(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 September 2005 (01.09.2005)

PCT

(10) International Publication Number
WO 2005/079716 A1

(51) International Patent Classification[7]: A61F 9/00, 9/04

(21) International Application Number:
PCT/GB2005/000535

(22) International Filing Date: 16 February 2005 (16.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
GB 0403370.0 16 February 2004 (16.02.2004) GB

(71) Applicant *(for all designated States except US)*: **KEEPSIGHT LIMITED** [GB/GB]; 93 Chilton Way, Hungerford, Berkshire RG17 0JF (GB).

(71) Applicant and
(72) Inventor: **ARDEN, Bernard, Geoffrey** [GB/GB]; 16 Noel Road, London N1 9HA (GB).

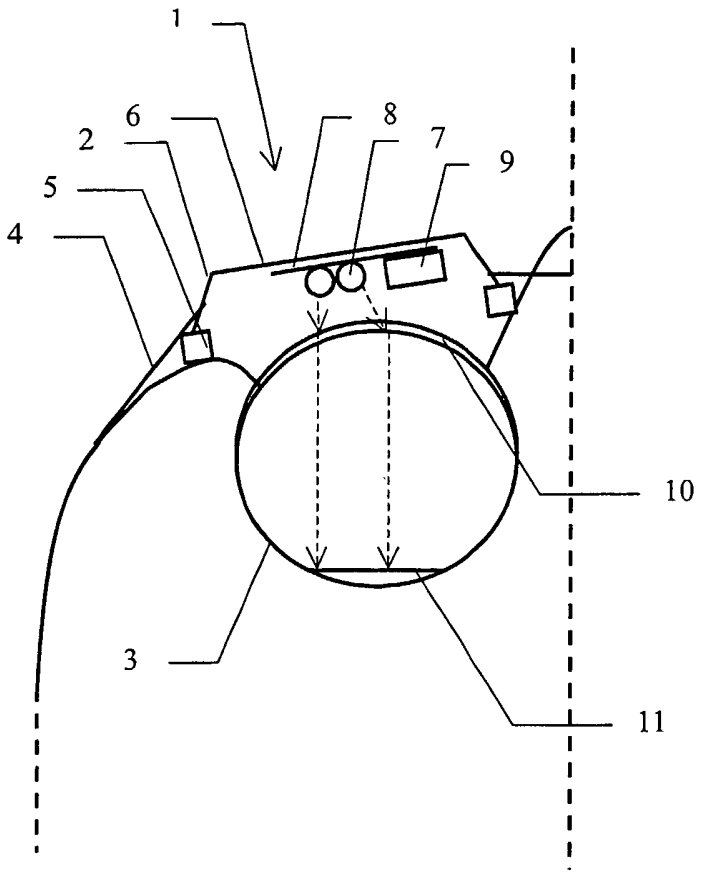
(74) Agents: **CROSS, James, P., A.** et al.; R.G.C. Jenkins & Co., 26 Caxton Street, London SW1H 0RJ (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,

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(54) Title: METHOD AND DEVICES FOR PREVENTING RETINAL DISEASES



(57) Abstract: The specialised cells in the retina that detect dim Tight (called "rods") have a variable sensitivity. After a period in darkness, they become reliable and nearly noise-free single-quantum detectors. This is achieved by a unique method of operation that uses all the oxygen that can be supplied to the cells. If, in disease, the delivery of oxygen is slightly impaired (anoxia), the retina sends out chemical 'distress signals' that encourage the abnormal growth of new blood vessels. Such anoxia and the development of these new vessels is the cause of Diabetic Retinopathy in persons whose general vasculature elsewhere in the body is adequate to local demands. This maximal rod sensitivity only occurs in sleep: hence by preventing dark-adaptation during sleep, periods of anoxia may not occur and the development of diabetic retinopathy may be slowed or stopped. Dark adaptation is prevented by wearing a device, similar to a pair of goggles, which emits light onto the eyelids when the user is asleep. The light is preferably green, around 480 nm, and is sufficiently intense to prevent dark adaptation but not so intense as to disturb the user. The light may be generated by an electrical light source, such as an LED, or a luminescent light source.

WO 2005/079716 A1

SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Method and Devices for Preventing Retinal Diseases

Field of the Invention

The present invention relates to a method and devices for prevention of certain retinal diseases, or at least for inhibiting their progression.

Background of the Invention

Three common blinding diseases – Diabetic Retinopathy (DR), Retinopathy of prematurity (ROP) in oxygen-treated neonates, and Age-related Macular Degeneration (AMD)- are peculiar to the eye. The hallmark of these conditions is angiogenesis, the formation of new blood vessels, but the processes which give rise to them are apparently confined to the retina. One feature that distinguishes the retina from other parts of the Central Nervous System (CNS) and from other organs is the presence of large numbers of specialised photoreceptor cells – 140,000,000 rods and 6,000,000 cones. Recent discoveries have detailed various mechanisms of angiogenesis in the eye (reference [1] below) so it is now becoming meaningful to ask what local factors might account for the especial damage to the retina in DR, ROP, and AMD.

Diabetes and diabetic retinopathy are increasing rapidly. The loss of vision is a most severe complication, and is very expensive for the community. Over 200 million persons in the Western world are at risk from loss of vision from diabetic retinopathy and other blinding diseases of the retina.

References [17] and [18] below show that defects of retinal function in diabetic persons may be instantly reversed by inhalation of oxygen. Reference [91] below shows that continuous breathing of oxygen (via nasal tubes) for several weeks can improve the structure of the retina in diabetic maculopathy. The amount of extra oxygen provided is only about 2-4%. The treatment

would require the patient to carry around an oxygen bottle, which is neither cheap nor convenient.

Statement of the Invention

According to one aspect of the present invention, there is provided a device for preventing or inhibiting a disease of the retina by preventing complete dark adaptation of the eye. The device is arranged to be worn and used while the user is asleep, and to emit light on the anterior surface of the closed eyelid or eyelids.

Preferably, the light is green, most preferably having a dominant wavelength of 480 nm, because such light, filtered through the lids, would provide retinal illumination centred at 510 nm. This wavelength is close to maximal absorption wavelength of rod cells. The light intensity is sufficient, after attenuation by the eyelid, to prevent complete dark adaptation of the eye. The intensity may be sufficient to semi-saturate the rod signalling mechanism, for example between 1 and 30 quanta per second per rod.

Preferably, the light intensity is not sufficient to arouse the user when the eyelids are closed. The intensity with the eyes open may be near the colour vision threshold so hues are just visible but the gamut is much reduced. Hence, with closed lids the light is perceived as dim and unarousing, and is tolerable during sleep.

Preferably, the device is arranged to be worn comfortably and securely by a sleeping user. The device is preferably light and semi-flexible, and may be secured by an adjustable headband. The device is preferably arranged to illuminate both eyes of the user, preferably symmetrically.

In one embodiment, the device includes one or more light-emitting diodes arranged to illuminate the eye or eyes of the user. Preferably, the device includes a power supply for the diodes.

