A biosensor canalicular stent is provided having at least one incorporated biosensor for monitoring one or more properties of tear fluid. The stent is designed for insertion into either or both of the lacrimal canaluli of an eyelid. When positioned in the canalculus, the incorporated biosensor is brought into contact with tear fluid draining from the eye through the upper or lower punctum, through the canalculus, and thence to the nasolacrimal sac and out to the nasal cavity via the nasolacrimal duct. The tear fluid biosensor is capable of measuring one or more properties of tear fluid, such as the level of glucose. Information about the measured properties of the tear fluid are transmitted by the device to a receiver outside the eye. Alternative embodiments measure physiological properties of the eye by utilizing sensors that can come into contact with the tear film or the sclera or cornea of the eye, e.g., to measure changes in eye curvature or intraocular pressure. Methods of using the canalicular biosensor stent to monitor bodily functions and physiological properties of a patient via a sensor stent positioned in the patient's canalculus are also disclosed.
BIOSENSOR CANALICULAR STENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to US provisional application no. 62/153,022 filed April 27, 2015, and to US provisional application no. 62/244,621 filed October 21, 2015.

FIELD OF THE INVENTION

The invention relates to a lacrimal stent capable of detecting and monitoring properties of a bodily fluid, e.g., tear fluid, and/or intraocular pressure. The stent is constructed of a biocompatible material, preferably silicone, and is designed for insertion into the upper and/or lower canaliculus of the lacrimal drainage system of the human eyelid. Methods of detecting and monitoring properties of tear fluid, e.g., glucose levels, and intraocular pressure are also disclosed.

BACKGROUND OF THE INVENTION

Diabetes Mellitus (DM) is the most common endocrine disease in the world and is expected to triple in prevalence due to an aging population and increasing longevity in diabetic patients (http://www.cdc.gov/media/pressrel/2010/rl01022.html). About 29.1 million Americans have diabetes, and one-quarter of them do not know they have it (http://www.cdc.gov/media/pressrel/2010/rl01022.html). The number of patients diagnosed with diabetes has increased 7-fold during the last 20 years. If this current trend continues, the population of diabetes patients will be 350 million in 2030, meaning that 7 million people will be added annually.

Self-monitoring by patients diagnosed with a chronic or progressive disease is vital. Billions of patients worldwide take regular readings of bodily conditions to monitor the progression or effectiveness of treatment for chronic disease processes such as diabetes and hypertension. Studies of diabetes self-care have shown that self-efficacy, or the patient's assessment of their capability to organize and execute a treatment regimen, is an essential

Patient non-compliance (failure to adhere to testing, management, and recommended healthcare advice) is a serious healthcare concern that poses a great challenge to the successful delivery of healthcare. Thirty-two million Americans use three or more medicines daily and 75% of adults are non-adherent in one or more ways. The economic impact of non-adherence is estimated to cost $100 billion annually (http://www.epill.com/statistics.html). Patient non-compliance is not only limited to the failure to take medication, but also the failure to make lifestyle changes, undergo tests including self-testing or keep appointments with physicians. Diabetes was the seventh leading cause of death in 2010, and is the leading cause of new cases of blindness among adults under age 75, cases of kidney failure, and incidence leg and foot amputations among adults not due to accident or injury. People with diagnosed diabetes have medical costs that are more than twice that of those without the disease.

Total costs of diagnosed diabetes in the United States in 2012 was estimated at $245 billion: $176 billion for direct medical costs and $69 billion in reduced productivity. After adjusting for population age and sex differences, average medical expenditures for patients diagnosed with diabetes were 2.3 times higher than for patients in the absence of diabetes. Centers for Disease Control and Prevention, *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States*, 2014, Atlanta, GA: U.S. Dept. of Health and Human Services; 2014. It has been estimated that 100% compliance with a prescribed drug regimen would reduce the risk of kidney disease, stroke, heart failure or amputation caused by diabetes by 13.6%. This would reduce the costs of treatment by $9.3 billion per year. Kockaya et al., *Innovations in Pharmacy*, 2(2): 1-8 (2011).

Self-monitoring of blood glucose (SMBG) has been used in diabetic patients for over 25 years. Patients with Type 1 diabetes should monitor their capillary blood glucose concentration at least three or four times daily, and patients with Type 2 diabetes should probably monitor their capillary blood glucose concentration at least twice a day. See, American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement), *Diabetes Care*, 24(Supp. 1):S33-S43, (2001). These factors contribute directly to patient non-compliance. Currently, regular capillary blood glucose concentration testing and monitoring is accomplished by utilizing a finger-stick test, which many patients
find inconvenient, uncomfortable and cost-prohibitive. Research has shown that increased
self-monitoring of blood glucose is associated with improved glycemic control (Strowig et al., "Improved glycemic control in intensively treated type 1 diabetic patients using blood

Care, 21:1694-1698 (1998)). Despite this improvement, however, patients often do not
adhere well to this aspect of the diabetes regimen. A study using a large national sample of
patients with Type 2 diabetes found that 24% of insulin-treated patients, 65% of those on oral
medications, and 80% of those treated by diet and exercise alone either never performed self-
monitoring of blood glucose or did so less than once per month (Harris, "Frequency of blood

Care, 24: 979-982 (2001)). Daily self-monitored blood glucose (at least one blood glucose
check per day) was reported by only 39% of patients treated with insulin and just 5% of those
treated with either oral medications or diet and exercise. Ibid.

Complications due to non-compliance can be extremely detrimental to the patient’s
health and their disease management.

Medical need and the invasive nature of finger-stick blood sugar testing has led to
research and development of alternative methods to assess blood glucose levels in diabetic
patients.

U.S. Pat. No. 6,120,460 ("the ‘460 patent") teaches the utilization of a contact device
placed on the surface of the eye equipped with sensors to detect physical and chemical
parameters of a bodily fluid coming into contact with the sensors, then transmitting a signal
indicative of a property of the bodily fluid. Preferably the signals are transmitted
continuously as electromagnetic waves, radio waves, infrared radiation and the like. The
system utilizes eyelid motion and/or closure of the eye lid to activate a microminiature radio
frequency sensitive transensor mounted in the contact device. The ‘460 patent teaches that
the contact device remains in contact with the conjunctiva of the eye. In one embodiment,
the system comprises a contact device in which a microminiature radio frequency transensor
is mounted in the contact device which in turn is placed on the surface of the eye which is
capable of detecting chemical compounds, electrolytes, glucose level, cholesterol level, and
the like on the surface of the eye.

U.S. Pat. Nos. 8,090,426 ("the ‘426 patent") and 8,364,232 ("the ‘232 patent") describe
a plug for insertion into the superior or inferior punctum of the eyelid having a channel
therethrough to admit tear fluid and allow its passage through the plug. The plug is equipped with a biosensor in communication with the channel that is adapted to measure a property of tear fluid. One embodiment of the plug is described that is equipped with an enzyme cartridge having an enzyme such as glucose oxidase capable of reacting with glucose in tear fluid to yield a chemical byproduct (hydrogen peroxide) that is detectable by an electrode in communication with the plug channel that acts as an optical or amperometric sensor. The results of the biosensor detection is transmitted electronically to a receiver for analysis outside the eye.

There are inherent weaknesses in the design of the biosensor plug disclosed in the '426 and '232 patents, including its small size, its ability to migrate or be easily dislodged, possible granuloma formation or infection, and a design relying on the flow-through passage for the tears to effect tear fluid analysis.

The small size of the plug (e.g., 2.0 mm x 1.0 mm x 0.5 mm) could make it challenging to incorporate the necessary microchip hardware and biosensors needed for reliable biochemical testing. Additionally, the small size of the plug may make distal migration and embedding of the plug into the lacrimal canaliculus more likely and consequently lead to infection, irritation, tearing, and discharge. Serious negative consequences of punctal plug installation include pyrogenic granuloma formation and uncontrollable excess tearing, both of which conditions require prompt medical attention and occasionally emergency removal. Lacrimal canaliculus embedding and possible infection may require major lacrimal surgery to remove the plug. Conversely, if a plug is shaped, e.g., with a self-retaining collar, so as to remain at the punctum, its small size and placement may lead to extrusion and loss of the plug during even the gentlest rubbing of the eye.

