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Erlach et al.

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(54) **NANODEVICES, MICRODEVICES AND SENSORS ON IN-VIVO STRUCTURES AND METHOD FOR THE SAME**

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(76) Inventors: **Julian Van Erlach**, Clifton Park, NY (US); **Arlen L. Olsen**, Clifton Park, NY (US); **Jeffrey M. Smith**, Pittsfield, MA (US); **Laura B. Smith**, Pittsfield, MA (US); **Gerald E. Bender**, Cheshire, MA (US); **Audra L. Stinchcomb**, Latham, NY (US); **Denis P. Donnelly**, Saratoga Springs, NY (US); **James E. Peterson**, Starkville, MS (US); **Roger D. Whitmer**, Pittsfield, MA (US); **Gerald F. Dudding**, Clifton Park, NY (US); **Mark D. Scott**, Surrey (CA)

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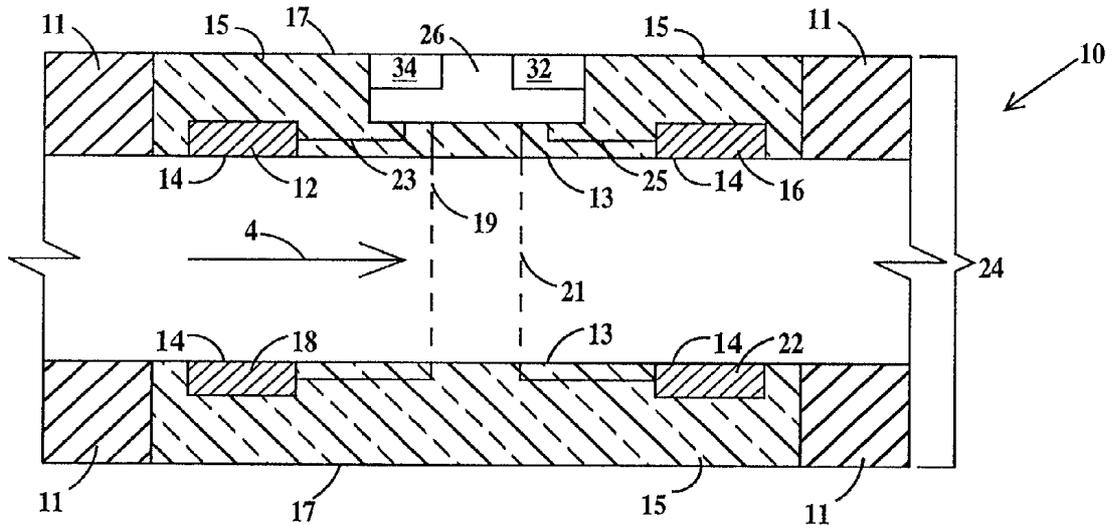
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(57) **ABSTRACT**

An in-vivo method and apparatus is disclosed that comprises at least one sensor for determining changes in a human's or an animal's body and reporting said changes outside the body. The sensor may be embedded in a sheath. The apparatus may be used to monitor chemical or physical changes in the body fluids. Alternatively, the apparatus may be used to monitor and regulate chemical or physical levels in humans and animals.

Correspondence Address:
Schmeiser, Olsen & Watts
Suite 201
3 Lear Jet Lane
Latham, NY 12110 (US)

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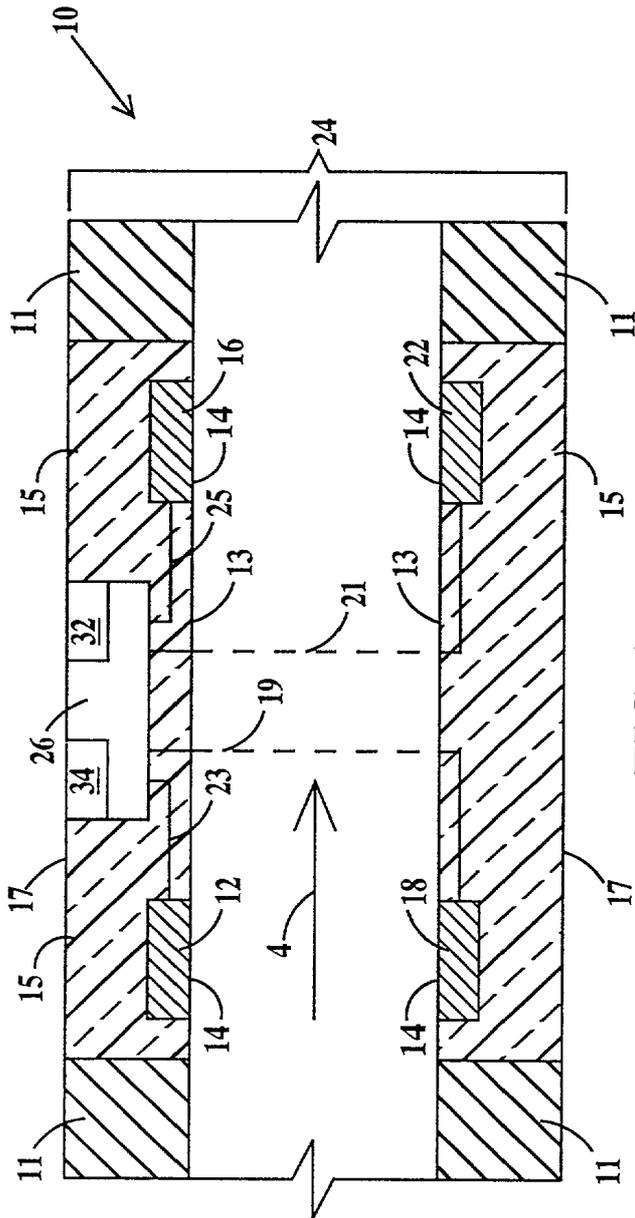