In another embodiment, the device includes a non-electrical luminescent light source arranged to illuminate the eye or eyes of the user. The light source may for example be chemoluminescent or phosphorescent. The phosphorescent

material may be subjected to radiation from a low-activity radioactive substance, such as tritium. The radioactive substance may be encapsulated with the phosphorescent material

According to another aspect of the present invention, there is provided a method of preventing the onset of a disease of the retina by illuminating the eyelid or eyelids of the user by means of the device, while the user is asleep. Preferably, the method comprises illuminating the eyelids in this way for most of the time that the user is asleep, preferably from the time the condition is first diagnosed, and preferably every night.

The specialised cells in the retina that detect dim light (called "rods") have a variable sensitivity. After a period in darkness, they become reliable and nearly noise-free single-quantum detectors. This is achieved by a unique method of operation that uses all the oxygen that can be supplied to the cells. If, in disease, the delivery of oxygen is slightly impaired (anoxia), the retina sends out chemical 'distress signals' that encourage the abnormal growth of new blood vessels. Such anoxia and the development of these new vessels is the cause of Diabetic Retinopathy in persons whose general vasculature elsewhere in the body is adequate to local demands. For most people, this maximal rod sensitivity only occurs in sleep: very few people live under circumstances in which rod vision alone is used for any great length of time, such as walking in the country without any artificial illumination at night. Even driving at night uses powerful headlamps and involves illumination of the visual scene to a level where cones function. Hence by preventing dark adaptation during sleep, periods of anoxia that would otherwise occur will be greatly reduced in number and duration and the development of retinal diseases such as diabetic retinopathy or age-related maculopathy may be slowed or stopped.

As a result of the treatment in one embodiment of the invention, the amount of oxygen required by the retina decreases by about 50%, at times when the demand is greatest, and is therefore be more effective, better directed, cheaper, and more acceptable than other forms of treatment.

Brief Description of the Drawings

Figure 1 is a horizontal half-sectional diagram through the eye of a user wearing a device according to a first embodiment of the invention;

Figure 2 shows the left hand side of the device of the first embodiment substantially as seen by the user when putting the device on;

Figure 3 is a graph showing the response of rod and cone cells as a function of wavelength.

Figure 4 is a horizontal half-sectional diagram through the eye of a user wearing a device according to a second embodiment of the invention;

Figure 5 shows the left hand side of the device of the second embodiment, substantially as seen by the user when putting the device on;

Figure 6 is graph of the spectral emissivity of chemoluminescent and phosphorescent material suitable for use in the device according to the second embodiment; and

Figure 7 is graph of the decay of emission intensity of the chemoluminscent material.

Description of Embodiments

The medical theory underlying the embodiments of the invention will first be discussed. References in square brackets are to the Reference section at the end of this description.

Diabetic Retinopathy

Diabetes - experimental and clinical - selectively damages retinal microvessels. Elsewhere the diabetic state causes thickening of capillary basement membrane, but only in retinal blood vessels is there loss of pericytes, and swelling and damage to capillary endothelial cells that result in the capillary dropout, microaneurysms, leakage, cellular damage and new blood vessel growth that characterises DR [6]. This indicates that local factors unique to retina provoke DR although retina is often considered "an approachable part of the brain" [7]. The main difference between retina and

brain tissue is, of course, the photoreceptors. Their signal transduction mechanism, found in no other neurone, is very energy-demanding. In darkness the surface membrane of the rod outer segment is leaky, and water and sodium enter, to be extruded by pumps in the inner segment. Light seals the leaks in the outer segment, reduces or stops the dark current and promptly halts the pump action, reducing metabolism and oxygen uptake. The maximum magnitude of the dark current under strict dark-adapted conditions indicates that the rod circulates its entire cytosol volume in 30 seconds [8] and this process produces more heat and consumes more oxygen than any function in any other cell. The photoreceptor layers are avascular, and the oxygen supply is normally barely sufficient. This explains why dark adapted sensitivity in normal persons begins to drop when there is a slight reduction of inspired oxygen, equivalent to ascending to 3,000 feet [9], and loss of dark adaptation is the first symptom in a variety of pathological conditions, ranging from *polycythaemia vera* to partial carotid occlusion, before other functions fail [10-12].

Experiments with oxygen microelectrodes in normal eyes show a precipitous drop in pO_2 as the microelectrode passes from the level of the choroidal blood vessels to fall to a minimum in the vicinity of the rod mitochondria [13-14]. In dark-adapted eyes this minimum pO_2 tension is zero, but even during a brief flash of light it reaches 30 mm Hg [15]. Unlike brain cells, rods can apparently function in such ultra-low oxygen environments but their intense activity in darkness reduces the pO_2 of the inner retina, a region served by blood vessels that penetrate inward from the vitreal surface. Therefore, when rods operate at maximum sensitivity, with less than optimal oxygen supply, a relative anoxia develops in less distal portions of the retina.

Clinical diabetic retinopathy appears to develop years after the condition is diagnosed. But during the preclinical period, although the fundus is normal (stage 0), psychophysical and electrophysiological experiments demonstrate that anomalies are developing, especially in rod vision (reviewed in [16]). It has been shown that several of these losses can be promptly though partially

reversed by inhaling oxygen from a face mask [17-19]. Therefore, even at stage 0, there must be a degree of oxygen lack in the retina of diabetics. Thus the loss of dark adaptation in diabetics with stage 0 is explicable. Diabetes causes a series of slight changes in the circulation: glycosylated Hb has a Michaelis-Menton curve shifted slightly to the right, basement membranes thicken, and RBC walls stiffen slightly, reducing ease of transport through the capillaries. Oxygen demand may be increased, as an intracellular 'pseudohypoxia' develops, associated with high levels of glucose and Advanced Glycation Endproducts (AGEs) - and autoregulation of (retinal) capillaries diminish. In most tissues, these modifications would be of little consequence: but the retina has very little reserve capacity, and slight reductions in oxygen supply would tend to decrease the pO_2. This cannot fall below the zero level found in the region of the rod mitochondria, but proximal and distal to this point, PO2 will be reduced. This concept is supported by findings in diabetic cats, where it has been found that retinal oxygen tension is reduced relative to normal, even in regions with no fluorescein angiographic evidence of actual capillary dropout [20].

