Journal of the Uveitis Information Group | 2 £

uveitis

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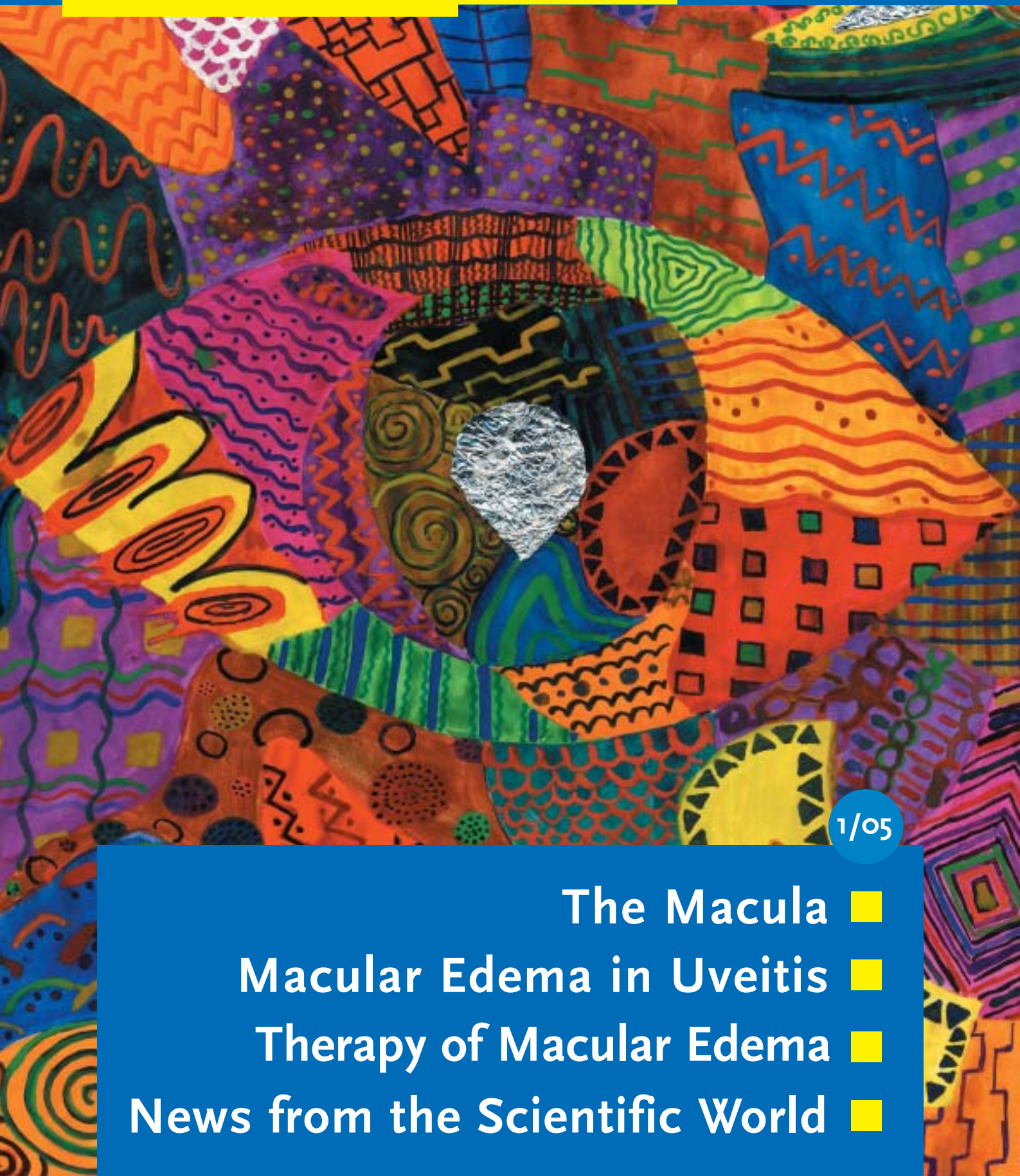
INFLAM'OEIL



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Cover Picture - Katharina Semmler, Germany

Editorial

In the year 1998, the German Uveitis Patient Interest Group **DUAG** published the first issue of a journal called "***uveitis***", two years after the inauguration of this group in 1996. Such a journal was created to improve the contact to patients, but also to ophthalmologists (who in Germany are 10% of the members!).

After a first meeting of different countries uveitis patient groups in Mestre, Italy, September 2004, the idea was seeded to use the experience the **DUAG** has achieved in creating such a journal and to bring out such an issue in English and French, in addition to the German one: same articles, different languages. As the major topic of such an edition we have chosen probably the most important complication for uveitis patients, the macular edema.

Now, after 5 months of preparation and hard work, we hope that this edition fulfils your expectations: to learn about the uniqueness of macular structure, the importance of macular edema, and finally to explain strategies we ophthalmologists have to fight against this complication. Patient reports show how individually macular edema is influencing life and how, by different means, it can be cured.

Since 2003 the **DUAG** has given awards for the best published scientific reports about uveitis. In this edition the 6 award winning papers will be presented. So I wish this "new" journal in three languages the same success as we have with the German edition alone. There are still many topics from the field of uveitis which need more explanation in different languages for the future.

Manfred Zierhut,
Professor of Ophthalmology, University Eye Clinic of Tübingen, Germany, April 2005

Editorial

In the new millennium, uveitis remains a potentially sight-threatening disease and requires sophisticated diagnostic and major therapeutic strategies in severe cases. Created by a few patients and parents of children with uveitis, the French association of patients with intraocular inflammation, **Inflam'oeil**, was born in April 2002 and the first issue of its journal, **Tyndall**, was published the same year. This group has the same goals as other European Associations, including education and support of patients with intraocular inflammation.

It is a great pleasure and a privilege to assist the birth of the European Patient Interest Association along with different pioneer countries, hopefully joined as soon as possible by other contact groups. There is no doubt that patients with uveitis need more medical and social information and the idea of a European journal is a major step to achieve these needs. **EUPIA** will not replace national Associations, but will be more powerful to encourage research, new diagnostic and therapeutic developments in the field of uveitis. Our collaboration and union will allow us to discuss with health authorities and pharmaceutical laboratories in order to improve the management of our patients.

Bahram Bodaghi,
Professor of Ophthalmology, University of Paris VI,
Pitié-Salpêtrière Hospital, April 2005

Editorial

The Dutch uveitis contact group is a young society which emerged in 2002 out of the need of patients to find trustworthy information about uveitis. The mission of the group is to educate and support those affected by uveitis.

Because uveitis is such a complex disease and consists of many distinct entities, research into the cause and treatment is very expensive. The chronicity of the disease, its frequent exacerbations, confusion about the availability, efficacy and side-effects of diverse medical treatments, stressful worries about the possible visual loss, all this makes the patients with uveitis exceptionally sensitive to a reduction in the quality of available medical services. The project of the joint European Patient Interest Association might therefore play an important role in the development and availability of treatments and stimulation of research in the field of uveitis. Already now many of the leading uveitis researchers and clinicians volunteered their time to develop educational materials for the Journal and Internet web site. I believe that the European collaboration will have also more impact on the development and availability of new treatments for patients with uveitis.

Aniki Rothova,
Professor of Ophthalmology, FC Donders Institut for Ophthalmology,
University of Utrecht, The Netherlands,
Medical Advisor of the Dutch Uveitis Contact Group, Utrecht,
April 2005

Editorial

It is exciting to see the development of a European Uveitis Patient Support Group which has naturally arisen from the success of each countries individual Patient Groups. The commonality of need and support between countries has brought us all together in the aim to widen support and enhance the profile of uveitis.
I wish the group well in their endeavours and it is a great pleasure to help endorse the first publication of hopefully many alongside future expansion of the group. Empowering patients support is essential for education of and support to patients, and educating Doctors on the needs of our patients.

Well done and I wish you every success for the future

Andrew Dick,
Professor of Ophthalmology, University Eye Clinic of Bristol,
UK, April 2005

Editorial

In recent years, it has become clear that the patient support groups play an important role in preventing blindness that is so often seen in long-standing uveitis. The support groups have been instrumental in disseminating information about patient care, current treatment modalities and supporting research.

I had the pleasure of participating in the international uveitis patient support group meeting held in Venice, Italy and meeting the representatives of various national organizations. It is impressive that the support groups publish periodicals in various languages emphasizing recent developments in uveitis treatment. There is no doubt that the support group publications will bring together various national organizations, clinicians and researchers in enhancing the patient care and in prevention of uveitis related blindness all over the world. The International Uveitis Study Group (**IUSG**) clinicians support the efforts of the groups and several members of **IUSG** look forward to actively participate in accomplishing the goals of the support groups.

Narsing A. Rao,
Professor of Ophthalmology, President of the International Uveitis Study Group, Los Angeles, April 2005

The Macula

The macula is one of the most important structures of the eye. Unfortunately very often this central small structure is involved in chronic uveitis. In this article, **Bahram Bodaghi**, *Professor of Ophthalmology at the University of Paris VI, Pitié-Salpêtrière Hospital, describes the anatomy of the macula and its layers, finally also, why it is so important.*

The macula is the central part of a layer of the eye called the retina

The retina, undeniably one of the most important components of the human eye, is the paper-thin tissue that lines the back of the eye (*Figure 1*) and contains the light-sensing cells, the **photoreceptors** (rods and cones) that convert light images into nerve impulses and transmit them through the **optic nerve** to the brain, where the image is interpreted and sight is achieved. It comprises two different structures: the **neurosensory retina** with its 9 layers and the retinal **pigment epithelium**, which is outside the neurosensory retina and next to the choroidal layer.

What are "Macula" and "Fovea"?

The word "**macula**" translates from the Latin as "spot". The **macula lutea**, also called the yellow spot, is a small and highly sensitive part of the retina responsible for detailed central vision. Its diameter is approximately 5.5 mm and it is situated nearly 4 mm temporally and 1 mm inferiorly from the centre of the optic disc (*Figure 2*). The macular area can be further subdivided into several zones. At its centre is a highly specialized area, the **fovea**, which allows high quality vision. It measures approximately 1.5 mm or one disc diameter in size. The central floor of the fovea is called the **foveola**. The fovea is a depression in the retinal surface (*Figure 3*).

Figures 1 - 3 see page 10 and 11.

The different layers of the macula

Anatomically the fovea is that portion of the macula that contains only a few layers of the retina (Figure 4 side 14): the internal limiting membrane, the outer plexiform layer and the outer nuclear layer (including the so called ganglion cells, bipolar cells and horizontal cells), the cones as the only photoreceptor type, and the retinal pigment epithelium. The rest of the retina is used for peripheral vision and generates the full extent of the visual field. Two types of

Title

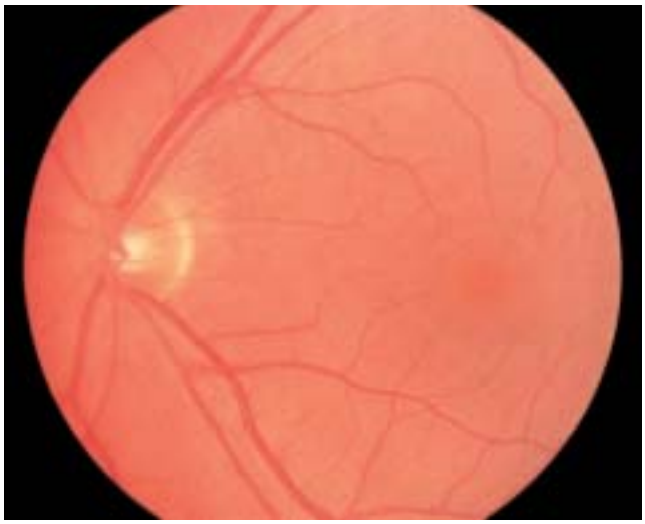


Figure 1 left:
This picture shows the posterior segment of a healthy left eye, as it appears in the ophthalmoscope of an ophthalmologist. The comparison with figure 2 demonstrates on the left side the optic nerve with arterial and venous vessels, at the middle of the right side, where the macula is situated, a reduction of vessels.

