structures, either through compression or infiltration, any type of focal neurologic symptoms may occur, such as cognitive and behavioral impairment, personality changes, hemiparesis, (hemi) hypesthesia, aphasia, ataxia, visual field impairment, facial paralysis, double vision, tremor etc. These symptoms are not specific for brain tumors - they may be caused by a large variety of neurologic conditions (e.g. stroke, traumatic brain injury). What counts, however, is the location of the lesion and the functional systems (e.g. motor, sensory, visual, etc.) it affects.

A bilateral temporal visual field defect (bitemporal hemianopia—due to compression of the optic chiasm), often associated with endocrine dysfunction—either hypopituitarism or hyperproduction of pituitary hormones and hyperprolactinemia is suggestive of a pituitary tumor.

### **Brain tumors in infants and children**

In 2000 approximately 2.76 children per 100,000 were affected by a **CNS tumor** in the United States. This rate has been increasing and by 2005 was 3.0 children per 100,000. This is approximately 2,500-3,000 pediatric brain tumors occurring each year in the US. The tumor incidence is increasing by about 2.7% per year. The CNS Cancer survival rate in children is approximately 60%. However, this rate varies with the age of onset (younger has higher mortality) and cancer type.

In children under 2, about 70% of brain tumors are medulloblastoma, ependymoma, and low-grade glioma. Less commonly, and seen usually in infants, are teratoma and atypical teratoid rhabdoid tumor.

### **Signs and symptoms**

- **Headaches:** This was the most common symptom, with 46% of the patients reporting having headaches. They described the headaches in many different ways, with no one pattern being a sure sign of brain tumor. Many - perhaps most - people get headaches at some point in their life, so this is not a definite sign of brain tumors. You should mention it to your doctors if the headaches are: different from those you ever had before, are accompanied by nausea / vomiting, are made worse by bending over or straining when going to the bathroom.(1)
- **Seizures:** This was the second most common symptom reported, with 33% of the patients reporting a seizure before the diagnosis was made. Seizures can also be caused by other

things, like epilepsy, high fevers, stroke, trauma, and other disorders. (3) This is a symptom that should never be ignored, whatever the cause. In a person who never had a seizure before, it usually indicates something serious and you must get a brain scan.

A seizure is a sudden, involuntary change in behavior, muscle control, consciousness, and/or sensation. Symptoms of a seizure can range from sudden, violent shaking and total loss of consciousness to muscle twitching or slight shaking of a limb. Staring into space, altered vision, and difficulty in speaking are some of the other behaviors that a person may exhibit while having a seizure. Approximately 10% of the U.S. population will experience a single seizure in their lifetime. • Nausea and Vomiting: As with headaches, these are non-specific - which means that most people who have nausea and vomiting do NOT have a brain tumor. Twenty-two percent of the people in our survey reported that they had nausea and /or vomiting as a symptom.

Nausea and / or vomiting is more likely to point towards a brain tumor if it is accompanied by the other symptoms mentioned here.

- Vision or hearing problems: Twenty-five percent reported vision problems. This one is easy - if you notice any problem with your hearing or vision, it must be checked out. The eye doctor is the first one to make the diagnosis - because when they look in your eyes, they can sometimes see signs of increased intracranial pressure.
- Problems with weakness of the arms, legs or face muscles, and strange sensations in your head or hands. Twenty-five percent reported weakness of the arms and/or legs. Sixteen percent reported strange feelings in the head, and 9% reported strange feelings in the hands. This may result in an altered gait, dropping objects, falling, or an asymmetric facial expression. These could also be symptoms of a stroke. Sudden onset of these symptoms is an emergency - you should go to the emergency room. If you notice a gradual change over time, you must report it to your doctor.
- Behavioral and cognitive problems: Many reported behavioral and cognitive changes, such as: problems with recent memory, inability to concentrate or finding the right words, acting out - no patience or tolerance, and loss of inhibitions - saying or doing things that are not appropriate for the situation.