The central passage or channel of the biosensor plug of the '426 patent, which is designed as a flow-through passage for tears, is also a potentially detrimental feature, as occlusion of the passage with debris will lead to malfunctioning of the plug and possible toxicity to the eye and lacrimal system. Also, the required continuous flow-through penetration of tear fluid through the instrument may lead to continuous assay of a static sample rather than monitoring the true composition of constantly renewed tear fluid entering the eye.

U.S. Pat. No. 8,985,763 ("the '763 patent") describes facilitation of communication by embedding chips or integrated circuits into a dual-layer contact lens. U.S. Pat. No. 8,870,370
"the '370 patent") describes contact lenses that facilitate antenna communication via sensor impedance modulation. In a stated embodiment, a system can include a contact lens and a radio frequency (RF) reader. The contact lens can include: a substrate; an RF antenna, disposed on or within the substrate; and a sensing component (e.g., a glucose sensing component), disposed on or within the substrate, and directly coupled to the RF antenna. A drawback of this design is the utilization of a contact lens on the surface of the eye. Daily and/or chronic contact lens wear may and has resulted in vision loss and blinding disease. Since the cornea is avascular tissue, it derives its oxygen supply via the tear film. The oxygen supply is replenished with each blink of the eye, which also induces a micro-movement of a properly fitted contact lens. Poorly-fitting contact lenses, improper care, use while swimming, and overnight usage severely deplete the oxygen supply, create stagnation, allow pathogens to enter the cornea and cause a suffocation of the corneal tissue. The dual-layer design may cause additional oxygen desaturation of the tear film because of its enhanced thickness, thereby reducing oxygen transmission. This poorly-oxygenated state and conditions are conducive to infectious keratitis. Additionally, since the cornea is a much more penetrable tissue compared to the sclera, it is unknown if the electromagnetic energy emitted by such a contact lens could potentially harm the intraocular tissues. This could potentially cause an iritis, uveitis, vitritis and/or retinitis with an inherent risk of blindness.

Chronic contact lens wear has additional vision-threatening risk factors on the eye, including corneal neovascularization, corneal abrasion, conjunctivitis, risks associated with corneal transplant surgery, corneal perforation, blindness, and loss of the eye.

Although the glucose monitoring devices described above provide several advantages compared to the current industry standard finger-lancing tests, the drawbacks of said systems make it clear that there is a continuing need for improved wearable/implantable biosensors, particularly those capable of monitoring and transmitting glucose levels to aid the treatment and/or management of diabetes.

**SUMMARY OF THE INVENTION**

The present invention relates to a canalicular stent (also referred to as a "lacrimal stent") capable of detecting and monitoring properties of a bodily fluid from the eye and/or intraocular pressure (IOP), and capable of being inserted into the superior and/or inferior canaliculus of the human eyelid. In a preferred embodiment of the invention the stent is
capable to detecting and monitoring properties of tear fluid. The stent is constructed of a biocompatible material, preferably silicone, and is designed for insertion into the upper and/or lower proximal portion of the lacrimal drainage system of the human eyelid, i.e., the superior and/or inferior canaliculus. In preferred embodiments, the proximal portion of the stent, designated herein as the head, is designed to be in direct contact with and to sense properties of the tear film on the surface of the eye. The sensing mechanism(s), preferably located within the head of the stent, is/are capable of determining various biochemical properties of the human body, for example, glucose levels.

In a preferred embodiment, a canalicular stent for measuring at least one property of tear fluid is provided, said canalicular stent comprising an elongated body adapted for placement into at least one canaliculus of a human eyelid, such that the body of the stent extends from the punctum through the vertical canaliculus and at least partly traversing the horizontal canaliculus, said body housing at least one biosensor capable of measuring at least one property of tear fluid, said biosensor being positioned in the body of the stent so as to be exposed to contact with tear fluid making contact with the outer surface of the stent, said body further housing apparatus for generating a signal corresponding to a property of tear fluid measured by said biosensor. In a more preferred embodiment the stent according to the invention is configured to have a head portion, connecting to a neck portion, in turn connecting to an elongated body that extends in a roughly 90° angle from the longitudinal axis of the head and neck portions, such that the stent fits the general shape of the canaliculus from the punctum through the vertical canaliculus and into at least a portion of the horizontal canaliculus, optionally extending to the common canaliculus and protruding slightly into the nasolacrimal sac. See Figs. 4A, 4B, 6A and 6B. A canalicular stent of this configuration may be advantageously positioned so that the head portion is adjacent the punctum or protrudes slightly therefrom, so that the head is in contact with the tear lake forming near the caruncle of the eye. In such a configuration, the biosensor of the biosensor canalicular stent is preferably located in the head portion of the stent, so as to come into direct contact with the tear lake. In alternative embodiments, the biosensor may be located in the neck or body portions, with the sensor located in the stent so as to be in open communication with an outer surface of the stent that will directly contact tear fluid passing around the stent through the lacrimal drainage system, when the stent is in position in a canaliculus of a patient's eyelid.
In a preferred embodiment, the biosensor is positioned at the proximal end of the elongated body so as to be immediately adjacent or protruding from the punctum when the stent is in place in the canaliculus of a human eyelid.

In one embodiment, the stent is adapted for insertion into the superior canaliculus of a human eyelid.

In another embodiment, the stent is adapted for insertion into the inferior canaliculus of a human eyelid.

In an alternative embodiment, the stent is adapted for insertion into both the superior canaliculus and the inferior canaliculus of a human eyelid, and wherein said biosensor is generally centrally located within the body of the stent.

In a preferred embodiment of the canicular stent of the invention, the distal end(s) of the stent body, with respect to the position of the biosensor, is/are furnished with self-anchoring devices effective to prevent migration of the stent from the original position of its placement in the eyelid.

In another embodiment of the stent, after placement in the canaliculus of the eyelid, the biosensor is in contact with tear fluid in the tear lake at the nasal end of the eye.

In a preferred embodiment of the invention, the biosensor is capable of measuring the level of glucose present in tear fluid, which in turn is an indicator of blood glucose level. Such measurements are useful, for example, to monitor glycemic index in a patient with a metabolic disorder such as diabetes, which measurements can assist in the patient being able to regulate food intake, administer insulin, or take other steps to treat or manage the disorder.

In additional embodiments, the biosensor is capable of measuring tear film osmolality, tear film biochemistries, and/or tear film pharmacology (i.e. drug content or concentration).

In further embodiments, the biosensor is capable of detecting blood components, measuring systemic and ocular blood flow, measuring heart rate and respiratory rate, tracking operations, detecting ovulation, detecting radiation and drug effects, detecting intraocular pressure (IOP), detecting blood alcohol level, assisting in diagnosis of ocular and systemic disorders, and the like.

In preferred embodiments, the biosensor continuously or periodically measures a glucose level in the tear fluid.
In some embodiments of the invention, the biosensor generates a signal that may be received by data collection apparatus outside the eye. In other embodiments, the signal is stored in a memory chip housed within the body of the stent, and/or the stent further comprises apparatus for transmitting said signal.

In preferred embodiments, the apparatus for transmitting the signal transmits the signal to a receiver located outside the stent, and preferably, the receiver is an external device outside the human body in which the stent is placed.

In one embodiment, the receiver is part of a smartphone, hand-held computer, or external monitor, e.g., wearable activity monitors (such as Fitbit® wristband analyzers).

Additional embodiments of the invention provide a method of measuring a property of tear fluid in a human eye comprising the steps of providing a lacrimal stent housing at least one biosensor capable of measuring at least one property of tear fluid, said stent being sized and shaped for placement into at least one canaliculus of a human eyelid, such that the stent extends from the punctum through the vertical canaliculus and at least partly traversing the horizontal canaliculus; inserting the stent into a canaliculus of a human eyelid and positioning the stent so that tear fluid from the human eye impinges on the biosensor housed in said stent; measuring at least one property of said tear fluid impinging on said biosensor; and transmitting information corresponding to said at least one property measured by said biosensor.

