No. 2020-1510

In the United States Court of Appeals for the Federal Circuit

ARBMETRICS, LLC,

Plaintiff-Appellant,

v.

DEXCOM INC.,

Defendant-Appellee.

Appeal from the United States District Court
for the Southern District of California, No. 3:18-cv-00134-JLS-MSB.
The Honorable **Janis L. Sammartino**, Judge Presiding.

BRIEF OF PLAINTIFF-APPELLANT, ARBMETRICS, LLC

TIMOTHY E. GROCHOCINSKI
JOSEPH P. OLDAKER
NELSON BUMGARDNER ALBRITTON P.C.
15020 South Ravinia Avenue, Suite 29
Orland Park, Illinois 60462
Telephone: (708) 675-1974

Counsel for Appellant

FORM 9. Certificate of Interest

Form 9
Rev. 03/16

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Arbmetrics, LLC **v.** Dexcom Inc.

Case No. 20-1510

CERTIFICATE OF INTEREST

Counsel for the:
☐ (petitioner) ☒ (appellant) ☐ (respondent) ☐ (appellee) ☐ (amicus) ☐ (name of party)

Arbmetrics, LLC

certifies the following (use "None" if applicable; use extra sheets if necessary):

1. Full Name of Party Represented by me	2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:	3. Parent corporations and publicly held companies that own 10 % or more of stock in the party
Arbmetrics, LLC	Arbmetrics, LLC	None

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (**and who have not or will not enter an appearance in this case**) are:

See Attachment A

March 6, 2020
Date

/s/ Timothy E. Grochocinski
Signature of counsel

Please Note: All questions must be answered

Timothy E. Grochocinski
Printed name of counsel

cc: All counsel of record via CM/ECF

Reset Fields

FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47. 4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary).

NONE

3/6/2020
Date

/s/ Timothy E. Grochocinski
Signature of counsel

Please Note: All questions must be answered

Timothy E. Grochocinski
Printed name of counsel

cc: All counsel of record via CM/ECF

Reset Fields

ATTACHMENT A

Brandon C. Fernald (SBN 222429)
FERNALD LAW GROUP
510 West Sixth Street, Suite 700
Los Angeles, California 90014
Telephone: 323.410.0320
Facsimile: 232.410.0330
Email: brandon.fernald@fernaldlawgroup.com

Edward R. Nelson, III
Texas Bar No. 00797142
NELSON BUMGARDNER ALBRITTON PC
3131 West Seventh Street, Suite 300
Fort Worth, Texas 76107
Telephone: 817.377.9111
Email: ed@nbafirm.com

Brent Bumgardner
Texas Bar No. 00795272
NELSON BUMGARDNER ALBRITTON PC
3131 West Seventh Street, Suite 300
Fort Worth, Texas 76107
Telephone: 817.377.9111
Email: brent@nbafirm.com

TABLE OF CONTENTS

CERTIFICATE OF INTEREST ……..…….. i

TABLE OF AUTHORITIES …….. vii

STATEMENT OF RELATED CASES …….. 1

APPELLATE JURISDICTIONAL STATEMENT ……. 1

STATEMENT OF THE ISSUES ……. 2

STATEMENT OF THE CASE ……..……. 2

I. The ’225 Patent …….……. 2

II. The Claim Construction Order ….…….. 4

SUMMARY OF THE ARGUMENT …….. 5

ARGUMENT ……... 7

I. Standard of Review for Claim Construction …….. 7

II. The District Court Erred in Its Construction of “emulsion” …….. 8

A. The District Court’s Construction of “emulsion” is Contrary to the Intrinsic Evidence ……. 8

i. The District Court’s construction is contrary to claim 5 of the ’225 patent …… 9

ii. The District Court’s construction is contrary to the ’225 patent specification ……. 13

iii. The File History Does Not Require the Claimed Emulsion be Limited to Liquids ……. 15

B. The District Court’s Factual Finding Regarding the Extrinsic Evidence Constitutes Clear Error …….. 17

C. The District Court's Construction is Also Internally Inconsistent 20

D. Arbmetrics' Proposed Construction Should Have Been Adopted 21

III. The District Court Erred in Its Construction of "oxygen dissolving substance" …….. 22

A. The District Court Erred by Not Considering Clear Disclaiming Statements by the Patentee ……. 22

B. The District Court Erred by Defining the Term Only in Relation to Solubility, Not Permeability …….. 26

C. Arbmetrics' Alternative Proposed Construction Should Have Been Adopted ……. 28

IV. The District Court Erred in Its Construction of "in contact with" …..... 29

A. The District Court's Construction of "in contact with" is Contrary to the Intrinsic Evidence ……. 29

B. The District Court's Construction of "in contact with" is Inconsistent With Its Construction of "intimate contact" …….. 32

C. The District Court's Construction of "in contact with" is Not Required by the Extrinsic Evidence ……... 33

V. The District Court Erred in Its Construction of "electrode" ……...….. 35

A. The District Court's Construction is Contrary to the Intrinsic Evidence ……. 36

B. The District Court's Construction is Contrary to the Extrinsic Evidence ……. 40

VI. The District Court Erred in Its Construction of "hydrocarbon oils or solids" ……. 42

CONCLUSION AND RELIEF SOUGHT ……. 45

ADDENDUM

CERTIFICATE OF SERVICE

CERTIFICATE OF COMPLIANCE

TABLE OF AUTHORITIES

Cases	**Page(s)**
Advanced Magnetic Closures, Inc. v. Rome Fastener Corp., 607 F.3d 817 (Fed. Cir. 2010) …….	19, 33, 40
Cardsoft, LLC v. Verifone, Inc., 807 F.3d 1346 (Fed. Cir. 2015) ……...	45
Eli Lilly and Company v. Teva Parenteral Medicines, Inc., 845 F.3d 1357 (Fed. Cir. 2017) ...……	45
Hill-Rom Servs. v. Stryker Corp., 755 F.3d 1367 (Fed. Cir. 2014) ……..	6, 23, 29, 41, 43
Inverness Med. Switzerland GmbH v. Warner Lambert Co., 309 F.3d 1373 (Fed. Cir. 2002) ……...	13, 15, 25, 39
Liebel-Flarsheim Co. v. Medrad, Inc., 358 F.3d 898 (Fed. Cir. 2004) …….	12, 15, 25, 39
Omega Eng'g v. Raytek Corp., 334 F.3d 1314 (Fed. Cir. 2003) ……...	6, 23, 28
Persion Pharm. LLC v. Alvogen Malta Operations Ltd., 945 F.3d 1184 (Fed. Cir. 2019) ……...	8, 17
Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005) ……...	*passim*
Power Mosfet Techs., L.L.C. v. Siemens AG, 378 F.3d 1396 (Fed. Cir. 2004) ……...	39
Regents of Univ. of Cal. V. Dakocytomation Cal., Inc., 517 F.3d 1364 (Fed. Cir. 2008) ……...	45
SimpleAir, Inc. v. Sony Ericsson Mobile Communs. AB, 820 F.3d 419 (Fed. Cir. 2016) ..……..	7