## Diagnosis

Although there is no specific clinical symptom or sign for brain tumours, slowly progressive focal neurologic signs and signs of elevated intracranial pressure, as well as epilepsy in a patient with a negative history for epilepsy should raise red flags. However, a sudden onset of symptoms, such as an epileptic seizure in a patient with no prior history of epilepsy, sudden intracranial hypertension (this may be due to bleeding within the tumour, brain swelling or obstruction of cerebrospinal fluid's passage) is also possible.

Symptoms include phantom odours and tastes. Often, in the case of metastatic tumours, the smell of vulcanized rubber is prevalent.

Imaging plays a central role in the diagnosis of brain tumours. Early imaging methods— invasive and sometimes dangerous—such as pneumoencephalography and cerebral angiography, have been abandoned in recent times in favour of non-invasive, high-resolution modalities, such as computed tomography (CT) and especially magnetic resonance imaging

(MRI). Benign brain tumours often show up as hypodense (darker than brain tissue) mass lesions on cranial CT-scans. On MRI, they appear either hypo- (darker than brain tissue) or isointense (same intensity as brain tissue) on T1-weighted scans, or hyperintense (brighter than brain tissue) on T2-weighted MRI. Perifocal edema also appears hyperintense on T2-weighted MRI. Contrast agent uptake, sometimes in characteristic patterns, can be demonstrated on either CT or MRI-scans in most malignant primary and metastatic brain tumours. This is due to the fact that these tumours disrupt the normal functioning of the blood-brain barrier and lead to an increase in its permeability.

Electrophysiological exams, such as electroencephalography (EEG) play a marginal role in the diagnosis of brain tumours.

The definitive diagnosis of brain tumour can only be confirmed by histological examination of tumour tissue samples obtained either by means of brain biopsy or open surgery. The histologic examination is essential for determining the appropriate treatment and the correct prognosis. This examination, performed by a pathologist, typically has three stages: interoperative examination of fresh tissue, preliminary microscopic examination of prepared tissues, and followup examination of prepared tissues after immunohistochemical staining or genetic analysis.

### **Treatment and prognosis**

Many meningiomas, with the exception of some tumors located at the skull base, can be successfully removed surgically. In more difficult cases, stereotactic radiosurgery, such as Gamma Knife radiosurgery, remains a viable option.

Most pituitary adenomas can be removed surgically, often using a minimally invasive approach through the nasal cavity and skull base (trans-nasal, trans-sphenoidal approach). Large pituitary adenomas require a craniotomy (opening of the skull) for their removal. Radiotherapy, including stereotactic approaches, is reserved for the inoperable cases.

Although there is no generally accepted therapeutic management for primary brain tumors, a surgical attempt at tumor removal or at least cytoreduction (that is, removal of as much tumor as possible, in order to reduce the number of tumor cells available for proliferation) is considered in most cases. However, due to the infiltrative nature of these lesions, tumor recurrence, even following an apparently complete surgical removal, is not uncommon. Postoperative radiotherapy and chemotherapy are integral parts of the therapeutic standard for malignant tumors. Radiotherapy may also be administered in cases of "low-grade" gliomas, when a significant tumor burden reduction could not be achieved surgically.

Survival rates in primary brain tumors depend on the type of tumor, age, functional status of the patient, the extent of surgical tumor removal, to mention just a few factors.

Patients with benign gliomas may survive for many years while survival in most cases of glioblastoma multiforme is limited to a few months after diagnosis.

The main treatment option for single metastatic tumors is surgical removal, followed by radiotherapy and/or chemotherapy. Multiple metastatic tumors are generally treated with radiotherapy *and* chemotherapy. Stereotactic radiosurgery, such as Gamma Knife

radiosurgery, remains a viable option. However, the prognosis in such cases is determined by the primary tumor, and it is generally poor.

A shunt operation is used not as a cure but to relieve the symptoms. The hydrocephalus caused by the blocking drainage of the cerebrospinal fluid can be removed with this operation.