In preferred embodiments of the methods of the invention, at least one measured property of tear fluid in a human eye is glucose level.

In one embodiment of the methods of the invention, the information is transmitted to and/or stored in a memory chip housed within the stent and/or the stent further comprises apparatus for transmitting the information to a receiver outside the stent, including but not limited to smartphones, hand-held computers, or external monitors, e.g., wearable activity monitors (such as Fitbit® wristband analyzers).

In some embodiments, the stent may also be designed to maintain patency in narrowed or stenosed lacrimal passages and may therefore be useful in the treatment of excess tearing.

BRIEF DESCRIPTION OF THE DRAWINGS
**Fig. 1** is an illustration of particular anatomical features of the human eye showing the structures comprising the lacrimal drainage system.

**Fig. 2** is an illustration of the layers of precorneal tear film on the surface of the eye.

**Figs. 3A, 3B, and 3C** are a series of illustrations depicting the operation of the lacrimal pump in a human eye during blinking. **Fig. 3A**: In the relaxed state, the puncta lie in the tear lake. **Fig. 3B**: With eyelid closure, the orbicularis contracts. The pretarsal orbicularis squeezes and closes the canaliculi. The preseptal orbicularis, which inserts into the nasolacrimal sac, pulls the sac open, creating a negative pressure that draws the tears into the nasolacrimal sac. **Fig. 3C**: With eyelid opening, the orbicularis relaxes, and the elastic forces create a positive pressure in the nasolacrimal sac, that propels the tears down the nasolacrimal duct and into the nasal cavity.

**Figs. 4A and 4B** are a perspective view and a cross-sectional view, respectively, of a monocanalicular stent in accordance with one embodiment of the present invention. Internal features of the stent structure are illustrated using dotted lines or cutaway sections.

**Figs. 5A and 5B** are an illustration of a bicanalicular stent in accordance with an alternate embodiment of the present invention. **Fig. 5A** shows a bicanalicular stent prior to insertion in a patient, together with flexible stainless steel probes that may be used to guide insertion. The flexible probes for use in inserting the ends of the bicanalicular stent into the superior and inferior canaliculi via the puncta are separate instruments, removed after insertion is completed. **Fig. 5A** shows one probe separated from the stent, while another probe is shown engaged with one end of the stent, in the configuration for positioning the stent in one canaliculus of a patient. **Fig. 5B** shows the bicanalicular stent of Fig. 5A in place, occupying the inferior and superior canaliculi of the right eye of a patient. A biosensor is centrally located on the body of the stent, with the stent positioned so that the biosensor engages the tear lake adjacent the caruncle of the eye. The central portion housing the biosensor has an elongated section or arm extending from either side, and each arm is inserted into the adjacent canaliculus. In the embodiment illustrated, the arms are sufficiently long to extend through the horizontal canaliculi and into the common canaliculus adjacent to the nasolacrimal sac, and the ends of the arms are equipped with vanes to help retain the stent in position.

**Fig. 6A** is an illustration depicting the positioning of a monocanalicular stent according to the invention in the inferior lacrimal canaliculus. **Fig. 6B** is an illustration
depicting the positioning of a monocanalicular stent according to the invention in the superior lacrimal canaliculus.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a lacrimal stent capable to detecting and monitoring properties of a bodily fluid, e.g., tear fluid. The stent is made of a biocompatible material, preferably silicone, and is designed for insertion into the upper and/or lower proximal portion of the lacrimal drainage system of the human eyelid. In a preferred embodiment, the stent detects and monitors glucose levels in tear fluid and wirelessly transmits the information to an external device. In one embodiment, the stent does not have an internal passage, is made of solid silicone, and houses a biosensor that directly contacts the tear lake in the caruncular region of the eyelid. In one embodiment, the biosensor comprises glucose oxidase and measures tear glucose levels via the biocatalytic oxidation of glucose. In alternative embodiments, the stent biosensor does not require a chemical reaction and therefore avoids any potential risks of toxicity to the eye, to the lacrimal system, and to the systemic condition of the patient.

Canalicular stents, also known as lacrimal stents, are known in the art and are commercially available, see, for example Mini-Monoka Monocanalicular Stent (SI-1500) or Self-Retaining Bicanaliculus Intubation Set (SRS) II(SI-129-0/1/2u) both available from FCI Ophthalmics, Pembrook, Massachusetts. Known uses of lacrimal stents include treatment of canalicular lacerations, punctal stenosis and/or horizontal lacrimal duct obstruction. The canaliculi of the lacrimal drainage system can be obstructed or stenotic as a congenital condition, or acquired as a result of trauma, such as lacerations, inflammation, or side effects of chemotherapy, or the obstruction can be idiopathic. Once obstructed, tears can no longer drain from the surface of the eye through the lacrimal drainage system into the nose. As a result tears well up in the eye, and run down the face. Excess tearing blurs the vision and the patient has to constantly dab the eye.

Excess tearing resulting from acquired canalicular obstruction may be relieved by resolving the underlying medical cause, if known. For instance, if the obstruction is due to a nasal infection, treatment of the underlying infection may resolve the obstruction. If the obstruction persists, or if the root cause cannot be addressed, insertion of a canalicular stent is indicated to re-establish the flow of tear fluid out of the eye and through the nasolacrimal
drainage system. See, Fig. 1 and Figs. 3A-3C. When canalicular stent insertion is performed
as a primary procedure to alleviate excess tearing or to improve tear flow, the success rate is
79% - 96%.

The inherent need of a passive mechanism to determine tear biochemistry, for
example glucose monitoring in diabetic patients, has led to the invention of the present
biosensor canalicular stent. The present invention provides a lacrimal stent equipped with a
tear fluid-sensitive biosensor and suitable electronic circuitry for storing or transmitting
biosensor data. Such a biosensor-equipped stent is capable of being inserted into the superior
and/or inferior canaliculus of the human eyelid, detecting and/or monitoring at least one
property of tear fluid (such as glucose levels), and wirelessly transmitting the information
pertaining to the measured property of tear fluid to an external device or alternatively storing
the information for later reading by an external monitoring device.

Unlike prior art devices, the biosensor lacrimal stent of the present invention
incorporates a unique combination of features that makes it the ultimate implantable monitor
of tear film biochemistry. The size and placement location of the canalicular stent makes it
possible to accommodate the necessary sensors and hardware to accurately monitor and
subsequently transmit data to an external receiver. This is an advantage over other devices
intended for placement in or near the eye, such as contact lenses or punctal plugs, where the
space for biosensors and electronic hardware is extremely limited, either by the size of the
device or by the intended location: The need for transparency in a contact lens and the need
to avoid obscuring the vision of the wearer with opaque biosensors and electronic
components limits the utility of contact lens devices that incorporate biosensors. Similarly,
the small size of a punctal plug places limits on the size of biosensors and accompanying
electronics for transmitting or storing biosensor signals, and punctal plug design makes
extrusion and migration a distinct disadvantage in comparison to the present canalicular stent.

Punctal plugs are typically indicated for "dry eye", or situations in which it is desired
for an efficiently functioning lacrimal drainage system to be made less functional, in order to
cause accumulation of tears in the eye and prevent normal drainage. Where punctal plugs
have been adapted to include tear fluid biosensors, the typical function of the punctal plug,
i.e., to diminish tear flow by interfering with lacrimal drainage, is not indicated and may in
fact be undesirable. For this reason a punctal plug modified for tear fluid measurement is
provided with a flow-through passage to admit the passage of tears through the plug and out
through the lacrimal drainage system. See, e.g., U.S. Pat. No. 8,090,426 (Figs. 4, 5, 8). The flow-through channel intended to admit tear fluid shields and encapsulates tear fluid from the dynamic nasolacrimal drainage system of the eye. Tear fluid reacting inside the plug may become a static tear fluid sample that does not circulate through the device and provide for the replacement of the sample penetrating the plug channel with fresh tear fluid. Additionally, occlusion of the flow-through channel may further confound the accuracy of the sensed properties of tear fluid entering the channel, and insufficient exchange of the channel's contents with the general tear fluid circulation may also lead to irritation or inflammation of the eye or the canaliculus.