Teleflex, Inc. v. Ficosa N. Am. Corp.,
299 F.3d 1313 (Fed. Cir. 2002) 13, 15, 25, 39

Union Carbide Corp. v. Am. Can Co.,
724 F.2d 1567 (Fed. Cir. 1984) ,,,..... 18

Statutes / Rules

28 U.S.C. § 1295(a)(1) 1

28 U.S.C. § 1338(a) 1

28 U.S.C. § 1400(b) 1

28 U.S.C. § 2107 1

FED. R. APP. P. 4(a)(4)(B)(i) 1

Manual of Patent Examining Procedures § 2173.05(h) 45

STATEMENT OF RELATED CASES

There have been no other appeals before this or any other appellate court stemming from the civil action giving rise to this appeal. Counsel is not aware of any other case, other than the present, which may be directly affected by this Court's decision.

APPELLATE JURISDICTIONAL STATEMENT

Appellant, Arbmetrics, LLC ("Arbmetrics" or "Appellant") brings this Appeal from the District Court to the United States Court of Appeals for the Federal Circuit in accordance with 28 U.S.C. § 1295(a)(1). *See* FED. R. APP. P. 4(a)(4)(B)(i).

This case arose, and arises, under the United States Patent Laws, and jurisdiction exists in accordance with, and pursuant to, 28 U.S.C. §§ 1338(a) and 1400(b). Arbmetrics appeals the Order on Claim Construction of the District Court construing certain claim terms of U.S. Patent No. 6,343,225 ("the '225 patent") ("Claim Construction Order") as well as the District Court's Order Entering Final Judgment ("Final Order"), which was based on the Claim Construction Order. The Final Order is final because final judgment was entered on January 28, 2020. Appx00007-00008, Appx00056.

This appeal has been timely taken within thirty (30) days of the entry of final judgment pursuant to 28 U.S.C. § 2107. Appx00007-00008, Appx00056. The Notice of Appeal was timely filed on February 10, 2020. Appx00056.

STATEMENT OF THE ISSUES

1. Did the District Court err in its construction of the term "emulsion?"

2. Did the District Court err in its construction of the term "oxygen dissolving substance?"

3. Did the District Court err in its construction of the term "electrode?"

4. Did the District Court err in its construction of the term "in contact with?"

5. Did the District Court err in its construction of the term "hydrocarbon oils or solids?"

STATEMENT OF THE CASE

This matter is the appeal of the District Court's Claim Construction Order and subsequent Final Order. Following entry of judgment, Arbmetrics timely appealed to this Court. Appx00007-00008, Appx00056.

I. The '225 Patent.

On January 29, 2002, the United States Patent and Trademark Office duly and legally issued the '225 patent, entitled "Implantable Glucose Sensor." Appx00028. Dr. Leland C. Clark, Jr. (hereinafter "Dr. Clark") is the sole inventor of the inventions claimed in the '225 patent. *Id.* Dr. Clark was an American biochemist whose career spanned more than six decades. He is widely recognized as the "father of biosensors" and for his invention of the oxygen electrode in the 1950's, commonly

referred to as the "Clark electrode." Appx02115-02116, Appx02313 (147:7-20), Appx02314 (150:13-151:2). A select few of the accolades Dr. Clark achieved in his career include the bestowal of the NIH Research Career Award in 1962 (more than thirty years prior to the filing of the '225 patent) and the Horace Mann Award for Service to Humanity in 1984 (more than ten years prior to the filing of the '225 patent). Appx02115-02116. Dr. Clark is a named inventor on more than thirty issued United States Patents. His inventions have been widely commercialized, many of which are still in use today. At least one publication has referred to him as "The Edison of Medicine."

The subject matter of the '225 patent pertains to work completed later in Dr. Clark's career, related to reducing the oxygen sensitivity of enzyme-based polarographic electrodes for implantable biosensors. Appx00028-00046, Appx01749-01754. Claim 1 of the '225 patent is directed to an implantable sensor for detecting a concentration of an organic substrate. Appx00045. The text of claims 1 and 5 is set forth below with claim terms that are the subject of this appeal set forth in bold:

> 1. An implantable sensor for sensing a concentration of an organic substrate, the sensor comprising:
>
> a conductive **electrode**; and
>
> a stabilized enzyme **emulsion in contact with** the **electrode**, the enzyme **emulsion** comprising:
>
> an oxidase enzyme that quantitatively oxidizes the organic substrate;
>
> a water immiscible **oxygen dissolving substance** emulsified

> into intimate contact with the enzyme to provide oxygen; and
>
> a protein crosslinking agent to crosslink and insolubilize the enzyme forming a stabilized gel comprising crosslinked protein and particles of said **oxygen dissolving substance**.
>
> 5. The implantable sensor of claim 1, wherein the **oxygen dissolving substance** is selected from the group consisting of perfluorocarbons, silicone oils, fluorosilicone oils, aromatic and aliphatic **hydrocarbon oils or solids**, carotenoids and steroids.

Id. Claim 1 and dependent claims 2, 5, 7, and 8 were asserted against Dexcom in this matter.

II. The Claim Construction Order.

On December 30, 2019, the District Court issued its Claim Construction Order. Appx00009-00027. The below table summarizes the District Court's constructions. The terms construed by the District Court that are the subject of this appeal are bolded.

