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[54] **IMPLANTABLE GLUCOSE SENSOR**

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[73] Assignee: **The University of Kansas,** Lawrence, Kans.

[21] Appl. No.: **682,560**

[22] Filed: **Apr. 9, 1991**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 511,049, Apr. 19, 1990, abandoned.

[51] **Int. Cl.**[5] **A61B 5/00**

[52] **U.S. Cl.** **128/635**; 204/403; 204/415

[58] **Field of Search** 128/635; 204/403, 415

[56] **References Cited**

U.S. PATENT DOCUMENTS

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4,671,288	6/1987	Gough	128/635

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OTHER PUBLICATIONS

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Salkind et al., "Improving . . . Stability", Med. Inst., vol. 15, No. 2, Mar.–Apr. 1981, pp. 126–127.

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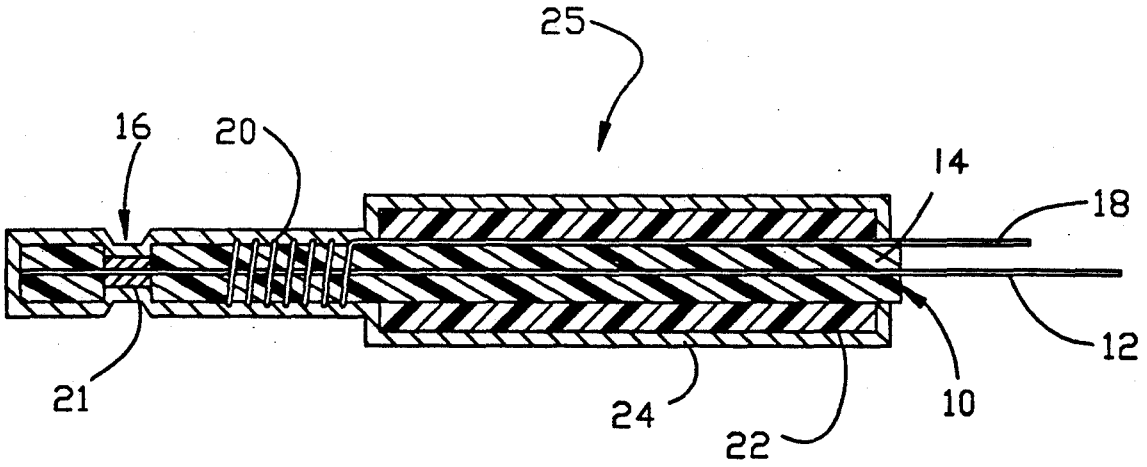
[57] **ABSTRACT**

Implantable enzymatic sensors (**25, 43, 44**) for biochemicals such as glucose are provided having an ideal size and geometry for optional long term implantation and linear responses over the concentration ranges of interest. The sensors (**25, 43, 44**) include an elongated body (**10, 26, 46**) supporting an indicating electrode section having an appropriate enzyme immobilized thereon to present an enzymatic indicating surface (**21, 33, 54**). A permeable synthetic polymer membrane (**24, 42, 56**) is applied over the sensor body (**10, 26, 46**) to protect the enzyme and regulate diffusion of analyte therethrough, to ensure linearity of sensor response. The sensors (**25, 43**) are of flexible design and can be implanted using a catheter. Alternately, the sensor (**44**) includes an internal indicating electrode body (**46**) housed within an apertured, hollow needle (**48**). A holder (**66**) affixed to the needle (**48**) allows for easy manipulation and implantation of the sensor (**44**).