The stent of the present invention does not have an internal passage, is preferably made of solid, inert material such as silicone, and houses a biosensor that directly contacts the tear lake in the caruncular region of the eye or contacts tear film in a protected area of the eye such as the conjunctival fornix. The biosensor canalicular stent of the invention is not a contact lens and therefore avoids the significant morbidity associated with contact lens use and abuse and avoids the possible risk of blindness. Since the canalicular stent of the invention is placed within one or both of the lacrimal canaliculi of one or both eyes of a patient, physical or electromagnetic impingement on the sensitive tissues of the cornea is avoided. The configuration of the biosensor canalicular stent of the invention removes the biosensor and biosensor electronics from the more penetrable corneal tissue and allows for significantly less electromagnetic energy in proximity to the eye surface. Its juxtaposition next to the sclera (and not the cornea) make it a safer tear film biosensing device, in comparison to devices placed in direct contact with the cornea (such as contact lenses).

In preferred embodiments, the proximal portion of the stent, designated herein as the head, is designed to be in direct contact with and to sense properties of the tear film. The sensing mechanism(s), preferably located within the head of the stent, is/are capable of determining various biochemical properties of the human body, for example, glucose levels.

In a preferred embodiment, the stent detects and monitors glucose levels in tear fluid and wirelessly transmits the information to an external device. In a preferred embodiment, the stent does not have an internal passage, is made of solid material that is inert to bodily fluids and tissues with which it makes contact, and houses a biosensor at its proximal end that directly contacts the tear lake in the caruncular region of the eyelid. In preferred embodiments, the biosensor contains glucose oxidase and measures glucose levels in tear
fluid via the biocatalytic oxidation of glucose in the presence of glucose oxidase. In
alternative embodiments, or embodiments measuring alternative biomarkers in tear fluids, or
embodiments incorporating instruments for measuring other features of the eye than tear fluid
such as intraocular pressure, the biosensors do not require a chemical reaction and thereby
may avoid the potential or perceived risks of toxicity to the eye, to the lacrimal system, and to
the systemic condition of the patient.

The biosensor canalicular stents of the present invention are constructed using
biocompatible materials that are non-immunogenic and substantially inert with respect to
body tissues the stents come into contact with. The biocompatible material will not degrade
in the presence of bodily substances such as proteases and will encapsulate and protect the
sensor electronics that are embedded in the stent. Suitable biocompatible materials include,
but are not limited to, polyurethanes, hydrocarbon polymers, polyacrylic esters, silicone
polymers, and the like. In a preferred embodiment, the lacrimal stent of the invention is
made of silicone and is designed for insertion into the upper and/or lower proximal portion of
the lacrimal drainage system of the human eyelid. Preferably the stent is sized and shaped to
extend from the punctum at its proximal end, where its tear fluid biosensor will be most
advantageously located, through the vertical canaliculus, and into the horizontal canaliculus
(see Figs. 1, 6A and 6B). In an alternative embodiment, the stent is a bicanalicular stent
having a centrally located biosensor housing to be positioned in contact with the tear lake at
the caruncle of the eye and having two lateral arms extending from either side of the central
section housing the biosensor, the arms being sized and shaped for placement of one arm
through the superior punctum extending into the superior canaliculus and the other arm
through the inferior punctum extending into the inferior canaliculus (see Fig. 5B).

The present invention is better understood in view of the anatomical review and non-
limiting examples below.

The human lacrimal system is divided into a secretory apparatus and an excretory
apparatus. The secretory apparatus is of ectodermal embryologic origin and is comprised of
the main lacrimal gland and the accessory glands of Krause and Wolfring. These glands are
responsible for secreting the intermediate aqueous layer of the tear film, which is comprised
of three parts.

Referring to Figure 1, the general anatomy of the lacrimal drainage system of the eye
is illustrated. The main lacrimal gland 10 is divided into an orbital lobe and a palpebral lobe
by the superior transverse ligament. Eight to twelve lacrimal ducts (not shown) empty aqueous tears from this gland into the superior cul-de-sac and onto the surface of the conjunctiva of the eye (E). Ocular surface irritation initiates tear production from the lacrimal gland.

The accessory glands of Krause and Wolfring (not shown) are located within the superior fornix and at the superior border of the tarsus, respectively. Previously thought of as being responsible for basal secretion, recent evidence suggests that these glands may be responsible for reflex tearing as well. The aqueous (watery) part of the tear film secreted by these glands mixes with mucin secreted by conjunctival goblet cells and lipid (oil) produced by the meibomian glands of the eyelid margin.

The lacrimal drainage system is accessed through a lacrimal punctum 11 located at the end of each eyelid closest to the nose. Each punctum 11 opens into an essentially L-shaped tube known as the canaliculus. The punctum of the upper eyelid leads to the superior canaliculus, and the punctum of the lower eyelid leads to the inferior canaliculus. The shorter leg (approximately 2 mm) of the L-shaped canaliculus, known as the vertical canaliculus 12, leads to the longer portion (approximately 8 mm) of the canaliculus, known as the horizontal canaliculus 13. Superior and inferior canaliculi (12, 13) in most individuals join to form a common canaliculus 14 immediately adjacent and emptying into a nasolacrimal sac 15. Tear fluid accumulating in the nasolacrimal sac 15 are expelled by contraction of the sac by blinking through the nasolacrimal duct 16, and thence into the nasal cavity.

Figure 2 diagrammatically shows the composition of tear film that normally coats the surface of the eye. An oily outer lipid layer 20, formed of material secreted by the meibomian glands, reduces evaporation, provides lubrication for eyelid passage over the globe of the eye, and prevents tear overflow. An inner mucin layer 21 allows for even distribution of the tear film over the surface of the eye (E), stabilizes the tear film via co-action with the lipid layer 20, and acts as a barrier against bacteria and foreign particles.

An aqueous layer 22 of fluid secreted by the lacrimal gland and accessory glands of Krause and Wolfring form a middle layer sandwiched between the outer oily layer 20 and inner mucin layer 21. Besides water, this aqueous layer 22 is composed of electrolytes (such as sodium, potassium, chloride, bicarbonate, magnesium, and calcium), solutes (such as urea, glucose, lactate, citrate, ascorbate, and amino acids), and immunoglobulins (such as IgG, IgM, IgA, IgD, and IgE). Other constituents of the aqueous layer 22 include lysozyme, B-
lysin, and lactoferrin. The main functions of the aqueous layer include supplying oxygen to the avascular cornea, anti-microbial action, smoothing surface irregularities of the cornea, and washing away foreign debris. This main component of the tear film is an ultrafiltrate of the blood and serves as an excellent source material for biochemical analysis for computation of various biochemical and gas levels in the bloodstream, including critical metabolites such as glucose, urea, catecholamines, and lactate, as well as gases such as oxygen and carbon dioxide. Furthermore, any exogenous substances found in the bloodstream such as drugs, radioactive compounds, and the like are also present in the tear fluid.

Thus, tear fluid can provide a less invasively obtained sample for analysis compared to blood or plasma sampling. For example, the present invention may be utilized to take measurements of electrolytes, pH, osmolarity, body temperature, acid and lactate, creatine, lipids, blood gases, mediators of inflammation, endocrine hormones, liver and other tissue enzymes, coagulation factors, albumin, lactoferrin, and proteins, among others. Analysis of tears can be used to accurately determine the level of glucose in diabetics.