Research to treatment with the VSV-virus

In 2008, Researchers of the Yale University, led by Dr. Anthony van den Pol, have discovered that the Vesicular stomatitis virus, or VSV-virus, can infect and kill brain tumors, without affecting the other brain cells. The oncolytic properties of the virus, which normally applies to cancer cells, have shown to apply to brain tumors as well.

In the research, a human brain tumor was implanted into mice brains. The VSV-virus was injected via its tail and within 3 days all tumor cells were either killed or dying. On the 10,000 infected tumor cells, only one healthy brain cell was affected 'on accident'.

Research to virus-treatment like this has been some years old, but no other viruses have shown to be as efficient or specific as the VSV-virus. Future research will focus on the risks of this treatment, before it can be applied to humans.

[http://en.wikipedia.org/wiki/Brain\\_tumor](http://en.wikipedia.org/wiki/Brain_tumor)

## USHER SYNDROME

A leading cause of deaf-blindness, **Usher syndrome** (sometimes referred to as "**Usher's syndrome**") is a relatively rare genetic disorder that is associated with a mutation in any one of 10 genes. Other names for Usher syndrome include **Hallgren syndrome**, **Usher-Hallgren syndrome**, **rp-dysacusis syndrome** and **dystrophia retinae dysacusis syndrome**. Usher syndrome is incurable at present; however, using gene therapy to replace the missing gene, researchers have succeeded in reversing one form of the disease in knockout mice.

This syndrome is characterized by deafness and a gradual vision loss. The hearing loss is associated with a defective inner ear, whereas the vision loss is associated with retinitis pigmentosa (rp), a degeneration of the retinal cells. Usually, the rod cells of the retina are affected first, leading to early night blindness and the gradual loss of peripheral vision. In other cases, there is early degeneration of the cone cells in the macula, leading to a loss of central acuity. In some cases, the foveal vision is spared, leading to "doughnut vision"; central and peripheral vision are intact, but there is an annulus around the central region in which vision is impaired.

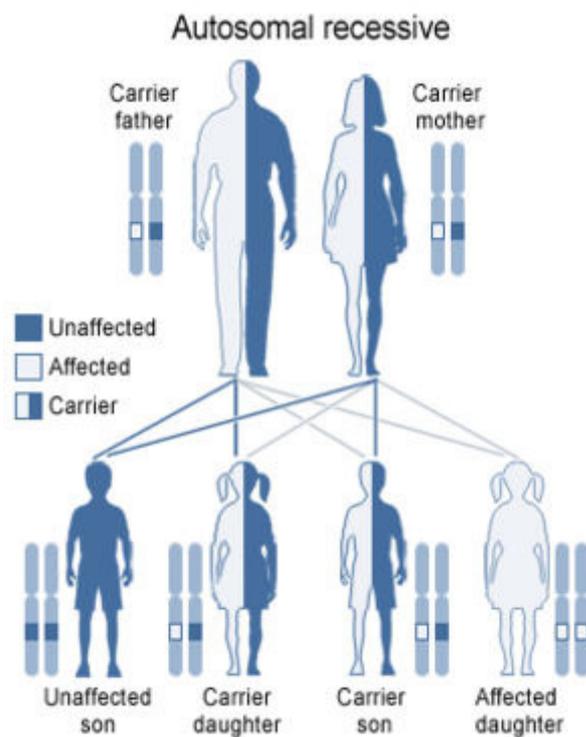
Usher syndrome has three clinical subtypes, denoted as I, II and III in decreasing order of severity. People with Usher I are born profoundly deaf, and begin to lose their vision in the first decade of life. They also exhibit balance difficulties and learn to walk slowly as children, due to problems in their vestibular system. People with Usher II are also born deaf, but do not seem to have noticeable problems with balance; they also begin to lose their vision later (in the second decade of life) and may preserve some vision even into middle age. People with

Usher syndrome III are not born deaf, but experience a gradual loss of their hearing and vision; they may or may not have balance difficulties.