Claim Term	District Court's Construction
"**emulsion**" (claim 1)	"a mixture of two or more immiscible liquids, in which one liquid is dispersed in another liquid"
"**oxygen dissolving substance**" (claim 1)	"a substance in which oxygen is preferentially soluble in comparison to water"
"oxygen dissolving substance emulsified into intimate contact with the enzyme" (claim 1)	"oxygen dissolving substance [as defined above] emulsified into very close contact with the enzyme"

"**electrode**" (claim 1)	"a solid electric conductor through which an electric current enters or leaves a substance"
"**in contact with**" (claim 1)	"touching"
"**hydrocarbon oils or solids**" (claim 5)	"oils or solids composed only of carbon and hydrogen"
"water immiscible" (claim 1)	"will not mix with or dissolve in water"

Id.

SUMMARY OF THE ARGUMENT

The District Court's Claim Construction Order suffers from several flaws. First, the District Court applied the abrogated *Texas Digital* framework in reaching its erroneous constructions. In contravention of the proper claim construction methodology articulated in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1320-21 (Fed. Cir. 2005), the District Court first determined what it deemed to be the plain and ordinary meaning of a term, based on its review of extrinsic dictionary definitions advanced by Dexcom that were divorced from the intrinsic evidence, and then purported to use the patent specification as a check on those definitions. This approach has been squarely rejected by this Court. *Phillips*, 415 F.3d at 1320-21.

For example, the District Court construed the term "emulsion" as limited to liquids despite the fact that claim 5, and the '225 patent specification, explicitly state

that the claimed "emulsion" can include solid components. Appx00045 (claim 5), Appx00042 (8:12-17, 8:48-56).

Second, where clear and unequivocal disclaimer was present, the District Court ignored the same instead opting once again for a definition based on extrinsic evidence divorced from the patent specification. For example, with respect to the term "oxygen dissolving substance" the District Court ignored the fact that the patentee distinguished the prior art Wilkins reference on the basis that the substances disclosed in Wilkins (*i.e.,* graphite, nylon, polyethylene, and polystyrene) were not oxygen dissolving. Appx03482-03483. In other words, in distinguishing Wilkins the patentee disclaimed what an "oxygen dissolving substance" can be. *Id.* Despite this, in contravention of this Court's binding precedent, the District Court's Claim Construction Order ignores the patentee's prosecution history statements. *Omega Eng'g., Inc. v. Raytek Corp.,* 334 F.3d 1314, 1324 (Fed. Cir. 2003) ("where the patentee has unequivocally disavowed a certain meaning to obtain his patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of surrender").

Finally, the District Court improperly narrowed the scope of certain claim terms absent lexicography or disavowal in contravention of this Court's long-standing precedent. *See e.g., Hill-Rom Servs. v. Stryker Corp.,* 755 F.3d 1367, 1371-72 (Fed. Cir. 2014). For example, with respect to the terms "electrode," "in contact

with," and "hydrocarbon oils and solids," the District Court adopted improperly narrow constructions proposed by Dexcom that are inconsistent with the intrinsic evidence and the plain and ordinary meaning of these terms. As such, the District Court's Claim Construction Order must be reversed, and this matter should be remanded for further proceedings consistent with this Court's mandate.

ARGUMENT

I. Standard of Review for Claim Construction.

In *SimpleAir, Inc. v. Sony Ericsson Mobile Communs. AB,* this Court set forth the standard of review for a district court's claim construction ruling as follows:

> The ultimate construction of claim language is a question of law reviewed *de novo*, based upon underlying factual determinations reviewed for clear error. *Teva Pharms. USA, Inc. v. Sandoz, Inc*., 135 S. Ct. 831, 837-39, 190 L. Ed. 2d 719 (2015). "[W]hen the district court reviews only evidence intrinsic to the patent (the patent claims and specifications, along with the patent's prosecution history), the judge's determination [as to claim construction] will amount solely to a determination of law, and the Court of Appeals will review that construction *de novo*." *Id*. at 841. "If, on the other hand, a district court resolves factual disputes over evidence extrinsic to the patent, we 'review for clear error those factual findings that underlie a district court's claim construction.'" *Cardsoft, LLC v. VeriFone, Inc*., 807 F.3d 1346, 1350 (Fed. Cir. 2015) (quoting *Teva*, 135 S. Ct. at 842). "[I]t is not enough that the district court may have heard extrinsic evidence during a claim construction proceeding—rather, the district court must have actually made a factual finding in order to trigger *Teva*'s deferential review." *Id*.

820 F.3d 419, 425 (Fed. Cir. 2016). Under the clearly erroneous standard of review, this Court defers to the District Court's factual findings unless, considering the

totality of the evidence, it is "left with the definite and firm conviction that a mistake has been committed." *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.,* 945 F.3d 1184, 1189-90 (Fed. Cir. 2019).

II. The District Court Erred in Its Construction of "emulsion."

A. The District Court's Construction of "emulsion" is Contrary to the Intrinsic Evidence.

The District Court construed the term "emulsion" to mean: "a mixture of two or more immiscible liquids, in which one liquid is dispersed in another liquid." Appx00015-00017, Appx00027. In reaching this conclusion, the District Court correctly framed the parties' dispute as follows: "The dispute therefore centers around whether the emulsion described in Claim 1 of the '225 Patent should be limited to liquids, as Defendant contends, or whether it should include any mixtures of immiscible components, as Plaintiff contends." Appx00015. As stated in the Claim Construction Order, the District Court sided with Dexcom and erroneously found that the term "emulsion" must be comprised of two or more immiscible liquids and cannot include a solid. Appx00015-00017, Appx00027.

The fact that the District Court reached an incorrect construction is likely due to its failure to apply the proper claim construction methodology. In performing its analysis, the District Court appears to have started with Dexcom's proposed construction, which was based on numerous dictionary definitions, and then used the patent specification as a check on those dictionary definitions, attempting to

explain away any portion of the intrinsic evidence that was inconsistent with Dexcom's dictionary based proposal. Appx00015-00017. This approach is contrary to the proper methodology articulated in *Phillips*, and instead follows the abrogated *Texas Digital* claim construction framework. *See Phillips*, 415 F.3d at 1320-21. As this Court held in *Phillips*,

> … the *Texas Digital* approach limits the role of the specification in claim construction to serve as a check on the dictionary meaning of a term if the specification requires the court to conclude that fewer than all dictionary definitions apply, or if the specification contains a sufficiently specific alternative definition or disavowal. That approach, in our view, improperly restricts the role of the specification in claim construction.