Figures 3A, 3B, and 3C illustrate the excretory apparatus of the eyelid and nasal cavity. The excretory structures are of ectodermal embryologic origin and include the canaliculi, the nasolacrimal sac, and the nasolacrimal duct. The entrance to the lacrimal drainage system is through puncta located medially on the upper and lower eyelid margin. The puncta are slightly inverted, lying against the globe of the eye (E) within the tear lake. Each punctum is surrounded by a cylinder of tissue called the ampulla. Each punctum opens to a tubular canaliculus connecting to the nasolacrimal sac and thence to the nasal cavity via the nasolacrimal duct. The section of the canaliculus adjacent the punctum is a vertical tubule of approximately 2 mm called the vertical canaliculus (12 in Fig. 1). The canaliculus turns roughly 90 degrees and runs 8 to 10 mm medially and horizontally to connect to the nasolacrimal sac. This longer portion of the canaliculus is called the horizontal canaliculus (13 in Fig. 1). In 90% of patients, the canaliculi combine to form a common canaliculus (14 in Fig. 1) before entrance into the lacrimal sac. A fold of tissue, known as the valve of Rosenmüller, functions as a one-way valve to prevent tear reflux.

Referring to Figure 3B, the act of blinking causes the tear fluid draining through the canaliculi to collect in the nasolacrimal sac. Referring to Figure 3C, the act of opening the eye following a blink, in turn, causes tear fluid collected in the nasolacrimal sac to
empty into the nasal cavity via the nasolacrimal duct 16. The nasolacrimal duct 16 measures approximately 12 mm in length and travels through the bony nasolacrimal canal to empty into the nasal cavity through an opening in the inferior meatus.

Evaporation from the tear film (Fig. 2) accounts for 10-20% of tear elimination.

Referring to Figures 3A, 3B and 3C, most of the tear flow is actively pumped from the tear lake 5 by actions of the orbicularis muscle in effecting eye blinking. In the mechanism described by Rosengren-Doane, the orbicularis muscle contraction forces the eyelids medially, producing positive pressure in the nasolacrimal sac 15, and thereby forces tears into the nasal cavity. As the eyelids open and move laterally, negative pressure is produced in the nasolacrimal sac 15 which causes the puncta 11 to pop open and draw tears from the eye surface into the canaliculi 13, and the lacrimal pump recycles.

The unique constituents of tears and the physiology of tear flow provide suitable conditions for the biosensor canicular stent to be an ideal monitor of tear fluid. Placement of the stent may be performed on an outpatient basis in the office by an ophthalmologist or other health care professional. The device is easily inserted as a minor procedure, and may remain in place for long periods without replacement. Typical installation periods will be from several weeks to a year or longer. Placement of a lacrimal stent does not prevent tear flow through the canaliculus in which it is positioned. The active pumping action of the lacrimal drainage system propels tear fluid through the canaliculi, and the peristaltic movement of the tear fluid continues along the outer body of the stent and into the nasolacrimal sac. For this reason, the lacrimal stent is not designed with openings to admit tears or any sort of an internal channel through which tear fluid is expected to pass; the biosensor portion of the biosensor canicular stent of the invention is located so as to be contiguous or flush with one or more surfaces of the stent, preferably the head as pictured in Figure 4A, that directly encounter tear fluid in its normal flow through the lacrimal drainage system.

As shown in Figure 4A, one embodiment of the invention, which is a monocanalicular biosensor stent 41, is a unitary device comprising interconnected sections, i.e., a head (42), a neck (43), a body (44), and a tail (45). The tail section 45 culminates in a closed tip 46, which is advantageously rounded or pointed in shape to ease smooth insertion into the canaliculus of a patient's eyelid. The stent embodiment pictured in Figure 4A shows an opening 51 in the head portion that extends along the length of the tail 45 to the tip 46, which
is closed. This tubular opening 51 is to accommodate a probe or stylus (not shown) that is inserted through the opening and provides a means for guiding the stent into place. After the stent is in position (see Figures 6A and 6B), the guiding probe or stylus is removed, leaving the stent in place. In an alternative embodiment, the stent 41 will not have any opening 51 or extended lumen through the tail 45 but instead will be solid. For a solid-body stent, an alternative tip 46A may be advantageously used, having a notch 48 on the outer surface of the tail 45 near the tip 46A, configured to receive the tip of a probe or stylus that will facilitate pushing the stent into place in a patient's canaliculus. See, also, Figure 5A.

Figure 4B shows a frontal cross-section of the stent 41 illustrated in Figure 4A, showing the head 42, neck 43, and body 44 sections, and the opening 51 defining the lumen for accepting the guiding probe or stylus (not shown) for positioning of the stent 41.

Figures 4A and 4B also show a cylindrical cavity 50 extending from the outer surface of the head 42 and housing a biosensor 47 with electronic circuitry 49 for storing and/or transmitting measurement information from the biosensor 47. The circuitry 49 may include its own power source or may be powered intermittently by electromagnetic radiation from a portable source being brought near enough to the patient's eye to power the stent. The biosensor 47 and/or circuitry 49 may be permanently enclosed in the head/neck/body portion (42, 43, 44) of the stent 41, or alternatively, the stent may be configured so that the biosensor 47 or the biosensor and electronic circuitry 47, 49 both may be extracted from the stent for replacement and/or downloading of stored data outside the patient's body. Figure 4B additionally shows an optional antenna 49A extending from the electronic circuitry 49. Such an antenna may extend for part or all of the length of the tail 45 of the stent or be configured in a coil along any length of the stent, to increase the range of any signals transmitted by the circuitry 49.

Referring to Figure 5A, a bicanalicular embodiment of the lacrimal stent 41 of the invention is illustrated, together with probes 53A, 53B that may be used to push the respective ends of the bicanalicular biosensor stent 41 into the superior and inferior canaliculi of a patient, so that both the upper canaliculus and the lower canaliculus of one eye of a patient are occupies by the stent (see Fig. 5B). The structure of the bicanalicular stent 41 may be viewed as a central body portion 44 with essentially symmetrical tail sections 45 extending bilaterally from the central body portion 44. The ends of the tail sections 45 advantageously have pointed or rounded tips 46 that reduce resistance during insertion.
Additionally, preferred embodiments may also be constructed with flanges or vanes 52 that help to anchor the stent in place and reduce if not eliminate shifting of position along the longitudinal axis of the stent 41. For insertion and positioning of the tail sections 45 of the stent 41, notches 48 are provided that will accept the end of a probe (53A, 53B). Figure 5A shows one probe 53A as a separate instrument apart from the stent 41, and another probe 53B that is inserted into a notch 48 at the tip 46 of one tail section 45 of the stent 41, the probe 53B being in position for use to guide that end of the stent 41 into one canaliculus of a patient's eyelid. The probes 53A, 53B may be made of any material, provided the shaft of the probe is rigid enough for use in positioning the probe. Preferably such probes are made of stainless steel.

Referring to Figures 5A and 5B, it is seen that the central body 44 of the bicanalicular stent 41 encompasses a biosensor 47 and compatible electronic circuitry 49 for powering the biosensor, receiving biosensor signals, and transmitting information received from the biosensor to a receiver outside the patient's body.

Figure 6A shows placement of a monocanalicular biosensor stent 41 of the invention into the inferior lacrimal canaliculus 13 leading from a patient's eye (E). The stent 41 is configured so that the head portion 42 protrudes slightly from the punctum 11 to contact the tear lake adjacent the caruncle of the eye (E), the neck 43 and body 44 occupy the verticle canaliculus (see Fig. 1, feature 12), with the stent tail 45 extending at roughly 90 degrees from the body 44 through the horizontal canaliculus. As shown in Figure 6B, the monocanalicular stent 41 may alternatively be placed into the superior lacrimal canaliculus. As pictured in Figures 6A and 6B, the monocanalicular stent 41 is positioned so that the biosensor 47 in the head portion 42 is in contact with the tear lake of the eye (E) and the neck, body, and tail sections (43, 44, 45, respectively) of the stent 41 extend through the punctum of the eyelid, through the vertical canaliculus, along the horizontal canaliculus, and protrude slightly into the nasolacrimal sac 15. In other embodiments the tail 45 of the stent 41 may be shorter or may be made shorter by clipping in order to extend through only a part of the length of the canaliculus 13. It is advantageous that at least a portion of the stent extends into the horizontal canaliculus, as this enhances the stable positioning of the stent and makes inadvertent removal or migration of the stent virtually impossible. In some embodiments, the stent will be shaped and sized to extend from the punctum, all the way through the canaliculus, ending at or even extending slightly into the nasal passage. In
alternative embodiments, the biosensor 47 may extend away from the stent, outside the punctum to position the biosensor in a particular desired location for exposure to fresh tears. The tear lake adjacent the caruncle of the eye is a preferred location, but specific mention is made of the conjunctival fornix (under the eyelid), which some practitioners regard as exhibiting tear fluid in its purest form.