Usher syndrome I and II are associated with a mutation in any one of six or three different genes, respectively, whereas only one mutation has been linked with Usher III. Since Usher syndrome is inherited in an autosomal recessive pattern, both males and females are equally likely to inherit Usher syndrome. Consanguinity of the parents is a risk factor. Since Usher syndrome mutations are recessive, if both parents have Usher syndrome in the same gene, all their children are overwhelmingly likely to have the same condition; by contrast, the children of a mixed marriage (one parent with Usher syndrome and the other with wild-type genes) are overwhelmingly likely to *not* have the condition, although they will be all carriers. First recognized in the 19th century, Usher syndrome was the first condition to demonstrate that phenotypes could be inherited in tandem; deafness and blindness are inherited together, but not separately. Animal models of this human disease (such as knockout mice and zebrafish) have been developed recently to study the effects of these gene mutations and to test potential cures for Usher syndrome.

Usher syndrome is named after the British ophthalmologist Charles Usher, who examined the pathology and transmission of this illness in 1914 on the basis of 69 cases. However, it was first described in 1858 by Albrecht von Gräfe, a pioneer of modern ophthalmology. He reported the case of a deaf patient with retinitis pigmentosa, who had two brothers with the same symptoms. Three years later, one of his students, Richard Liebreich, examined the population of Berlin for disease pattern of deafness with retinitis pigmentosa. Liebreich noted that Usher syndrome is recessive, since the cases of blind-deafness combinations occurred particularly in the siblings of blood-related marriages or in families with patients in different generations. His observations supplied the first proofs for the coupled transmission of blindness and deafness, since no isolated cases of either could be found in the family trees.

### Symptoms and subtypes



U.S. National Library of Medicine



Usher syndrome is inherited in an autosomal recessive pattern. The genes implicated in Usher syndrome are described below.

Usher syndrome is responsible for the majority of deaf-blindness. The word *syndrome* means that multiple symptoms occur together, in this case, deafness and blindness. It occurs in roughly 1 person in 23,000 in the United States, 1 in 28,000 in Norway and 1 in 12,500 in Germany. People with Usher syndrome represent roughly one-sixth of people with retinitis pigmentosa.

Usher syndrome is inherited in an autosomal recessive pattern. "Recessive" means that both parents must contribute an appropriate gene for the syndrome to appear, and "autosomal" means that the gene is *not* carried on one of the sex chromosomes (X or Y), but rather on one of the 22 other pairs. (See the article on human genetics for more details.)

The progressive blindness of Usher syndrome results from retinitis pigmentosa. The photoreceptors usually start to degenerate from the outer periphery to the center of the retina including the macula. The degeneration is usually first noticed as night blindness (nyctalopia); peripheral vision is gradually lost, restricting the visual field (tunnel vision), which generally progresses to complete blindness. The qualifier *pigmentosa* reflects the fact that clumps of pigment may be visible by an ophthalmoscope in advanced stages of degeneration.

Although Usher syndrome has been classified clinically in several ways, the prevailing approach is to classify it into three clinical sub-types called Usher I, II and III in order of decreasing severity of deafness. Usher I and II are the more common forms; the fraction of people with Usher III is significant only in a few specific areas, such as Finland and Birmingham. As described below, these clinical subtypes may be further subdivided by the particular gene mutated; people with Usher I and II may have any one of six and three genes mutated, respectively, whereas only one gene has been associated with Usher III. The function of these genes is poorly understood as of yet. The hearing impairment associated with Usher syndrome is better understood: damaged hair cells in the cochlea of the inner ear inhibit electrical impulses from reaching the brain.

### **Usher syndrome I**

People with Usher I are usually born deaf and often have difficulties in maintaining their balance owing to problems in the vestibular system. Babies with Usher I are usually slow to develop motor skills such as walking. Worldwide, the estimated prevalence of Usher syndrome type I is 3 to 6 per 100,000 people in the general population.