Phillips, 415 F.3d at 1320. Such "heavy reliance on the dictionary divorced from the intrinsic evidence," such as that done by the District Court, "risks transforming the meaning of the claim term to the artisan into the meaning of the term in the abstract, out of its particular context, which is the specification." *Id.* at 1321. As a result of applying the wrong framework, the District Court reached a construction for "emulsion" that is contrary to the '225 patent claims and specification and must be reversed.

(i) The District Court's construction is contrary to claim 5 of the '225 patent.

Claim 5 of the '225 patent, which depends from claim 1, explicitly states that the "oxygen dissolving substance," which is part of the claimed "emulsion," can be a solid. Appx00045 (claim 5). Specifically, claim 5 recites a Markush group that

states the "oxygen dissolving substance" may be "hydrocarbon oils or solids." *Id.* Since one of the major components of the claimed "enzyme emulsion" may be a solid (*see e.g.,* claim 5), the term "emulsion" should not be limited to mixtures of two liquids as contended by Dexcom.

Likewise, the claims and the '225 patent specification provide other examples of "oxygen dissolving substances" that are solids. Appx00045 (claim 5), Appx00042 (8:12-17, 8:48-56). For instance, claim 5 also provides that the "oxygen dissolving substance" may be a steroid. Appx00045 (claim 5). The '225 patent specification describes such steroids as "cortical steroids," which are solid substances. Appx00042 (8:12-17, 8:48-56), Appx01760 (Smith Decl. ¶ 48).[1] Despite this, the District Court found that the claimed "emulsion" cannot include solids.

"It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips,* 415 F.3d at 1312 (internal citations omitted). By requiring that the claimed emulsion be "a

[1] In addition, the '225 patent specification goes beyond solids and liquids and also states that gases can be part of the claimed emulsion. *See* Appx00042-00043 (8:14 (silanes, which are gases), (8:53) steroids, which are solids, (8:56) tiny solids, (9:8-12) gas bubbles). This is further evidence that the term "emulsion" is not limited to only liquids. *Id*. In addition, Dexcom's technical expert, Dr. Weber, agreed that steroids are an example of a solid oxygen dissolving substance. Appx03564 (89:11-14).

mixture of two or more immiscible liquids" the District Court's construction violates this bedrock principle and, therefore, must be reversed.

The District Court's contention that "whenever the '225 Patent describes solids used in the emulsion, it is describing solids that have been dissolved in solution – in other words, liquid," is incorrect and directly refuted by the intrinsic evidence. Appx00045 (claim 5), Appx00042 (8:12-17, 8:48-56). First, claims 1 and 5 do not require that any component of the claimed "enzyme emulsion" be dissolved in solution. Appx00045 (claims 1, 5). When the patentee wanted to require a component be dissolved he said so. Appx00045 (claim 9), Appx00046 (claim 17). For example, claim 9 requires "an electron transport compound *dissolved in* the water immiscible oxygen dissolving substance." Appx00045 (claim 5). As another example, claim 17 requires "an electron transport compound dissolved in the perfluorocarbon liquid." Appx00046 (claim 17). Claims 1 and 5 do not have such a requirement.[2] *Compare* Appx00045 (claims 1, 5) *with* Appx00045 (claim 9), Appx00046 (claim 17).

Second, the patent specification does not support the District Court's erroneous conclusion. Notably, the District Court does not cite any portion of the

[2] In addition, when the patentee wanted to limit the claimed "oxygen dissolving substance" to a liquid he also said so. For example, claim 6 states, "wherein the oxygen dissolving substance is a perfluorocarbon liquid." Appx00045 (claim 6). As another example, claim 14 requires "a perfluorocarbon liquid." Appx00046 (claim 14). Claims 1 and 5 are not so limited. Appx00045 (claims 1, 5).

intrinsic record in support of its statement that "whenever the '225 Patent describes solids used in the emulsion, it is describing solids that have been dissolved in solution – in other words, liquid." Appx00016. Rather, the District Court merely cites to page 18 of Dexcom's claim construction brief, in which Dexcom argues that the plain language of claim 5 specifically defining the "oxygen dissolving substance" as a "solid" does not actually mean that the oxygen dissolving substance is a solid. Appx00016, Appx02334. Instead, Dexcom contends that this language means that a solid is "dissolved in solution." Appx02333-02334. However, there is no language in claims 1 or 5 requiring that any component of the claimed "enzyme emulsion" be dissolved in solution and there is no disclosure in the '225 specification requiring that any solid be dissolved. Appx00045 (claims 1, 5).

Further, the fact that certain portions of the '225 patent describe features of certain embodiments as liquids, aqueous, or droplets does not warrant limiting the claimed emulsion to liquids. Appx00040 (4:49-53), Appx00041 (5:25-29), Appx00042 (7:55-65, 8:23-29) (the excerpts relied on by Dexcom). Claim 5 specifically states that at least the "oxygen dissolving substance" of the claimed emulsion can be a solid. Appx00045 (claim 5). This Court has repeatedly held that courts may not import limitations from embodiments disclosed in the specification in order to limit or otherwise vary the meaning of the claim language. *See e.g., Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 905-06 (Fed. Cir. 2004);

Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1327-28 (Fed. Cir. 2002); *Inverness Med. Switzerland GmbH v. Warner Lambert Co*., 309 F.3d 1373, 1379 (Fed. Cir. 2002) ("It is improper to limit the claim based on a preferred embodiment of the invention."). When the patentee wanted to limit the claimed "oxygen dissolving substance" to liquids he stated as much. Appx00045 (claim 6 – "wherein the oxygen dissolving substance is a perfluorocarbon liquid").[3]

In sum, nothing in the intrinsic record supports the District Court's conclusion that any solids in the claimed emulsion (*e.g.,* those claimed by claim 5) must be first dissolved in liquid form. It is well established that "the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips,* 415 F.3d at 1312. The District Court simply decided to ignore the plain language of the claims in lieu of a construction based on extrinsic dictionary definitions. This is improper and requires reversal.

(ii) The District Court's construction is contrary to the '225 patent specification.

In addition to the plain language of the patent claims, the District Court's construction of "emulsion" is also contrary to the '225 patent specification. The specification of the '225 patent is explicit that the materials comprising the

[3] Perfluorocarbons can also be a solid. Appx02122-2123 (Smith Rebuttal Dec., ¶ 33). However, in claim 6 the patentee chose to limit the state of perfluorocarbon to liquid. Appx00045 (claim 6).