FIG. 1

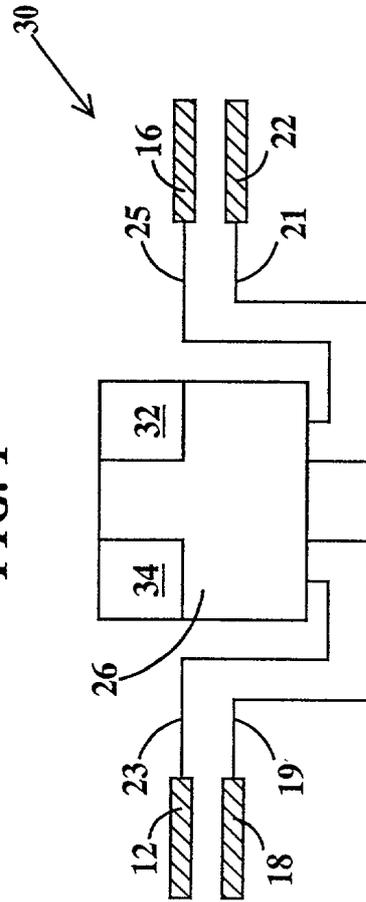


FIG. 2

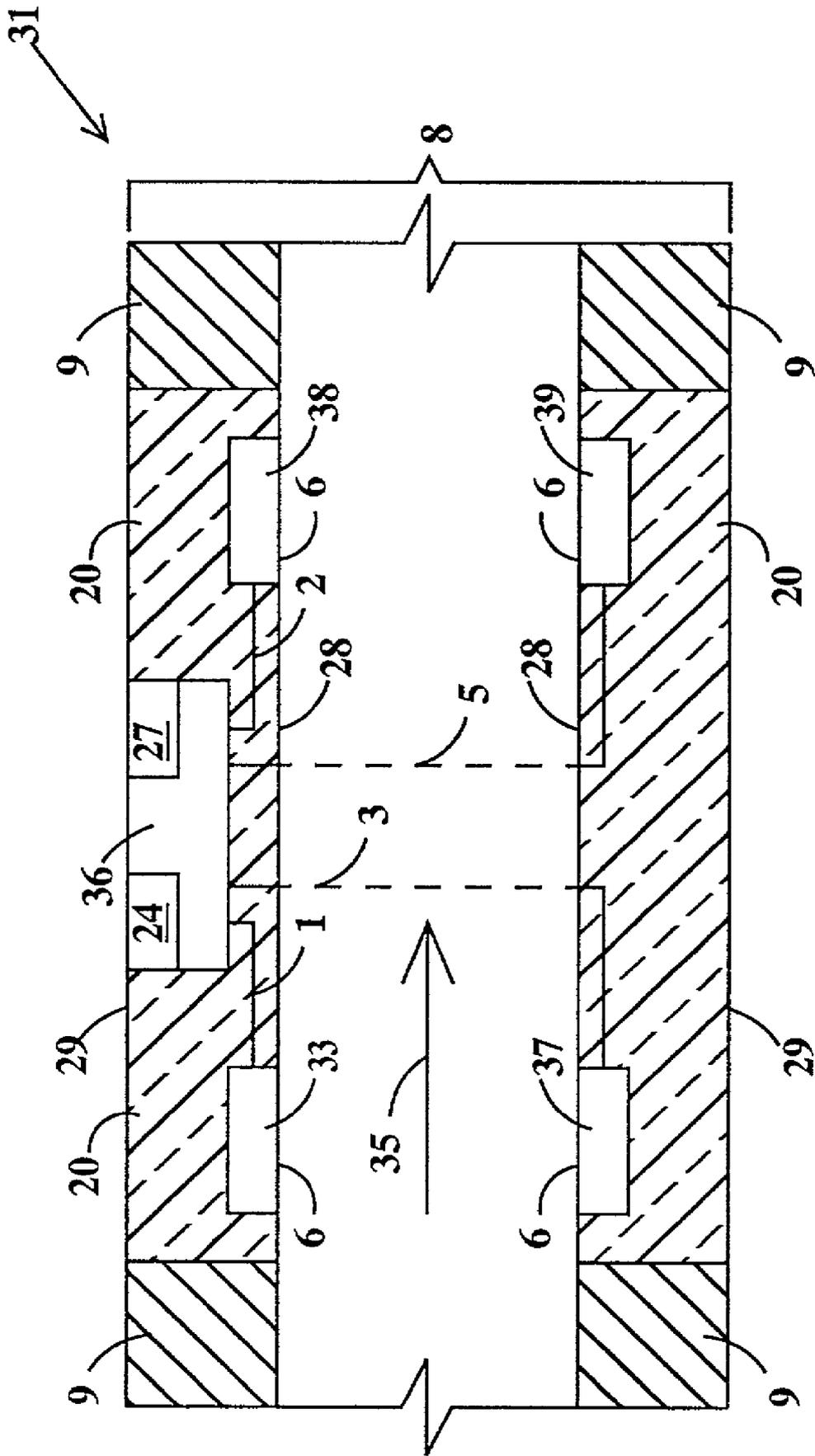


FIG. 3

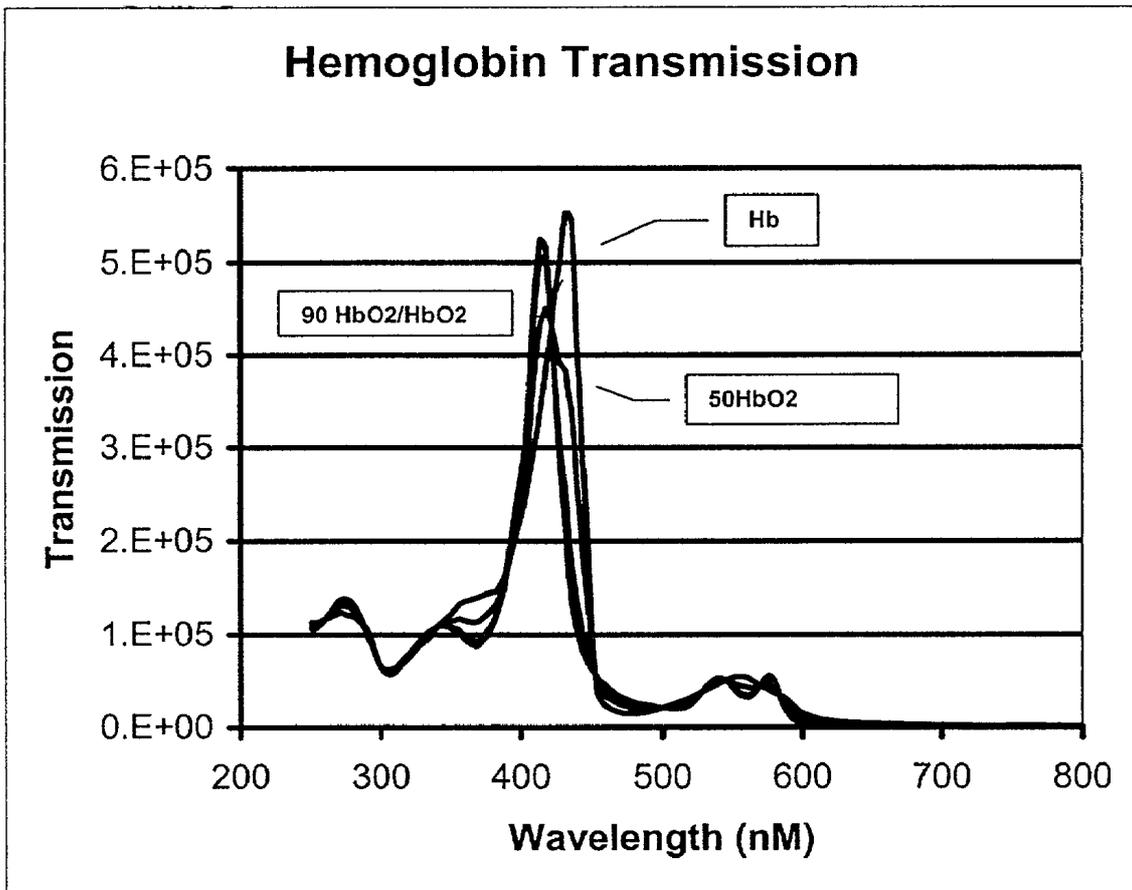


FIG. 4

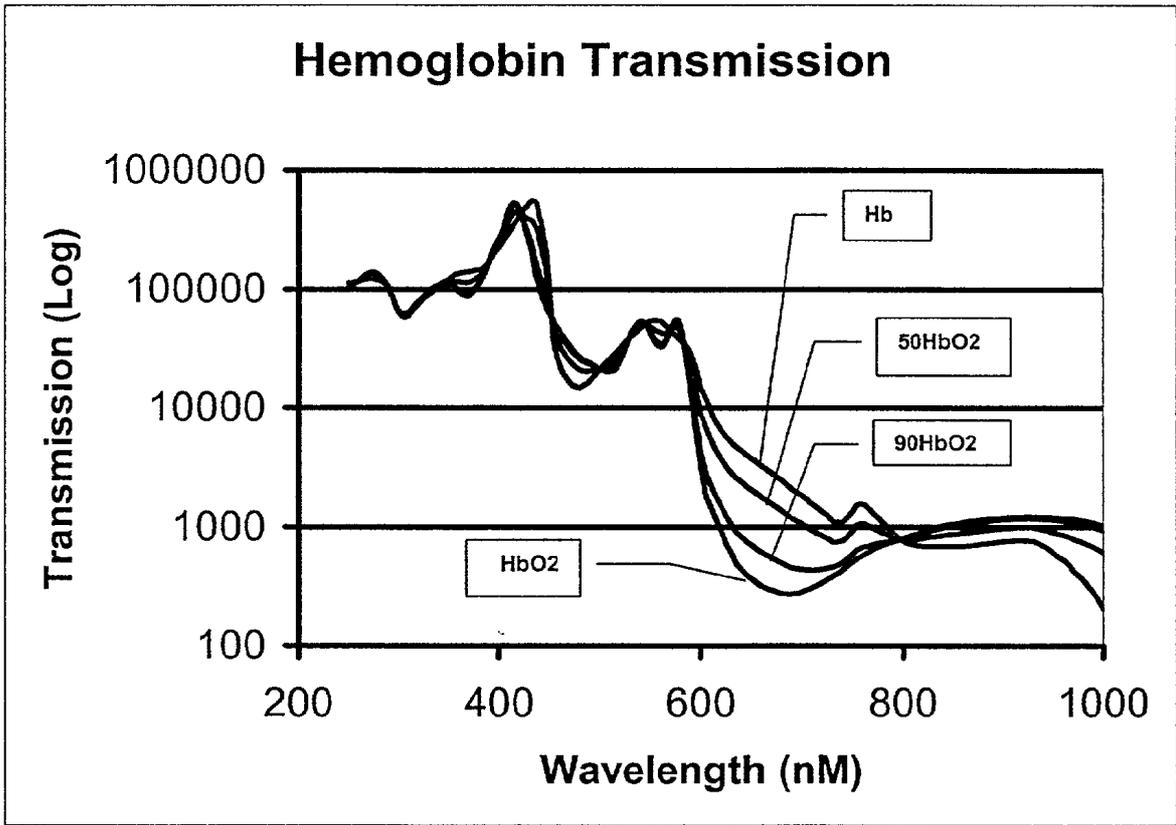


FIG. 5

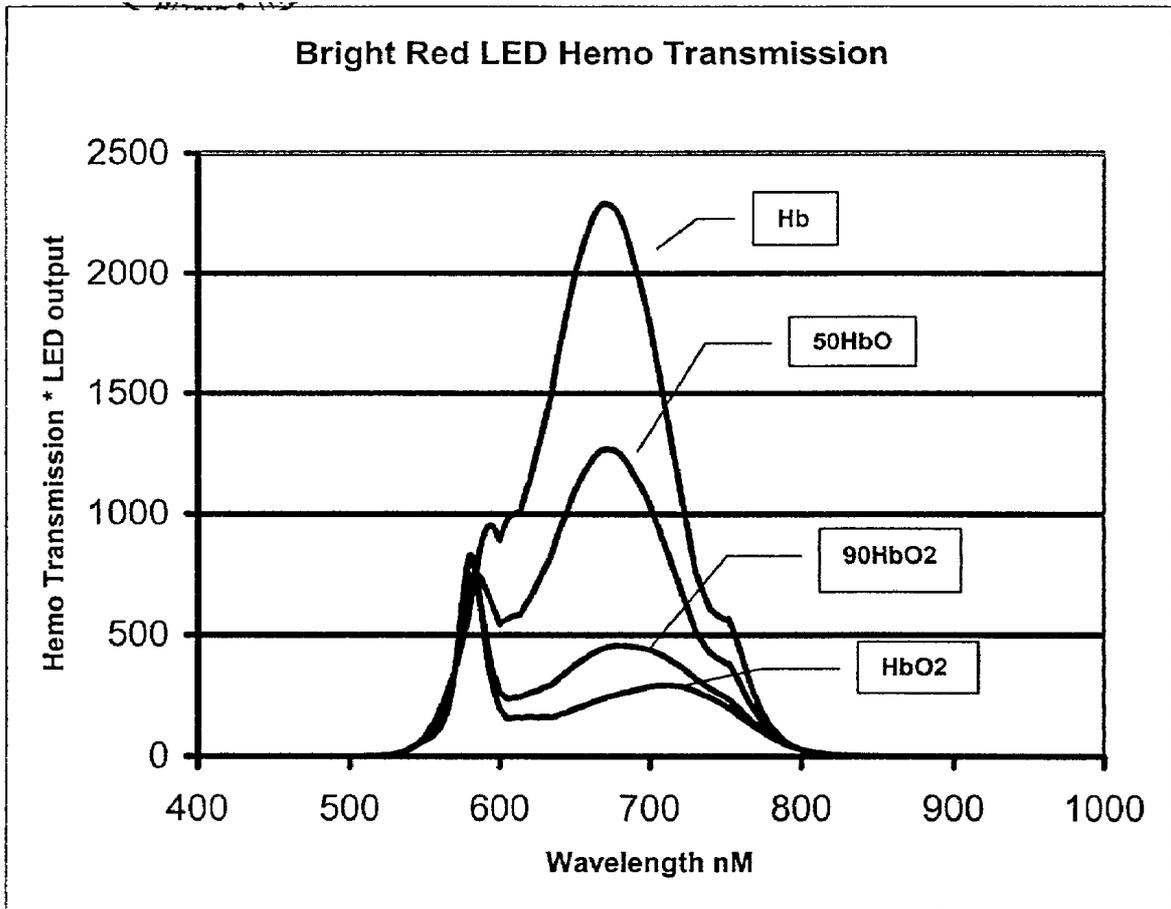


FIG. 6

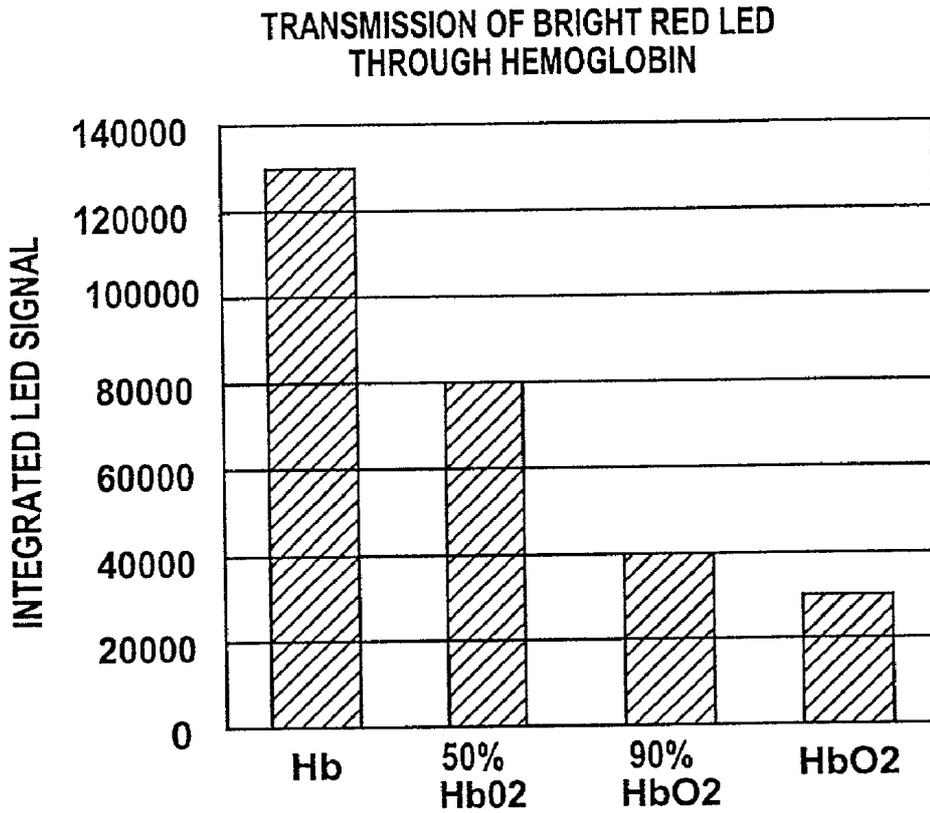


FIG. 7