Hyperglycaemia is the first signal to trigger the onset of DR and the cascade of metabolic and biochemical changes. High levels of intracellular glucose cause, among other changes, a state of 'pseudohypoxia' in retinal cells (Wiliamson, Brownlee). (Pseudo)hypoxia may upregulate factors such as vascular endothelial growth factor-A (VEGF) [1]. VEGF is a prime regulator of angiogenesis and vascular permeability (reviewed in [21]). Evidence is available for a role of VEGF-A in the early stage of DR, as retinal VEGF expression by activated Müller cells is increased a few weeks after the onset of diabetes in rats [23- 28]. Intracellular 'pseudohypoxia', high levels of glucose and AGEs all induce increased VEGF expression in cells *in vitro* [22]. We suggest that in pre-clinical DR, the increased anoxia associated with complete dark adaptation is a crucial and necessary driving force of VEGF upregulation in the presence of chronic hyperglycaemia. This hypothesis is supported by experiments in a rat model of early diabetes. In these animals,

12 hours of darkness caused an increase of VEGF almost perfectly correlated with the increase in lactate suggesting a switch from aerobic to anaerobic metabolism [35]. Therefore even in the preclinical phase of diabetic retinopathy, dark-adapted rods are instrumental in the increase of VEGF expression. VEGF overexpression may reflect a stress response enabling survival of vascular and neuronal cells, but it also induces early BRB breakdown [31], leucocyte adhesion to retinal vessels [29], and causes swelling and proliferation of endothelial cells [30] within days.

Once this increase is established, repeated insults cause replicative senescence of endothelial cells resulting in the vascular changes seen in clinical DR, which, themselves lead to a vicious circle of ischaemia, VEGF production, endothelial swelling and capillary non-perfusion, reinforcing the production of anoxia [30]. This scheme of events can easily be envisaged against the background of rod-induced anoxia. Later, when clinical DR is established, hard exudates demonstrate the capillary leakage, and capillary dropout and neovascularization can be seen: the anoxia associated with DR is evident. The role played by VEGF-A and its receptors in this stage is very well documented [1].

Evidence is plentiful for the suggestion that "rod driven anoxia" triggers the changes that cause DR. As predicted, DR does not occur in patients doubly afflicted with diabetes and retinitis pigmentosa [16] because rod outer segments are reduced. Proliferative DR may even regress when an anti-angiogenic state develops in retinal degeneration [39]. In the mitochondrial disorder MIDD 3243, which begins in adult life, diabetes is characteristic, and DR commonly occurs unless a retinal degeneration also develops [36-38]. Some longstanding diabetics (types I and II) develop no signs of DR at all. In a group of these, it has been shown that the upregulating effect of anoxia on blood white cell VEGF production is greatly reduced (and by implication, in all cells) [40]. However, the best evidence of the importance of anoxia is the success of the common treatment of DR, pan-retinal photocoagulation [22], which was introduced to destroy retinal tissue thought to be liberating

"toxins", but which may work simply by destroying enough rods to increase retinal pO_2 [23].

Of course several systems contribute to diabetic retinopathy. The effect of glucose and insulin is well known, and the polyol pathway, and pseudohypoxia that is associated with NAD-NADH levels all can cause retinal damage. But, for example while knockout of rods prevents any vascular proliferation in experimental oxygen induced retinopathy, knockout of insulin receptors which are indirectly necessary for VEGF activity reduces vascularisation by 50% [41]. Almost the only time human rods ever dark adapt (and maximise their oxygen needs) is during sleep. Our hypothesis predicts that if persons with diabetes and grade 0 - I retinopathy were to sleep in light levels of 1-10 cd/m^2, sufficient light would pass through the lids to protect against DR (consideration of the quantity of light required can be found in [24]). Other testable predictions are that (i) elderly diabetics who suffer from sleep apnoea would have considerably more DR than diabetics who did not, (ii) at high latitudes an annual maximum frequency of DR incidence would be reported in early spring, with a minimum in early autumn, but would be much less in equatorial zones.

Age-related macular degeneration

Age related maculopathy is a multifactorial condition, and a genetic component has been analysed [42]. However, the rapidly increasing prevalence suggests environmental factors [43-45] and this is also indicated by histopathologic studies (see below). The natural history shows that after the age of 55, increasing numbers of persons develop large "soft" drusen, and the number of these increase with time. The drusen are seen in the posterior pole, often in a ring peripheral to the macula [46]. The drusen are the clinically visible indicators of a collection of abnormal material between Bruch's membrane and the RPE and Bruch's and the choroid, known as basal laminar and basal linear deposit [47-49]. The RPE also becomes loaded with characteristic lipofuscin granules, which are a result of phagocytosis of ROL

fragments, and incomplete digestion [50-51]. The volume of shed outer segments is ~2 μm^3 per rod per day [5] and ~ 30 outer segments contact each RPE cell. Analysis of the material [52-4] shows it contains lipids which are highly oxidised, suggesting the formation by reactive oxygen species. The origin of this material is thought to be the photoreceptor outer limbs and represents the inability of senescent RPE to properly digest phagocytosed ROL. This failure leads to the accumulation of the deposits, in both the " dry" and "wet" forms of ARMD [55]. At the same time, abnormalities in the choroid occur [56]. Thus, although there is some correlation between atherosclerosis and Alzheimer's, ARM appears to be another disease whose manifestations are due to a local retinal factor [57].

Visual functions are affected early in the condition [58-67] and it is reported that dark adaptation is slowed and less complete even in the early stages, although recently, a similar finding has been made for blue cone vision [65, 68-70]. Like DR, there is an asymptomatic "preclinical" stage but during this stage, drusen can be seen, pigment irregularities have been reported, and subtle losses of rod and cone function occur. The histologically verified loss of rods in the region of highest density [71] has suggested that the condition is caused by the death of rods, but at such a stage there is also evidence of an obstructive barrier between choroid and RPE [72-3], which hinders the diffusion of oxygen from the choroid, and abnormal biochemical and immunocytological findings have been reported. With the loss of rods irregularities and patchy diminution of choroidal blood flow may be seen in aging eyes [74]. The causal relationships of these different findings are obscure. It may be that the primary disorder is a defect in the RPE. Curcio [71] raises the possibility that rod death leads to the loss of a trophic factor that is necessary for normal cone function. However, in various other forms of night blindness, with absent or very reduced rod function, macula degeneration does not occur as an early event. The early stage of ARM occurs with little obvious symptomatology, but after some time, subjective visual disturbance occurs associated with a change in retinal appearance. In the

"dry" form, a limited retinal geographic atrophy eventually occurs. The fovea can be spared. In other cases, there is growth of choroidal new vessels through Bruch's into the subretinal space, local oedema, and leakage. At this stage there is metamorphopsia, considerable reduction in acuity and obvious retinal damage. At such a stage the condition is often termed Age-Related Macular Degeneration.