9 Claims, 3 Drawing Sheets



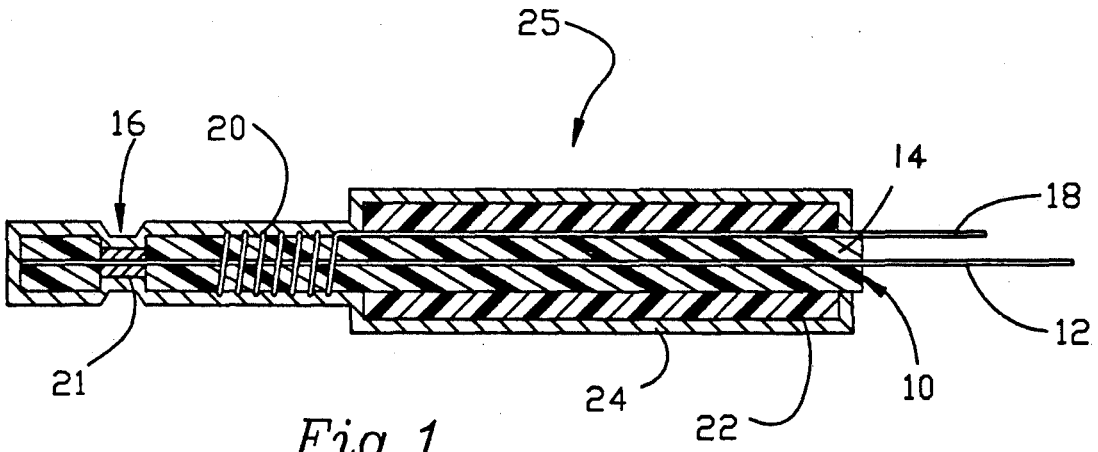


Fig. 1.

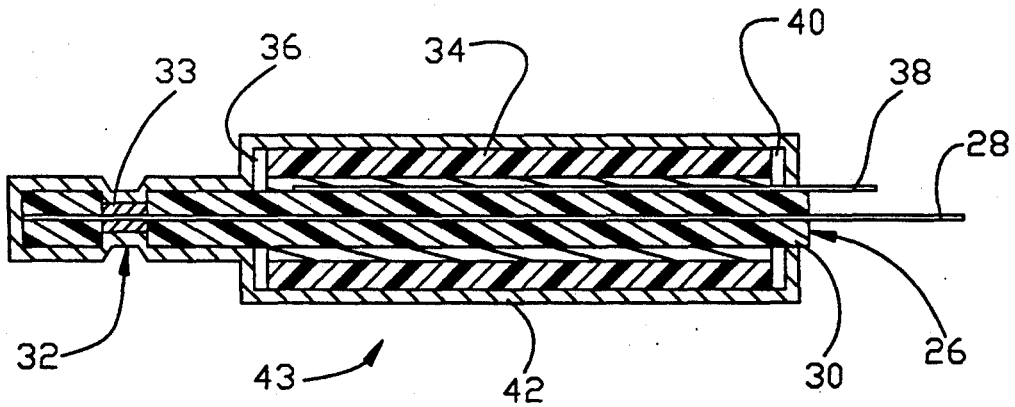


Fig. 2.