Usher syndrome type I can be caused by mutations in any one of several different genes: CDH23, MYO7A, PCDH15, USH1C, and USH1G. These genes function in the development and maintenance of inner ear structures such as hair cells (stereocilia), which transmit sound and motion signals to the brain. Alterations in these genes can cause an inability to maintain balance (vestibular dysfunction) and hearing loss. The genes also play a role in the development and stability of the retina by influencing the structure and function of both the rod photoreceptor cells and supporting cells called the retinal pigmented epithelium. Mutations that affect the normal function of these genes can result in retinitis pigmentosa and vision loss.

## **Usher syndrome II**

People with Usher II are generally hard-of-hearing rather than deaf, and their hearing does not degrade over time; moreover, they generally have a normal vestibular system. Usher syndrome type II occurs at least as frequently as type I, but because type II may be underdiagnosed or more difficult to detect, it could be up to three times as common as type I.

Usher syndrome type II may be caused by mutations in any of three different genes: USH2A, GPR98 and DFNB31. The protein encoded by the USH2A gene, usherin, is located in the supportive tissue in the inner ear and retina. Usherin is critical for the proper development and maintenance of these structures, which may help explain its role in hearing and vision loss. The location and function of the other two proteins are not yet known.

## **Usher syndrome III**

By contrast, people with Usher III experience a *progressive* loss of hearing and roughly half have vestibular dysfunction. The frequency of Usher syndrome type III is highest in the Finnish population, but it has been noted rarely in a few other ethnic groups.

Mutations in only one gene, the CLRN1 gene, have been linked to Usher syndrome type III. The CLRN1 gene encodes Clarin-1, a protein that is important for the development and maintenance of the inner ear and retina. However, the protein's function in these structures, and how its mutation causes hearing and vision loss, is poorly understood as yet.

## **Differential diagnosis**

Since Usher syndrome is incurable at present, it is helpful to diagnose children well before they develop the characteristic night blindness. Some preliminary studies have suggested that as many as 10% of congenitally deaf children may have Usher syndrome. However, a misdiagnosis can have bad consequences, e.g., if the parents elect to give the child cochlear implants.

The simplest approach to diagnosing Usher syndrome is to test for the characteristic chromosomal mutations. An alternative approach is electroretinography (ERG), although this is often disfavored for children, since its discomfort can also make the results unreliable. Parental consanguinity is a significant factor in diagnosis. Usher syndrome I may be indicated if the child is profoundly deaf from birth and especially slow in walking.

Thirteen other syndromes may exhibit signs similar to Usher syndrome, including Alport syndrome, Alstrom syndrome, Bardet-Biedl syndrome, Cockayne syndrome, spondyloepiphyseal dysplasia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hurler syndrome (MPS-1), Kearns-Sayre syndrome (CPEO), Norrie syndrome, osteopetrosis (Albers-Schonberg disease), Refsum's disease (phytanic acid storage disease), and Zellweger syndrome (cerebro-hepato-renal syndrome).

## **Genes associated with Usher syndrome**

Several genes have been associated with Usher syndrome using linkage analysis of patient families and DNA sequencing of the identified loci. A mutation in any one of these genes is likely to result in Usher syndrome. The clinical subtypes Usher I and II are associated with

mutations in any one of six (USH1B-G) and three (USH2A,C-D) genes, respectively, whereas only one gene, USH3A, has been linked to Usher III so far. Two other genes, USH1A and USH2B, were initially associated with Usher syndrome, but USH2B has not been verified and USH1A was incorrectly determined and does not exist. Research in this area is ongoing.

Using interaction analysis techniques it could be shown that the identified gene products interact with one another in one or more larger protein complexes. If one of the components is missing, this protein complex cannot fulfill its function in the living cell and it probably comes to the degeneration the same. The function of this protein complex has been suggested to participate in the signal transduction or in the cell adhesion of sensory cells.