The RPE controls the vascularity of the choroid. There is a normal strong polarisation of the secretion of VEGF basolaterally [75], and this paracrine relationship with the choriocapillaris [76] is disturbed by changes in Bruch's that forms a barrier to aqueous diffusion from the choroid. Even in the earliest stages, there may be retinal and RPE hypoxia because of the high metabolic requirements of the retina. Any diminution of VEGF secretion into the choroid will cause choriocapillaris atrophy and reduce the oxygen supply to the overlying RPE and retina. Thus ageing changes enter a vicious circle, and alteration in RPE function eventually leads to further relative atrophy of choriocapillaris, the deposition of basal deposits, the relative impermeability of Bruchs, and documented loss of rod and blue cone function. At this clinical stage considerable retinal and RPE hypoxia upregulates VEGF, but transfer to the choriocapillaris is so reduced that a higher critical concentration may develop in the outer retina, or proximal to Bruchs, triggering CNV [75,77,78]. Alternatively the anoxia can cause death of RPE and retina in geographic atrophy. Although many factors contribute to this sequence of change, material shed from the rods is responsible for the barrier to fluid transfer, and the metabolic demands of rods contribute heavily to anoxia and VEGF upregulation. This suggests that were rods to be absent the changes associated with ARM would develop more slowly. A small number of scattered laser burns in ARM reduces drusen, and can stabilise retinal function [79-86]. The choroidal Neovascularization Prevention Trial (CNPT) [87] also determined this, but the immediate incidence of neovascularisation following their protocol was so high recruitment was terminated. However, after 5 years, the patients' vision was not worse than controls, so that some retardation in

development of ARMD must have occurred. The longest small trial shows that the production of "wet" AMD is reduced 8 years after lasering. The mechanism whereby such light lasering removes drusen at least temporarily, and apparently arrests the progress of retinal degeneration is not fully established. However, there is evidence that many more burns, applied to persons with much milder ARM, can have beneficial outcome.

In type II diabetics ARM occurs at a similar frequency to normal controls [88]. However after PRP, there is a marked reduction in the prevalence of wet and dry AMD [89] and there is much anecdotal evidence to the same effect. All this suggests that an important factor in the development of ARM may be a relative anoxia in the outer part of the retina/RPE complex. The reported increase in cytokine formation [90] is of course consistent with a local relative anoxia. It is necessary that such anoxia would be worse during periods of dark adaptation. It is possible that the condition would progress more slowly if such periods were avoided.

Hence, DR and/or ARM could be avoided by preventing dark adaptation of the eyes during sleep. The following embodiments of the invention provide a device for preventing dark adaptation during sleep.

Device

In a general embodiment of the invention, there is provided a wearable device for preventing dark adaptation of the eye of the wearer when asleep. The device includes a light source which emits light onto the eyelid of the wearer. The light has properties selected so as to prevent dark adaptation without disturbing the wearer's sleep. Preferably, the light is low-intensity, substantially constant green light.

Figures 1 and 2 show the left hand side of the device 1 in a first embodiment of the invention. The right hand side (not shown) is symmetrical with the left hand side. The device 1 has a frame 2 which is secured around the eyes 3 with a headband 4, like a pair of goggles. The edges of the frame 2 are lined with a soft foam material 5 which contacts the user around the bridge of the nose and

the orbit of the eyes and prevents other parts of the device 1 from touching the eyelid or eye. The front of the frame is covered with plastic sheet 6.

Preferably, the frame 2 is flexible for comfortable wear by different users. The headband 4 may be elastic and/or adjustable, for the same reason.

A pair of light sources 7 are mounted on respective substrates 8 within the frame 2 so as to emit light towards the eyes. Each light source 7 may comprise one or more light-emitting diodes (LED's), preferably subminiature LEDs. The light sources 7 may be powered by an external battery 9, but it is preferred that the battery 9 is integral, that is mounted directly or indirectly on the frame 2. The battery 9 is preferably rechargeable. In a preferred embodiment, the device 1 includes an induction charger and a rechargeable battery 9, to allow the device 1 to be conveniently recharged between uses.

A protective pad (not shown) may be disposed between the substrate 8 and the eye 3, with an aperture or window allowing light from the light source 7 to fall upon the eyelid 10. The window may include a filter if this is necessary to achieve the spectral and intensity requirements of light falling on the closed eyelid 10.

The light sources 7 and battery 9 are selected, and the arrangement of the light sources 7 within the frame 2 designed, to emit light onto the surface of the eyes satisfying the following requirements. The light must inhibit dark adaptation of the retina 11 when the eyelid 10 is closed, but should not disturb the sleep of the user. Preferably, the power requirement of the light sources should be as low as possible, so that a small, integral battery 9 can be used.

In this embodiment, these requirements are satisfied by a selection of both wavelength and intensity for the light. The sensitivity of rods varies with wavelength within the visible spectrum, as shown in Figure 3, with a maximal absorption at 498 nm with a half-bandwidth of approximately 40 nm. The attenuation of light by the eyelids also varies with wavelength, becoming lower at longer wavelengths. For example, at 510 nm the attenuation is about 2 $\log_{10}$ unit (i.e. 10^2 intensity reduction, or 99% attenuation), and at 630 nm, about 0.5 $\log_{10}$ unit. Convolving the sensitivity of the rods with the

attenuation of the eyelids gives an optimum wavelength of 480nm. Hence, LED's emitting predominantly around 480 nm were chosen in this embodiment. After filtering by the eyelid, the light has a peak intensity of about 510 nm. Deviation from the emitted or filtered wavelength is possible within a range of about 400 to 550 nm, as can be seen from Figure 3, but leads to the following disadvantages. First, less light is absorbed by the rods, so a higher intensity is required. Second, the light will be absorbed more strongly by cone cells, leading to a greater perception of colour by the user and hence more potential to disturb the user's sleep.

The intensity requirement of the light is determined as follows. A surface illumination that is just visible to the dark-adapted eye is <1 μ microcd.m^{-2} [A7]. The relationship between visual threshold with eyes open and closed at different wavelengths is given in [A6]: pp 305-316. Alternatively the quantity of light required is that required to semi-saturate the rod signalling mechanism, i.e. 1-30 quanta/second/rod. The radiometric units can be translated into simple psychophysical measurements, using the following relationships:

Visual sensation occurs in darkness when 1 rod in 200 absorbs 1 quantum/second.

The relationship between background illumination (I) and a light flash that is just visible (ΔI) is given by (ΔI)/ (I) = Constant. Consequently, a background that increases (ΔI) by 200-2000 times is sufficient for the purposes of reducing sensitivity and the need for oxygen in the retina.

The colour vision threshold is 1000-3000 times the absolute threshold of vision. Increasing rod threshold to this level would prevent dark adaptation. At such lighting levels, hues are just visible, but the colour gamut is much reduced. Thus a user can immediately discover how dim and un-arousing such a light level is.

In the embodiment, the mean quantity of light emitted, measured at the surface of the closed lid, is log 5.7 microcd.m^{-2}. The current drawn from the battery 9 was 1 mA.

The light intensity may be variable, for example by ± 1.5 $\log_{10}$ unit, for research purposes, but the light intensity is preferably fixed at an optimum level, since the minimum intensity required does not vary greatly between users.

The light intensity is preferably substantially constant and/or does not fluctuate rapidly while the device 1 is in use, and the device preferably includes no other light sources having substantially different spectral characteristics from the light sources 7. Hence, the device differs significantly from light goggles intended to alter the mental state of the user by various means of illumination including flashing red and green LED's at a much higher intensity than is required to inhibit dark adaptation of the eye, in a way likely to disturb a user's asleep.

A device 1 in a second embodiment is shown in Figures 4 and 5, which are similar to Figures 1 and 2; similar parts to those of the first embodiment carry the same reference numerals. The second embodiment differs from the first embodiment by having a self-contained non-electrical luminescent light source 7', instead of the LED's 7, substrate 8 and battery 9. The luminescent light source produces light having the desired characteristics described above.