In the embodiment depicted in Figures 4A, 6A and 6B, the tear fluid biosensor is located at the head 41 and, when the stent 41 is in position, is in direct contact with the tear lake region of the nasal portion of the eyelid. This region is constantly bathed by fresh new tears after each blink of the eye. The biosensor 47 detects the biochemical properties of the tear film and transmits these data via microchip circuitry 49 housed in the neck and body portion 43, 44 of the stent. Further propagation of this information is relayed to an optional antenna (e.g., Fig. 4B, feature 49A) located in the tail 45 of the stent 41. The longer aspect of this part (tail) of the stent allows it to accommodate a longer antenna for proper wireless transmission of this collected data via RFID (Radio-frequency Identification) to an external source or monitor such as a smartphone or wearable activity monitors downloaded with the proper software application.

In an alternative embodiment illustrated in Figure 5A, the biosensor canalicular stent is shaped and sized for bicanalicular placement, so that a centrally located biosensor section 47 may be positioned at the tear lake and anchored in place by two tail sections 45, which are shaped for insertion into the two lacrimal canaliculi (one arm extending into each canaliculus). The bicanalicular design is shown in Figure 5A, and its positioning with respect to the anatomical structures of the lacrimal drainage system is depicted in Figure 5B. In this bicanalicular embodiment, the tail ends 46 have self-anchoring devices 52 to allow for secure placement of the device. In the embodiment illustrated in Figure 5B, the elongated body of the stent includes a centrally located housing having a biosensor 47 which is in direct contact with the tear film in the region of the caruncle of the eye (E). During each blink, fresh new tears bathe the biosensor, which senses the biochemical properties of the tear fluid in contact with the biosensor. Data from the biosensor interaction with tear fluid are then transmitted to a microchip 49 located within the body of the stent. Further propagation of this information is relayed to an antenna located within one or both arms 45 of the stent. The longer aspect of this part of the stent allows it to accommodate a longer antenna for proper wireless transmission of this collected data via RFID (Radio-frequency Identification) to an external
source or monitor such as a smartphone or wearable activity monitors downloaded with the proper software application.

In preferred embodiments, the biosensor incorporated into the stent, e.g., the head of the stent as shown in Figure 4A, or the centrally located biosensor housing as shown in Figure 5A, will be a glucose sensor capable of capturing data indicative of blood glucose level in the patient bearing the stent. Suitable glucose sensors or electronic glucose sensors and/or hardware for storage and/or transmission of the detected or measured information for use in the stents according to the present invention are known and available commercially. See, e.g., Peng et al., "Miniature Enzymatic Biosensors for Tear Glucose Measurement in Capillary Tubes," *ECS Trans.*, 50(12): 13-21 (2013); M.K. Chu, K. Mitsubayashi, "Soft Contact-lens Sensor for Monitoring Tear Sugar as Novel Wearable Device of Body Sensor Network, published online, Knowledge Systems Institute, www.ksi.edu/seke/Proceedings/dmsll/DMS/2_Kohji_Mitsubayashi.pdf; or those disclosed in U.S. Pat. No. 8,870,370, issued to Otis, et al. A particular type of biosensor that may be used in the stent of the present invention is described in U.S. patent publication no. US 2014/0081105 Al, incorporated herein by reference. This type of biosensor utilizes glucose oxidase as a bioreceptor for glucose (biomarker). The biocatalytic oxidation of glucose in the presence of glucose oxidase is a two-step process consisting of enzymatic oxidation of glucose by glucose oxidase in which the co-factor flavin-adenine dinucleotide (FAD) is reduced to FADH2 followed by oxidation of the enzyme co-factor by molecular oxygen with formation of hydrogen peroxide. The reaction may be described as follows:

\[
\text{Glucose} + \text{O}_2 \xrightleftharpoons{\text{Glucose Oxidase}} \text{Gluconic Acid} + \text{H}_2\text{O}_2
\]

The amount of hydrogen peroxide (H2O2) generated is an indication of the amount of glucose in the tear liquid and is measured potentiometrically (see, US 2014/0081105, page 2). The glucose oxidase is preferably coated on a biocompatible outer surface of the biosensor canalicular stent.

The preferred configuration and methods for measurement of blood components and chemical species in the tear fluid and/or surface of the eye is based on electrodes associated with enzymatic reactions providing an electrical current that can be radio transmitted to a
remote receiver providing continuous data on the concentration of species in the tear fluid or a quality of the surface of the eye. The preferred method and apparatus for glucose level measurement uses the enzyme glucose oxidase which catalyzes a reaction involving glucose and oxygen in association with electrochemical sensors mounted in the stent device that are sensitive to either the product of the reaction, an endogenous co-reactant, or a coupled electron carrier molecule such as the ferrocene-mediated glucose sensors, as well as the direct electrochemical reaction of glucose at the catalytic metal electrode.

Referring again to Figure 4A, glucose and oxygen present in the tear fluid contact a layer of glucose oxidase enzyme coated on the surface of the sensor 47, e.g., on the head 42 of the stent device 42. Flow of tears across and around the stent, passing through the lacrimal drainage system, provides a continually replenished source of reactants to the enzyme substrate of the sensor. The preferred embodiment utilizes amperometric glucose biosensors with the biosensors based on biocatalytic oxidation of glucose in the presence of the enzyme glucose oxidase. This is a two-step process consisting of enzymatic oxidation of glucose by glucose oxidase in which the co-factor flavin adenine dinucleotide (FAD) is reduced to FADH2 followed by oxidation of the enzyme co-factor by molecular oxygen with formation of hydrogen peroxide. Glucose concentration can be measured either by electrochemical detection of an increase of the anodic current due to hydrogen peroxide (product of the reaction) oxidation or by detection of the decrease in the cathodic current due to oxygen (co-reactant) reduction. The detection system preferably has an enzyme electrode in contact with the tear fluid and/or surface of the eye capable of measuring the oxidation current of hydrogen peroxide created by the stoichiometric conversion of glucose and oxygen in a layer of glucose oxidase. The glucose sensor is preferably electrochemical in nature and based on a hydrogen peroxide electrode which is converted by immobilized glucose oxidase which generates a direct current depending on the glucose concentration of the tear fluid. The enzyme electrode of the sensor responds to changes in the concentration of both glucose and oxygen, both of which are substrates of the immobilized enzyme glucose oxidase. Alternatively, the sensor can be made responsive to glucose only by operating in a differential mode. The enzymatic electrodes built into the stent device may be placed in contact with the tear fluid or the surface of the eye and the current generated by the electrodes according to the stoichiometric conversion of glucose, are subsequently converted to a frequency radio signal and transmitted to a remote receiver, with the current being
proportional to the glucose concentration according to calibration factors.

The signals can be transmitted using the various transmission systems previously
described with an externally placed receiver demodulating the radio frequency signal to a
voltage, and the glucose concentration being calculated from the voltage and subsequently
displayed on a LED display. The receiver may be further connected with a computer for
further processing and analysis of the signal.