"emulsion" are not limited to liquids. Appx00045 (claim 5), Appx00042 (8:12-17, 8:48-56). In describing the claimed emulsion, the '225 patent states: "[e]ssentially, tiny **solid or liquid particles** of a material that readily dissolve oxygen are held in intimate contact with an oxygen utilizing enzyme which is preferably **in insoluble form**." Appx00042 (8:56-59) (emphasis added). In other words, the '225 patent specification explicitly states that the particles that make up the emulsion can be "solid or liquid particles." *Id*. The District Court's construction, limiting the claimed emulsion to "liquid particles," is directly contradicted by the '225 patent specification. *Id*.

In an attempt to support its construction, the District Court sought to distinguish this excerpt of the '225 patent specification not with evidence, but merely with another citation to Dexcom's brief, stating: "as Defendant notes, 'the sentence seems to describe the gel formed after the emulsion is crosslinked, rather than before as in the claims." Appx00016. This argument is nonsensical and does not support limiting the claimed emulsion to liquids. First, the '225 patent specification at 8:56-59 is describing the claimed emulsion and explicitly states that the claimed emulsion can contain "solid or liquid particles." Appx00042. Second, the inconsistency of the District Court's construction is highlighted by its acknowledgment that a "gel" includes a solid. Appx00016 ("the sentence seems to describe the gel formed after the emulsion is crosslinked"). The plain language of claim 1 requires that the

"enzyme emulsion" comprise the "gel" referenced by the District Court. Appx00045 (claim 1).[4] It is therefore impossible for the claimed "enzyme emulsion" to *comprise the gel* (as required by claim 1) and simultaneously *not be able to include a solid* as required by the District Court's construction. Appx00015-00017, Appx00027. Finally, even if it were assumed that Dexcom were correct, which it is not, the fact that this excerpt "seems to describe the gel" does not warrant limiting the scope of the claimed emulsion to only liquids. *See e.g., Liebel-Flarsheim*, 358 F.3d at 905-06; *Teleflex,* 299 F.3d at 1327-28; *Inverness Med.*, 309 F.3d at 1379.

(iii) The File History Does Not Require the Claimed Emulsion be Limited to Liquids.

The District Court, once again citing only Dexcom's brief, held that in the prosecution history, "the patentee distinguishes a prior art reference, U.S. Patent 5,431,160 ("Wilkens") (*sic*), because Wilkens discloses a suspension or gel – both of which may contain solids – rather than an emulsion." Appx00016-00017. This holding is simply wrong. In distinguishing Wilkins, the patentee stated,

> Such gels are known in the art and are used by **Wilkins**. However, the stabilized gel of the instant invention also contains an emulsion of an immiscible oxygen dissolving substance.

[4] The District Court's explanation, which is merely an adoption of a sentence from Dexcom's brief, also arguably reads a method step into claim 1, which is an apparatus claim. *See e.g., IPXL Holdings, LLC v. Amazon.com, Inc.,* 430 F.3d 137, (Fed. Cir. 2005) (holding that a single claim covering both an apparatus and a method of use of that apparatus is indefinite).

Appx03482 (emphasis in original). In other words, the patentee acknowledged that Wilkins disclosed a gel and then went on to state that the instant invention also claims a stabilized gel. *Id.* The patentee did not distinguish Wilkins because it discloses a gel. Rather, on this point the patentee agreed that both Wilkins and the claimed invention disclose a gel. The District Court's holding that Wilkins was distinguished on this basis is simply incorrect.

The patentee then went on to actually distinguish Wilkins, stating:

> Applicant contends that **Wilkins** does not teach the formation and use of an (*sic*) stabilized enzyme emulsion containing an immiscible oxygen dissolving substance. The fine particles of graphite used by **Wilkins** are immiscible but do not constitute an oxygen dissolving substance. Oxygen is not preferentially soluble in graphite – it is barely soluble if at all. Nor is oxygen particularly soluble in nylon, polyethylene or polystyrene. Because the device of **Wilkins** does not contain an emulsion of an immiscible oxygen dissolving substance, it cannot be said to anticipate the present invention.

Appx03483 (emphasis in original). In other words, applicant distinguished Wilkins based on the fact that the particles found in the Wilkins reference, specifically particles of graphite, nylon, polyethylene, and polystyrene, are barely oxygen dissolving if at all, and therefore do not disclose the claimed "enzyme emulsion," which requires an oxygen dissolving substance. *Id.,* Appx02120-02121 (Smith Rebuttal Decl., at ¶¶ 26-28). In sum, there are no statements in the prosecution history that limit the claimed "emulsion" to liquids.

B. The District Court's Factual Finding Regarding the Extrinsic Evidence Constitutes Clear Error.

As a threshold matter, the extrinsic evidence does not need to be considered to determine that the District Court's construction of "emulsion" is incorrect and must be reversed. As discussed above, the intrinsic evidence requires that the District Court's construction of "emulsion" be reversed. Setting this aside, the District Court also erroneously held that the extrinsic evidence supports Dexcom's – *i.e.,* the District Court's – construction. Appx00017. In support of this conclusion the District Court only cited to Dexcom's claim construction brief, quoting Dexcom's assertion that "all of the dictionaries and texts relied on by both parties define emulsion as a dispersion of two or more liquids." *Id*. This is incorrect.