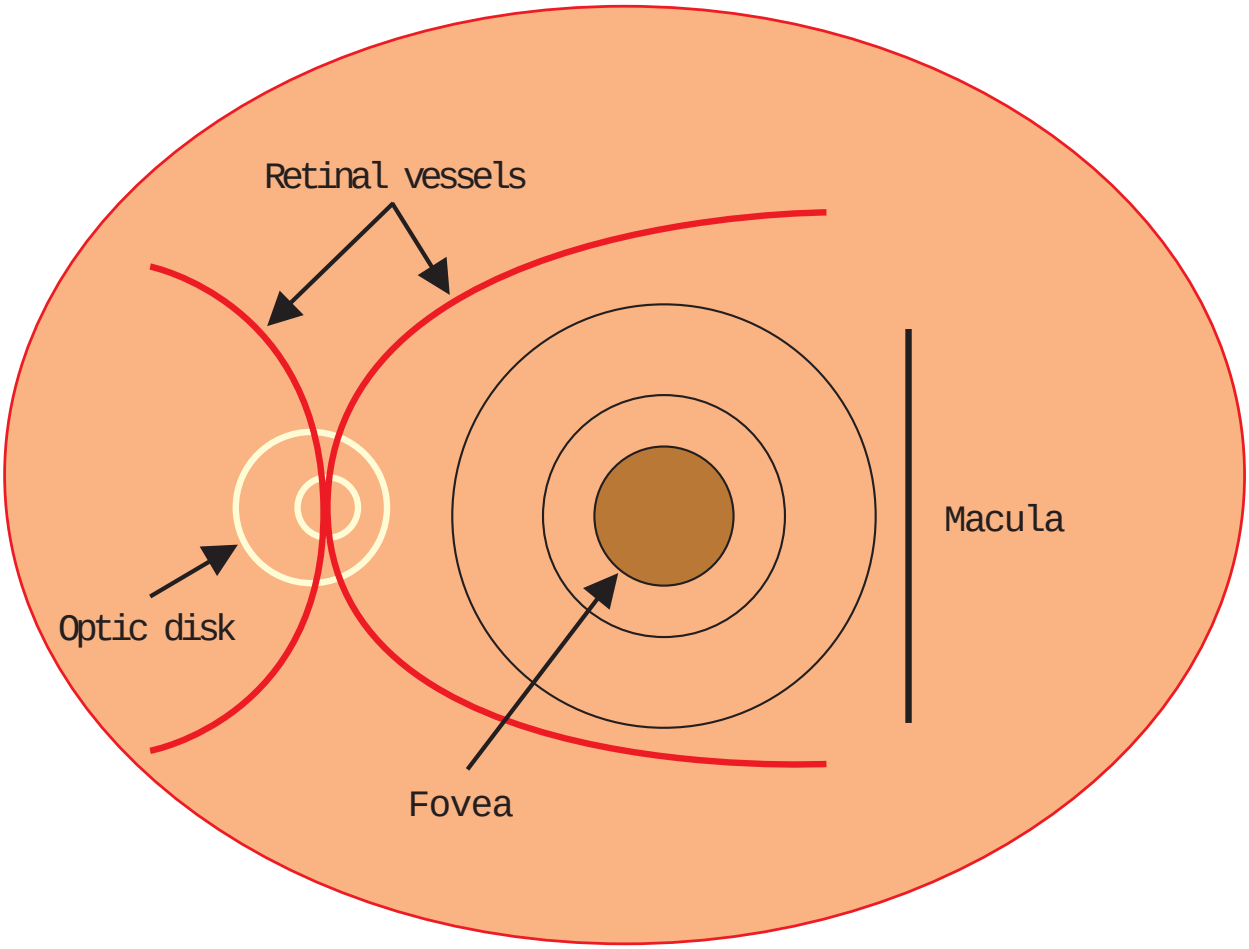


Figure 2:
Schematic presentation of the posterior pole of the eye.

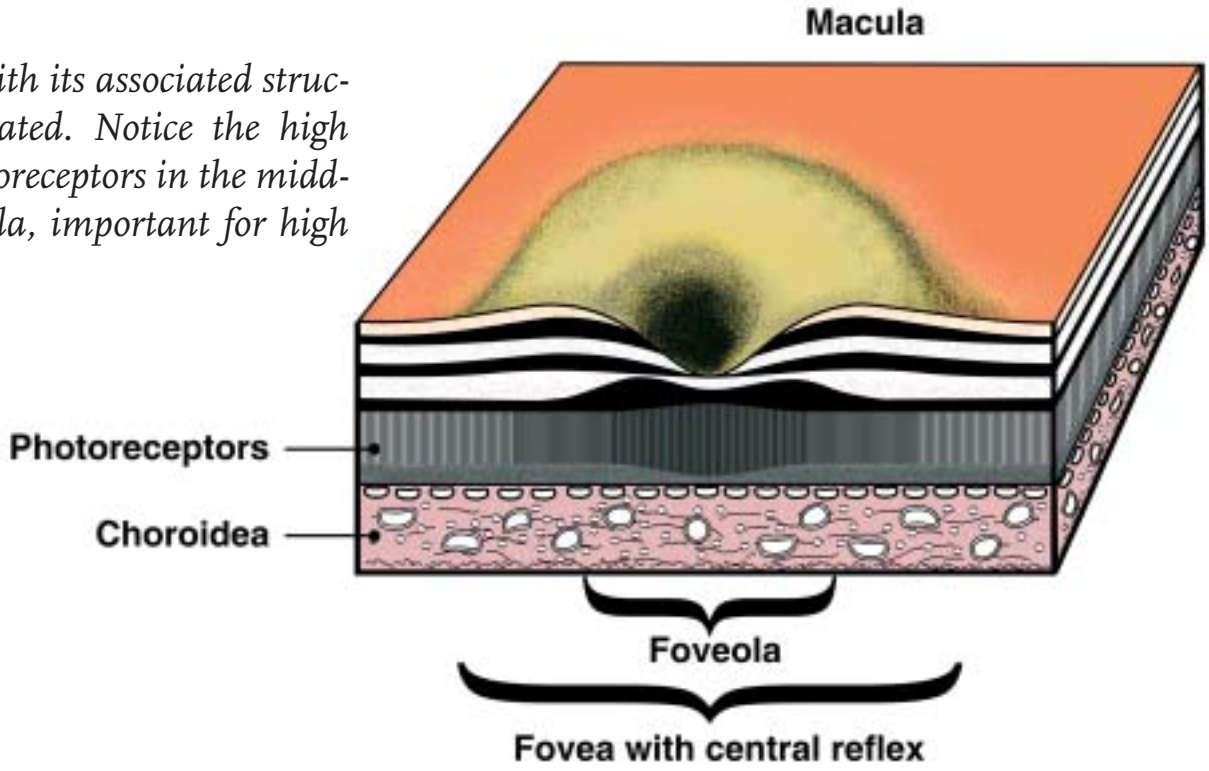


Figure 3 right:
The Macula with its associated structures is illustrated. Notice the high density of photoreceptors in the middle of the macula, important for high visual acuity.

photoreceptors have been described: cones are concentrated at the macula and are responsible for acuity and colour appreciation. Rods are for vision in low light (or "night vision") and detection of movements. They are distributed throughout the rest of the retina. There are no rods in the fovea. There are about 110,000 to 115,000 cone cells in the fovea and only about 25,000 cones in the tiny foveola. The retinal pigment epithelium is a single layer of pigmented cells which are essential to photoreceptor physiology. These cells recycle vitamin A for the formation of photo pigments, transport water and metabolites, renew photoreceptors and help to reduce damage by scattered light. The **pigment epithelial cells** in the macula are more columnar and have a greater concentration of melanin and lipofuscin granules than in the remainder of the retina. Xanthophyll is present in the fovea, located probably in the outer plexiform layer. These properties are what make the macula appear dark when the back of the eye is examined. The absence of retinal vessels around the fovea is another cause of the dark appearance of the macula. The **blood supply of the retina** is derived from the central retinal artery and vein, but also from the choroidal network. Both systems are required for normal function. However, the macular blood supply depends totally on the choroidal system. Interestingly, the **blood-retinal barrier**, consisting of **tight junctions** between the endothelial cells of retinal vessels and between retinal pigment epithelial cells isolates the

retinal and the macular environment from the systemic circulation. Disruption of the barriers may happen during different abnormal conditions, such as uveitis.

How do we see with the macula?

The process leading to the perception of an image by the brain, "**sight**", is complex. The macula allows us to appreciate detail and perform tasks that require **central vision** such as reading and recognizing faces. Visual acuity is a measure of the ability of the eye to see that two closely positioned objects are separate. The angle between these two objects is measured as 1 minute of arc. Letters on the Snellen chart are based on multiples of these angles. When we look directly at something far or near, the light from that object forms an image on our macula. A healthy macula ordinarily is capable of achieving 20/20 (or 6/6 in metric) ("normal") vision or visual acuity. However, an eye's best visual acuity may be less, for example 20/40 (6/12). That eye can perceive the same detail at 20 feet that a 20/20 eye can perceive from 40 away. In contrast,

