Ten years of progress in ophthalmology

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Refer this article as: Sahel, J., Ten years of progress in ophthalmology, Points de Vue, International Review of Ophthalmic Optics, N65, Autumn 2011
Publication date : 10/2011

After decades of progress in glaucoma surgery and topical therapies, concomitant progress made in high output sequencing in genetics, modern imaging and the coming of age of molecular medicine have now enabled much progress to be made in ophthalmology over several years, with still more yet to come.

Today, giant leaps are being made in ocular surface imaging, a technique that is now capable of achieving the level of cellular resolution of the retina and the optic nerve. Optical Coherence Tomography (OCT) is used to visualise all the cells in the retina. With adaptive optics (2005), a complementary technique, each individual photoreceptor is distinguished. Numerous therapeutic paths have been successfully explored, such as micro nutrition in AMD prevention (2001), anti-VEGF (2006) for the treatment of AMD. And yet, at the same time, blindness due to degenerative diseases of the retina is increasing in developed countries due to the ageing of the population. Over 50 million people in Europe and the USA and over 7000 million worldwide are affected by low vision. These figures are also on the increase due to lifestyles: diabetes and high blood pressure, and they are set to double by 2020. Gene therapy, cellular therapy, nanotechnologies, synthetic biology, pluridisciplinary approaches (biology, physics, mathematical tools) are all new tools and new approaches which, in the long term, should enable us to meet the challenge of the ageing population and its health implications.

Age-related macular degeneration (AMD)

In developed countries, age-related macular degeneration (AMD) affects 10% of the population over the age of 50 and 25% of people over the age of 80. AMD affects almost 1.3 million people in France, where it has become the top cause of blindness and visual deficiency after the age of 50. As its name indicates, AMD affects the central area of the retina (macular). There are three stages in the pathology, "age-related maculopathy" (small retinal deposits, often asymptomatic, are observed on examination of the fundus), the "dry" or atrophic form which is observed due to gradual disappearance of the cells in the macular (developing more slowly) and the so-called "wet" neovascular or exudative form, which develops very quickly and corresponds to a proliferation of abnormal vessels (neovessels) under the influence of various growth factors including VEGF (Vascular Endothelial Growth Factor). Ten years ago treatments of neovessels in AMD were based on photo-coagulation by laser, which slowed the development of lesions but was still extremely damaging for the retina. In 2000, dynamic phototherapy (PDT) arrived in the therapeutic arsenal,
but it is only useful in certain clinical forms and has only a limited and palliative effect. A recent major advance is treatment of the neovascular form of AMD using anti-VEGF drugs injected into the eye once a month. Available since 2006, anti-VEGF drugs result in improved vision in 40% of cases and stabilisation in 90% of cases, by means of repeated intra-vitreal injections. Today research is being directed to ways in which to reduce the frequency of re-injection by attempting to extend the length of treatment efficiency. One of the innovative ways is the use of a VEGF Trap, for which the phase III results are looking promising. Current very promising research work is targeting other cells involved in the macular degeneration process. It is based around molecules whose action combines with that of the anti-VEGF drugs: these are anti-PDGF, which inhibit the cells that regulate the blood flow from the vessels they surround, anti-integrins, monoclonal antibodies which attempt to restrict the fixing of certain cells that are responsible for the neovascularisation phenomenon and anti-complements which appear to be showing remarkable results in association with anti-VEGF treatments. On the other hand, there is still no treatment for atrophic AMD, which is characterised by a reduction in choroidal vascularisation and atrophy of photoreceptors, preceded by the accumulation of deposits. This form is currently the object of intense research. We are seeing the emergence of several strategies: preventing oxidative damage, removing inflammation, and preserving photoreceptors (neuro-protection). A diet rich in omega 3 or docosahexaenoic acid (DHA) ("fatty" fish), lutein (contained in spinach, broccoli and cabbage) and antioxidants (vitamins C and E and zinc) would reduce the risk of developing the disease. Over the past few years, several genetic mutations predisposing to AMD have been identified. In the future these discoveries could be used for the development of new therapies.

Diabetic retinopathy (DR)

Diabetes is recognised as being the leading cause of acquired blindness in western countries, in adults between the ages of 25 and 74. Treated diabetes concerns around 4% of the French population, i.e. over 2.5 million people. The prevalence of diabetic retinopathy (DR) increases with the length of time a patient has suffered from diabetes and with the level of chronic hyperglycemia. Without the relevant treatment, DR can lead to partial or total loss of vision, whence the importance of regular screening, where considerable progress has been made and which can now be carried out using colour photography of the retina, using "non-mydriatic retinography", retinal angiography with fluorescein and an examination of the macular by OCT. The best treatment for DR is certainly good balancing of the diabetes and of blood pressure. Combined with common treatments such as laser operations and intra-vitreal injection of corticoids, this balance is the key to the combat against DR. Surgical treatment of DR, vitrectomy, has witnessed considerable progress thanks to better knowledge of the physiopathology and development of the disease. Surgical indications and instrumentation and techniques have also developed extremely rapidly. Antiangiogenic drugs, resulting from research undertaken to halt AMD, are a new therapeutic class in the treatment of DR. Amongst the drugs that are now arriving for the primary and secondary prevention of DR (active ingredients taken orally and capable of reducing the incidence and slowing the progress of DR), there are a specific inhibitor of the beta protein isoform kinase C (ruboxistaurin), inhibitors of the bradykinin pathway and an AT1 angiotensin II receptor antagonist (candesartan).