In one example, the luminescent light source 7' comprises a hollow capsule of Pyrex™ glass coated on its interior surface with phosphor, and containing tritium gas as a source of beta radiation for inducing phosphorescence in the phosphor. Products having a phosphorescent arrangement of this type are commercially available from SRB Technologies (UK) Ltd. of Berkshire UK. In the present example, the capsule is manufactured as a disc conforming to the dimensions of the eye and fixed within the device of the second embodiment. The tritium gas is a low-activity radioactive source and therefore safe for domestic use. The emission spectrum of the luminescent light source is shown in Figure 6.

In another example, the luminescent light source 7' comprises a phosphorescent material without an integrated source of radiation. For example, the luminescent light source 7' may comprise a substrate coated

with phosphorescent material, which is irradiated by UV light and then fixed within the device 1 shortly before use. The UV light may be provided by an electrically powered UV light source in a housing for irradiating the phosphorescent material while preventing leakage of UV light.

In another example, the luminescent light source 7' comprises chemoluminescent material, in the form of a thin hollow transparent or semi-transparent disc containing fluorescent dye and an oxidizing agent separated by a barrier. The barrier is broken shortly before use, causing the oxidizing agent and the dye to mix and emit light, and the disc is then fixed for use within the device 1. A similar reaction is used within commercially available light sticks. However in this embodiment, the disc is made to conform to the dimensions of the eye and arranged immediately in front of the eye. Chemoluminescent discs of suitable dimensions are available from Omniglow Ltd. of Salisbury, UK; however, these are intended for signage or other displays. Novelty spectacles having frames composed of thin chemoluminescent tubes are also available from Glowsticks Direct of Newport, Isle of Wight, UK, but these are clearly unsuitable for wearing overnight in bed, as they are likely to become dislodged and/or apply excessive pressure to the wearer's head. Moreover, the chemoluminescent tubes are not positioned directly in front of the user's eyes.

The spectral emission characteristic of a chemoluminescent light source suitable for use in the second embodiment is shown in Figure 6, and the decay of its luminous intensity is shown in Figure 7; the intensity decays slowly over 8 to 10 hours and is sufficient for one night's treatment, but new chemoluminescent sources are used each night.

No source of electrical power is required in the second embodiment, so that the device 1 may be particularly light, convenient and cheap to manufacture.

In some examples of the second embodiment, the luminescent light source 7' may be flexible, and the device 1 as a whole may be flexible, for greater comfort when worn in bed. For example, the device 1 may comprise a band of flexible material to which the luminescent light source is fixed, and may be

detachable. The device 1 may include one or more pockets of transparent flexible material for removably holding the luminescent light source 7'. The luminescent light source 7' may alternatively be fixed directly onto the user's eyelids with clinical adhesive tape or an adhesive patch provided on the luminescent light source 7', with a removable backing layer.

Other light sources have been contemplated by the inventor, and may be used if suitable. For example, bioluminescent light sources would be suitable if they could be made tolerant of the conditions in which the device 1 is intended to be used. Electroluminescent light sources are currently unsuitable for use in the device 1 because they require a high voltage (110 V), and generate a high-pitched whine, but would otherwise be suitable if these problems were overcome. In either embodiment, it is not essential that the device 1 block some or all of the background illumination, but this may be advantageous in a product which is also intended as a light mask, such as may be worn while travelling, to block out ambient light.

Preventative Treatment

A method of treatment to prevent or inhibit the onset of DR and/or ARM will now be described. A patient wears the device 1 substantially every night for a period of at least 6 months, and preferably for at least two years. Every 6 months, standard 4 view fundus photographs are taken to observe the stage of retinopathy. The patient may already be suffering from mild stage 1 background diabetic retinopathy, or may have stage 0 retinopathy (i.e. a normal fundus). The treatment may at least slow or halt the progression of diabetic retinopathy.

Alternative embodiments

The above embodiments are described by way of example and the invention is not restricted to them. Alternative arrangements of the device 1 may be contemplated, so long as they can be worn by a user when asleep without being dislodged. The device may take the form of headwear also having some

other purpose, such as the light mask described above. If for any reason it is desired to treat one eye only, then the light source may be arranged to illuminate only one eye, in which case the device may take the form of an eye patch, for example.

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A7 Le Grand Y Light Colour and Vision Chapter 10 fig 64. pg 242. Chapman and Hall London 1962).

Claims

1. A light-emitting device suitable for wearing by a user, comprising a light source for emitting light onto at least one eye of the user such that dark adaptation of the eye is inhibited without substantially disturbing the user when asleep.

2. A device according to claim 1, wherein the intensity of the light is sufficient to cause on average at least one quantum of the light per second to be absorbed per rod.

3. A device according to claim 2, wherein the intensity of the light is sufficient to cause on average between 1 and 30 quanta of the light per second to be absorbed per rod.

4. A device according to any preceding claim, wherein the mean intensity of the light, incident on the closed eyelid, is at least log 5.7 microcd.m^{-2}.

5. A device according to any preceding claim, wherein the mean intensity of the light, incident on the closed eyelid, is at or below the colour vision threshold of the eye.

6. A device according to claim 5, wherein the mean intensity is 0.1 candela or less.

7. A device according to any preceding claim, wherein the light is green.

8. A device according to claim 7, wherein the wavelength of the light emitted onto the eye is predominantly at or around 480 nm.

9. A device according to claim 7 or 8, wherein the wavelength of the light is such that the light falling on the retina of the eye when the eyelid is closed is predominantly at or around 510 nm.

10. A device according to any preceding claim, wherein the intensity of the light is substantially constant.

11. A device according to any preceding claim, wherein the light source comprises one or more light-emitting diodes.

12. A device according to any preceding claim, arranged to emit the light onto both eyes of the user.

13. A device according to any preceding claim, including means for securing the light source relative to the eye when the user is asleep.

14. A device according to claim 13, wherein the means for securing is a headband.

15. A device according to any preceding claim, arranged to block ambient light from the eye.

16. A device according to any preceding claim, wherein the light source is electrically powered.

17. A device according to claim 16, wherein the light source comprises one or more light-emitting diodes.

18. A device according to any one of claims 1 to 15, wherein the light source is luminescent.

19. A device according to claim 18, wherein the light source is chemoluminescent.

20. A device according to claim 18, wherein the light source is phosphorescent.

21. A device according to claim 20, including a source of radiation arranged to induce phosphorescence.

22. A light-emitting device suitable for wearing by a user when asleep, including a luminescent light source arranged to emit light onto at least one eye of the user.

23. A light-emitting device according to claim 22, wherein the luminescent light source is chemoluminescent.

24. A light-emitting device according to claim 22, wherein the luminescent light source is phosphorescent.

25. A device according to claim 24, including a source of radiation arranged to induce phosphorescence in the phosphorescent material.