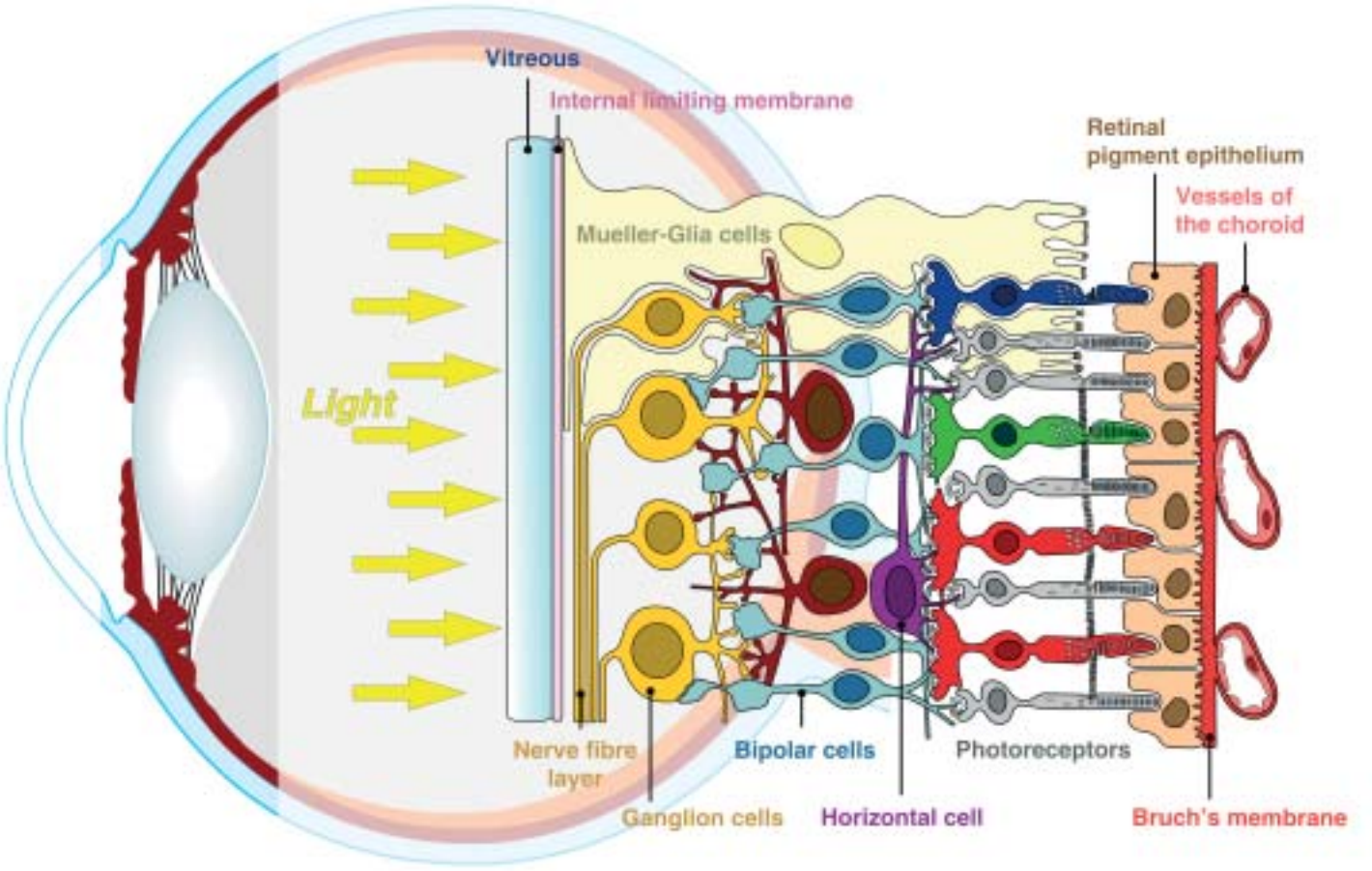


Figure 4: The retina consists of various layers, more details in the text.

some people are capable of 20/10 vision, which is twice as good as 20/20. Vision this acute may be due to the presence of more cones per square millimetre of the macula than in the average eye, enabling that eye to distinguish much greater detail.

We see colours only in the macula!

Furthermore, the foveal area is the main portion of the retina used for colour discrimination. To see any colour, cone cells first must be stimulated by light. "Red-sensitive" cones are most stimulated by light in the red to yellow range, "green-sensitive" cones are maximally stimulated by light in the yellow to green range, and "blue-sensitive" cones are maximally stimulated by light in the blue to violet range. Accordingly, due to their respective sensitivities to long (L), medium (M), and short (S) wavelengths, they also are referred to as "L" cones, "M" cones, and "S" cones. Our eyes are sensitive to light which lies in a very small region of the electromagnetic spectrum called "visible light", corresponding to a wavelength range of 400 - 700 nanometres (nm) and a colour range of violet through to red. The visible colours from shortest to longest wavelength are: violet, blue, green, yellow, orange, and red. The white light is a mixture of the colours of the visible spectrum. Black is a total absence of light. Collectively, the photoreceptors in the human eye are most sensitive to wavelengths between 530 and 555 nanometres, which is bright green tending toward yellow.

Fundus examination allows ophthalmologists to analyse the macula. Furthermore, macular function may be tested by using different techniques. The **Amsler test** is probably one of the easiest and convenient ways for this purpose. The Amsler grid (see page 15) is a 10 cm x 10 cm line grid comprising 0.5 cm squares. The subject holds the chart at a comfortable reading distance with one eye covered, and fixes on the dot at the centre of the grid. The grid area corresponds roughly with that of the macula. Any significant macular disease will usually be apparent as a distortion or as a missing area (scotoma). Other specialized tests such as **fluorescein angiography**, **optical coherence tomography** and **electrophysiology** may be used to analyse the macula.

Macular degeneration is the most common reason for blind registration in the Western world. It is associated with increasing age and is typically bilateral. It results in loss of central vision only. Thus peripheral vision, important for navigation (that is finding our way around streets and the house etc), is retained. Macula may be involved in other ocular conditions such as uveitis but also in diabetes.

Title

Macular edema in uveitis

Especially chronic long lasting uveitis can result in macular edema. In this article, **Prof. Dr. Aniki Rothova**, *from the Uveitis Center, FC Donders Institute of Ophthalmology, at the University Medical Center Utrecht, the Netherlands describes what a macular edema is, what the symptoms are, and how we can diagnose this complication.*

What is cystoid macular edema?

Cystoid macular edema is a swelling of a small area of the retina (called the macula) which is responsible for central vision. The disorder is characterized by an accumulation of fluid (edema) in many cyst-like (cystoid) areas, hence its name, cystoid macular edema, or in short CME.

The development of edema accompanies all sorts of inflammations in the human body. Edema is caused by the fluid, which leaks through the inflamed vessels. However, there is a big difference between edema in the eye and other parts of the body (e.g. skin). Slight edema of the skin might be completely unnoticed by the patient. However if a small volume of fluid is situated in the macula, it decreases central visual acuity, at first temporarily. If it persists for a longer period of time, it might affect vision permanently. CME presents most commonly late in the course of uveitis and is an important complication of uveitis because it usually determines the visual function of the patients with chronic disease. It is treatable during its initial stage and rarely causes a permanent loss of vision, but the recovery is often a slow, gradual process. However, if CME persists and remains untreated, the cystoid spaces might join together and form a large cyst which interferes with vision. This cyst may burst causing a hole in the retina to appear. The cells of the central retina may be destroyed by the long term fluid build-up and a central retinal scar develops. At this late stage, the treatment for CME is not effective anymore.

The symptoms of macular edema.

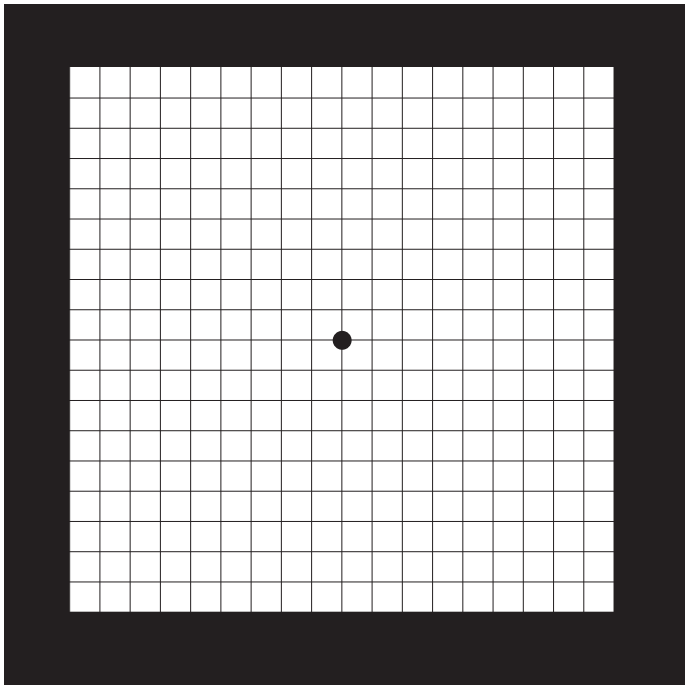
CME is a painless complication of uveitis. The eye looks normal but patients experience reduced vision in the form of blurring, darkening or distorted (crooked, wavy) images. Often the amount of retinal edema and symptoms will be unequal between the two eyes.

The Amsler chart (*Figure 1a*, see page 15) is an useful tool for monitoring the central visual field and distortion of

vision caused by CME (*Figure 1b*) (see page 16). It is a simple way to detect early and sometimes subtle visual changes in the macula. With the Amsler grid, each eye is tested separately which helps to recognize visual symptoms which are in one eye only.
Blurring occurs usually in the center of the visual field and (part of the) object might disappear when the eye tries to focus or fix on it. It can also appear like one is looking through cellophane paper. Visual loss may progress slowly over a period of months and this can be very annoying because of the inability to focus.

In the early stages, the visual acuity might still be normal when measured in the ophthalmologist's office with strong illumination and high contrast letter charts, but patients can already notice slight distortions (straight lines may appear wavy, especially when reading) and small fragments of visual fields may be missing. Colors might also look different through an eye with cystoid macular edema. Contrast sensitivity (e. g. visual acuity in dim light) is also diminished in the early stages of CME, even in the patients with normal vision in situations with sufficient light and contrast circumstances.

Figure 1a Amsler-chart:
1. *Use the chart with one eye shut, and with reading glasses on if used.*
2. *Hold the chart at your normal reading distance.*
3. *Fix on the central point, and see whether any part of the grid is missing, blurred or any lines are distorted.*



How can we diagnose macular edema?

It is very difficult to detect CME during a routine examination. A suspicion of CME is often based on the patient's symptoms and ophthalmoscopy, but for the definitive diagnosis, confirmation with one of the following dedicated tests is needed: **fluorescein angiography** and **optical coherence tomography (OCT)**.

1 OPHTHALMOSCOPY

An ophthalmoscope is an instrument that allows the ophthalmologist to view the retina. Usually, the patient has had dilating drops prior to the examination. A strong light from the ophthalmoscope and a magnifier permit the ophthalmologist to see the details of the macula. The ophthalmologist observes the edema as a glistening area in the macula and sometimes the cysts can also be seen. However, the ophthalmoscopic picture is usually not sufficient for the diagnosis and evaluation of the severity of CME.