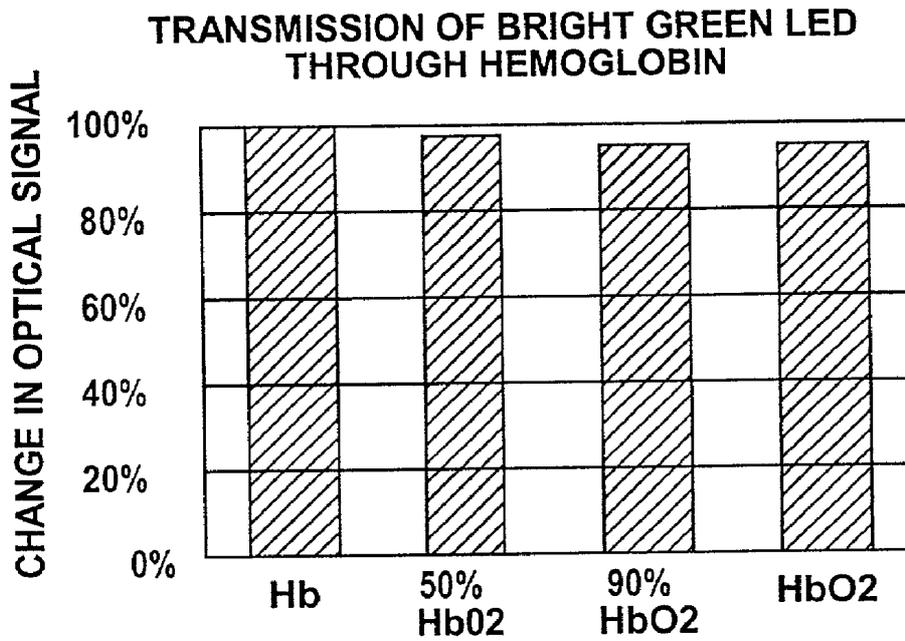


FIG. 8

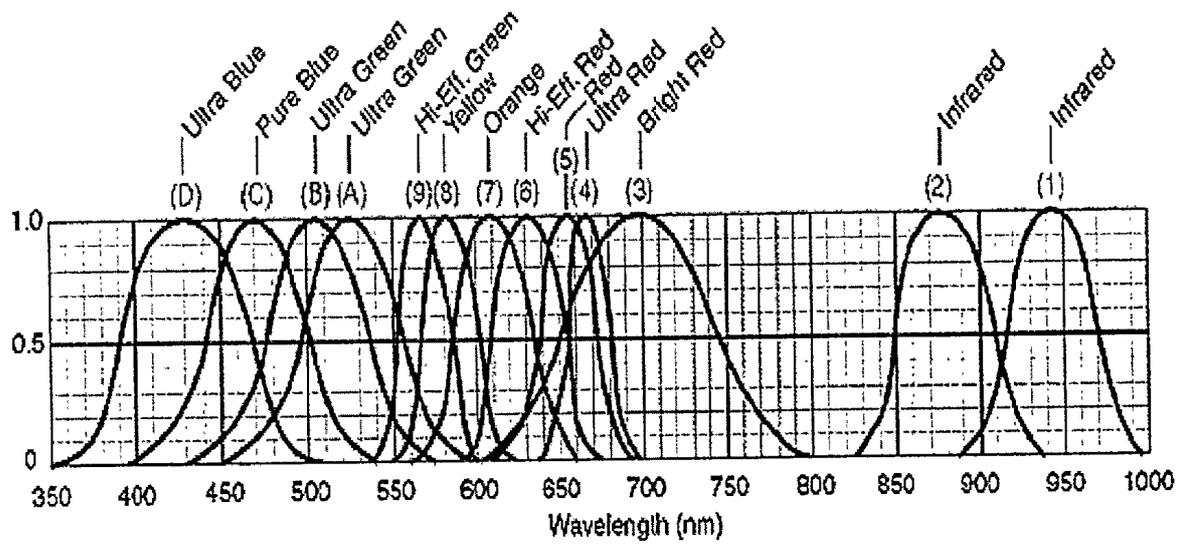


FIG. 9

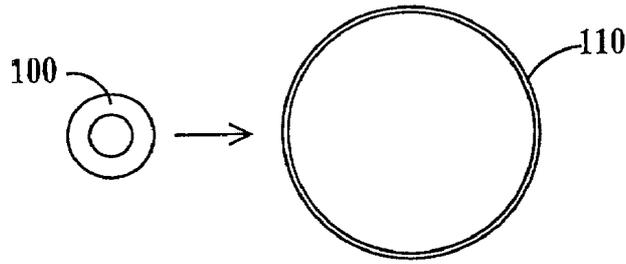


FIG. 11

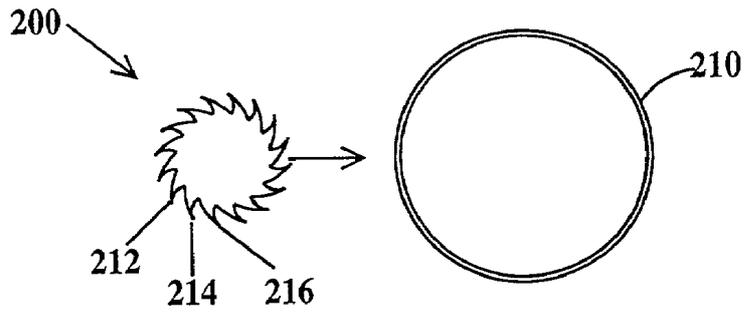


FIG. 12

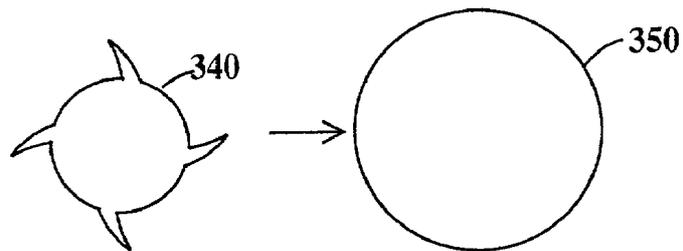
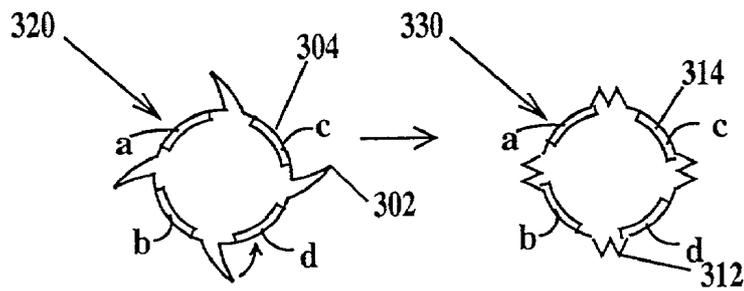
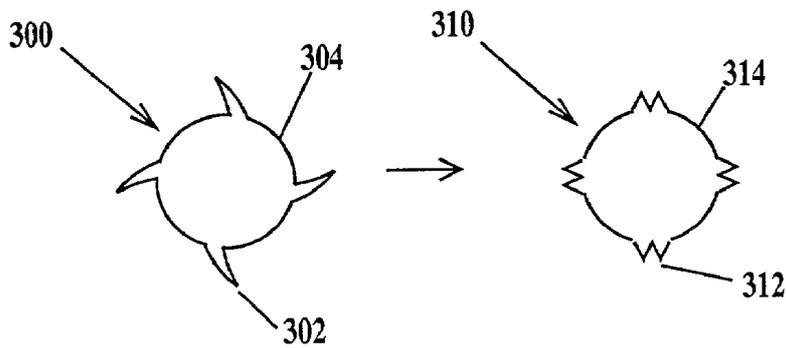