For instance, the New Encyclopedia Britannica indicates that the term "emulsion" is often applied to mixed systems that may be characterized as solutions, suspensions, or gels. Appx01807-01810. A "photographic emulsion" is one example of such a system. *Id*. A person having ordinary skill in the art would have known that a "photographic emulsion" is a mixture of a crystalline silver halide dispersed within a gel (*i.e.,* not a mixture of only liquids, but includes a solid). Appx01758 (Smith Decl., at ¶ 42). Additionally, Dexcom argued in its claim construction briefing that "suspensions" and "gels" include "solid particles dispersed in liquids." Appx02333-02334. As such, a person of ordinary skill in the art in the 1990's would have understood that the term "emulsion," on its own, clearly does not

apply to only mixtures of two or more liquids. Appx01757-01761, Appx02118-02125.[5]

Further, Dexcom's extrinsic evidence does not mandate that the term "emulsion," be limited to mixtures of liquids. For instance, several dictionary definitions used by Dexcom in the deposition of Arbmetrics' expert, Dr. Smith, recognize that a photographic emulsion comprises solid particles suspended in a gel,

[5] In its Claim Construction Order, the District Court failed to identify the relevant art and the qualifications of a person of ordinary skill in the art at the time of invention. This was despite the fact that a dispute between the parties existed concerning both of these issues. Arbmetrics contends that the relevant field of art is implantable sensors for analyte measurements and person of ordinary skill in the art at the time of invention would have had at least a bachelor's degree in chemistry, biochemistry, physics, chemical engineering, or biomedical engineering, and at least three years of experience in the development of implantable systems for blood glucose (or other analyte) monitoring systems. Appx01715-01716, Appx01754, Appx02114-02117. Dexcom contended that the relevant art of the '225 patent is "electrochemistry" and that a person of ordinary skill in the art at the time of invention would have had "at least a Bachelor's degree and at least five years of experience, or a Ph.D. degree and at least two years of experience, where the degree was in the field of chemistry, electrochemistry, or a closely related discipline, and where the experience was practical laboratory experience in making electrochemical sensors." Appx02215-02216. Dexcom's expert Dr. Weber testified that he had no experience in developing implantable sensors in the 1990's. Appx02284-02285 (30:19-34:16) (he began work with implantable sensors in the 2000's). As such, Dr. Weber was not a person of ordinary skill in the art at the time of the invention of the '225 patent. Therefore, his opinions regarding what a person having ordinary skill in the art would have understood at the time of invention are unsubstantiated and the testimony he has provided in conjunction with this matter should be afforded little weight. *Union Carbide Corp. v. Am. Can Co*., 724 F.2d 1567, 1572 (Fed. Cir. 1984) (discounting the testimony of one who fails to show skill in the relevant art or whose opinion is without factual support). In contrast, Dr. Smith, Arbmetrics' expert, is one of ordinary skill in the art. Appx01746-01748, Appx01780-01786, Appx02114-02117.

or describe an "emulsion" as a "suspension," in direct contravention to Dexcom's alleged meaning of that term. Appx02170-02171 (148:8-25, 151:6-24) (noting the Concise Oxford Dictionary (1999) definition of "emulsion" includes "crystals of a silver compound dispersed in a medium such as gelatin"), Appx02171-02173 (152:22-153:6, 156:15-157:20) (noting the American Heritage Dictionary (1994) provides a first definition of "emulsion" that includes "a suspension," and a second definition includes "silver halide grains in a thin gelatin layer"), Appx02174-02175 (161:14-162:18, 164:2-8) (noting the American Heritage Science Dictionary (2005) defines "emulsion" as "a suspension"). In addition, Dexcom's extrinsic evidence explicitly states that an "emulsion" can include an emulsifying agent, which can be a solid. Appx02979-02984, Appx03000-03006.

The District Court's Claim Construction Order completely ignores the extrinsic evidence presented by Arbmetrics. Arbmetrics provided detailed testimony from its expert, Dr. Smith, evidencing that the District Court's construction is incorrect and that Arbmetrics' proposed construction should have been adopted. Appx01757-01761, Appx02118-02125. The District Court's Claim Construction Order did not even acknowledge Dr. Smith's opinions. Appx00015-00017. The District Court's failure to consider all of the evidence in its analysis also constitutes clear error. *See Advanced Magnetic Closures, Inc. v. Rome Fastener Corp.*, 607

F.3d 817, 831 (Fed. Cir. 2010) (noting that a district court is required to "consider all the evidence").

In sum, when viewed in its entirety, the extrinsic evidence demonstrates that there are multiple different types and definitions of emulsions, all of which are not limited to "a mixture of two or more immiscible liquids." The District Court's unsupported holding to the contrary constitutes clear error and should be reversed.

C. The District Court's Construction is Also Internally Inconsistent.

The District Court incorrectly construed the term "emulsion" to be limited to liquids. However, in construing the term "oxygen dissolving substance," which is discussed *infra* in Section III, the District Court held that that the term is not limited to liquids and specifically noted that the "term is described as a solid in both Claim 5 and the specification." Appx00021-00023, Appx00027. It is not disputed that the claimed "oxygen dissolving substance" is part of the claimed "emulsion." Appx00045 (claim 1). As such, the Claim Construction Order holds that the claimed "emulsion" cannot include a solid, but that the claimed "oxygen dissolving substance," which is part of the claimed emulsion, can be a solid. Appx00015-00017, Appx00021-00023, Appx00027. This is nonsensical and highlights why the District Court's construction of "emulsion" is incorrect and must be reversed.

D. Arbmetrics' Proposed Construction Should Have Been Adopted.

In contrast to the District Court's construction, Arbmetrics' proposed construction is consistent with the intrinsic and extrinsic evidence. Arbmetrics' proposed that the term "emulsion" should be construed to mean: "a mixture of two or more immiscible components, in which one component is dispersed in another component." Appx00015, Appx01717-01721. This construction is consistent with claim 1, which defines the "enzyme emulsion" as a "stabilized gel." Appx00045 (claim 1). It is well understood that a gel can include a solid dispersed in a liquid, and the District Court acknowledged this in adopting Dexcom's arguments concerning solids in the "crosslinked gel." Appx00015-00017. The District Court's construction, which requires that a liquid be dispersed in a liquid is contrary to the plain language of claim 1, which states that the claimed enzyme emulsion is a "stabilized gel" (*e.g.,* a solid dispersed in a liquid).

Arbmetrics' proposed construction is also consistent with claim 5, in that it allows for solids to be present in the claimed emulsion, which is explicitly required by claim 5. Appx00045 (claim 5). Further, Arbmetrics' proposed construction is consistent with the '225 patent specification, which explicitly states that the particles that make up the emulsion can be "solid or liquid particles." Appx00042 (8:12-17, 8:48-56). Finally, Arbmetrics' proposed construction is also consistent with the extrinsic evidence, which clearly demonstrates that the term "emulsion" is not

limited to only liquids but can also include solid components. Appx01757-01761, Appx01807-01810, Appx02118-02125, Appx02170-02175, Appx02979-02984, Appx03000-03006.