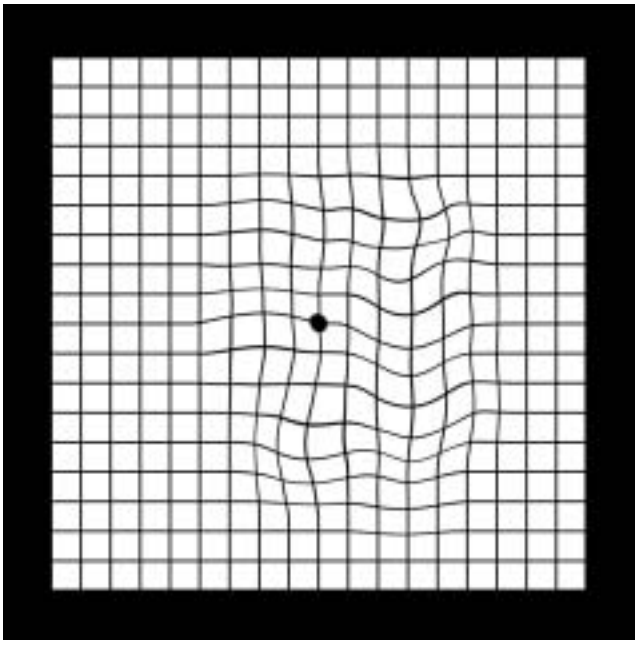


Abb. 1 b Amsler-chart: an illustration of how the chart might be perceived in a patient with CME

2 FLUORESCEIN ANGIOGRAPHY

is a procedure which uses a specialized camera system to take a series of photographs of the structures in the back of the retina. The photography technique uses fluorescein, a yellow dye that is injected into a vein in the arm and thereafter travels through the blood circulation. As the dye passes through the blood vessels of the retina, which will happen in a matter of seconds, a special camera flashes a blue light into the eye and takes multiple photographs of the retina. Fluorescein might also be orally taken, which is valuable in children, but the quality of the photographs is usually less then with intravenous injection. Fluorescein angiography can supply valuable information about the accumulation of fluids in the cysts in the macular area, information otherwise unavailable. In addition, the activity of inflammation, typified by leaky vessels near the macula, might also be determined from the photographs. Fluorescein is safe to use. Rarely, a patient may have an allergic reaction to the dye. Fluorescein angiography may occasionally be associated with

nausea that typically passes very soon after dye injection. Fluorescein can cause a patient's skin, eyes and urine to appear somewhat yellow for the first 24 hours following administration.
Fluorescein angiography is often confused with X-ray angiography where an iodine conjugate is injected into a vessel. Fluorescein does not contain iodine and, therefore, may be used in patients allergic to iodine. Fluorescein angiography is a photographic test and does not expose the patient to radiation or x-rays.

■ The figures *2a* and *2b* show the fluorescein dye (the white areas) as it fills the retinal blood vessels (*2a*, normal appearance) and the leakage of fluid with cysts in the macula indicating the edema (*2b*, CME).

3 OPTICAL COHERENCE TOMOGRAPHY (OCT)

is a new non-contact, non-invasive imaging technique. OCT is similar to ultrasound scan imaging except that light instead of sound waves is used to reveal specific layers of the retina. The resolution of OCT is much higher than that of ultrasound scanning. The test takes approximately five minutes per eye, and simply requires the patient to sit still and look in a specific direction while the scan is made; no substances are administered to the patient. The OCT scan can be used to visualize the

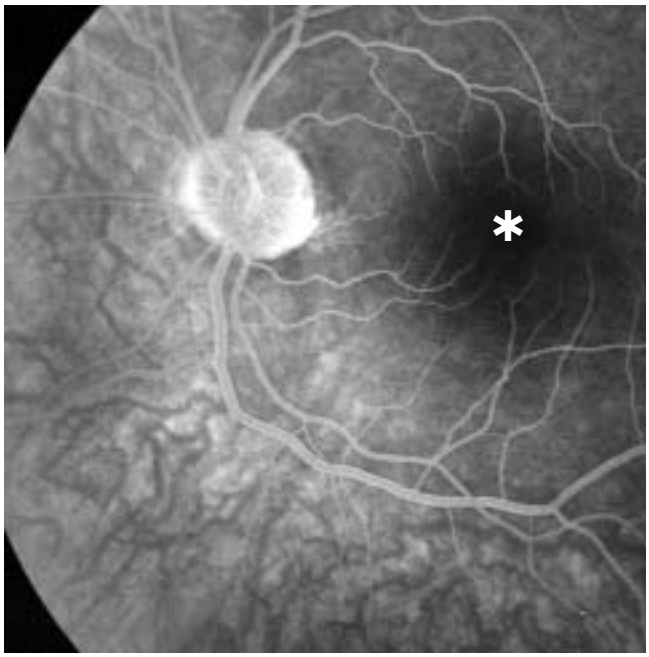


Figure 2a:
Fluorescein angiography in healthy eye. The macula (✱) shows no Fluorescein.

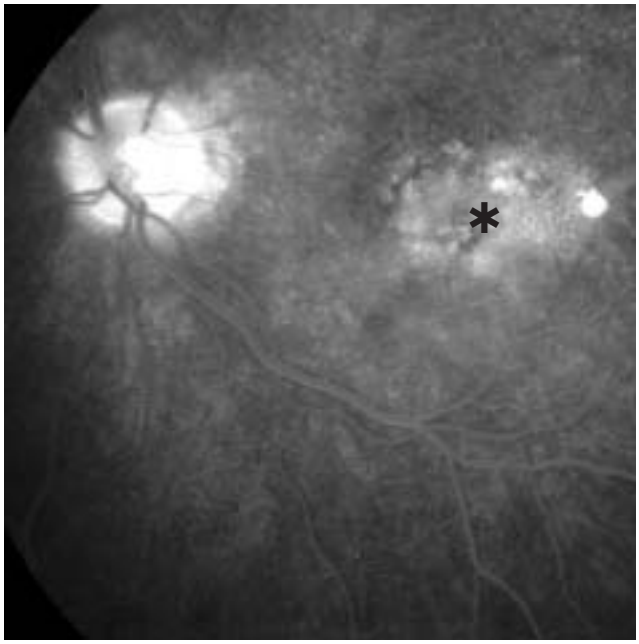


Figure 2b:
Fluorescein angiography in patient with CME. The macula (✱) filled with Fluorescein.

edema in the macula, to determine the exact location of the fluid (*Figure 3a, 3b*) and to calculate the volume of the fluid (the severity of the CME). In clinical practice, OCT images add information to the results of fluorescein angiography and are especially useful when evaluating the effects of treatment and eventually also to plan surgical strategies with minimal discomfort for the patient.

Conclusions:

CME is a major complication of uveitis and may negatively influence visual acuity. Early detection and treatment of CME are important to prevent the visual loss in uveitis. The new OCT method allows the precise evaluation of CME and thereby monitoring the efficacy of treatment, with the benefit of a non-contact, non-invasive method.

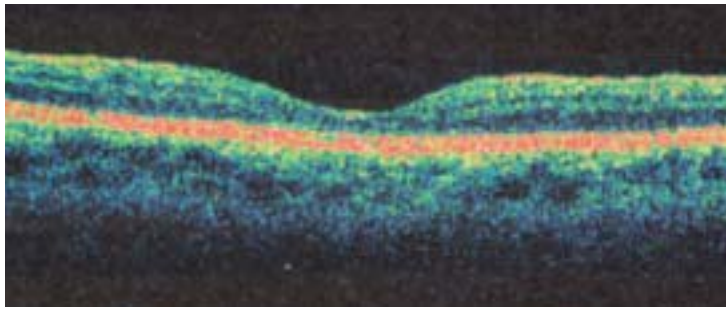


Figure 3a: OCT, normal situation

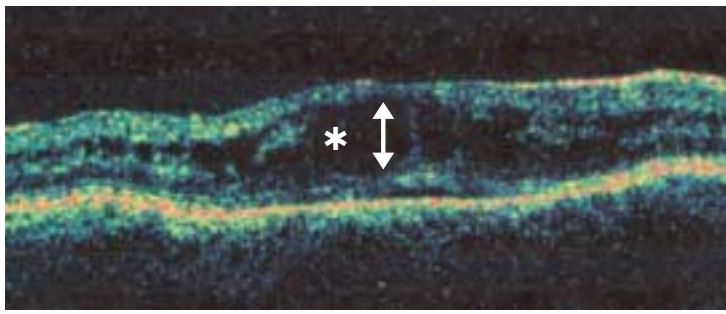


Figure 3b: OCT, in a patient with CME. The arrow shows the amount of fluid in the macular edema (black structure). The height (↕) of the edema (✱) can be measured.

Therapy of Macular Edema

Macular edema can be very significant for many patients regarding their visual prognosis. The extent of the vision impairment is particularly dependent of the size and duration of the macular edema. This and the likeliness of recurrent edema determine the efficacy of a therapy. In the following article the current therapeutic options will be explained and evaluated.
In the first part, **Dr. Christoph Deuter** *reports on drug therapy and its limits. If medication does not help anymore, in some cases surgical options might lead to successful treatment of the edema, as* **Prof. Dr. Bartz-Schmidt** *reports in the second part.*

Pharmacotherapy of the Macular Edema in Patients with Uveitis

Christoph Deuter, MD, Department of Ophthalmology, University of Tübingen, Germany

Cystoid macular edema is the most common cause for a persisting impairment of vision in patients suffering from uveitis. Early onset of therapy, even if vision is still good, is crucial.

Can drops alone be helpful?

With few exceptions (see later: Surgical Therapy), the macular edema needs systemic drug treatment, i.e. oral medication. Eye drops alone are not sufficient. Unfortunately, it still happens that uveitis patients with macular edema are treated for months or even years with corticosteroid eye drops alone without effect. In too many cases their central vision thus gets permanently impaired.

Corticosteroids and Acetazolamide

However, proven to be effective is a systemic therapy with corticosteroid tablets or, especially in unilateral cases, into the orbital floor (parabulbar or retrobulbar). Corticosteroids have an antiinflammatory action and furthermore do a good job dehydrating the edema and tightening blood vessels. Treatment with corticosteroids should be initiated in an appropriate dosage (e.g. 1 mg prednisolone per kg bodyweight). During the course, slow reductions of 10 mg per week till 30 mg, then in 5 mg steps and, below 20 mg, in 2.5 mg steps should be applied. Acetazolamide in tablets (e.g. Diamox®, Diuramid®) can help reduce the edema by gently dehydrating.

An adequate initial dose of 250 mg twice daily with afterwards, a slow dose reduction of 1/2 a tablet every 2 – 4 weeks, later 1/4 a tablet every 2 – 4 weeks, depending on the response of the macular edema, has been shown effective in our hands. As acetazolamide causes loss of potassium, this has to be substituted regularly. Administration of magnesium helps to prevent possible formation of kidney stones.

If the macular edema relapses after cessation of corticosteroids and acetazolamide or the edema can be kept in remission only by maintaining high doses of the two drugs, (which is not wise for a long time due to their side effects) immunosuppressive agents such as cyclosporine A are usually indicated. These drugs, also administered as tablets, act similarly to corticosteroids, thus helping to reduce their dose. If macular edema occurs during active uveitis, for example during an acute inflammatory phase, the medications mentioned before will usually be effective to reduce it.

Are there new effective medications?

Unfortunately, there are patients in whom the uveitis itself is quiet or already "burned out", who still have persistent or chronic macular edema. In these cases, conventional options of drug therapy with corticosteroids, acetazolamide or immunosuppressants often fail. Here, new therapeutic tools have to be investigated and invented. First reports nourish hope as biologics (e.g. Interferon alpha and TNF-alpha-antagonists) are effective especially in those cases of macular edema which were resistant to therapeutic attempts so far. To date, these drugs have no formal approval for the treatment of macular edema. The "off-label-use" of these, often very expensive medications, is usually not paid for by the public health insurance.

Surgical Therapy of macular Edema in Uveitis

Prof. Dr. Karl-Ulrich Bartz-Schmidt,
Department of Ophthalmology,
University of Tübingen, Germany

Surgical treatment is an option, if there are adhesions between the vitreous and the retina in the macular area. These adhesions (*Figure 1 page 22*) can cause traction on the retina which is detectable by optical coherence tomography (OCT). This non invasive imaging tool can help monitor the outcome of therapy in terms of preservation of the macula structures. Unfortunately, the improvement of vision is sometimes lacking, as the edema has caused structural changes of the retina (e.g. thinning of tissue layers resulting in atrophy) persisting even when the edema has been successfully removed. Surgical options are the application of corticosteroids

into the vitreous or the removal of membranes at the border of vitreous and retina.