Glaucoma

Glaucoma is one of the major causes of blindness in the world: there are currently over 60 million people suffering from glaucoma and over 7 million of them are blind. These are figures that are set to increase still further over the coming years due to the increase in life expectancy. In France over a million people are concerned by the disease, of whom 800,000 have been diagnosed and are being
treated, but about 400,000 remain undetected. Glaucoma is a serious eye disease, characterised by damage to the optic nerve. Treatment aims to reduce ocular pressure by all means possible. There are 3 main types of treatment used to reduce intra-ocular pressure: drugs, laser and surgery. Anti-glaucoma drugs (eye drops) reduce pressure in the eye either by reducing the production of aqueous humour (betablockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors), or by increasing its elimination (cholinergic drugs). Considerable progress has been made over these past fifteen years with the appearance of a new therapeutic class, prostaglandins, which in just a few years has become the top therapeutic class being prescribed. The years 2000 have seen a trend towards an improvement in the drugs present on the market, with prolonged release forms and fixed associations. The latter are of major interest and studies have confirmed the superiority of an association of two molecules, compared to each of the products used separately (e.g. beta-blockers plus prostaglandins). The years 2005-2010 saw the era of local tolerance. A major role played by preservatives, revealing the long term local effects of eye drops (allergy, chronic irritation, toxic reactions, destruction of the lachrymal film) has been described by Christophe Baudouin's team. Preservative-free eye drops have now gradually appeared on the market, with the aim of optimising local tolerance of a treatment used over a prolonged period of time. One of the greatest advances made over these past few years concerns the diagnosis of glaucoma which can now take place earlier and earlier. Technological progress made in imaging of the optic nerve and the layer of nerve fibres in the retina can be used to diagnose glaucoma right from the very early stages and foresee improved success for the treatment. The therapeutic arsenal has also developed with surgery that is both more precise and less invasive.

Cataract

Cataract is a disease linked to aging, which affects more than one in five people over the age of 65 and almost one in two after the age of 75. Although curable, cataract is still the leading cause of blindness in the world. Every year, 600,000 cataract operations take place in France, to replace the damaged crystalline with a flexible artificial lens. These implants are becoming increasingly sophisticated, well tolerated and in certain cases, even capable of correcting myopia.

Diseases of the cornea

There are hundreds of diseases of the cornea, and numerous treatments exist, from eye drops through to corneal transplant. In France every year over 4,000 people undergo a corneal transplant, which is efficient at 5 years in over 80% of cases. Cellular therapy also constitutes real hope for these diseases. When the cells in the cornea can no longer renew themselves correctly, therapy enables input of new cells from the other eye, or from a related donor. Transplanting stem cells from the same patient (taken from the patient's mouth) is yet another innovative therapy.

Genetic diseases of the retina

Age is not the only cause of retinal deterioration. Several genetic diseases affect children or young adults. Pigmentary retinopathies (PR) affect between 1/3000 and 1/5000 people in the general population, i.e. 20,000 people in France. Almost 70 genes are involved in PR, whence the difficulty of creating therapies against the cause of the disease. The artificial retina is one area of research which is giving encouraging results. Transplant of stem cells from which healthy retinal cells develop is also currently being explored. For Stargardt's disease, the onset of which happens most
often between the ages of 7 and 12, and which causes irreversible vision loss, similar research to that for RP is being carried out, particularly gene therapy. Important progress has already been made in the diagnosis and treatment of monogenic diseases, such as Leber's congenital amaurosis. Several clinical trials are on-going to treat this devastating disease using gene therapy. Other progress made with research concerns the development of protective factors, to slow or halt the degeneration of photoreceptors, particularly cones. This treatment could be applied not only to all forms of PR but also to AMD.

**Conclusion**

Vision is essential for our relations with the world, for life integrated into our surroundings. It is therefore crucial to preserve or restore good quality, functional and lasting vision as essential for our health and our well-being as well as being a major challenge for our society. Curative treatments, based on genetics, neuroprotection and tissue repair are laying the foundations for future innovations and developments in molecular medicine will enable us to take up this challenge, whereas rehabilitation, based on capacities that can be preserved, will enable patients to live better lives on a daily basis, thanks to the therapeutic progress made.