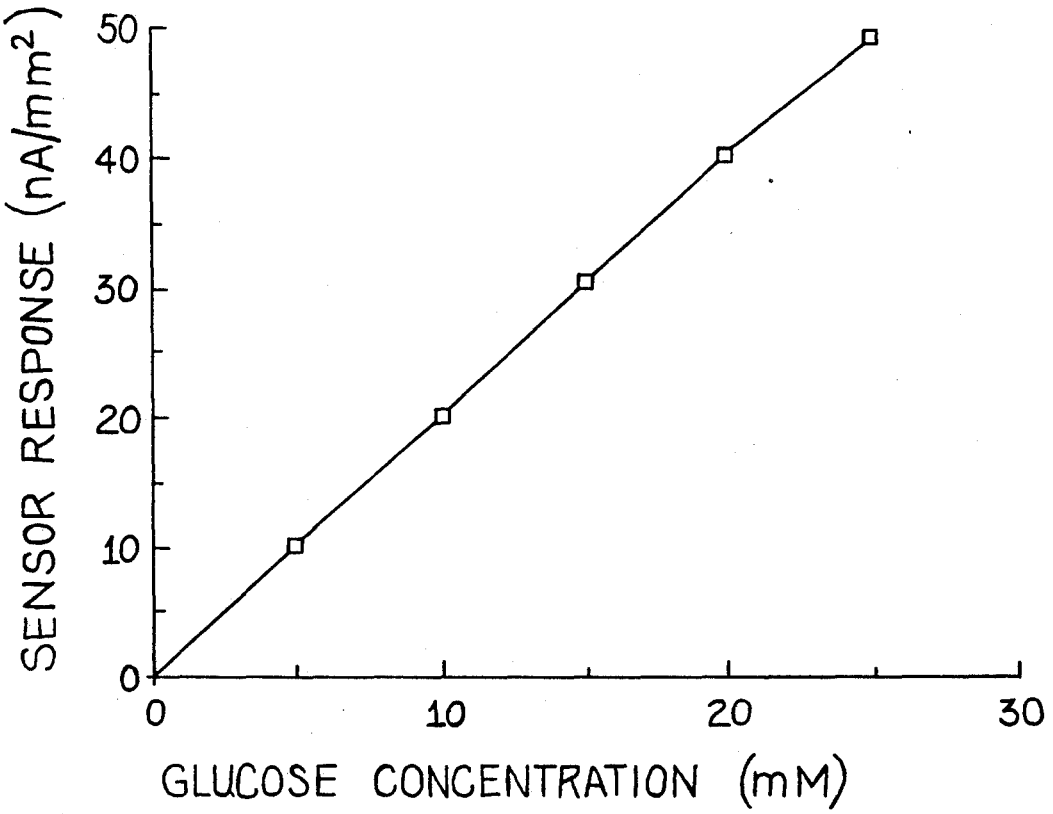
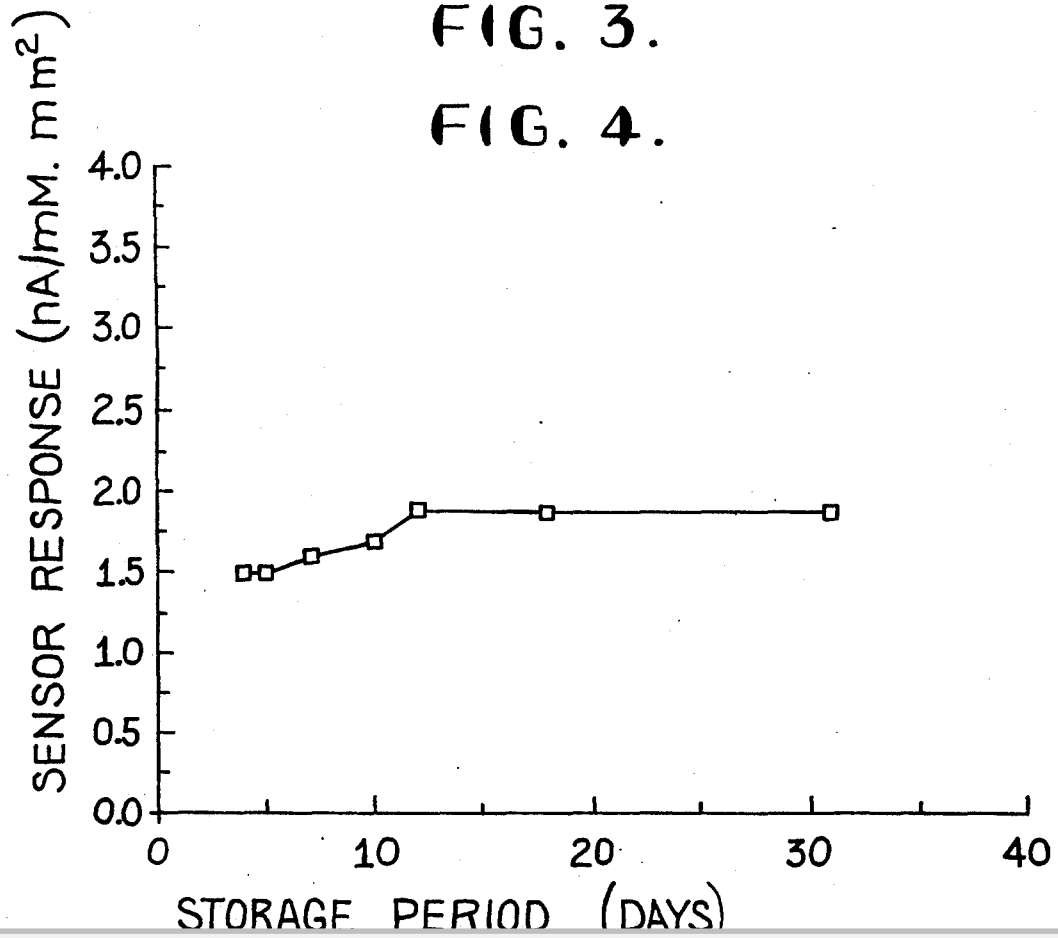


FIG. 3.

FIG. 4.