Injection of corticosteroids into the vitreous

Injection of crystalloid corticosteroids became popular in recent years as it seems to have relatively low risks and can be performed easily. In half of the patients, however, a secondary increase of intraocular pressure has been observed. This indicates further medical, sometimes even surgical treatment (filtration surgery). Injecting crystalloid corticosteroids can also cause cataract or infection of the eye (endophthalmitis). The injection has thus to be done very carefully under sterile conditions in the operating room according to the guidelines of the ophthalmological societies. In first clinical trials, uveitis patients receive corticosteroids via a small drug delivery tool implanted into the vitreous cavity fixed by sutures in the sclera. This drug delivery tool is designed to release small amounts of corticosteroids continuously over years to reduce uveitis and thus the macular edema. The results are so promising that this implant under the name of Retisert, has just recently been approved in the USA. However there is a increased incidence of cataract formation and intraocular pressure also seems to be elevated.

Removal of the vitreous

A different approach has to be taken in eyes, where inflammatory processes have caused membrane formation between retina and vitreous. These membranes, inducing traction on the macula, cannot be treated by medication. Surgical intervention seems to be much more effective in these cases. By removing the vitreous (vitrectomy), we are able today to reach the border between retina and vitreous. After injection of certain colour pigments (e.g. indocyan green or trypane blue) into the vitreous to make the epiretinal layer visible (*Figure 2 page 23*) we can remove the tractional membrane using a microscope with high magnification (*Figure 3 page 23*). After the removal of such tractional membranes, the central area of the retina undergoes reorganisation and restructuring. After 6 to 8 weeks, this may result in a significant increase of vision in some patients. Typical complications of a vitrectomy can occur in these patients too, e.g. retinal detachment in approximately 3 to 5% of the cases. One year postoperatively, nearly half of the patients develop cataract, which should be surgically treated without further delay. Nevertheless vitrectomy is very effective in patients with tractional retinal membranes.

What may the future bring?

Generally, the treatment of macular edema is by medication. Here we have to observe closely results of new substances, such as the anti-VEGF-drugs, which are used in age-dependent macular degeneration, but can also be applied in selected cases of macular edema in an "off-label-use". Further alternatives may be modified corticosteroids (anacortafacetate), which decrease the incidence of their secondary adverse effects. They can be injected below the eye lid (parabulbar) or behind the ophthalmic bulb (retrobulbar), without the risk of intraocular infections. Major steps towards a better treatment can be expected from new drugs, achieving approval in the near future, not only for patients suffering from age-dependent macular degeneration but also from chronic uveitis and inflammatory macular edema.

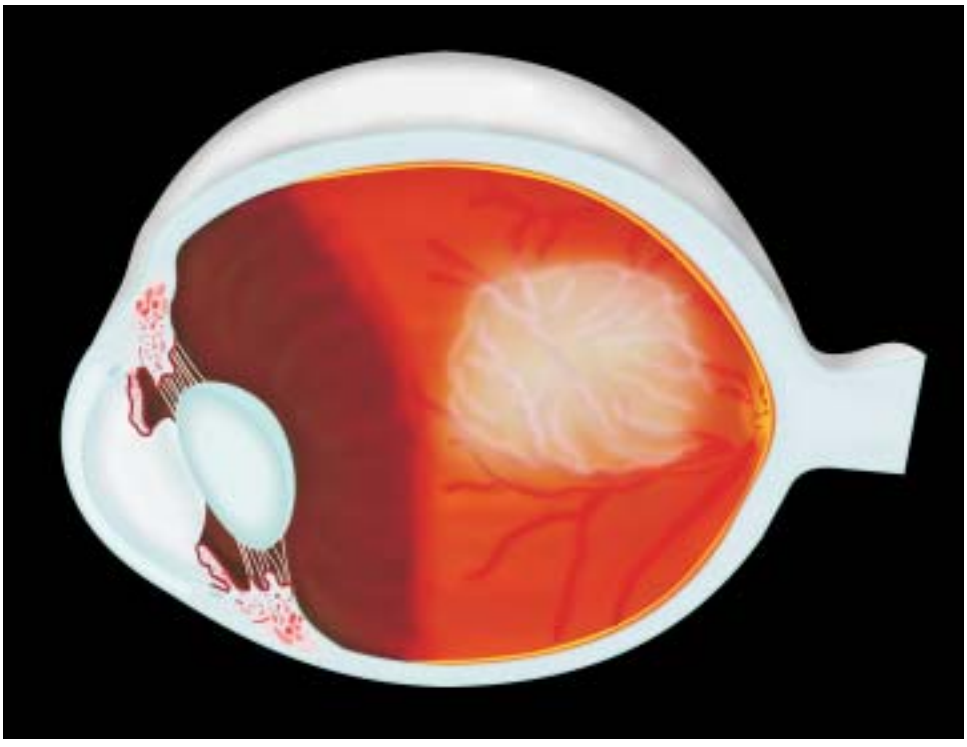


Figure 1: *On the macula a fine membrane (epiretinal gliosis) has formed which can probably induce or maintain severe macular edema.*

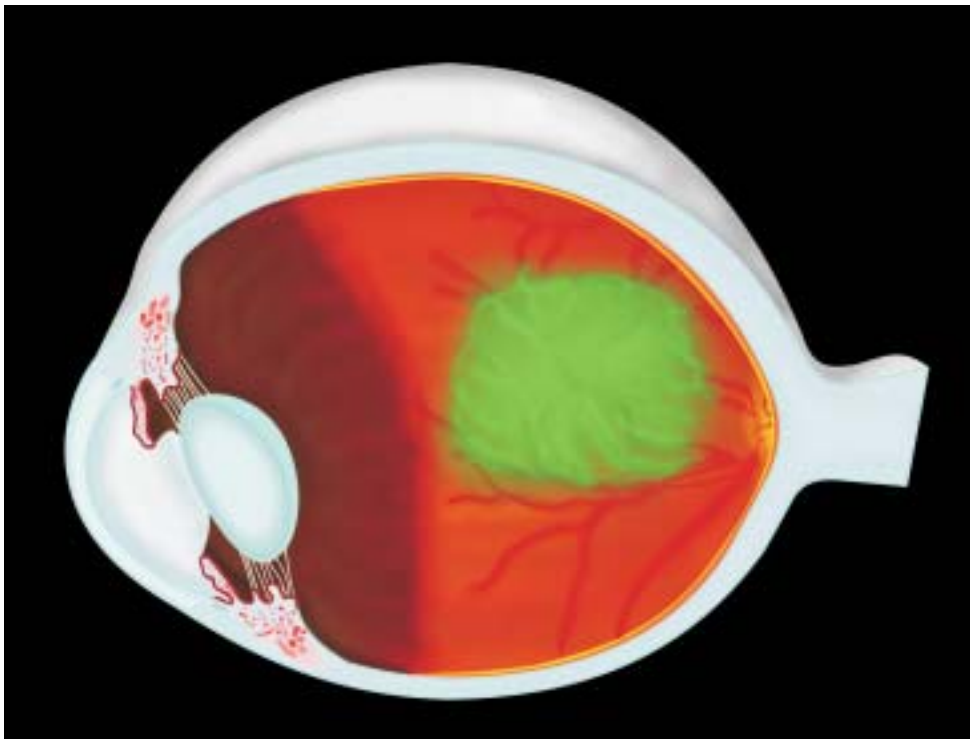


Figure 2: *This membrane can be stained. So demarcation to normal retina is much better.*

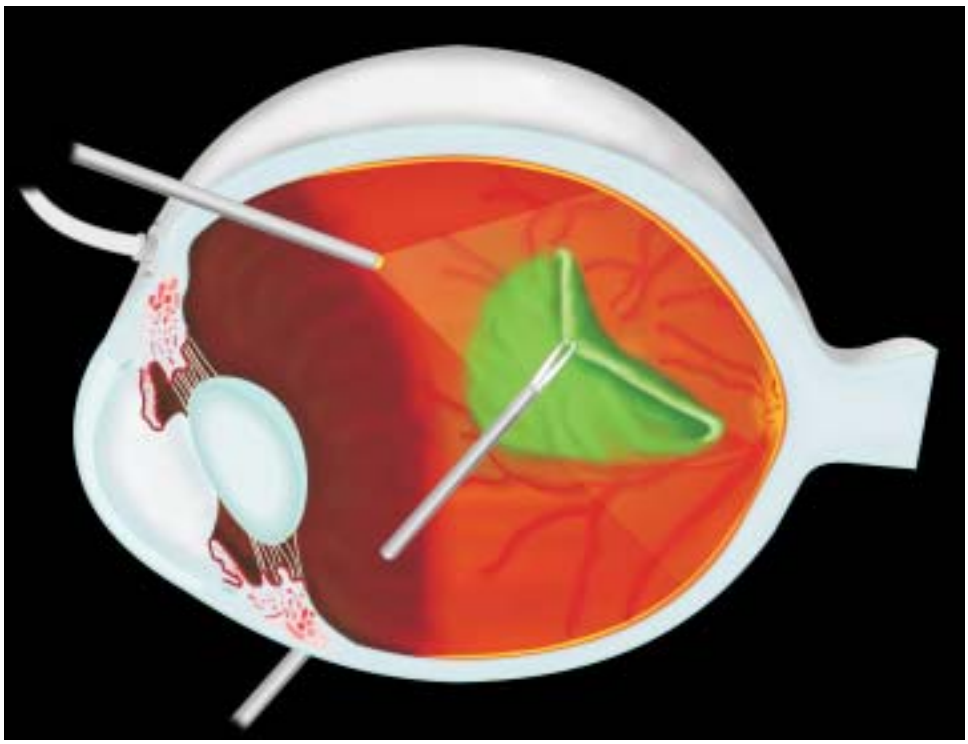


Figure 3: *The membrane can be removed by using a spatula and then tweezers.*

Macular Edema in Uveitis

Patient Report from Germany

How I fought against uveitis and macular edema

Five years ago, an effective therapy treated the uveitis (iritis) and even reduced the persisting macular edema. My vision improved from 8/20 to 20/20 and my ability to work was preserved.

Before that I underwent a whole spectrum of standard treatment twice, with multiple eye drops, Acetacolamide, Diclofenac and corticosteroids orally. There were also corticosteroid injections next to the eye, with some side effects, but they were the only effective options. Afterwards I could only see properly for two or three days.

Success through Corticosteroids and very slow weaning

The breakthrough was achieved by an initial high dose of cortiocosteroid eye drops, followed by very slow tapering off. Starting applications three times, then twice and once a day, I reached a maintenance dose of a drop every other day. Overall it took me five months which even for experienced uveitis patients is a very long period of time.

Attempts to apply the drops at less frequent intervals caused a recurrence of inflammation. Thus I had to increase the dosage for a short period of time, however, I could reduce it relatively quickly to the one drop every other day. For me it was better to apply the drops just before night time. With this therapy I can suppress inflammation and now I am on top of the disease for more than five years now! The injections seem to have had an initial beneficial effect which probably is the reason why this low dose of corticosteroids now gives me long lasting relief.