In sum, the District Court's construction of "emulsion" is contrary to the evidence and must be reversed. Arbmetrics' proposed construction, which is consistent with the evidence, should be adopted.

III. The District Court Erred in Its Construction of "oxygen dissolving substance."

The District Court construed to the term "oxygen dissolving substance" to mean "a substance in which oxygen is preferentially soluble in comparison to water." Appx00023, Appx00027. This construction is incorrect for two reasons: (1) it incorrectly defines the term in relation to the solubility of water instead of adopting the patentee's disclaiming statements made during prosecution, and (2) it defines the term only in relation to solubility instead of solubility or permeability.[6]

A. The District Court Erred by Not Considering Clear Disclaiming Statements by the Patentee.

As discussed above, in distinguishing Wilkins the patentee stated:

> Applicant contends that Wilkins does not teach the formation and use of an (*sic*) stabilized enzyme emulsion containing an immiscible oxygen dissolving substance. The fine particles of graphite used by Wilkins are immiscible but do not constitute an oxygen dissolving substance. Oxygen is not preferentially

[6] For the reasons discussed above in Section II, the District Court correctly held that the term "oxygen dissolving substance" is not limited to liquids.

> soluble in graphite – it is barely soluble if at all. Nor is oxygen particularly soluble in nylon, polyethylene or polystyrene. Because the device of Wilkins does not contain an emulsion of an immiscible oxygen dissolving substance, it cannot be said to anticipate the present invention.

Appx3483. Through this interaction with the patent examiner, the patentee excluded graphite, nylon, polyethylene, and polystyrene from the definition of an "oxygen dissolving substance," because these substances do not have a high enough oxygen dissolving characteristic (*e.g.,* solubility). *Id.* These statements constitute clear and unequivocal disclaimer that must be accounted for in the construction of the term "oxygen dissolving substance." *See Omega Eng'g,* 334 F.3d at 1323-25. In this excerpt, the patentee is setting the threshold that determines whether or not a substance is oxygen dissolving (*i.e.,* is its oxygen dissolving property higher than graphite, nylon, polyethylene, and polystyrene). In other words, the patentee is making clear (*i.e.,* disclaiming) that graphite, nylon, polyethylene, and polystyrene are not oxygen dissolving substances, as claimed. *Hill-Rom Servs.*, 755 F.3d at 1371 (disavowal occurs where the specification or prosecution history make clear that the invention does not include a particular feature). The District Court's failure to even address this excerpt from the file history constitutes error. *Phillips,* 415 F.3d at 1317 ("a court 'should also consider the patent's prosecution history, if it is in evidence'"). At a minimum, the term "oxygen dissolving substance" should be construed to be a substance having a higher oxygen solubility or permeability than particles of

graphite, polyethylene, polystyrene, and nylon.

Further, the fact that the '225 patent specification mentions in a few instances water solubility in passing does not overcome the patentee's disclaiming statements and mandate that the term be construed in relation to water. Appx00040 (3:33-40), Appx00042 (7:38-40), Appx00043 (10:27-32), Appx00045 (13:2-4). In support of its holding that the oxygen dissolving property of the claimed "oxygen dissolving substance" should be defined in comparison to water, the District Court cites two excerpts from the '225 patent, neither of which warrants the District Court's construction. Appx00022.

The District Court cites to column 10, lines 27-29 (incorrectly identified in the Claim Construction Order as 3:33-40), which states "[t]his limits the distance that oxygen must diffuse through a poor oxygen carrier **such as** water." Appx00043. This statement is referencing oxygen transport, which is a different phenomenon than solubility. *Id.* Rather, oxygen diffusion is related to permeability, which the District Court incorrectly held "has no place in the construction of this term." Appx00022. In addition, this specification excerpt does not mandate that materials with a lower oxygen dissolving characteristic than water should be excluded from the claimed invention, as it implies that oxygen will in fact diffuse through water in various embodiments. Appx00043 (10:27-29).

The other excerpt relied on by the District Court is column 13, lines 2-4, which

states, "[a]n advantage is that steroids, like perfluorocarbons, are much better at dissolving oxygen than is water." Appx00022, Appx00045. First, this statement is made in the context of addressing the problem of leukocyte accumulation, which may compromise the accuracy of the glucose readings, via the use of steroids as an "anti-inflammatory, anti-leukocyte compound,"[7] not in the context of the claimed "oxygen dissolving substance." *Id.* Second, the fact that the patentee states that "steroids, like perfluorocarbons, are much better at dissolving oxygen than is water" does not mandate that the term "oxygen dissolving substance" be limited as such. This Court has repeatedly held that courts may not import limitations from embodiments disclosed in the specification in order to limit or otherwise vary the meaning of the claim language. *See e.g., Liebel-Flarsheim*, 358 F.3d at 905-06; *Teleflex,* 299 F.3d at 1327-28; *Inverness Med.*, 309 F.3d at 1379.

In sum, there is nothing in the intrinsic evidence that warrants limiting the term "oxygen dissolving substance" to substances with a higher oxygen solubility than water. In contrast, the patentee's disclaiming statements in distinguishing Wilkins require that the term be construed to include substances having a higher oxygen solubility than particles of graphite, polyethylene, polystyrene, and nylon

[7] The concept of using steroids as an "anti-inflammatory, anti-luekocyte compound" is addressed by unasserted claim 13, which depends from claim 1. Appx00046 (claim 13). It is not addressed by claims 1 or 5, which discuss using steroids as oxygen dissolving substances. *Id.*

(*i.e.,* the substances the patentee disclaimed as non-oxygen dissolving).

B. The District Court Erred by Defining the Term Only in Relation to Solubility, Not Permeability.

The District Court also erred by holding that "permeability has no place in the construction of this term." Appx00022. Notably, the District Court provides no citation or support for this erroneous holding. *Id.* Further, as discussed above, the District Court erred by relying upon excerpts of the '225 patent specification discussing oxygen diffusion, a concept related to the permeability of materials, in support of its incorrect construction. *Id.,* Appx00043 (10:27-29). This is because the '225 patent specification discusses the "oxygen dissolving substance" in terms of its oxygen solubility or oxygen permeability. Appx00041 (5:24-26), Appx00042 (7:46-54, 8:21-22).