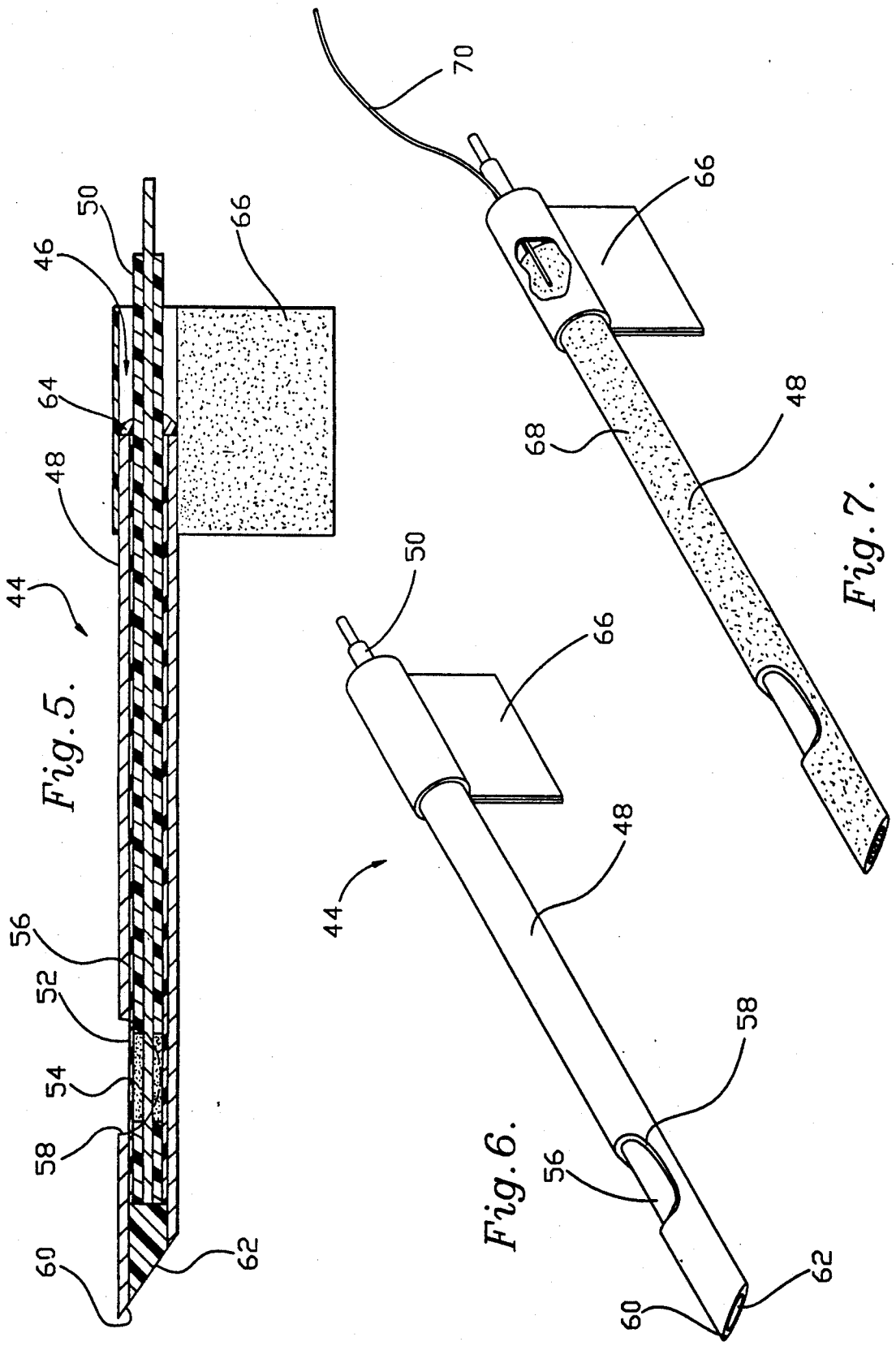


Fig. 5.

Fig. 6.

Fig. 7.

IMPLANTABLE GLUCOSE SENSOR

This is a continuation-in-part of application Ser. No. 07/511,049, filed Apr. 19, 1990, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is broadly concerned with a subcutaneously implantable enzymatic sensor characterized by small size, optimum geometry and linearity of sensor response over the concentration range of interest. More particularly, it is preferably concerned with an implantable glucose sensor of this type designed to provide, in conjunction with a suitable signal processing unit, a current which is proportional to subcutaneous glucose concentration. In preferred forms, glucose sensors of the invention are based on the enzyme-catalyzed oxidation of glucose to gluconic acid and hydrogen peroxide, the latter being monitored amperometrically by the sensors.