I am not really afraid of adverse side effects; however, I would rather get along without the drops. Compared to earlier times where I had to apply the drops more often – up to seven times a day – I have reduced the overall dose of corticosteroids quite significantly. I have skipped the side effect prone steroid tablets and other medication. The cataract has progressed, if any, only minimally.

Immunosuppression and surgery not necessary

From today's point of view, I could have spared many medications and the visits in three ophthalmology departments. In one of them, Sandimmune (active agent: cyclosporin A) was prescribed to suppress the overactive immune system which most likely causes my uveitis. I did not fulfil this prescription for many reasons. Furthermore, an "epiretinal gliotic change of the macula" was diagnosed. I was referred to another department for a "second opinion regarding a possible surgical treatment of the macula". The diagnosis was found to be incorrect. Later, an ultrasound exam of the eye was recommended to see whether the vitreous body had still contact to the retina. Otherwise, a vitrectomy, the surgical removal of the vitreous body would have been suggested.

No exaggerated expectations, please!

I do not want to give a wrong notion or claim, that there are no selected cases in which immunosuppressive medications such as Sandimmune or a vitrectomy might be necessary. In my case, however, things fortunately turned out to be different. Whether this will or will not stay the way it has over the years I don't know.

As there are many types of uveitis, not every patient may take for granted that this therapy will be right for her or him. If their disease were to be judged similar to mine, chances are that in some cases this therapy might be feasible. Of course, the therapy should always and only be done in consent with and under supervision of an ophthalmologist.

Günter Rönne

Patient Report from France

I was 57 years old, as blind as a bat due to myopia (-8 dioptres). It all happened just before Christmas when days were the shortest. It became difficult to drive because I could not distinguish the road from the kerb and because large flares appeared around lights. The consulted ophthalmologist diagnosed an anterior uveitis in the right eye and prescribed steroid eye-drops and eye-drops to dilate the pupil. During the spring, the left eye was also involved. After a remission period until summer, I suddenly could not read the small characters of my newspaper anymore. I deciphered with difficulty, because in one word some characters were dark and the others grey and blurred. The words moved on the page during reading. The pictures were distorted. It was hazardous to drive a car. At hospital, the medical team diagnosed a bilateral macula oedema and proposed investigations to find possible underlying disorders for the uveitis. What beautiful holidays! Because no aetiology was found, a treatment using intravenous corticosteroids (Solumedrol) was started. The first day of treatment, my vision dramatically improved. What a pleasure to read during the 3 days of staying at the hospital. I had no side effects, no insomnia nor hyper excitability during the treatment. I learned to eat without salt and low amount of sugar, a regimen I followed for several years, during the slow decrease of oral corticosteroids. My vision is often blurred by floaters in my eyes, but the macula oedema did not appear again since that treatment.

C. A.

Patient Report from the United Kingdom

I live in the Shetland Isles, the furthest north you can get in the UK. We have a small local hospital and the nearest major hospital is in Aberdeen, 300 km away by boat or plane.

I have retinal vasculitis, a condition that rapidly affected my right eye approximately 13 years ago, resulting in the loss of the eye some time later (due to secondary rubeotic glaucoma). I am going to describe my memories of how I developed retinal vasculitis and associated cystoid macular edema (CME) in my left eye. Needless to say, any visual loss in my left eye was going to be particularly noticeable.

When the macular edema started

During a 5-year spell after the loss of the right eye, I had a symptom less left eye, and found virtually no problems with the monocular vision. I continued with my occupation as a dentist.

The inflammation in my left eye started with some quite subtle visual signs, seeing some tiny dots and 'flickering' of the vision.

This was swiftly diagnosed in Aberdeen and aggressive therapy commenced. There followed quite long periods of inflammation and treatment. It may be useful to point out that, at this time, I knew very little about my condition and couldn't really name it. However, during spells of high dosage steroids, and immunosuppressive therapy, I don't recall being particularly worried and wasn't really seriously considering losing the ability to practise dentistry. There are some important factors to consider here. One reason there was little concern was the fact that there was an ethos throughout the medical and nursing staff at Aberdeen that allowed me to feel confident that I was receiving the best care possible. The way things were being explained to me meant that I didn't feel that I would need to suddenly read up and quickly find about this condition. Getting to know about my condition has been very useful and I would recommend it to any patient, but it can take time. If there is a lack of communication between patient and doctor, then the patient may feel the need to find outside sources of information and support more urgently.

There is another theory, which may explain why, in my case, I don't recall being particularly anxious about what was going on. On high dosages of steroids, I remember not really being worried about anything other than when the next bar of chocolate was coming from. This 'euphoric' state, which is not uncommon with high dosage steroids, is likely to produce some strange disproportionate responses to dealing with

uveitis. These side effects of steroids can start pretty quickly and a knowledge gained early on of the possible side effects would be useful for patients. For example, to be aware of weight gain as a side effect and to be able to prevent it with care over diet and exercise **before** it became a problem would be really useful to patients.

It is difficult to remember during the initial stages of the vasculitis in the left eye what visual problems I had. I do, however, remember very clearly the day I was walking along the hospital corridor and noticing that parts of people's faces were 'missing'. I was getting around the hospital without any difficulty and I remember clearly a feeling of real curiosity but not worry about these missing faces. It was just very hard to work out why it was just faces. Very soon, I was soon to discover problems reading. I know now that I was beginning to get an insight into the meaning of **central vision**.

This was **macula edema**. Any patient, with this, will in one way or another start to deal with the concept of central vision. Whether by experimentation or by reading up about it, any patient who is affected by a central vision loss would, I believe benefit working out and learning about this thing we have taken for granted all our lives, so much so that we probably don't know what it is, until it is taken away.

What is Central vision?

To be able to explain what central vision is to relatives, a friend, and work colleagues goes much of the way to explaining the effects of macula oedema.

From a patient's point of view, this is the way I explain central vision:

I ask someone to 'fix' his or her gaze on a picture or some other fixed point on the wall. I then hold up a sheet of paper at the edge of their field of vision. There will be something very clearly written on the paper, like 'Ab 37'. I will ask them to confirm when they can see the sheet of paper in the 'edge' of their vision. Getting them to concentrate on the picture on the wall all the time and not to move their gaze even for a moment, I then ask them if they can not only see the sheet of paper but also if they can tell me what is written on the paper. They realise whilst they can see that it is a sheet of some kind, perfectly well, they can't tell what is written on it.

Whilst getting to him or her to keep their gaze fixed, I now walk round slowly until I superimpose the sheet of paper over the picture so that they can suddenly both 'see' the sheet and also read the writing on it.

In this way, this simple test gets over to someone what central vision is more effectively than trying to describe it in words. This exercise is very good for children and adults alike and gives someone with no vision problems an idea of the problem that people with

macula edema may experience.
One difficulty I have found is explaining why I can go skiing but can't recognise my daughter's face 5 metres away.
The exercise can be repeated with a picture of a familiar face. The fact that there is a picture of a face is picked up well before the face is recognised (this can only be achieved when the face is in direct line of the fixed gaze).

What has been done for my macula edema?

From my point of view, it was the visual outcome of macula edema, which concerned me. It is very easy as a patient to be unaware of whether your current regime of drugs is treating your uveitis or your macula edema. There is an important distinction to be made because of the fact that persistent macula edema can occur in 'quiet' uveitis. It is probably always a good idea if patients know if their uveitis is quiet or not.

Macula edema can be treated and was successfully treated with immunosuppression in my case. I am still left with some central vision loss. In time, I adapted to central vision loss in different ways. Some ways are virtually automatic. Memory is called upon much more. I began to realise that I was recognising people by their gait or posture. It is interesting to find out that things like gait and posture are almost unique to each person.

Whilst these adaptive mechanisms are very useful, the best adaptive means are those, which utilise various forms of magnification. With central vision loss, if any detailed matter such as text or faces can be made to fill the field of vision then they can be recognised. An Optometrist who specialises in low vision is extremely useful in this respect and my life was transformed when I met Karon, my practitioner who is based at my eye clinic. I made use of different types of magnification aid and now have a large collection that can be used for all sorts of different tasks.

I have given an account of my experiences of macula edema. I realise that, like cases of uveitis, there is a huge range of variety between individual cases. I only had brief experience of the distortion of straight lines, for example. I am not sure if macular edema and central vision loss are always closely linked, but I think to understand what is going on with any visual effects of macula edema, then it is important to have a good basic understanding of central vision. It is, after all, a fascinating subject to learn about.

Phil Hibbert

UIG intern

The European Uveitis Patient Interest Association An Idea for the future

There seems to be a chance for a European Uveitis Group in the near future. This is the report of a first meeting, **Matthias Nahm** *from Germany and* **Lancelot Pecquet** *from France describe the participating groups an the projects of a European Group.*

On September the 19th 2004 Prof. Zierhut, president of the German Uveitis Patient Interest Group (**DUAG**), had invited representatives of uveitis patient interest groups and opthalmologists from different countries for a meeting. This was established as a "satellite meeting" of the "International Uveitis Study Group (**IUSG**)" in Mestre/Venice. Besides Prof. Rao, United States of America, representatives from Great Britain, France, Spain, Italy, The Netherlands, Austria and Germany attended. The intention was to have an exchange of information on an international level and also to estimate the need and possibility for an international uveits patient interest group.

Each representative of the countries gave the overview on history, structure and current activities of their uveitis association. According to this the associations were founded between 1996 and 2003. The number of members differs from 50 to 800 people. Three countries are publishing newsletters and send them regulary to group members for free. In average the association fee amounts to 25 € . Every patient interest group has its own homepage:

Great Britain: www.uveitis.net
France: www.inflamoeil.org
Netherlands: www.uveitis.nl
Germany: www.duag.org

Most groups are focusing on patient information and support.

The participants of the countries agreed to establish a "European Uveitis Patient Interest Association (**EUPIA**)" and to work for it. Two goals should be implemented for the next couple of months:

1. **A common publication in the languages English, French and German.**
2. **An international homepage containing amongst others links to the uveitis patient groups of the countries.**

The discussion on the use of lists of uveitis specialists on websites showed that there was much work to be done to achieve this. The same is true for the possibilities to find sponsors on an international level and for the necessity to form a platform to accelerate the development on new drugs. The participants came to an agreement to continue the discussion on these topics more intensively via email and further meetings. The questions mentioned above should also be discussed in the patient groups of each country.

After nearly three hours, it became clear that there is a strong wish for an international uveitis patient interest group. The participants stressed that the arrangement of the group should focus on a European perspective, but it must remain accessible and relevant for participants from different countries. The next meeting will be associated with the "International Ocular Inflammation Society (**IOIS**) Symposium" in Granada, Spain in May 2005.

The summary of the meeting is available in the internet under:
www://lancelot.pecquet.org/hidden/IUSGproceedingsIUS6 2004/index.html.

Matthias Nahm, Representative of the German Uveitis Patient Interest Group, **DUAG**

Lancelot Pecquet, Representative of the French Uveitis Patient Interest Group, **Inflam´oeil**

Group photo: from the left to the right side: C. Rosenthal, M. Nahm, P. Hibbert, C. Edelsten, J.d.Vos, M. Becker, L. Pecquet, M. Zierhut, A. Leonardi

Cultural Corner

Pictures and memories

Ever since man started recording his existence with drawings on cave walls, pictures have been an integral way of helping us to record and revisit our memories. The form that these pictures take has obviously changed considerably over the years.