26. A device according to any one of claims 22 to 25, wherein the light source is arranged directly in front of the eye.

27. A device according to any one of claims 22 to 26, wherein the intensity of the light is at or below the colour threshold of the eye, when incident on the closed eyelid.

28. A method of preventing or inhibiting the progression of a retinal disease, comprising wearing a device according to any preceding claim, while asleep.

29. A method according to claim 28, wherein the device is worn over a period of at least 6 months.

30. A method according to claim 28 or 29, wherein the disease is diabetic retinopathy.

31. A method according to claim 28 or 29, wherein the disease is age-related maculopathy.

Fig. 1

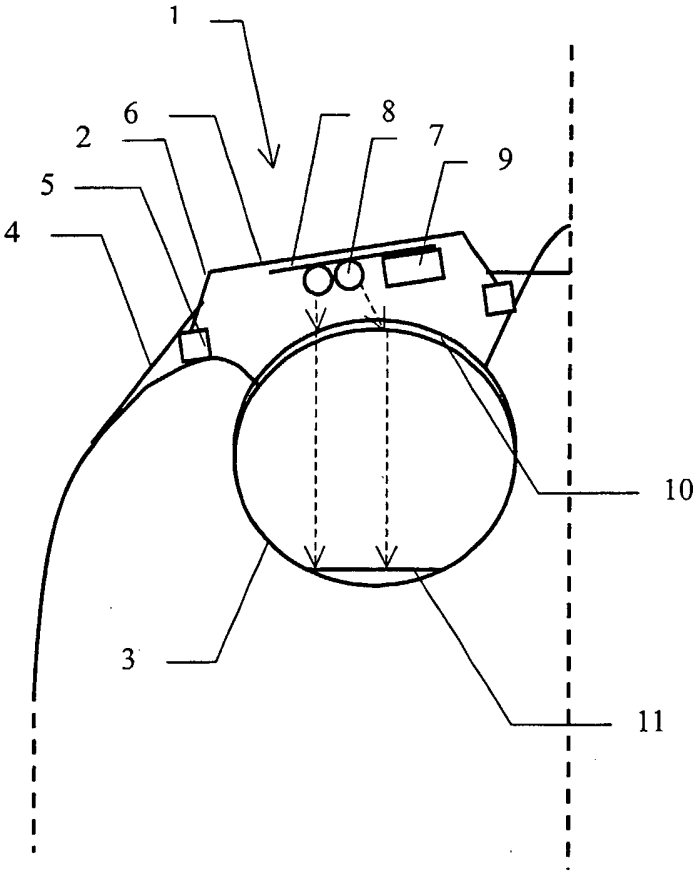
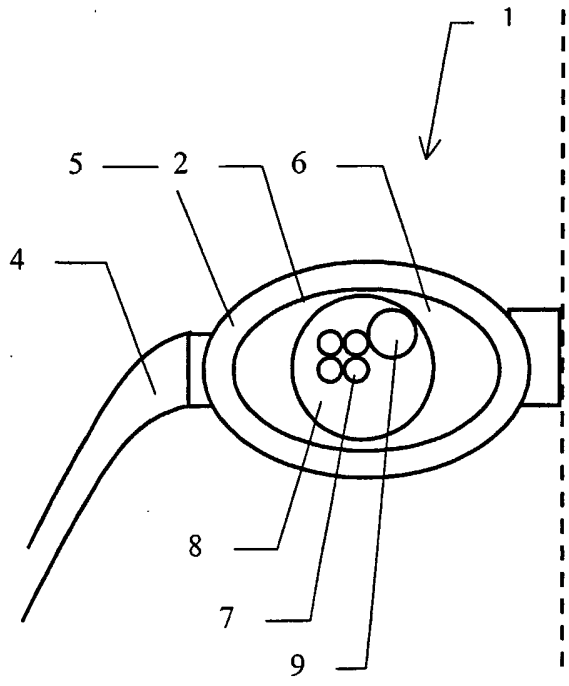