2. Description of the Prior Art

There have been a great many attempts in the past to develop viable implantable sensors for continuous in vivo measurements of biochemicals. For example, considerable effort has been made to devise reliable implantable sensors for monitoring glucose concentrations in blood. Such determinations are useful in a variety of applications, e.g., in the treatment of diabetics. One difficulty in providing a reliable implantable glucose sensor is that glucose levels in the bloodstream of a patient vary on a time basis and are normally dependent upon the physical activity of the individual, his food, beverage and sugar intake, his metabolic rate, and other individualized factors. Furthermore, the geometry of the sensor must be such as to adapt to implantation in a living patient.

Glucose sensors have been proposed in the past which rely upon the well-established enzyme-catalyzed oxidation of glucose wherein glucose and oxygen function as substrates for the enzyme glucose oxidase in the production of gluconic acid and hydrogen peroxide, the latter being monitored amperometrically. See, for example, U.S. Pat. Nos. 3,539,455 to Clark and 4,671,288 to Gough.

Although the idea of an implantable enzymatic glucose sensor is not per se new, considerable difficulty has been encountered in producing reliable, cost-efficient devices of this character. For example, many proposed sensor geometries are simply not realistically implantable, at least for the periods of time required for adequate clinical glucose monitoring. Thus, the devices proposed in the '288 Gough Patent, because of a requirement of multiple electrodes carried within a tubular needle, inevitably are of such diameter as to be uncomfortable to the user and not practical for extended implantation. Furthermore, many prior sensors do not exhibit a stable and linear response, particularly over extended times of implantation, and do not give accurate and reliable results. Finally, fabrication of prior glucose sensors has presented formidable difficulties, to the extent that only about one in five sensors produced by conventional techniques are deemed usable. This obviously represents a considerable inefficiency, to the point that no truly successful implantable glucose sensor has heretofore been produced on a large scale.

SUMMARY OF THE INVENTION

The present invention overcomes the problems outlined above, and provides a greatly improved enzymatic sensor specifically designed for long-term implantation in a patient. The sensor is adapted for positioning in an environment characterized by the presence of biological molecules which are substrates for or products produced by enzymes, in order to determine the presence of such biological molecules. While the principles of the invention may be used in the fabrication of glucose sensors, the invention is not so limited. Indeed, the sensors in accordance with the invention may be produced using a wide variety of immobilized enzymes, for the detection of an equally large number of analytes. Exemplary enzymes and their corresponding substrates are given in U.S. Pat. No. 4,721,677 to Clark, and this patent is incorporated by reference herein.

In any event, the enzymatic sensors in accordance with the invention preferably are in the form of an elongated body supporting at least an indicating electrode, with the indicating electrode presenting a section adapted for exposure to the biological environment. The indicating electrode section has an enzyme operably immobilized thereon to present an enzymatic indicating surface. A number of variants are possible for the reference electrode. For example, use may be made of an externally applied electrocardiogram skin electrode (an 8 mm disk covered with silver chloride and available as Model E-243 from the Phymep Company, 21 Rue Campoformio, Paris, France), or a reference electrode which is implanted with the indicating electrode.

In one specific embodiment employing an implanted reference electrode, the indicating surface of the indicating electrode and the reference electrode are laterally spaced apart along the length of the body and each substantially circumscribes the latter and is substantially exposed to the biological environment when the sensor is placed therein. Use of such circumferentially extending enzymatic indicating surfaces and reference electrodes sections is believed to be an important aspect of this embodiment. Alternately, the reference electrode section may comprise a conductive salt bridge circumscribing the body and lying in a plane transverse to the longitudinal axis of the body; in this case, a reference electrode is placed in electrical contact with the salt bridge, through use of a buffered electrolyte. In another embodiment, the reference electrode is simply placed adjacent the indicating electrode as a part of the overall sensor.

In preferred practice, the sensor body advantageously comprises an electrically conductive noble metal (e.g. platinum or platinum-iridium) electrode covered with electrically insulative material, with a portion of this material removed from the electrode to define an enzyme-receiving zone. Thus, a short length of Teflon (polytetrafluoroethylene) coated platinum-iridium wire may be provided, with a short section of the insulation removed intermediate the ends of the wire, so that respective segments of the insulating material are on opposite sides of and define a recessed enzyme-receiving circumferential zone. Alternately, the endmost portion of the Teflon may be removed, leaving a protruding exposed stretch of wire which defines the enzyme-receiving zone. An enzyme is operably immobilized on the exposed section of the platinum-iridium wire, by known means such as adsorption of the enzyme on a

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