The format in which we can record and archive our pictures is developing and changing at a staggering pace. This is exciting but it may be worth thinking about why we are recording all these pictures in the first place and what we are doing with them all.

What I would like to know is how long will the pictures we make today last?

It often seems that pictures grow in significance the older they get. Cave pictures have been found in sites such as Lascaux in France dating back thousands of years. These pictures may not be 'pin sharp' and they are certainly not very portable, but they have lasted an awfully long time. I wonder how long some of the pictures that are being stored on this laptop, which I am using now, will survive beyond this year, let alone many years or dare I suggest, centuries?

As picture making has evolved most types still have good longevity. There are some very old oil paintings, etchings etc around.

According to recent statistics, we are all taking phenomenal numbers of photographs, many more than ever before. We can now produce high quality images and using computers, digitally process and store these pictures. Yet the same recent statistics show us that we are actually saving only a tiny percentage of the images we record and printing even fewer.

It is tempting to believe that the pictures we record now will be around forever, but how many of us have pictures on a floppy disk. (No sign of floppy disk drive on any computer I've seen recently). Will old pictures survive in the future only through the efforts of enthusiasts prepared to convert old fashioned and long forgotten formats like the quaint old compact disc?
It may be worth looking at some of today's means of recording pictures. Inkjet printing is becoming the standard way of producing prints for most of us. The vast majority of inkjet prints we make today will have faded badly in

less than 10 years. It is possible to use a printer and inks, that will produce archival quality prints, but only a tiny percentage of inkjet printers are capable of this.

If we consider it important for our images to last to record our local area or family so that future generations can see them, then we may have to carefully think about the technology we use.

Pictures undoubtedly last longer as prints. I have recently unearthed a hoard of old family pictures dating back to the 1930's in some cases. Two things struck me; first, what good quality the pictures were and second, how well the pictures had lasted, with very little sign of fading.

We should also maybe think of making a lot more prints. We may well be able to retrieve pictures left on CD's but can we be sure that these discs will not be more easily lost than a box of old prints?

Let's not be too dismissive of modern technology though. There are some novel ways of looking at our pictures. There are even picture frames with their own hard drives, which can display a different picture every day for months. Our personal home computers will very soon be storing all our pictures on a hard disk making them available to be seen on the TV, printed to a wirelessly connected printer or sent onwards on the Internet.

Memory for most of us is visual for the most part, whether we look at a picture or visualise a remembered event. It is difficult to imagine how memories were passed on before we worked out how to paint images on the walls of caves.

Phil Hibbert

Physicians and Uveitis

News from the Scientific World

The Uveitis Awards from the German Uveitis Patients Interest Group (DUAG) 2004

Since 2003 the DUAG has supported uveitis research by donating awards to clinical and experimental uveitis research. In September 2004 the awards were presented along with the congress of the International Uveitis Study Group in Mestre near Venice in Italy. **Prof. Manfred Zierhut**, *the President of the DUAG, describes the way how the winners were found, what the topics of the winning papers were, but also, why patient interest groups should try to donate awards.*

Support the scientific research, and you will support patients

One of the main goals within the constitution of the DUAG is to achieve "support of scientific research". For a group with app. 800 members, this is not a simple task. With the help of **Bausch & Lomb Co.**, Rochester, USA, we were able to donate awards in 2003 and also in 2004. We would like to thank this company very much for their support!

How the winners were selected

As in the previous year awards were in two categories, in the fields of experimental and in clinical uveitis research. A team of 6 experts had to choose the best 3 publications in each field, published in the scientific literature of the year 2003. "Scientific Literature" relates to journals where articles undergo peer review (means likely to be important and new). This secures a high grade of quality in itself. The money award goes to the first author, the document of honour to the whole group.

In the first round, each expert had been asked to nominate what he or she thought are the best 4 articles. This resulted in a list of 17 clinical and 13 experimental articles. In the final round each expert had to give points to four of these nominated papers (5, 10, 20 and 30). In July (for the experimental awards) and in August (for the clinical awards) the winners were notified. Because no other uveitis award exists, the winners were very happy.

The award ceremony

In September, along with the Meeting of the International Uveitis Study Group in Venice-Mestre in Italy, the award ceremony took place. For the first time,

Physicians and Uveitis

the organisers invited the winners to present their award winning articles to the congress audience, a summary of which our readers will find on the following pages.

What was the content of the winning articles?

Until today the mechanisms leading to uveitis are not well known. Most of the work has to be undertaken in animal experiments. Especially mice and rats can develop a model which can mimic the human uveitis in very important parts. The first article investigates how the body achieves the ability to differentiate between foreign (should be destroyed by our own immune system, like bacteria) and our own or self components (must be conserved and protected against the autoaggressive immune system) in our body. The two other articles investigate cells which seem to be important for the initiation and perpetuation of the inflammation: the dendritic cells, and the microglial cells. The clinical articles reported about diagnostic, therapeutic and epidemiologic aspects of various uveitis entities. The first report dealt with the so-called TINU-syndrome that includes uveitis with renal inflammation. The authors found that genetic factors (HLA-antigens) seem to play a major role in recruiting this form of uveitis. The second paper reported about a new treatment for Behçet´s disease. This disease leads to generalized inflammation of nearly all vessels of the body, resulting in a most severe form of uveitis. Interferon-alpha has been shown to be extraordinarily successful in controlling the disease. The third article discloses very important facts about juvenile uveitis, one of the most challenging forms of uveitis.

Why do we need uveitis-awards?

The donation of the awards in Venice-Mestre appeared to be a great "Advertisement-Show", illustrating that patient interest groups are powerful and that they are really determined to fight this disease, and that they are strongly working for the support of uveitis research. In 2005, the awards will again be sponsored by Bausch & Lomb, but we also need the help of private sponsors. In the future, these awards, the only ones donated in the name of an ocular disease patient interest group, should become more famous. They should be working as a qualification criterion and be helpful to the winners for personal purposes and for recruiting research grants and thereby expending research into uveitis.

The Committee and the **DUAG** agree that in this year too all six awarded publications offer an important new aspect in the diagnostics and therapy of clinical uveitis or improve our knowledge regarding the mechanisms playing key

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roles in experimental uveitis, therefore probably delivering ideas for new therapeutic targets. To make new scientific results readily available as quickly as possible to ophthalmologists, but also to health insurers, may become a major goal for patient interest groups in all countries, for assuring a modern, success oriented diagnosis and therapy for uveitis-patients.

Fig.: 1st clinical award – from the left to the right side:
Rosenbaum J.T., Smith J.R., Levinson R.D, Zierhut M., Holland G.N.

Physicians and Uveitis

The clinical uveitis-awards

1st award **Levinson R.D, Parks M.S., Rikkers S.M., Reed E.F., Smith J.R., Martin T.M, Rosenbaum J.T., Foster C.S. Sherman M.D, Holland G.N.**

Strong Association between specific HLA-DQ and HLA-DR Alleles and the tubulointerstitial Nephritis and Uveitis Syndrome

Investigative Ophthalmology & Visual Science 2003;44:653-657

In this research project, uveitis groups from three universities collaborated in order to examine human leukocyte antigen (HLA) types in this very interesting disease. Tubulointerstitial nephritis and uveitis (TINU) syndrome is particularly interesting because it affects both the kidneys and the eyes with inflammation, but in the vast majority of cases the kidney disease improves on its own after a few weeks to a few months, but in more than half the cases the uveitis will be chronic or recurrent. Seventeen of 18 of our patients had chronic uveitis because this group was selected from patients in uveitis practices. Therefore, we are really looking at a particular subset of individuals with TINU syndrome who have chronic or recurrent uveitis.

We looked at HLA genes in our patients. There are hundreds of variations (alleles) of these genes, and most individuals have six. The products of these genes are HLA proteins that are found on the cell surface and allow communication between cells of the immune system. These HLA proteins present small segments of other proteins (called peptides) to receptors on immune cells called T lymphocytes, or T cells; if the T cell has a receptor that can respond to the HLA-peptide complex, then that T cell can be instructed either to respond with an immune response to any cell which has that peptide, or conversely be instructed that this is a "normal" peptide and no response is needed. That depends on the context, and there is still much to learn about this very central aspect of the immune response that helps to fight infection (for example when the peptide is from a bacteria or virus), but can also lead to inflammatory disease like uveitis.

We found that there were very strong associations with HLA-DRB*0102 and HLA-DRQA*01, and HLA-DQB1*05 alleles and TINU syndrome. The strongest association was with the HLA-DRB1*0102 which had a relative risk of almost 150! This is the highest for any class II (HLA-DR or DQ) association that we are

aware of in any disease. We are finding that Vogt-Koyanagi-Harada (VKH) disease, another entity with chronic anterior uveitis, also has an association with HLA-DRB1*01 in Hispanic individuals, and perhaps with HLA-DRB1*0102 particularly, but the association is nowhere nearly as strong. Other HLA associations that have been very strong in patients with uveitis have included HLA-B27 and iritis, and HLA-A29 is perhaps even more strongly associated with a disease called birdshot chorioretinopathy than HLA-DRB1*0102 was with TINU, but they seem to confer a similar level of risk.

Interestingly, there are some intriguing indications that the HLA-DQ5 association may also play a role in conferring risk for TINU syndrome. Previous smaller reports of HLA typing from various parts of the world showed different HLA-DR types, but all of those types are what we call "linked," i.e. can usually be found with, HLA-DQ5 in the same individual. In fact, in one report from Spain they found that 2 of 3 patients had a certain HLA-DR type, but interestingly all 3 patients had HLA-DQ5. It may well be that both specific HLA-DR and HLA-DQ types confer risk. There is some precedent for that in rheumatoid arthritis, and there has been a suggestion of that in VKH disease.

One of the strengths of this study was the collaboration between three different institutions. When studying rare diseases like uveitis, it is very important to have a collegial relationship and to combine efforts. It is hard to get meaningful information otherwise. This enabled us to see patterns that previous reports of only a few patients could not find. We are now looking at some other genes that could also have some promise in giving us additional information about the immunogenetics of uveitis.

2nd award

Kötter I., Zierhut M., Eckstein A. K., VontheimR., Ness T., Günaydin I., Grimacher B., Blaschke S., Meyer-Riemann W., Peter H.-H., Stübiger N.

Human recombinant Interferon alpha-2a for the Treatment of Behçet´s Disease with Sight threatening posterior or Panuveitis

British Journal of Ophthalmology 2003;87:423-431

Uveitis in patients suffering from Behçet´s disease can impair their vision quite significantly. In 70% of these patients, there is a generalized inflammation of the blood vessels (vasculitis), affecting several organs. In the eye, a posterior uveitis or vasculitis of the retinal vessels can develop. As a consequence, circulatory disorders like vessel occlusion of the retina, causing vision impairment, can be seen. Regardless of the current therapy used (for example corticosteroids, cyclosporine or azathioprine), several studies show that in the time course of 5 years, 25 to 50% of the patientswill suffer from the most severe vision impairment. In the awarded work our group showed in an open study (i.e. all patients received the medication to be examined) with 50 patients, that interferone-alpha-2a (RoferonA®, IFN-alpha) resulted in inflammation-free eyes in over 90% of the patients. This led to an improved (sometimes very impressive) vision which was maintained for a long period of time. In about a third of the patients, IFN-alpha could be weaned without a relapse of the uveitis. This has not been reported in any previous treatment studies. IFN-alpha will most likely improve the options to treat uveitis in the future and can maintain vision in patients with Behçet´s disease greatly. A randomized study (i.e. the study medications will be assigned to patients at random) in comparison to cyclosporine A, the standard medication so far, is currently under way in Germany.