FIG. 13

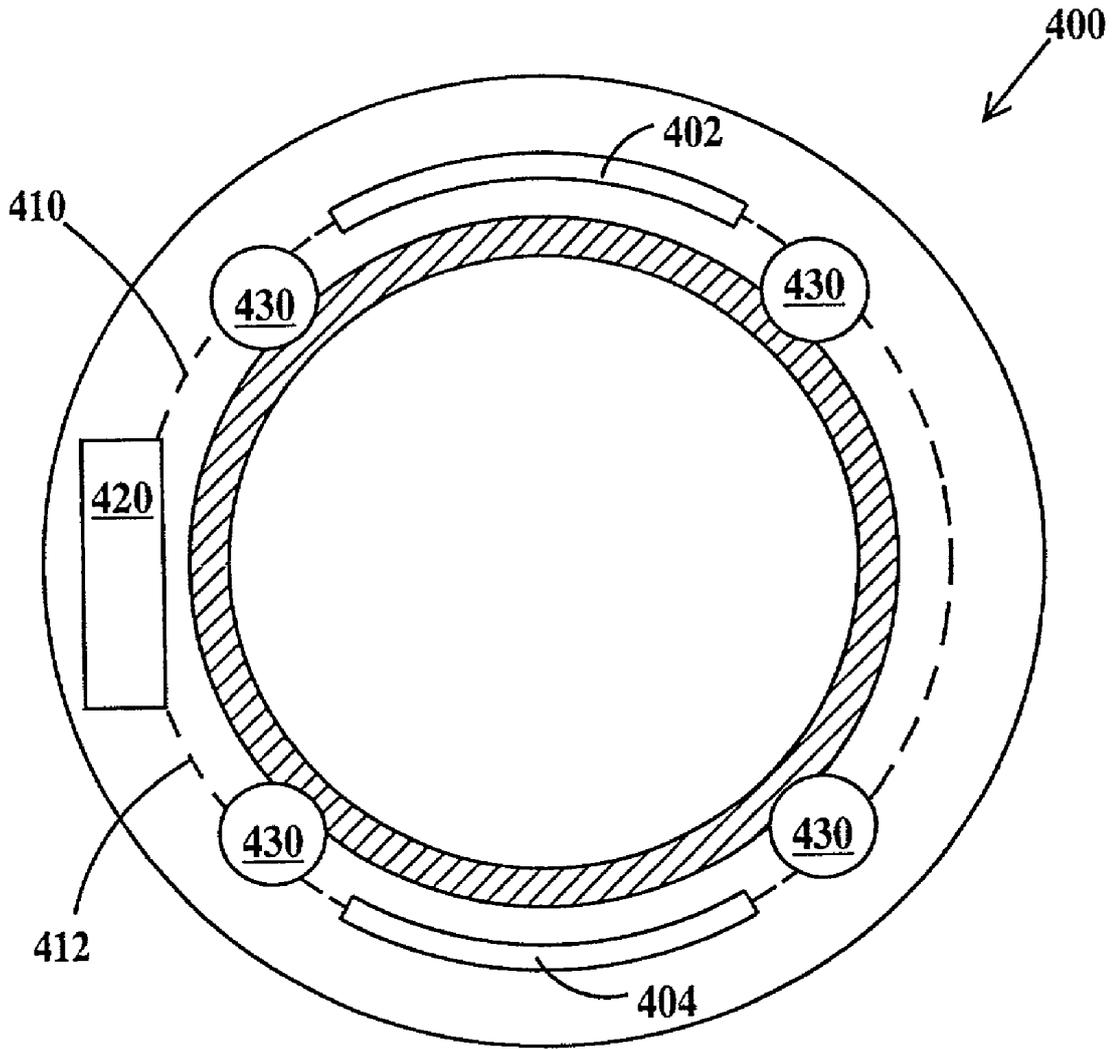


FIG. 14

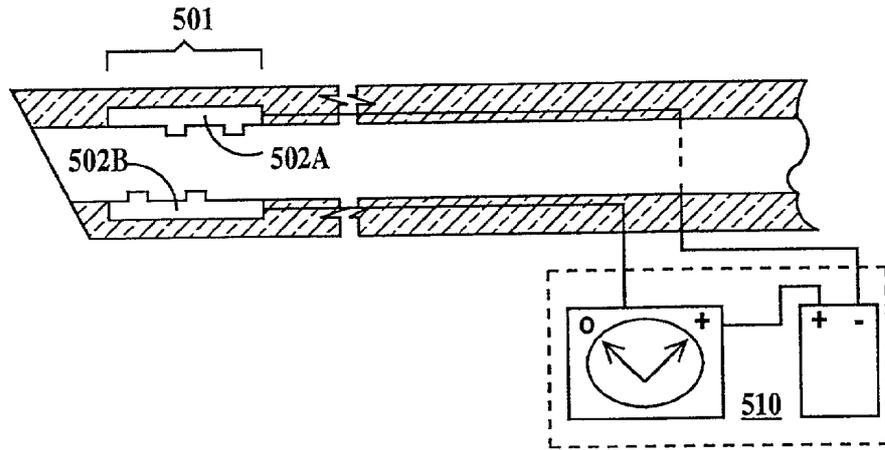


FIG. 15A

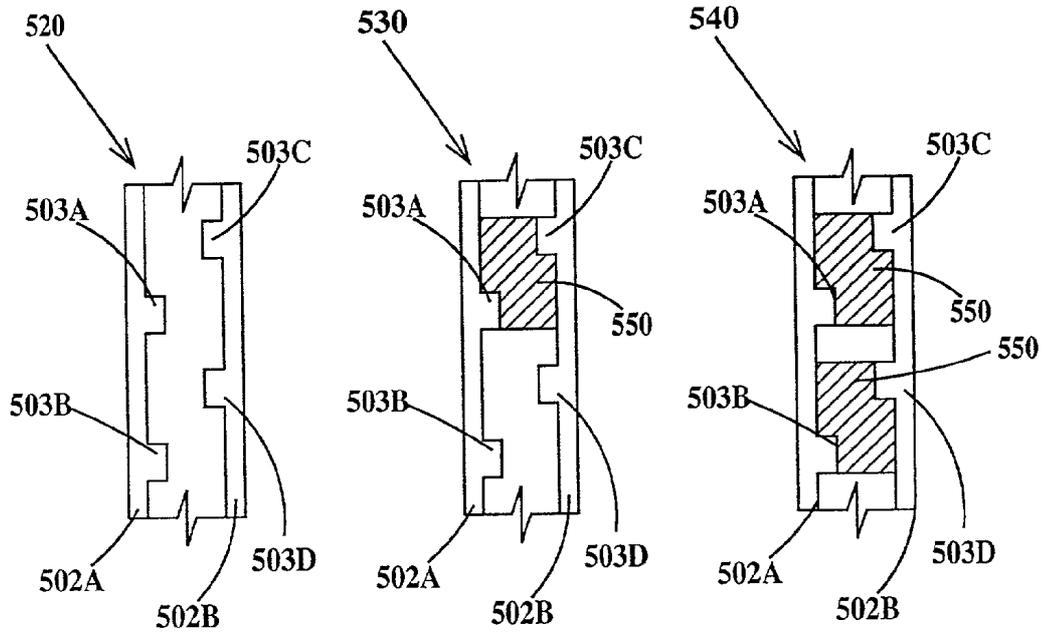


FIG. 15B

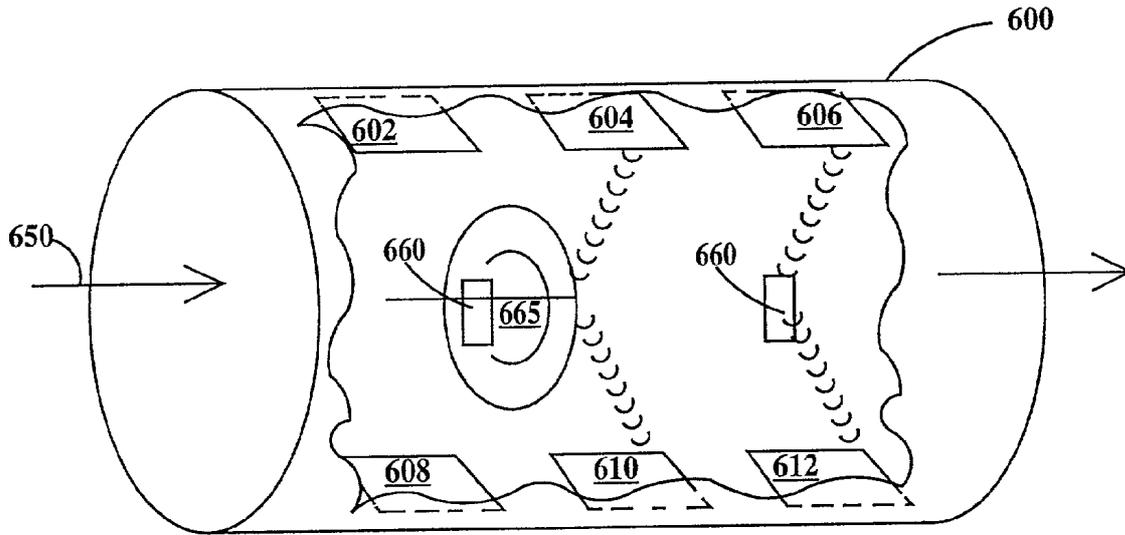


FIG. 16

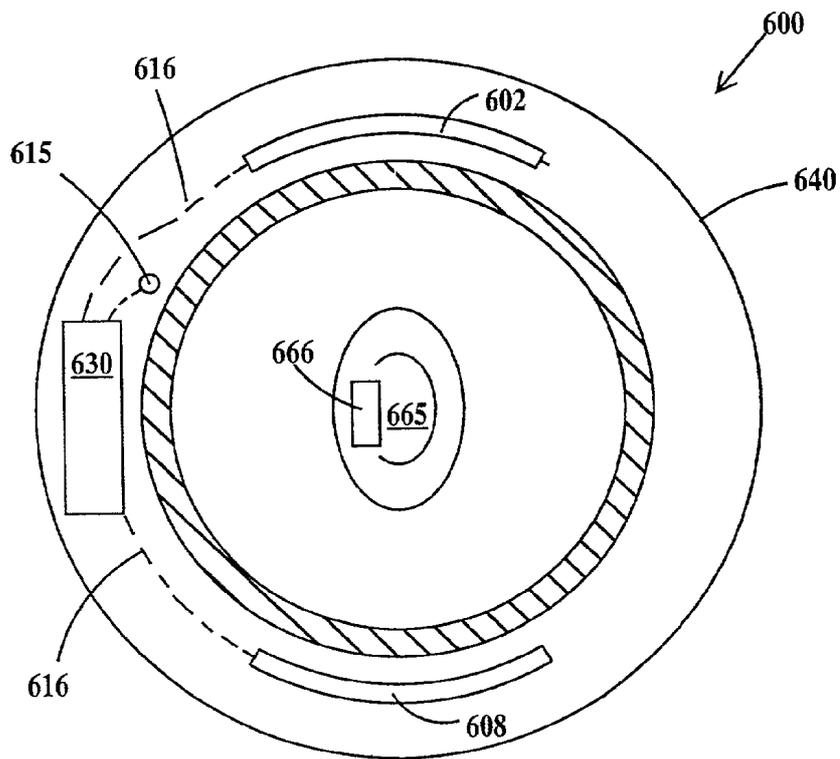


FIG. 17

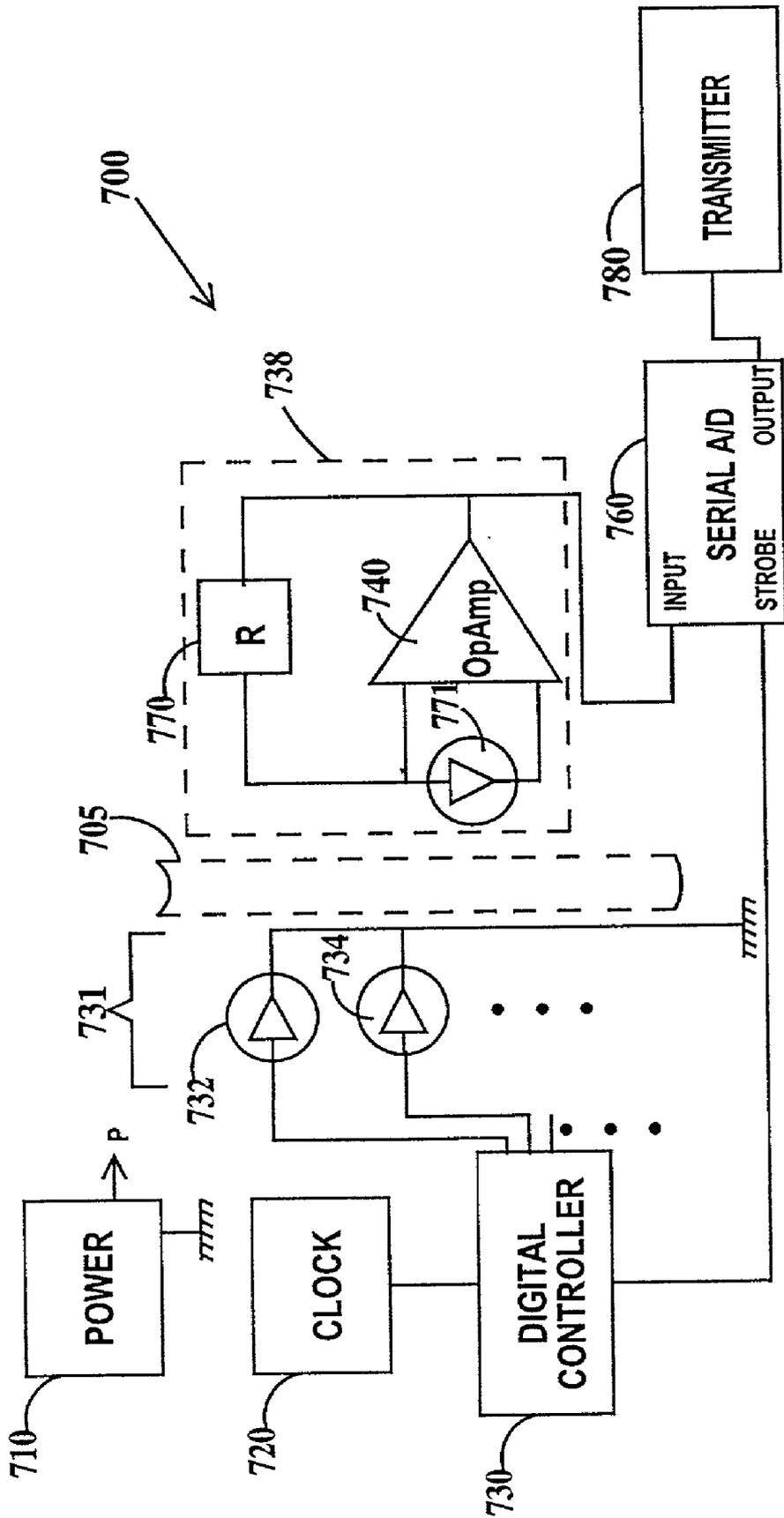


FIG. 18

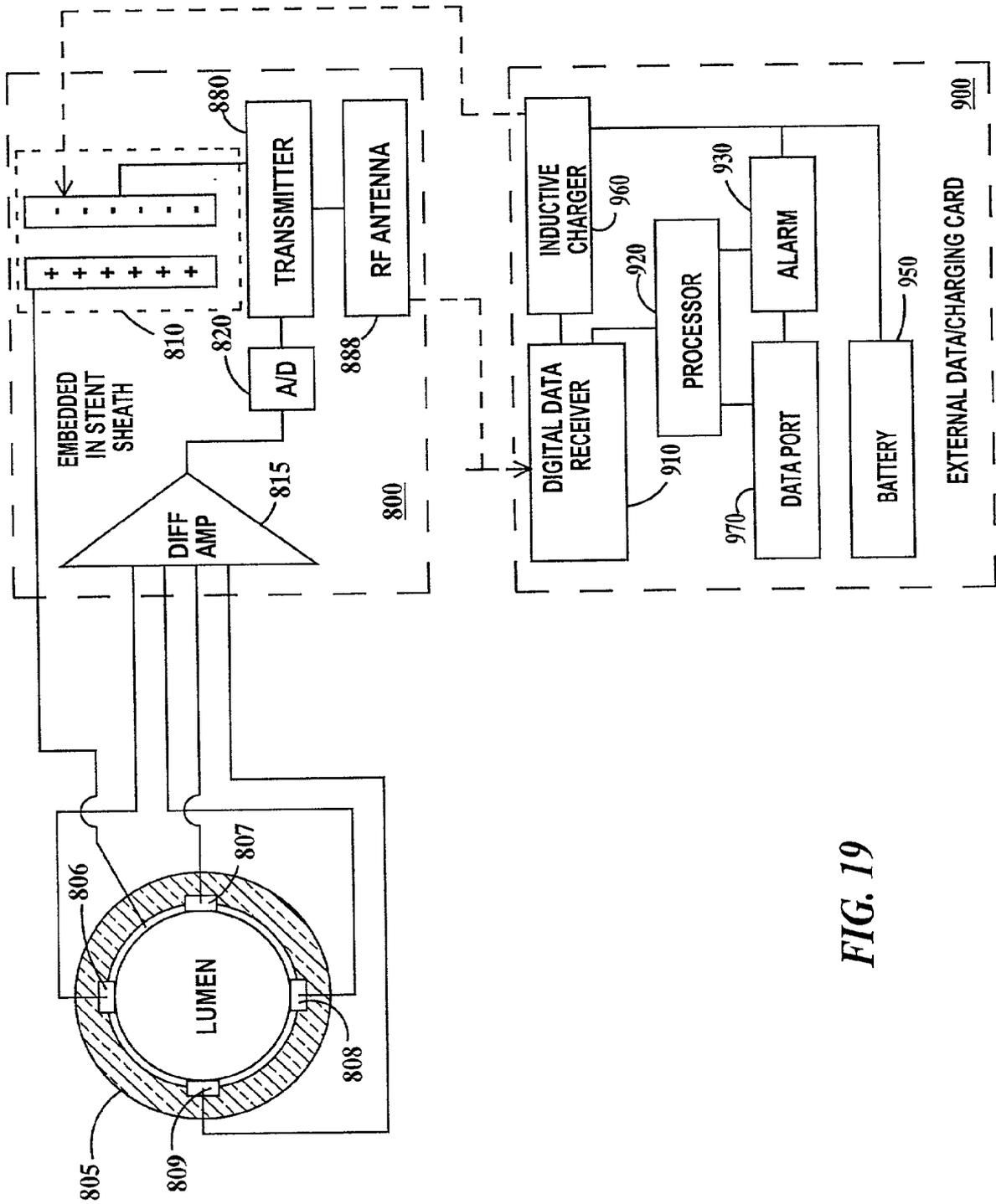


FIG. 19

NANODEVICES, MICRODEVICES AND SENSORS ON IN-VIVO STRUCTURES AND METHOD FOR THE SAME

BACKGROUND OF THE INVENTION

[0001] 1. Technical Field

[0002] This invention relates to a method and apparatus for forming devices on substrates and using these devices to provide in-vivo treatment of certain disease conditions in animals and humans. Specifically, the present invention relates to a method and apparatus for nanodevices, microdevi- ces, and sensors on in-vivo structures.

[0003] 2. Background Art

[0004] Typically diagnosis of animal and human diseases or body disfunctions involves testing a person's physical parameters such as blood pressure, temperature and pulse. Additionally, diagnosis commonly requires removing samples of blood and other body fluids and subjecting them to diagnostic tests to determine levels of enzymes, metabo- lites, toxins or other chemicals essential to life. Medical imaging instruments based on inter alia x-ray, ultrasound or magnetic resonance provide additional information used by the medical profession to diagnose causes of animal and human illness. Once diagnosed, the ailment may commonly be treated inter alia using drugs administered transdermally, orally or by injection.

[0005] Diagnosis and treatment by these common tech- niques may be difficult because physical and chemical testing is not sufficiently specific to the diseased or disfunc- tional part of the body. Also, drug effectiveness may be reduced because traditional methods of introduction are not specifically directed to the diseased or dysfunctional part of the body.

SUMMARY OF THE INVENTION

[0006] The present invention overcomes the deficiencies of the related art by providing an apparatus comprising nanodevices, microdevi- ces and sensors on in-vivo structures and method for the same. Also disclosed is a device that is insertable into a body passage or implantable into body tissue, wherein a sensor operatively attached to a device determines changes in body conditions, and wherein the apparatus reports the changes. The biosensors transmit wire- lessly outside or within the body.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] These and other features and advantages of this invention will be more readily understood from the follow- ing detailed description of the various aspects of the inven- tion taken in conjunction with the accompanying drawings in which:

[0008] FIG. 1 depicts a longitudinal cross-section of an apparatus of the present invention;

[0009] FIG. 2 depicts an expandable longitudinal cross section of a structure of an embodiment of the present invention;

[0010] FIG. 3 depicts a longitudinal cross-section of an apparatus, comprising light emitting devices and light sens- ing detectors operatively attached to an inner surface of a tube;

[0011] FIG. 4 depicts a hemoglobin transmission spec- trum, wherein an oxygen content of the hemoglobin ranges from 0-100%;

[0012] FIG. 5 depicts a hemoglobin transmission (Log) spectrum, wherein an oxygen content of the hemoglobin ranges from 0-100%;

[0013] FIG. 6 depicts a bright red light emitting diode transmission of hemoglobin, wherein an oxygen content of the hemoglobin ranges from 0-100%;

[0014] FIG. 7 depicts an integrated bright red light emit- ting diode transmission through hemoglobin, wherein an oxygen content of the hemoglobin ranges from 0-100%;

[0015] FIG. 8 depicts a percent change of an integrated bright green light emitting diode transmission through hemoglobin, wherein an oxygen content of the hemoglobin ranges from 0-100%;

[0016] FIG. 9 depicts a range of wavelengths and inten- sities for light emitting diodes;