A variety of materials can be used for the electrodes of a glucose monitoring sensor,
such as silver/silver chloride coded cathodes. Anodes may be advantageously constructed as
a platinum wire coated with glucose oxidase or preferably covered by an immobilized
glucose oxidase membrane. Several possible configurations for sensors using amperometric
enzyme electrodes which involves detection of oxidizable components can be used in the
stent devices of the invention. A variety of electrodes can be used in the device which are
capable of creating a stable working potential and output current which is proportional to the
concentration of blood components in the tear fluid and surface of the eye.

In addition to glucose detection, amperometric detection of a wide range of oxidizable
species can be accomplished using the stent device of the invention. Any sensor capable of
converting a biological variable to a voltage signal can be used in the stent device and placed
in the flow of tear fluid through the lacrimal drainage system for measurement of the
biological variables. Radio and sonic sensors to measure pressure, electrical changes,
dimensions, acceleration, flow, temperature, bioelectric activity and other important
physiologic parameters, and power switches to externally control such systems, have been
developed and are suitable for use in the sensor stents according to the invention. The
sensors can be automatically turned on and off with power switches externally controlling the
stent monitoring system or can be on continuously if adequate direct current (from an in situ
battery) or induction current is used. The use of integrated circuits and advanced transducer,
power source, and signal processing technology allow for extreme miniaturization of the
components, which permit several sensors to be incorporated into the biosensor canalicular
stent device without altering the standard dimensions of commercially available non-
biosensor stents. Radio frequency and ultrasonic microcircuits are available and can be used.
A number of different ultrasonic and pressure transducers are also available and can be used.

Alternative sensors such as microminiature gas-sensitive, such as oxygen-sensitive,
radio frequency transensors may be used, e.g., for measuring oxygen content of tear fluid or
estimating blood oxygen. Sensors for measuring other health parameters of interest may also be advantageously employed, for example, microminiature blood velocity-sensitive radio frequency transensors. Radio frequency sensors capable of measuring electrical resistance can monitor the effects of microorganisms, drugs, poisons and anesthetics.

The stents of the invention incorporate one or more sensors with dimensions and size chosen to fit within the available space of the body of a lacrimal stent. The sensor may consist of a passive or active radio frequency emitter, or a miniature sonic resonator, and the like which can be coupled with a miniature microprocessor mounted in the stent device. The sensors mounted in the stent device can be remotely driven by ultrasonic waves, infra-red radiation, or alternatively remotely powered by electromagnetic waves or by incident light. They can also be powered by microminiature low voltage batteries which are incorporated into the body of the biosensor canalicular stent.

In preferred configurations both single canalculus insertion or bicanalicular insertion designs may advantageously incorporate one or more micro-LED lights that can flash or remain lit for a period of time, e.g., to act as an alert for administration of insulin or alteration of blood glucose level. The glucose content in the tear film may be continuously or periodically monitored using the biosensor stents of the invention. Drastically elevated glucose levels or dangerously low glucose levels detected by the biosensor stent may be reconfirmed by conventional means, such as finger-stick blood glucose testing.

As disclosed herein, the canalicular stent is uniquely suited for incorporation of a biosensor that measures one or more properties of tear fluid. This makes biosensor canalicular stents according to this invention particularly adaptable to constant or even continuous monitoring of physiological properties from assaying tear fluid, preferred adaptive uses including but not limited to measurement of blood glucose level, detecting chemical compounds, measuring electrolytes, measuring cholesterol level, monitoring drug metabolism, detecting blood alcohol level or the level of other blood components. Whereas such levels are advantageously measured from analysis of tear fluid, the position of a canalicular stent also lends itself to measurement of other properties and bodily functions by incorporation of different sensors adapted to detection of other physiological phenomena.

For example, with suitable sensors incorporated into the body of the stent, a biosensor canalicular stent of the invention may also take measurements of heart rate or respiratory rate; detect drug effects, detect ovulation, detect radiation, or measure properties of the eye such as
changes in curvature, blink rate, intraocular pressure, and the like. Particular mention is made of sensor lacrimal stents adapted to measure intraocular pressure, e.g., as a means for tracking the progression of glaucoma in a patient.

Glaucoma is the second most common cause of blindness in the world according to the World Health Organization (WHO). Glaucoma is a group of eye diseases that cause progressive damage of the optic nerve at the point where it leaves the eye to carry visual information to the brain. If left untreated, most types of glaucoma progress gradually to worsening visual damage leading ultimately to blindness. Once incurred, visual damage is mostly irreversible, and this has led to glaucoma being described as the "sneak thief of sight".

Glaucoma is typically accompanied by high intraocular pressure (e.g., greater than 21 mmHg), although "normal-tension glaucoma" in individuals having intraocular pressure in the normal range of 12 - 21 mmHg is known. Treatments for glaucoma can reduce eye pressure but do not achieve a cure. Current treatments include medicines (such as eyedrops to lower IOP), laser surgery, or invasive surgery.

Similar to arterial blood pressure, intraocular pressure, or IOP, may vary from one individual to another. It is not constant and undergoes variations throughout the day, further influenced by our daily activities. To avoid optic nerve damage associated or accompanying changes in intraocular pressure, monitoring of IOP provides a treating physician with valuable data that can signal the need for glaucoma treatment or indicate a change requiring adjustment of treatment. Thus, frequent or continuous monitoring of eye pressure during the day and at night, when the patient is not at the doctor's office, can be essential to successful treatment.

Many biosensors for measuring intraocular pressure are known and several may be adapted to produce an IQP-measuring biosensor canalicular stent according to this invention. See, e.g., Triggerfish® continuous ocular dimensional change monitoring system (Sensimed AG, Lausanne CH) which provides a contact lens-type monitoring system that captures spontaneous circumferential changes at the corneoscleral area and transmits data to a portable recorder device worn by the patient. Other IOP measuring technologies that may be adapted to in situ pressure measurement by incorporation into a stent of this invention include but are not limited to Goldmann applanation tonometry, Pascal Dynamic Contour Tonometer (Ziemer Ophthalmic Systems AG, Port CH), Tono-Pe-n (Reichert Ophthalmic Instruments inc., Depew NY, US), Model 30 pneumatonometer (Reichert Ophthalmic insinmients Inc.).
See, Eisenberg, D., "Reconsidering the Gold Standard of Tonometry," *Glaucoma Today*, Early Spring 2011. See, also, U.S. 7,403,805, incorporated herein by reference. The biosensor canalicular stent having tonometric capabilities provides distinct advantages over extraocular and contact lens-type instruments in that it can provide constant or continuous readouts of TOP and avoids irritation of the cornea, as can occur with standard tonometric devices. The IOP stent can also provide pressure data away from the physician's office, without the use of anaesthetic eye drops. The patient can take a pressure reading at any time by pressing the device against the sclera or by simply looking toward their nose, depending on the type of IOP sensor. As with the tear film sensors, signals from the sensor may be recorded for later download in a resident microchip or transmitted via an antenna to a device such as a smartphone, computer, or other monitor, e.g., wearable activity monitors (such as Fitbit® wristband analyzers).

By appropriate selection of the suitable biosensor, a biosensor canalicular stent according to the present invention provides a way of monitoring a wide range of physiological properties including glucose level, blood components, systemic and ocular blood flow, heart rate, respiratory rate, tracking operations, ovulation, effects of radiation, drug effects, intraocular pressure, blood alcohol content, and ocular and systemic disorders. Stents according to the invention provide such measurements in a way that is less invasive, longer lasting, safer, less irritating, and more versatile than devices and methods previously available.

All patents, patent applications, patent application publications, and other publications cited or referred to herein are incorporated by reference to the same extent as if each independent patent, patent application, patent application publication or publication was specifically and individually indicated to be incorporated by reference.
CLAIMS:

The invention claimed is:

1. A biosensor canalicular stent for measuring at least one property of tear fluid comprising:

   an elongated body adapted for placement into at least one canaliculus of a human eyelid, such that the body extends from the punctum through the vertical canaliculus and at least partly traverses the horizontal canaliculus,

   said body housing at least one biosensor capable of measuring at least one property of tear fluid, said biosensor being positioned in the body of the stent so as to be exposed to contact with tear fluid making contact with the outer surface of the stent,

   said body further housing apparatus for generating a signal corresponding to a property of tear fluid measured by said biosensor.