Fig.: 2nd clinical award – from the left to the right side: Kötter I., Zierhut M.

3rd award

Edelsten C., Reddy M.A., Stanford M.R., Graham E.M.

Visual Loss associated with pediatric Uveitis in English primary and referral Centres

American Journal of Ophthalmology 2003;135:676-680

Previous studies of uveitis beginning in childhood have found that the condition is much rarer than in adults, its causes are very different and that the outcome is more severe. As childhood uveitis is so rare, the majority of studies have come from tertiary referral centres and these types of studies frequently overestimate the severity of disease because patients with complications are more likely to be referred to specialist centres.

In this study we examined the diagnosis and outcome of patients seen in district hospitals and compared them to those seen in two specialist units in London. In the UK patients are initially referred from their general practitioners or high-street opticians to district hospitals which each serve a distinct area of the country. As childhood uveitis is rare, the study required documenting all cases referred to three separate district hospitals over several years before an accurate estimate of the incidence and pattern of disease could be established.

The main findings of the study were that:
1] the frequency of uveitis in children is 4-5 less common than in adults
2] the types of uveitis developing in childhood differ in early and late childhood, and adult patterns of disease only start to develop in the late teenage years.
3] the majority of patients have isolated uveitis and are otherwise fit and healthy whereas majority of patients in specialist hospitals have uveitis associated with juvenile idiopathic arthritis
4] in this study we found no difference, in the general population, in the severity of uveitis starting in childhood compared to that starting in adulthood

We confirmed that uveitis starting in childhood is rare and the younger the population, the rarer it is: in children under the age of 5 uveitis develops in 3 per 100,000, which is less than 10% of the rate found in 40-50 year olds. Children under the age of eight most commonly develop a painless, chronic anterior uveitis that is usually associated with chronic arthritis: this group of patients is very overrepresented in the population of specialist hospitals.

Physicians and Uveitis

Children who develop uveitis between the ages of 8 and 16 are most likely to have a chronic posterior uveitis, and this is only rarely associated with other medical problems. If uveitis develops later it is most likely to be a short-lived painful anterior uveitis affecting one eye- acute anterior uveitis. This is the most frequent type of uveitis found in North European populations. We found that the majority of children developing uveitis in the district hospitals were otherwise fit and healthy and the survey of other recent studies also found that in those children with uveitis, who do not have chronic arthritis at the time of diagnosis, less than a third have other medical problems such as Behçet's disease, ankylosing spondylitis or sarcoidosis which are commonly associated with uveitis in adults.

We found that 17% of children with uveitis lost at least some vision in one eye and a similar proportion required surgery at some point- usually cataract surgery. These outcomes are no different to that found in our studies of adults with uveitis in district hospitals. A poor outcome appears more likely in those with chronic uveitis, whether anterior or posterior and we think that the poor outcome of childhood uveitis reported in previous studies, compared to adults, is largely due to the greater proportion of chronic uveitis seen in children in specialist centres, rather than young age being itself a major risk factor for poor outcome.

Children are of course more likely to present late and have irreparable damage to the eye at the time of diagnosis and so we must continue to direct every effort to screening high risk populations such as young children with arthritis. This study also demonstrated that there are significant differences in the type of uveitis seen in different countries as well as in different types of hospital in the same country. If we are to understand more about this condition then we need further studies of the differences in pattern of disease and outcomes in different countries.

Fig.: 3rd clinical award – from the left to the right side: Edelsten C., Zierhut M.

The experimental uveitis-awards

1st award

Avichezer D., Grajewski R.S., Chan C.-C., Mattapallil M.J., Silver P.B., Raber J.A., Liou G.I., Wiggert B., Lewis G.M., Donoso L.A., Caspi R.R.

An immunologically privileged retinal Antigen elicits Tolerance: major Role for central Selection Mechanisms

Journal of Experimental Medicine 2003;198:1665-1676

Experimental autoimmune uveitis (EAU) is a model for human uveitis that can be induced in susceptible animals by immunization with retinal proteins, such as interphotoreceptor retinoid binding protein (IRBP) or retinal arrestin. Uveitis patients often have an abnormal response to these antigens, which is thought to be involved in their disease. In order to avoid such a reaction against normal tissue components, the body has developed a process known as "self tolerance". This tolerance is normally induced and maintained by two pathways: central, which occurs in the thymus, a lymphoid organ overlying the heart where lymphocytes mature, and peripheral, which occurs in the tissue. Tissue-specific proteins (including at least some retinal proteins) are expressed in the thymus, and the maturing lymphocytes that recognize them are deleted or tolerated. Those that escape this process are tolerated in the periphery as they recirculate and encounter the antigen in healthy tissues. Retinal antigens are separated from the immune system by an efficient selecting filter called the blood-retinal barrier, suggesting that peripheral tolerance to retinal antigens is deficient and central tolerance may be the primary mechanism to achieve resistance to uveitis. Indeed, retinal antigens are detectable in thymus of EAU-resistant mice. However, they are not detectable by conventional methods in thymus of EAU-susceptible mice. We attempted to answer the question whether EAU susceptibility is due to lack of central tolerance to the uveitis target antigen, by comparing genetically engineered mice made deficient in IRBP, to "normal" mice from a highly EAU-susceptible strain. Using ultra-sensitive methods, we demonstrated that the normal mice do express a minute amount of IRBP in the thymus, demonstrable only at the single-cell level, which is not present in IRBP-deficient animals. This trace level of expression is functionally significant, because normal mice have dramatically reduced or changed immunological responses to IRBP compared to the deficient mice. Sophisticated thymus transplantation experiments between deficient and normal mice demonstrated that

deficient recipients of normal thymus responded like the normal donor, (and vice versa), proving that the pattern of response follows the thymus. Most importantly, normal recipients of IRBP-deficient thymus developed highly exacerbated EAU, which was much more rapid and severe than in normal recipients of normal thymus. Finally, we also demonstrated that regulatory cells coming out of the thymus are also involved in protecting susceptible mice from disease. Our results indicate that susceptible individuals exhibit a detectable level of tolerance to their uveitis target antigen, which is attributable to the vanishingly small expression of that target antigen in their thymus.
These findings increase our understanding of how the body attempts to turn off responses to components of the eye, and point to peripheral tolerance, rather than central tolerance, as the "weak link" that could be reinforced therapeutically to reduce pathological responses to retinal antigens.

Fig.: 1st experimental award – from the left to the right side: Avichezer D., Zierhut M., Caspi R.R.

Physicians and Uveitis

The experimental uveitis-awards

2nd award

Jiang H.-R., Muckersie E., Robertson M., Forrester J. V.

Antigen-specific Inhibition of experimental autoimmune Uveoretinitis by bone marrow-derived immature dendritic Cells

Investigative Ophthalmology & Visual Science 2003; 44: 1598-1607

Uveitis is a retinal antigen activated T cell-mediated autoimmune disease in the uvea and retina tissue. Recently research has focused on the function of dendritic cells. Dendritic cells are found in several places in the body (skin, mucosa, spleen, etc.). They are motile and can migrate in the blood and lymph organs. In essence, dendritic cells function to capture antigens and transport them to the antigen specific T cells, subsequently these T cells are induced to activate immune responses (Th1 response) such as initiating autoimmune responses or generate tolerance (Th2 or regulatory T cell response) which prevents the immune system responding to specific antigens. We investigated the effect of dendritic cell maturation status (ie the expression level of molecules such as MHC-II, CD86 and CD40) on T cell immune responses in vivo using experimental autoimmune uveoretinitis disease model which closely mimics human uveitis pathogenesis. Our results show that when we injected the immature dendritic cells (expressing low levels of MHC-II, CD86 and CD40) subcutaneously, the uveitis disease development was significantly inhibited and disease severity was reduced compared to control groups which had been treated with either PBS buffer or mature dendritic cells (expressing high levels of MHC-II, CD86 and CD40). We further investigated the mechanisms involved. We found immature dendritic cells induced Th2 and T regulatory cells in the nearby lymph nodes, as they produce high levels of proteins such as interleukin-5 and interleukin-10. This might explain the down-regulation of help 1 T cells mediated autoimmune response against retinal-antigen, therefore inhibited uveitis disease development. Overall, this work has given the evidence that immature dendritic cells can prevent uveitis disease development, and they might be used in the treatment of uveitis patients and other autoimmune diseases in the future.

Fig.: 2nd experimental award – from the left to the right side:
Jiang H.-R., Forrester J. V., Zierhut M.

3rd award

Rao N. A., Kimoto T., Zamir E., Giri R., Wand R., Ito S., Pararajasegaram G., Read R.W., Wu G.-S.

Pathogenic Role of retinal Microglia in experimental Uveoretinitis

Investigative Ophthalmology & Visual Science 2003 Jan; 44:22-31

In uveitis, loss of vision is primarily from damage to the retina. Although several mechanisms for the retinal damage have been proposed including infiltration of blood born cells, monocytes and macrophages. Several investigations have documented the infiltration of macrophages in the retina and subsequent retinal damage in uveitis. However, the stimulus for such cellular infiltration is not clear. In the retina there are cells which appear virtually identical to the macrophages and these cells are known as microglia. Normally microglia is dormant in the retina. These cells on activation may cause retinal damage similar to the damage produced by the macrophages. However, it has been challenge in differentiating activated microglia from the macrophages. Moreover, research on these cells is limited to brain and spinal cord where precise identification of the activated microglia was suboptimal.

We have taken a novel approach in identifying the activated retinal microglia and addressed the role of these cells in causing the retinal damage in uveitis. We approached this by studying the retinal damage in uveitis animals.

In accordance with the National Eye Institute (Bethesda, Maryland) guidelines for animal's research, we produced uveitis in a special strain of rats. These animals had minor surgery involving the back of the eye. Through this surgical procedure, a dye was introduced in to the nerve in the back of the eye and this dye was taken up by the retinal microglia and not by the macrophages. These observations were confirmed by current molecular biological techniques and by special microscopy called Confocal microscope.

Our study revealed that microglia is activated prior to the macrophage infiltration in the retina. The former cells released potent chemicals which initiated retinal damage. Subsequently, the macrophages arrived into the retina to clean the damaged retina. But non-reversible damage took place from the activation of microglia. This is the first research study revealing the importance of microglia

in uveitis unlike previous studies where macrophages were believed to cause retinal damage.

Because retinal damage in uveitis is caused by the initial activation of microglia, a better understanding of this process may lead to the development of novel, locally acting medications to prevent retina damage rather than current medication given either by mouth or by intravenous route. Such systemic treatment is associated usually with complications. These complications can be prevented by delivering the drug that neutralizes the activation of microglia locally in to the eye.

Fig.: 3rd experimental award – from the left to the right side: Rao N.A., Zierhut M.

Patient Groups & Information

Uveitis Information Group

A patient led information and support group.

Activities

- Provision of information and support by letter, phone and email.
- Public meetings around the UK.
- Web site

To Contact:

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