[0017] FIG. 10 depicts FIG. 3, further comprising a means for delivering a disease treatment agent through a wall of the tube; and

[0018] FIG. 11 depicts a cross-section of a sheath of the present invention;

[0019] FIG. 12 depicts a cross-section of an expandable sheath of the present invention;

[0020] FIG. 13 depicts a cross-section of an alternate expandable sheath of the present invention;

[0021] FIG. 14 shows a cross-section of an alternate expandable sheath of the present invention;

[0022] FIG. 15 shows a biodetection catheter;

[0023] FIG. 16 shows biodetection of nanodevices by a biosensor;

[0024] FIG. 17 shows a cross-section of the embodiment of FIG. 16;

[0025] FIG. 18 depicts an instrumented stent oximetry; and

[0026] FIG. 19 depicts a biosensor and external receiver and digital processor.

DETAILED DESCRIPTION OF THE INVENTION

[0027] FIG. 1 depicts a longitudinal cross-section of an in-vivo apparatus 10 that comprises a tube 24 having an inner surface 13, an outer surface 17 and a body 11. Hereinafter, a "tube" is a portion of an "internal medical device" such as a catheter, stent, endoscope, defibrillator or the like. The catheter, endoscope, or defibrillator may be used for biodetection of infection or patient monitoring, e.g., liver, heart enzymes and blood glucose. Hereinafter, a "stent" is a small, expandable wire mesh tube. The stent may be either a vascular stent or a urinary stent. The defibrillator is an implantable defibrillator such as that disclosed in U.S. Pat. No. 6,358,247 which is hereby incorporated by refer- ence. "Nanodevice(s)" may be any inorganic device on the order of magnitude of 1 nanometer (nm) to 800 nanometers. However, a typical nanodevice will be between 5-100 nm.

Examples of nanodevices include nanotubes, nanoparticles (such as lithium particles), buckyballs, and nanowires made from silicon, gallium nitride, zinc oxide and other semiconducting inorganic materials such as oxides of transition metals or semiconducting organic materials.

[0028] The body **11** further comprises conductive contacts **12**, **16**, **18**, and **22** operatively attached to and coplanar **14** with the inner surface **13** of the tube **24**. Referring to FIG. 1, contact **12** may be oriented opposite and parallel to contact **18**, and contact **16** may be oriented opposite and parallel to contact **22**. Alternatively, contact **12** may be oriented opposite and parallel to contact **18**, and contacts **16** may be oriented orthogonal to contact **22**. The body **11** of the tube **24** may be made from electrically insulating materials such as polyethylene, polypropylene, silicone elastomer, nylon, or polytetrafluoroethylene. The tube **24** may also be made from nitinol⁷, a typical nickel/tin metal alloy. The apparatus **10** further may include a microchip **26** that is electrically coupled to conductor **23** and to conductive contact **12** and additionally to conductor **25** and to conductive contact **16**. The microchip **26** further comprises an on-chip battery **32** or like source of electromotive force (EMF). The microchip is capable of passive remote EM interrogation. In addition the microchip **26** may further comprise a receiver/transmitter device **34**. The receiver/transmitter **34** may include an FM receiver having a receiving/transmitting antenna. Microchip **26** is conductively coupled to the receiving/transmitting antenna. When the body **11** of the tube **24** is made from electrical conductors such as metal or metal alloys such as nitinol⁷, the conductive components of apparatus **11** must be electrically insulated to prevent malfunction due to shorting. The microchip **26**, the conductors, **23**, **25**, **19**, and **21** and conductive contacts **12**, **16**, **18**, and **22** are encapsulated by insulator **15**. The insulator **15** may be made from silica, silicone elastomer, insulating plastics such as UltemTM from General Electric Co., nylon, acrylic, polypropylene, polyethylene or polytetrafluoroethylene or similar electrically insulating material.