### **Prospects for gene therapy**

Since Usher syndrome results from the loss of a gene, gene therapy that adds the proper protein back ("gene replacement") may alleviate it, provided that the added protein becomes functional. Recent studies of mouse models have shown that one form of the disease — that associated with a mutation in myosin VIIa — can be alleviated by replacing the mutant gene using a lentivirus. However, some of the mutated genes associated with Usher syndrome encode very large proteins — most notably, the USH2A and GPR98 proteins, which have roughly 6000 amino-acid residues. Gene replacement therapy for such large proteins may be difficult.

[http://en.wikipedia.org/wiki/Usher\\_syndrome](http://en.wikipedia.org/wiki/Usher_syndrome)

## **VITELLIFORM MACULAR DYSTROPHY OR VITELLIFORM DYSTROPHY**

**Vitelliform macular dystrophy** or **vitelliform dystrophy** is a genetic eye disorder that can cause progressive vision loss. This disorder affects the retina, specifically cells in a small area near the center of the retina called the macula. The macula is responsible for sharp central vision, which is needed for detailed tasks such as reading, driving, and recognizing faces.

Vitelliform macular dystrophy causes a fatty yellow pigment (lipofuscin) to build up in cells underlying the macula. Over time, the abnormal accumulation of this substance can damage cells that are critical for clear central vision. As a result, people with this disorder often lose their central vision and may experience blurry or distorted vision. Vitelliform macular dystrophy does not affect side (peripheral) vision or the ability to see at night.

Researchers have described two forms of vitelliform macular dystrophy with similar features. The early-onset form (known as **Best disease**) usually appears in childhood; however, the onset of symptoms and the severity of vision loss vary widely. The adult-onset form begins later, usually in middle age, and tends to cause relatively mild vision loss. The two forms of vitelliform macular dystrophy each have characteristic changes in the macula that can be detected during an eye examination.

### **Pathophysiology**

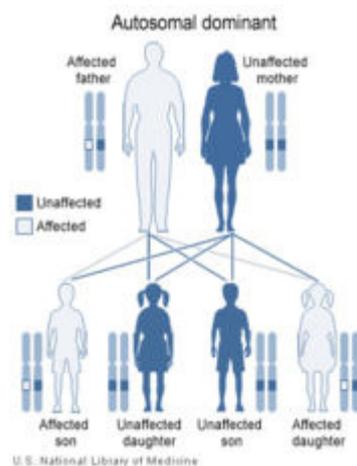
Mutations in the *RDS* and *VMD2* genes cause vitelliform macular dystrophy. Mutations in the *VMD2* gene are responsible for Best disease. Changes in either the *VMD2* or *RDS* gene can

cause the adult-onset form of vitelliform macular dystrophy; however, less than a quarter of cases result from mutations in these two genes. In most cases, the cause of the adult-onset form is unknown.

The *VMD2* gene provides instructions for making a protein called bestrophin. Although its exact function is uncertain, this protein likely acts as a channel that controls the movement of negatively charged chlorine atoms (chloride ions) into or out of cells in the retina. Mutations in the *VMD2* gene probably lead to the production of an abnormally shaped channel that cannot regulate the flow of chloride. Researchers have not determined how these malfunctioning channels are related to the buildup of lipofuscin in the macula and progressive vision loss.

The *RDS* gene provides instructions for making a protein called peripherin. This protein is essential for the normal function of light-sensing (photoreceptor) cells in the retina. Mutations in the *RDS* gene disrupt the structures in these cells that contain light-sensing pigments, leading to vision loss. It is unclear why *RDS* mutations affect only central vision in people with adult-onset vitelliform macular dystrophy.

### Inheritance



Best disease, the early-onset form of vitelliform macular dystrophy, has an autosomal dominant pattern of inheritance.

*Best disease* is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person has one parent with the condition.

The inheritance pattern of adult-onset vitelliform macular dystrophy is uncertain. Some studies have suggested that it may be inherited in an autosomal dominant pattern. Many affected people, however, have no history of the disorder in their family and only a small number of affected families have been reported.

[http://en.wikipedia.org/wiki/Vitelliform\\_macular\\_dystrophy](http://en.wikipedia.org/wiki/Vitelliform_macular_dystrophy)