2. The biosensor canalicular stent according to Claim 1, wherein said biosensor is positioned at the proximal end of the elongated body so as to be immediately adjacent or protruding from the punctum when the stent is in place in said human eyelid.

3. The biosensor canalicular stent according Claim 1 or 2, wherein the stent is adapted for insertion into the superior canaliculus of a human eyelid.

4. The biosensor canalicular stent according to Claim 1 or 2, wherein the stent is adapted for insertion into the inferior canaliculus of a human eyelid.

5. The biosensor canalicular stent according to Claim 1 or 2, wherein the stent is adapted for insertion into both the superior canaliculus and the inferior canaliculus of a human eyelid, and wherein said biosensor is generally centrally located within the body of the stent.

6. The biosensor canalicular stent according to any one of the preceding claims, wherein the distal ends of the stent body, with respect to the position of the biosensor, are furnished with self-anchoring devices effective to prevent migration of the stent from the original position of its placement in the canaliculus of the eyelid.
7. The biosensor canalicular stent according to any one of the preceding claims, wherein, after placement in the eyelid, the biosensor is in contact with tear fluid in the tear lake forming at the caruncle of the eye.

8. The biosensor canalicular stent according to Claim 1, wherein the biosensor is capable of measuring tear film glucose.

9. The biosensor canalicular stent according to Claim 1, wherein the biosensor is capable of measuring tear film osmolarity.

10. The biosensor canalicular stent according to Claim 1, wherein the biosensor is adapted to measure a glucose level in the tear fluid.

11. The biosensor canalicular stent according to Claim 10, wherein the biosensor makes continuous measurement of glucose level.

12. The biosensor canalicular stent according to Claim 10, wherein the biosensor makes periodic measurements of glucose level.

13. The biosensor canalicular stent according to Claim 1, wherein said signal is stored in a memory chip housed within the body of the stent.

14. The biosensor canalicular stent according to Claim 1, further comprising apparatus for transmitting said signal.

15. The biosensor canalicular stent according to Claim 14, wherein the apparatus for transmitting the signal transmits the signal to a receiver located outside the stent.

16. The biosensor canalicular stent according to Claim 15, wherein the receiver is an external device outside the human in which the stent is placed.
17. The biosensor canalicular stent according to Claim 16, wherein the receiver is part of a smartphone, hand-held computer, or external monitor, including wearable activity monitors.

18. A biosensor canalicular stent for measuring at least one physiological property of the eye, comprising:
   an elongated body adapted for placement into at least one canaliculus of a human eyelid, such that the body extends from the punctum through the vertical canaliculus and at least partly traverses the horizontal canaliculus,
   said body housing at least one biosensor capable of measuring at least one physiological property of the eye, said biosensor being positioned in the body of the stent so as to be exposed to contact with the tear film of the eye or the sclera of the eye,
   said body further housing apparatus for generating a signal corresponding to a physiological property detected by said biosensor.

19. The biosensor canalicular stent according to Claim 18, wherein the biosensor is capable of measuring tear film biochemistries.

20. The biosensor canalicular stent according to Claim 19, wherein the biosensor is capable of measuring tear film pharmacology (i.e., drug) content.

21. The biosensor canalicular stent according to Claim 18, wherein the biosensor is capable of: detecting blood components, measurement of systemic or ocular blood flow, measurement of heart rate or respiratory rate, tracking operations, detection of ovulation, detection of radiation or drug effects, detection of intraocular pressure, detection of blood alcohol content, or detection of at least one symptom of an ocular or systemic disorder.

22. The biosensor canalicular stent according to Claim 18, wherein the biosensor is capable of making tonometric measurements of intraocular pressure.

23. A method of measuring a property of tear fluid in a human eye comprising:
   providing a biosensor canalicular stent housing at least one biosensor capable of measuring at least one property of tear fluid, said stent being sized and shaped for placement
into at least one canaliculus of a human eyelid, such that the stent extends from the punctum through the vertical canaliculus and at least partly traverses the horizontal canaliculus;

inserting the stent into a canaliculus of a human eyelid and positioning the stent so that tear fluid from the human eye impinges on the biosensor housed in said stent;

measuring at least one property of said tear fluid impinging on said biosensor; and

transmitting information corresponding to said at least one property measured by said biosensor.

24. The method according to Claim 23, wherein said information is transmitted to a memory chip housed within said stent.

25. The method according to Claim 23, wherein said information is transmitted to a receiver located outside the stent.

26. The method according to Claim 25, wherein the transmitting step includes transmitting information to a receiver in a smartphone, hand-held computer, or external monitor, including wearable activity monitors.

27. The method according to Claim 23, wherein said at least one property of tear fluid is glucose level.

28. A method of measuring a physiological property in a human patient, comprising:

providing a biosensor canalicular stent housing at least one biosensor capable of measuring at least one physiological property of the patient's eye, said stent being sized and shaped for placement into at least one canaliculus of a human eyelid, such that the stent extends from the punctum through the vertical canaliculus and at least partly traverses the horizontal canaliculus;

inserting the stent into a canaliculus of a human patient's eyelid and positioning the stent so that the biosensor is exposed to contact with the tear film or sclera of the eye;

measuring at least one physiological property of the patient's eye from bringing the biosensor into contact with said tear film or said sclera; and
transmitting information corresponding to said at least one physiological property measured by said biosensor.

29. The method according to Claim 28, wherein said information is transmitted to a memory chip housed within said stent.

30. The method according to Claim 28, wherein said information is transmitted to a receiver located outside the stent.

31. The method according to Claim 30, wherein the transmitting step includes transmitting information to a receiver in a smartphone, hand-held computer, or external monitor, including wearable activity monitors.

32. The method according to Claim 28, wherein the biosensor is capable of: detecting blood components, measurement of systemic or ocular blood flow, measurement of heart rate or respiratory rate, tracking operations, detection of ovulation, detection of radiation or drug effects, detection of intraocular pressure, detection of blood alcohol content, or detection of at least one symptom of an ocular or systemic disorder.

33. The method according to Claim 28, wherein the biosensor is capable of making tonometric measurements of intraocular pressure.
## INTERNATIONAL SEARCH REPORT

**International application No.**
PCT/US16/29441

**A. CLASSIFICATION OF SUBJECT MATTER**

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<td>A61F9/007</td>
<td>-</td>
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</table>

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

<table>
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<tr>
<th>IPC(8):</th>
<th>CPC:</th>
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<tr>
<td>A61F9/007</td>
<td>-</td>
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</table>

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

- PatSear: US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC: Data; Orbit: Google/Google Scholar; PubMed/MEDLINE: 

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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<tbody>
<tr>
<td>X</td>
<td>US 2008/0103376 A1 (FELDER, RA) May 1, 2008 abstract; figures 4-5, 10; paragraphs [0005], [0025], [0037/0040], [0054]</td>
<td>1, 3/1, 4/1, 5/1, 8/11, 13/21, 23-32</td>
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<td>Y</td>
<td>US 6312393 B1 (ABREU, MM AM) November 6, 2001; column 118, lines 44-52</td>
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<td>Y</td>
<td>US 2014/0025022 A1 (QLT INC) January 23, 2014; abstract; claims 1-4</td>
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<td>A</td>
<td>US 5283063 A (FREEMAN, JM) February 1, 1994; entire document</td>
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</table>

Further documents are listed in the continuation of Box C. See patent family 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 application or patent 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
- "Y": document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "A": document member of the same patent family

Date of the actual completion of the international search: 05 July 2016 (05.07.2016)

Date of mailing of the international search report: 04 AUG 2016

Name and mailing address of the ISA/Authorized officer: Shane Thomas

P.O. Box 1450, Alexandria, Virginia 22313-1450

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

Form PCT/ISA/210 (sr.mlnd sheet) (lannary 2015)
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

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.: 6-7 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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 additional fees, this Authority did not invite payment of additional fees.

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 and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.