Fig. 2



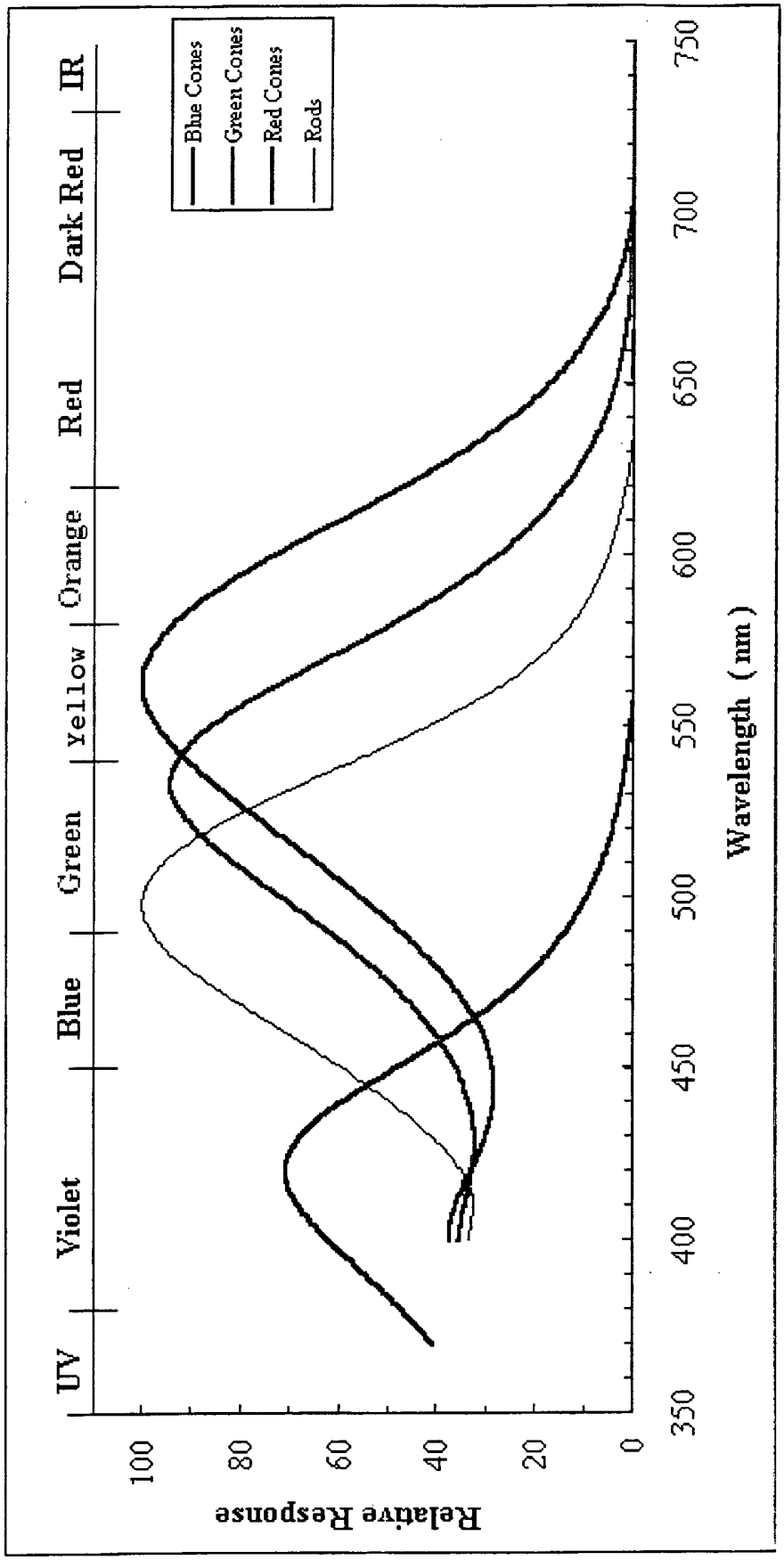

UV
Violet
Blue
Green
Yellow
Orange
Red
Dark Red
IR
Blue Cones
Green Cones
Red Cones
Rods
Relative Response
100
80
60
40
20
0
350
400
450
500
550
600
650
700
750
Wavelength (nm)

Fig. 3

Fig. 4

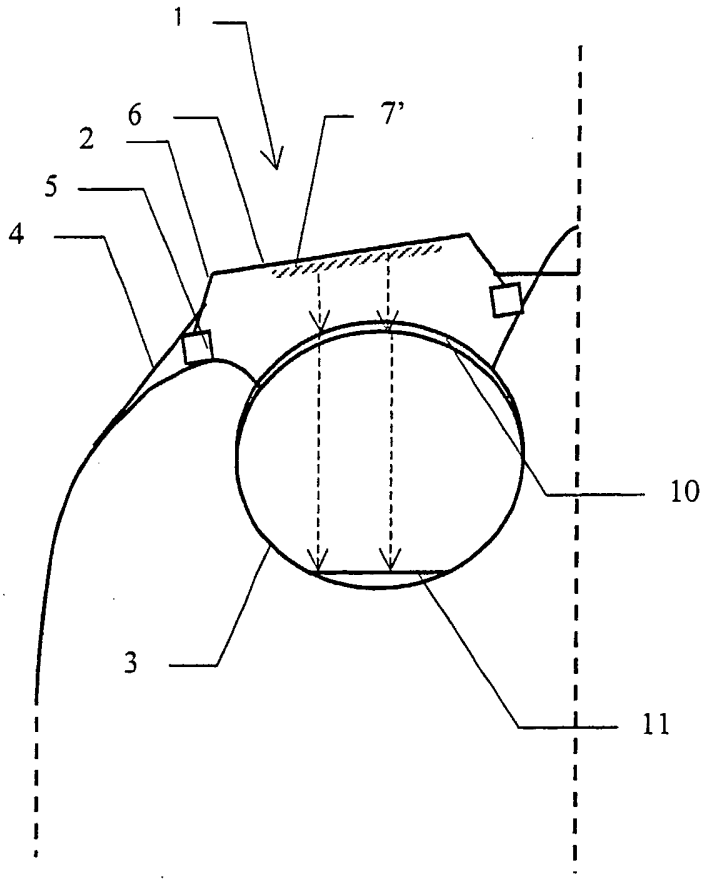
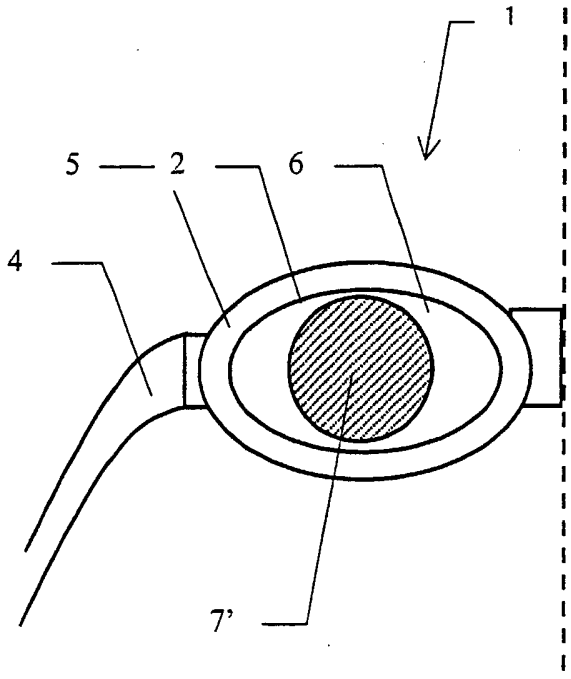