[0029] FIG. 2 defines a structure **30** comprising two circuits controlled by the microchip **36**. In one circuit comprising the microchip **26**, conductors **23** and **19**, the microchip **26** determines a resistance (R1) between the contacts **12** and **18** using Ohm's Law (see formula 1 infra). In a second circuit comprising the microchip **26**, conductors **25** and **21**, the microchip **26** determines a resistance (R2) between the contact **16** and **22**. R1 and R2 from the microchip **26** are transmitted through the animal's or human's skin using the transmitter/receiver **34**. Voltage and current values may be transmitted to the microchip **26** using the transmitter/receiver **34**. When the body **11** of the tube **24** is made from metal or metal alloy such as nitinol, the inner surface **13** and the outer surface **17** of the tube **24** may be electrically insulated by coating or sheathing (as described in FIGS. 11-13) with silica, silicone elastomer, insulating plastics such as UltemTM from General Electric Co., nylon, acrylic, polypropylene, polyethylene or polytetrafluoroethylene or similar electrically insulating material to avoid interfering with the determination of R1 and R2.

$$R=V/I. \quad (1)$$

[0030] (where R=resistance, V=voltage and I=current)

[0031] The circuits and field effect transistor (FET) devices in microchip **26** of FIG. 2 may be formed according

to a method of Dr. G. Julius Vansco et al., who demonstrated that self-assembled thin films of organic-organometallic diblock copolymers made up of poly(isoprene) and poly(ferrocenyldimethylsilane)(PFS) are promising candidates for nanolithography. ("Tying Top-Down to bottom Up," *Chemical and Engineering News*, 27, 28, Feb. 5, 2001. Hereinafter "nanolithography" is a form of lithography that provides resolution for forming electronic structures that have a maximum dimension equal to or greater than about 5 to 10 nanometers. Polymer chemistry can be used to produce nanometer-sized patterns on silicon wafers using one-step lithographic reactive-ion etching procedures. One key enabling tool for nanotechnology includes scanning probe techniques such as electrochemical atomic force microscopy. Another key tool to enable forming devices such as micro-chip **26** is chemical self-assembly. Hereinafter, "chemical self-assembly" is the self-organization of small molecular components to form complex functional structures." Hereinafter, "nanotechnology" is the study of forming miniaturized electronic devices that include devices that have a maximum dimension equal to or greater than about 5 to 10 μm).

[0032] Conductors **23**, **2519** and **21** illustrated in FIG. 1 may be formed according to a method of Christopher E. D. Chidsey et al., who demonstrated electron tunneling through oligophenylenevinylene (OPV) conductors having ferrocene at one end and thiol at the other "is so fast they could make good molecular wires." Christopher E. D. Chidsey et al., "Promising Lead for Molecular Wires," *Chemical and Engineering News*, 37, Feb. 26, 2001. Using OPV units from about 0.1 to 28 Angstroms (\AA) (from about 0.003 to 0.28 μm) having a ferrocene at one end and a gold electrode at the other, John F. Smalley et al. demonstrated no drop in a rate of electron transfer. Id. at 37.

[0033] Alternatively, conductors **23**, **2519** and **21** illustrated in FIG. 1 may be formed according to a method of Yuji Okawa et al. who used a scanning tunneling microscope (STM) to form electrically conductive polymer nanowires from 10,12-nonacosadiynoic acid shown in formula (2) infra. Y. Okawa et al., "Polymer Nanowires Connected by STM," *Chemical and Engineering*



[0034] *News*, 38, 38, Mar. 5, 2001. Hereinafter, "polymer nanowire" is a linear polymer chain having a length ranging from about 3 to 300 nm (from about 0.003 to 0.3 μm). Id. at 38. Okawa et al. reported "... demonstrating that we can initiate linearly propagating chain polymerization of organic molecules at any predetermined point and terminate it at another predetermined point with a spatial precision on the order of 1 nm. (0.001 μm)." Id.

[0035] In an embodiment of the present invention, referring to FIG. 1, the apparatus **10** comprises a tube **24** that may be inserted into a body passage that includes body passages that have a maximum diameter greater than or equal to about 5 to 10 μm . Lubricating the outer surface **17** of the tube **24** with materials such as petroleum jelly or mineral oil or compressing the tube **24** adapts the tube **24** for insertion. FIG. 1 illustrates that the body fluid in the vessel travels through the apparatus **10** in a direction depicted by arrow **4**. Hereinafter, a "vessel" is any artery, vein, capillary, duct or channel or the like in an animal or human body that carries body fluids. The microchip **26** supplies sufficient

EMF to the circuit comprising contacts **12** and **18** and to the circuit comprising contacts **16** and **22** to obtain a resistance in the range of about 50 to 310 ohms when the body fluid flows through the tube **24** in the direction of the arrow **4**. The microchip **26** transmits a value of **R1** and **R2**. Monitoring the values over time is used to indicate an onset of disease in the animal or human body.

[0036] In June, 1995, remarks of Dr. Alexander Wood were reported in which he stated a use of measurement of resistance of blood in humans. Dr. Wood reported "the ideal resistance of venous blood should be between 180 to 210 ohms." See "Fungal/Mycotoxin Conference: Excerpts From Dr. Wood's Presentation; Sept. 30 to Oct. 2, 1994," *Alt Healthwatch*, 143, 9-10 (1995). Dr. Wood further reported ". . . 1) [h]igh resistivity level, between 210 and 300 Ohms, indicates that there are not enough trace elements needed by the enzymes to digest food; 2) low resistivity level, dropping below 180 Ohms, indicates that the organs, such as the liver and the pancreas are beginning to show stress. Low resistivity also indicates the presence of a toxic load in the digestive system." See *Id.*, supra. Dr. Wood also reported "the ideal resistivity of saliva is about the same as for blood." See *Id.*, supra. In addition, according to Dr. Wood, "the ideal resistivity of urine is 30 Ohms. . . . The resistivity of the urine will rise dramatically to between 60 and 120 Ohms, a clear indication that the body's ability to eliminate waste is being compromised." See *Id.*, supra.

[0037] Referring to **FIG. 1**, when the tube **24** in an internal medical device or an apparatus **10** is a stent, the apparatus **10** may function as a typical stent in a post-angioplasty medical procedure. Throughout the specification, where a stent is referred to it is also understood that the stent may be any internal medical device as hereinbefore defined. With respect to a stent, it was first performed in the mid-1980s, and first approved by the FDA in the mid-1990s, stenting is a catheter-based procedure in which a stent (a small, expandable wire mesh tube) is inserted into a diseased artery to hold it open. Although stenting reduces a risk of a newly opened artery re-closing (restenosis), there is a need to monitor for restenosis. Hereinafter, "restenosis" is a proliferation of cell growth that causes inter alia varying degree of re-closing of the artery. The microchip **26** includes software that controls the function of the microchip **26** that includes accessing calibration files for correlating resistance to restenosis. The software on microchip **26** further controls transmitting **R1** and **R2** through the animal's or human's skin using the receiver/transmitter **34**. Since resistivity varies directly as a function of a diameter of the artery, comparison of a value of **R1** and **R2** over time indicates if a portion of the stent **24** has narrowed over time. Substantially similar reduction in the value of **R1** and **R2** over time anticipates collapse of the stent **24**.

[0038] Referring to **FIG. 1**, collapse of the stent **24** may cause a disease condition. Use of the alternative embodiment of apparatus **10**, described supra, wherein contact **12** may be oriented opposite and parallel to contact **18**, and contact **16** may be oriented orthogonal to contact **22** enables distinguishing between collapse of the stent **24** and restenosis. Biosensors would detect the vascular diameter and arrive at a given resistance for a given diameter. As diameter in the stent changes, so would the resistance. In the case of collapse of the stent **24**, resistance would remain constant across contacts orthogonal to one another, but resistance

would decrease across opposite and parallel contacts. The change in diameter may be determined by either one pair of biosensors or a plurality of biosensors.

[0039] In addition to the embodiment of the present invention using the apparatus **10** to monitor **R1** and **R2** in the animal's or human's body fluids, an alternative embodiment of the present invention is apparatus **10** further comprising a drug delivery system depicted in **FIG. 10** and described in associated text infra, to monitor and deliver a disease treatment agent such as rapamycin into the animal's or human's body fluid to retard or halt restenosis. Referring to **FIG. 1**, more than one apparatus **10** further comprising the drug delivery system depicted in **FIG. 10** infra may be used to detect restenosis or other disease condition resulting in change in the resistance between conductive contacts **12** and **18** or **16** and **22**. The microchip **26** of apparatus **10** includes software to network in-vivo between the stents. Hereinafter, "network" is a cross-functional communication between microchips to monitor **R1** and **R2** and provide a coordinated delivery of disease treatment agent.

[0040] In another embodiment of the present invention, **FIG. 3** depicts a longitudinal cross-section of an in-vivo apparatus **31**, comprising a tube **8**, that may be inserted into a body passage cavity or attached to an organ that includes vessels. The tube **8** may be adapted for insertion into the body vessel as described supra for **FIG. 1** and associated text. **FIG. 3** illustrates that the body fluid in the vessel travels through the apparatus **31** in a direction depicted by arrow **35**. The tube **8** that includes catheters and stents further comprises an inner surface **28**, an outer surface **29** and a body **9**. The body **9** further comprises light emitting diodes or lasers **33**, and **38** and light sensors **37** and a **39** operatively attached to and coplanar **6** with the inner surface **28** of the tube **8**. Referring to **FIG. 3**, light emitting diode or laser **38** may be oriented opposite and parallel to light sensor **39**, and light emitting diode or laser **33** may be oriented opposite and parallel to light sensor **37**. Alternatively, light emitting diode or laser **33** and light sensor **37** may be oriented in a non-opposite and non-parallel orientation to optimize a signal to noise ratio (S/N). Hereinafter, a "signal" is a response from a sensor due to absorption, transmission or fluorescence of light from a light emitting diode or laser by a chemical analyte or by a solid state photoreceptor such as that developed by Foveon, Inc. Hereinafter, "noise" is a response from sensor due to response of a sensor to light scattering of the light from a light emitting diode or laser. A test that a signal is real instead of noise is that the signal to noise ratio (S/N) is greater than 2.0. Hereinafter, a "chemical analyte" is an enzyme, metabolite, toxin or chemical essential to life. The body **9** of the tube **8** may be made from electrically insulating materials such as polyethylene, polypropylene, silicone elastomer, nylon, or polytetrafluoroethylene. The tube **8** may also be made from nitinol⁷, a typical nickel-titanium metal alloy. The apparatus **31** further comprises a microchip **36** that is electrically coupled to conductor **1** and to light emitting diode or laser **33** and additionally to conductor **2** and to light emitting diode or laser **38**. In addition, the microchip **36** may be electrically coupled to conductor **3** and light sensor **37** and additionally to conductor **5** and light sensor **39**. The microchip **36** may further comprise an on-chip battery **24** or like source of electromotive force (EMF). In addition the microchip **36** may further include a receiver/transmitter device **27**. The microchip **36**, the conductors, **1**, **2**, **3** and **5** and light emitting diodes or

lasers **33**, and **38** and light sensors **37** and **39** are encapsulated by electrical insulator **15** when the body **9** of the tube **8** is made from electrical conductors such as metal or metal alloys such as nitinol to prevent malfunction due to shorting. The insulator **15** may be made from silica, silicone elastomer, insulating plastics such as Ultem™ from General Electric Co., nylon, acrylic, polypropylene, polyethylene or polytetrafluoroethylene or similar electrically insulating material.