Fig. 5



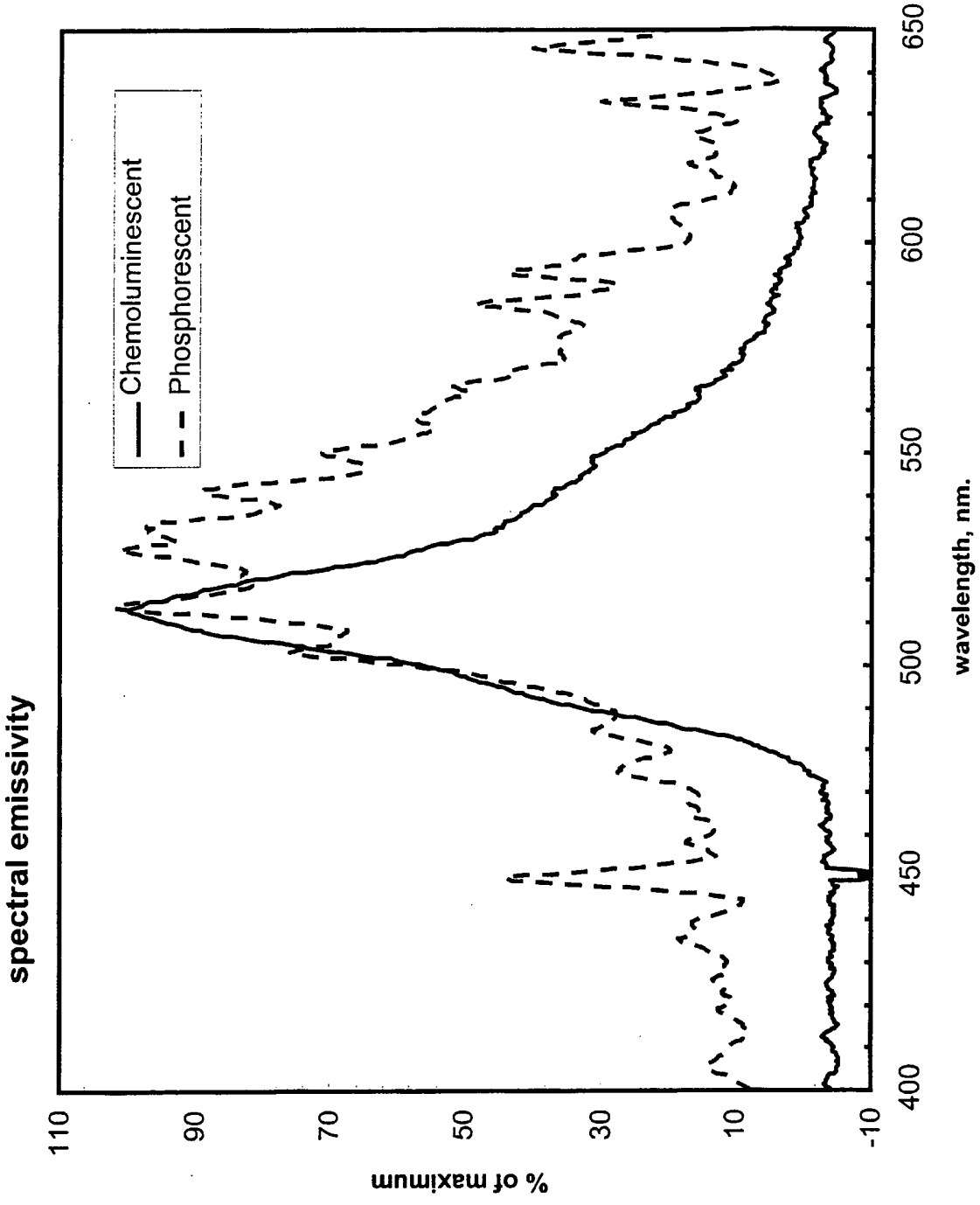

spectral emissivity
Chemoluminescent
Phosphorescent
110
90
70
50
30
10
-10
% of maximum
400
450
500
550
600
650
wavelength, nm.

Fig. 6

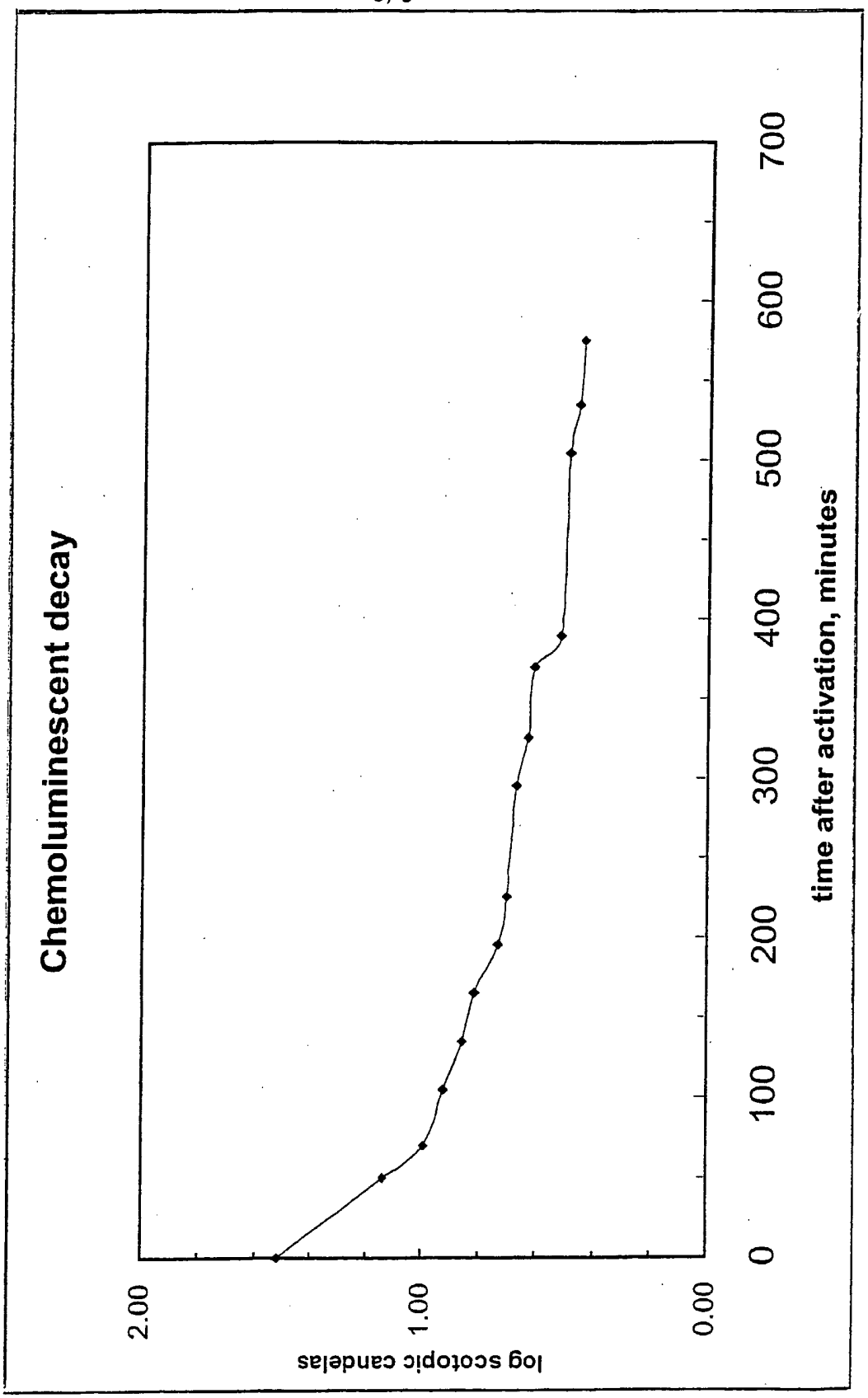

Chemoluminescent decay
log scotopic candelas
2.00
1.00
0.00
0
100
200
300
400
500
600
700
time after activation, minutes

Fig. 7

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/000535

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61F9/00 A61F9/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F A61H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARDEN G B; WOLF J E; TSANG Y: "Does dark adaption exacerbate diabetic retinopathy?" VISION RESEARCH, vol. 38, no. 11, June 1998 (1998-06), pages 1723-1729, XP002331531 ENGLAND Methods, Discussion	1,22
X	US 5 486 880 A (HOUSE ET AL) 23 January 1996 (1996-01-23)	1-6,9, 13,16-18
A	column 3, line 44 - column 4, line 25; figures	7,8
X	US 4 938 582 A (LESLIE ET AL) 3 July 1990 (1990-07-03) column 1, line 64 - column 2, line 65; figures	1,7,8,15
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2005	28/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ruff, C

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INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/GB2005/000535

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 396 259 A (MILLER ET AL) 2 August 1983 (1983-08-02) column 2, line 20 - column 3, line 19	1,7,8, 14,15
X	US 4 777 937 A (RUSH ET AL) 18 October 1988 (1988-10-18) column 2, line 53 - column 3, line 7	1,7,14, 15,20, 22,24, 26,27
X	US 6 319 273 B1 (CHEN JAMES C ET AL) 20 November 2001 (2001-11-20) column 9, line 42 - column 10, line 45; claim 3; figures 12,13	1,18,19, 22,23, 26,27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/000535

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 28-31
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ational Application No
PCT/GB2005/000535

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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