[0041] Referring to **FIG. 3**, when the tube **8** in apparatus **31** is a stent, the apparatus **31** may function as a typical stent in a post-angioplasty medical procedure. As described supra for **FIG. 1** and associated text, there is a need to monitor the stent **8** for restenosis. Formula **3** depicts an inverse square law relating light energy, luminescence (intensity) and distance between the source of the light, such as light emitting diodes **33** or **38** and a sensor of the light, such as a light sensors **37** or **39**.

$$\text{Light Energy} = \text{Intensity} / \text{distance}^2 \quad (3)$$

[0042] If X is the energy detected by a sensor of light when the source and the sensor are separated by 1 meter, 0.25 x will be the energy detected by the sensor of light when the same source and sensor are separated by 2 meters. Light sensors **37** and **39** respond to a light energy from light emitting diodes or lasers **33** and **38** over time and the response from light sensor **37** is electrically conducted to microchip **36** through conductor **3** and the response from light sensor **39** is electrically conducted to microchip **36** through conductor **5** over time. Hereinafter, the combined circuit comprising the light sensors **37** and **39**, light emitting diodes **33** and **38**, the microchip **36** and associated conductors **1**, **2**, **3** and **5** comprises a "monitoring circuit". Microchip **36** determines the light energy change over time using formula (3), and transmits the light energy change from light sensors **37** and **39** outside the animal's or human's body using the receiver/transmitter **27**. Monitoring the light energy from light sensors **37** and **39** over time is used to test for vascular patency in the animal or human body. Hereinafter, "vascular patency" is the state of an artery or vessel being open. Occlusion of the vessel by either collapse or blockage (e.g., clot formation) will alter light transmittance. Characteristics of light transmittance is a function of Diameter of the stent and the presence of serum and vascular cells (erythrocytes, leukocytes, and platelets).

[0043] In an alternative embodiment, **FIG. 4** depicts a transmission spectrum for hemoglobin having no oxygen, 50% oxygenated hemoglobin, 90% oxygenated hemoglobin and 100% oxygenated hemoglobin. **FIG. 5** depicts a hemoglobin transmission (Log) spectrum illustrating that the greatest variability in spectra from hemoglobin having the aforementioned levels of oxygen is in a range between about 600 nm and 800 nm.

[0044] **FIG. 6** depicts a transmission of bright red light emitting diode through hemoglobin having no oxygen, 50% oxygenated hemoglobin, 90% oxygenated hemoglobin and 100% oxygenated hemoglobin. A single photodiode would see the total integrated power of the product of the diode response and the hemoglobin transmission. The integrated power would be highest for the non-oxygenated blood and lowest for the 100% oxygenated hemoglobin. **FIG. 7** depicts an integrated bright red light emitting diode and hemoglobin transmission through hemoglobin having no oxygen, 50%

oxygenated hemoglobin, 90% oxygenated hemoglobin and 100% oxygenated hemoglobin.

[0045] **FIG. 8** depicts a transmission of bright green light emitting diode through hemoglobin having no oxygen, 50% oxygenated hemoglobin, 90% oxygenated hemoglobin and 100% oxygenated hemoglobin. The transmission of the bright green light emitting diode was insensitive to the oxygen percentage, since the transmission only diminished from 0-10% in the range from about non-oxygenated hemoglobin to 100% oxygenated hemoglobin. Since the bright green light emitting diode transmission was insensitive to the hemoglobin oxygen percentage, the bright green light emitting diode could act a reference that would correct for overall transmission changes due to physical light path length changes and fluid density changes. **FIG. 9** depicts a range of transmission wavelengths for light emitting diodes. As depicted in **FIG. 5** and described in associated text, a single bright red light emitting diode would see the total integrated power of the product of the diode response and the hemoglobin transmission.

[0046] Referring to **FIG. 3**, microchip **36** is used to process a response from the light sensor **37** from transmission using bright red light emitting diode **33** through hemoglobin, wherein the processing produces a signal, S1, that is transmitted through the animal's or human's skin. Microchip **36** is further used to process a response from the light sensor **39** from transmission using bright green light emitting diode **38** through hemoglobin, wherein the processing produces a signal, S2, that is also transmitted through the animal's or human's skin using receiver/transmitter **27**. Subtraction of S2 from S1 using commercially available computer software yields a corrected transmission signal, wherein the corrected transmission signal is proportional to a correct oxygenation level of the hemoglobin flowing through the apparatus **35**.

[0047] Another embodiment of the present invention is depicted in **FIG. 10**, comprising the apparatus **50** that may include delivering a disease treatment agent into the animal's or human's body fluid and monitoring for a disease condition. **FIG. 10** depicts **FIG. 3**, further comprising: a disease treatment agent reservoir **55** that is oriented coplanar **6** with the inner surface **28** of the tube **8**; a microchip **52** operatively coupled to a drug delivery circuit **57** that controls a rate of delivery of a disease treatment agent from the disease treatment agent reservoir **55** to the animal's or human's body fluid. The microchip **52** is also operatively coupled to the monitoring circuit depicted in **FIG. 3** supra and described in associated text.

[0048] Referring to **FIG. 10**, the animal's or human's body fluid flows through the apparatus **50** in a direction depicted by arrow **35**. If the tube **8** is a stent, thrombolytics such as those listed in Table 1 infra may be delivered by the apparatus **50** as the disease treatment agent. The disease treatment reservoir may be made from electroresponsive polymers such as poly(dimethylaminopropylacrylamide (PDMA PAA) poly(methacrylic acid), poly(acrylic acid), alginic acid gel, poly(allylamine) or from magnetically enhanced drug release polymer such as ethylene vinyl acetate copolymer (EVAc). Hereinafter, "electroresponsive polymers" are polymers which become permeable to disease treatment agents when electric current is passed through. Hereinafter, "magnetically enhanced drug release polymers"

are polymers which become permeable to disease treatment agents when subjected to a magnetic field. The reservoir **55** may be comprised of a plurality of smaller, individually addressable reservoirs, each containing a minimum desired dose.

[0049] Referring to FIG. 10, more than one apparatus **50** may be used to detect a disease condition detected by monitoring chemical analytes in the animal's or human's body fluids. The microchip **52** of apparatus **50** includes software to network in-vivo between the stents. Hereinafter, "network" is a cross-functional communication between microchips to monitor R1 and R2 and provide a coordinated delivery of disease treatment agent. Alternatively, the networking between microchips **52** in 2 or more stents **8** in the animal's or human's body fluid may be controlled by software located in a computer or other data processing device outside the body.

[0050] Referring to FIG. 10, the apparatus **50** may include one or more enzyme, sound, pressure pulse, pH and viral, bacterial or biochemical or other biochemical sensors to detect a disease condition. Hereinafter "disease condition" is pre-heart failure condition or abnormal heart beating through pressure/pulse detection and comparison to history. When the sensor detects sound, the determination of the disease condition may involve the Doppler effect. Hereinafter, "bio-chemical sensor" is a detector of a chemical substance or a vital process occurring in living organisms.

[0051] Disease treatment agents of the present invention, a dosage and a standard reconstitution volume required are listed in Table 1 infra.

TABLE 1

Disease Treatment Agent	Dose	Standard Reconstitution Volume
Streptokinase (SK) (Kabikinase, Pharmacia) (Streptase, Astra)	1,500,000 IU/60 min IV intercoronary: 20,000 IU bolus + 120,000/60 min	5 ml
Inexpensive, 5% patients allergic reaction		
Alteplase (tPA) (Activase, Genentech)	15 mg bolus 0.75 mg/kg/30 min (≤ 50 mg)	100 mg ~100 ml
10X SK cost, 580,000 IU/mg	0.5 mg/Kg/60 min (≤ 35 mg)	
Reteplase (rPA) (Retavase, Boehringer Mannheim) 10 U/17.4 mg	10 unit bolus 10 unit bolus 30 min later	2 ml
Anistreplase (Eminase, SmithKline Beecham) 5% patients allergic reaction	30 units IV over 2-5 min	
Tenecteplase (TNKase, Genentech) 200 U/mg	30-50 mg IV over 5 sec	6-10 ml

[0052] Referring to FIG. 10, when the tube **8** in apparatus **31** is a stent, the apparatus **50** may function to monitor for restenosis in a post-angioplasty medical procedure and to deliver a thrombolytic and thrombolytic dose that includes the thrombolytics listed in Table 1 supra.

[0053] The devices of FIGS. 1-3 and **10** may include a polymer coat for embedded circuitry, RF transmission device and pharmaceutical micro or nanotubes. The phar-

maceuticals may be embedded in a nanodevice such as nanotubes, nanoparticles or buckyballs. The nanodevices may be in a reservoir, in the stent or stent sheath. The luminal face of the stent will release the pharmaceutical by an induced signal via changes in a vascular occlusive event. One technique would be a current induced by changes in biopolymer permeability or gold.

[0054] Referring to FIG. 11, an elastic/stretchable sheath **100**, **110** is disclosed containing flexible circuitry. The sheath is made from a biocompatible material such as Gortex® (a waterproof breathable material), polytetrafluoroethylene, stainless steel, carbon structure (e.g., carbon nanotube/nanostructure), or other material as disclosed herein for sheath materials. The sheath is depicted prior to expansion **100** and after expansion **110**. Prior to expansion **100**, a balloon catheter is used to insert the sheath into the body. The sheath diameter is maintained by a rigid structure such as a stent (e.g., stainless steel mesh stent), catheter, or endoscope. The balloon catheter and rigid structure are used to expand the sheath into position.

[0055] FIG. 12 depicts a flexible/expandable stent sheath **200**, **210** containing multiple expansion sites **212**, **214**, **216**. The circumference of the sheathing contains a plurality of expansion sites. The sheath is made from a biocompatible material such as Gortex® (a waterproof breathable material), polytetrafluoroethylene, stainless steel, carbon structure (e.g., carbon nanotube/nanostructure), or other material as disclosed herein for sheath materials. Prior to expansion **200**, a balloon catheter is used to insert the sheath into the body. The balloon catheter expands the sheath **210**.

[0056] FIG. 13 depicts two alternative embodiments of a semi-rigid stent sheath with expansion folds. The two embodiments shown each depict a different configuration for the expansion folds. One type of expansion fold embodiment is a flexible hinge fold **300**. The fold expansion sites **302** located between semi-rigid sheath sites **304** maintain proper orientation of biodelectors (e.g., microdiodes). In the flexible hinge alternative **320** the flexible hinge region **322** folds flat towards the semi-rigid biodelectors a, b, c, d. The second type of expansion fold embodiment is an accordion fold **310**. The fold expansion sites **312** located between semi-rigid sheath sites **314** maintain proper orientation of biodelectors (e.g., microdiodes). The location of the biodelectors a, b, c, d in relation to the accordion folds is shown **330**. Flexible circuitry is present in the expansion folds of both alternatives. FIG. 13 also depicts the sheath prior to, and after, balloon angioplasty expansion. Prior to expansion **340**, a balloon catheter is used to insert the sheath into the body. The balloon catheter then expands the sheath **350**.

[0057] FIG. 14 shows a cross-section of a pharmaceutical delivery device. The pharmaceutical delivery device **400**. The pharmaceutical delivery device includes biosensors **402**, **404** for detecting an occlusive effect or change in diameter Dv. A signal is transmitted through circuit **410**, **412** to an integral microchip **420**. The circuit may include a nanowire or nanotube or standard circuitry with a biocompatible polymer such as polytetrafluoroethylene or other material as disclosed herein. The microchip **420** calculates the occlusive event and allows pharmaceutical release through microtube **430**.

[0058] FIG. 15 shows a biodetection catheter **500** having a biodelector **502** embedded in the luminal and external

surfaces of the catheter tip. The biodetector **502** includes circuitry as described in the embodiments of FIGS. **1-3, 10** and **14**. Alternatively, the microchip and sensor may be external and include an external indicator **510**. The biosensor will detect whether a substrate or occlusion is absent **520**, present **530** or whether an infection is present **540**.

[**0059**] FIGS. **16** and **17** disclose biodetection of nanodevices. A stent **600** is shown which includes biosensors **602, 604, 606, 608, 610,** and **612**. An RF antenna **615** is disclosed. The biosensors transmit data through circuits **616** to a microchip **630**. The circuitry is covered by a sheath or biocompatible material **640** as hereinbefore disclosed. Blood flows through the stent in the direction **650**. The blood includes nanodevices which are either extracellular **660** or intracellular **666**. The intracellular nanodevice is enclosed in a red blood cell **665** through a process such as reverse osmotic lysis or injection.

[**0060**] FIG. **18** shows instrumented stent oximetry circuitry **700** for biosensing bodily conditions about a stent **705**. The circuitry includes a power supply **710**, a clock **720**, a digital controller **730** which are operatively attached to photodiodes **732, 734** with tranconductance OpAmp **740**. The OpAmp **740** and circuit are attached to a serial A/D converter **760** which is attached to a transmitter **780** for conveying an RF signal to an external source.

[**0061**] FIG. **19** shows a circuit **800** embedded in a stent **805**. The circuit **800** includes an integral capacitor **810** operatively attached to an differential amplifier **815** and an A/D converter. The converter is attached to a transmitter **880** and an RF antenna **888**. External to the device is a receiver **900**. The receiver **900** may be in the form of a watch, necklace, palm pilot, computer, bracelet or the like. The receiver **900** receives a signal from the circuit **800** through a receiver **910** which processes the information in a processor **920** and provides an output such as an alarm **930**. The receiver may also include a battery **950**, an inductive charger **960** and a data port **970**.

We claim:

1. Apparatus comprising:
 - a stent; and
 - an expandable sheath, operatively attached to said stent.
2. The apparatus of claim 1, wherein said stent is a wire mesh tube.
3. The apparatus of claim 1, wherein said sheath is an electrically insulated material.
4. The apparatus of claim 3, wherein said electrically insulated material is selected from the group consisting of polyethylene, polypropylene, silicone elastomer, nylon, and polytetrafluoroethylene.
5. The apparatus of claim 3, wherein the electrically insulated material is a metal alloy.
6. The apparatus of claim 1, wherein the expandable sheath is a biocompatible material.
7. The apparatus of claim 6, wherein the biocompatible material is selected from the group consisting of waterproof breathable material, polytetrafluoroethylene, and carbon structure.
8. The apparatus of claim 1, wherein the expandable sheath includes a plurality of expansion sites.

9. The apparatus of claim 1, wherein the expandable sheath is selected from the group consisting of a flexible hinge fold and an accordian fold.

10. Apparatus comprising:

an expandable sheath; and

an electrical conductor operatively attached to said sheath.

11. The apparatus of claim 10, wherein the expandable sheath is a biocompatible material.

12. The apparatus of claim 11, wherein the biocompatible material is selected from the group consisting of waterproof breathable material, polytetrafluoroethylene, and carbon structure.

13. The apparatus of claim 10, wherein the expandable sheath includes a plurality of expansion sites.

14. The apparatus of claim 10, wherein the expandable sheath is selected from the group consisting of a flexible hinge fold and an accordian fold.

15. The apparatus of claim 10, further comprising a microchip.

16. The apparatus of claim 10, further comprising a receiver and transmitter.

17. Apparatus comprising:

a stent;

a biosensor operatively attached to said stent; and

a drug delivery system operatively attached to said biosensor to release a drug.

18. Apparatus comprising:

a stent having a sheath operatively attached thereto; and

a biosensor attached to said sheath.

19. A method for determining a body parameter of an animal comprising:

forming at least two sensors operatively attached to a sheath;

inserting the tube into the vessel; and

wirelessly transmitting a signal outside the body.

20. The method of claim 19, wherein the at least two sensors includes at least two electrodes, and wherein the at least two sensors comprises a circuit for measuring resistance.

21. The method of claim 19, wherein the at least two sensors includes at least one light source and at least one light detector and wherein the at least two sensors comprises a circuit for measuring light transmission.

22. The method of claim 21, wherein the at least two sensors further comprises a circuit for measuring light transmission from about 600 nm to about 800 nm.

23. The method of claim 21, wherein the at least two sensors further comprises a reference circuit for measuring light transmission from about 500 nm to about 600 nm.

24. The method of claim 19, wherein the at least two sensors include a north and south pole of a magnet and at least two electrodes, wherein the north and south poles are oriented orthogonal to a flow of a body fluid through the vessel, and wherein the electrodes comprise a circuit for measuring current.

25. An apparatus comprising:

a sheath having an inner and outer surface, wherein the outer surface is adapted for contacting a wall of a body

passage, and the inner surface forms a lumen for enabling flow of body fluids therethrough;

at least two sensors operatively attached to the sheath, for determining changes in a diameter of the lumen; and

a means for reporting the changes without an intervening wire.

26. The apparatus of claim 25, wherein the sensor determines changes due to collapse of the sheath.

27. The apparatus of claim 26, wherein a positive electrode and a negative electrode are operatively attached to the inner surface of the sheath, and wherein the sensor includes a means to measure a resistance between the electrodes.

28. The apparatus of claim 26, wherein the inner surface of the sheath includes at least one light emitting source and at least one light detector, and wherein the sensor includes means to measure an intensity of light transmitted by the light emitting source to the detector.

29. The apparatus of claim 26, wherein the inner surface of the sheath includes a device for generating a magnetic flux density in the lumen of the sheath, and wherein a positive electrode and a negative electrode are operatively attached to the inner surface of the sheath, and wherein the sensor includes means to measure a voltage between the electrodes.

30. An apparatus comprising:

a sheath having an inner and outer surface, wherein the outer surface is adapted for contacting a wall of a body passage, and the inner surface forms a lumen for enabling flow of body fluids therethrough; and

a light sensor, wherein the sensor is operatively attached to the inner surface of the sheath; and

a means for reporting the determination without an intervening wire.

31. The apparatus of claim 30, wherein an end of the fiber optic array contacts the body fluid.

32. The apparatus of claim 30, wherein a light emitting source is coupled to at least one fiber of the fiber optical array.

33. The apparatus of claim 30, wherein a light detector is coupled to an end of the at least one fiber of the fiber optical array, and wherein the end is proximal to the sensor.

34. The apparatus of claim 30, wherein a fluorescing chemical reagent is attached to an end of the at least one fiber, wherein the end is distal to the sensor and where the photoreceptor is a solid state device.

35. An apparatus comprising:

a microchip on a substrate that is insertable into an animal or human body;

at least one disease treatment agent that is releasable into the body; and

a sensor operatively attached to the microchip, wherein the microchip operatively receives feedback from the sensor for controlling an amount of the disease treatment agent in the body.

36. The apparatus of claim 35, wherein the microchip further includes circuitry, an RF antenna and a disease treatment agent permeable membrane, wherein a signal from the RF antenna increases the permeability of the disease treatment agent permeable membrane.

37. An apparatus comprising:

a catheter having an inner and outer surface, wherein the outer surface is adapted for contacting a wall of a body passage, and the inner surface forms a lumen for enabling flow of at least one disease treatment agent therethrough; and

a sensor operatively attached to the catheter for detecting changes in an amount of the disease treatment agent.

38. Apparatus comprising: an internal medical device; and a nanodevice operatively attached to said internal medical device. **39.** The apparatus of claim 38, wherein the nanodevice is selected from the group consisting of nanotubes, nanoparticles (such as lithium particles), buckyballs, and nanowires .

40. The apparatus of claim 38, wherein the internal medical device is selected from the group consisting of a stent, catheter, defibrillator and endoscope.

* * * * *

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[标]申请(专利权)人(译)	埃尔拉赫朱利安范 OLSEN ARLEN大号 SMITH JEFFREY中号 SMITH LAURA乙 BENDER GERALDê STINCHCOMB AUDRA大号 DONNELLY DENIS P PETERSON JAMESê 惠特默D罗杰 DUDDING GERALD°F SCOTT标记d		
申请(专利权)人(译)	埃尔拉赫朱利安范 OLSEN ARLEN L. SMITH JEFFREY M. SMITH LAURA B. BENDER GERALD E. STINCHCOMB AUDRA L. DONNELLY DENIS P. PETERSON JAMES E. 惠特默ROGER D. DUDDING GERALD F. SCOTT MARK D.		
当前申请(专利权)人(译)	埃尔拉赫朱利安范 OLSEN ARLEN L. SMITH JEFFREY M. SMITH LAURA B. BENDER GERALD E. STINCHCOMB AUDRA L. DONNELLY DENIS P. PETERSON JAMES E. 惠特默ROGER D. DUDDING GERALD F. SCOTT MARK D.		
[标]发明人	ERLACH JULIAN VAN OLSEN ARLEN L SMITH JEFFREY M SMITH LAURA B BENDER GERALD E STINCHCOMB AUDRA L DONNELLY DENIS P PETERSON JAMES E WHITMER ROGER D DUDDING GERALD F SCOTT MARK D		
发明人	ERLACH, JULIAN VAN		

OLSEN, ARLEN L.
 SMITH, JEFFREY M.
 SMITH, LAURA B.
 BENDER, GERALD E.
 STINCHCOMB, AUDRA L.
 DONNELLY, DENIS P.
 PETERSON, JAMES E.
 WHITMER, ROGER D.
 DUDDING, GERALD F.
 SCOTT, MARK D.

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摘要(译)

公开了一种体内方法和装置，其包括至少一个传感器，用于确定人体动物体内的变化并在体外报告所述变化。传感器可以嵌入护套中。该装置可用于监测体液中的化学或物理变化。或者，该装置可用于监测和调节人和动物的化学或物理水平。