While there are several passages in the '225 patent specification that discuss the concept of dissolving oxygen in terms of a substance's oxygen solubility (*see e.g.*, Appx00041 (5:24-26) ("[t]his is achieved by making a stabilized emulsion of the enzyme and a compound in which oxygen is extremely soluble")), it is clear the patentee intended to include oxygen permeability as another measure of a substance's oxygen dissolving properties. For instance, the '225 patent states, "[t]he speed of oxygen diffusion through a barrier" (*e.g.*, the permeability of the barrier) "is controlled by the thickness of the barrier and by the amount of oxygen that can dissolve in a unit thickness of the barrier. That is, making the barrier thinner, or

making the barrier dissolve more oxygen will increase the rate of oxygen diffusion." Appx00042 (7:46-54). This is a clear description of oxygen permeability through a barrier. The '225 patent goes on to state that "[t]he particles of these compounds act as stepping stones for oxygen to reach the electrode surface." *Id*. at 8:21-22. This is another example of a discussion of oxygen permeability. Therefore, the '225 patent specification discusses the concept of oxygen permeability, independent of oxygen solubility, as a factor that can be used to define the claimed oxygen dissolving substance. Appx00042 (7:46-54, 8:21-22), Appx01768-01772 (Smith Decl., at ¶¶ 80-81).

Moreover, the '225 patent specification uses the concepts of oxygen permeability and solubility *interchangeably* in the context of a material's "oxygen dissolving" properties. Appx00042 (8:48-54). The '225 patent specification explicitly states, "[t]he present invention, then, provides a greatly improved sensor by producing a cross-linked gel containing glucose oxidase or similar hydrogen peroxide-producing enzymes, an emulsified oxygen <u>binding/permeable</u> material, such as a perfluorocarbon, a silicone oil, a fluorosilicone oil, an aliphatic oil or organic compound such as a steroid, to carry oxygen to the enzyme." *Id.* (emphasis added). As such, the correct construction for the term "oxygen dissolving substance" should account for both oxygen solubility and oxygen permeability. The District Court's erroneous and unsupported conclusion that "permeability has no place in the

construction of this term" is directly contradicted by the intrinsic evidence and must be reversed.

C. Arbmetrics' Alternative Proposed Construction Should Have Been Adopted.

Arbmetrics' proposed that the term "oxygen dissolving substance" should be construed to mean: "a substance having a higher oxygen solubility or higher oxygen permeability than particles of graphite, polyethylene, polystyrene, and nylon." Appx01730, Appx03719, Appx03845.[8] This construction is consistent with the intrinsic evidence in that it accounts for the patentee's disclaiming statement made to overcome Wilkins. *Id.,* Appx03482-03483. In addition, Arbmetrics' proposed construction accounts for the fact that the patentee, throughout the intrinsic record, discussed the claimed "oxygen dissolving substance" in terms of its oxygen

[8] At the District Court, Arbmetrics proposed an alternative construction for "oxygen dissolving substance" of be "a substance having a higher oxygen solubility or higher oxygen permeability than at least one of a hydrocarbonaceous polymer (*e.g.*, graphite, polyethylene, or polystyrene) and an oxyhydrocarbon polymer. Appx00021, Appx01727-01731. The District Court rejected this construction because the terms "hydrocarbonaceous polymer" and "oxyhydrocarbon polymer" do not appear in the intrinsic record. Appx00022. As a threshold matter, the District Court's reasoning does not require rejection of Arbmetrics' proposal. With this proposal, Arbmetrics was simply trying to capture the substances disclaimed during prosecution of the '225 patent. Setting this aside, Arbmetrics' proposed construction for "oxygen dissolving substance" advanced on this appeal, which was also requested at the District Court, is congruent with the scope of the patentee's disclaimer. Appx01730, Appx03482-03483, Appx03719, Appx03845; *see Omega Eng'g,* 334 F.3d at 1324-25.

solubility and oxygen permeability. Appx00041 (5:24-26), Appx00042 (7:46-54, 8:21-22, 8:48-54), Appx01768-01774.

In sum, the District Court's construction of "oxygen dissolving substance" is contrary to the evidence and must be reversed. Arbmetrics' proposed construction, which is consistent with the evidence, should be adopted.

IV. The District Court Erred in Its Construction of "in contact with."

The District Court construed the term "in contact with" to mean "touching." Appx00020, Appx00027. In reaching this erroneous construction the District Court once again started with Dexcom's proposed construction, "touching," which was based on select excerpts from extrinsic dictionary definitions, and then consulted the '225 patent specification merely as a check. Appx00017-00020. This is not the proper claim construction methodology. *Phillips,* 415 F.3d at 1320-21. The result was a construction that improperly narrowed the scope of the term "in contact with" to "touching," absent lexicography or disavowal. *Hill-Rom,* 755 F.3d at 1371-72. In addition, the District Court's construction of "in contact with" – "touching" – is internally inconsistent with its construction of "intimate contact" – "very close touching." As such, the District Court's construction must be reversed.

A. The District Court's Construction of "in contact with" is Contrary to the Intrinsic Evidence.

The '225 patent discloses different types of contact, which requires that the term "contact" not be limited solely to direct contact or physical touching.

Appx00040 (3:33-42), Appx00041 (6:58-67), Appx00045 (claim 1). For instance, the '225 patent specification states:

> Generally the device is not directly in contact with the circulatory system so that formation of blood clots does not interfere with the operation. All of the body tissues come into glucose equilibrium with the blood fairly rapidly so that placement of the device in contact with the blood is not really required.

Appx00041 (6:62-67) (emphasis added). The primary purpose of a glucose sensor is to measure the glucose levels present in blood (*i.e.,* within the circulatory system) and the cited passage evidences that the device may merely be in communication with (or indirect contact with) blood and/or the circulatory system. *Id*. The District Court's conclusion that this excerpt, and Arbmetrics' proposed construction, means "that the glucose monitor is 'not really required' to be in communication with the blood" is unfounded. Appx00019. Rather, this passage makes clear that direct contact – *e.g.,* touching – is not required. Appx00041 (6:62-67). Further, contrary to the District Court's finding, Arbmetrics' proposed construction – *i.e.,* "in direct, indirect, or diffusional communication with" – is consistent with this specification passage, as it dictates that a glucose monitor may be in indirect contact or communication with the blood to affect the desired electrochemical reaction. Indeed, the specification discloses that the claimed implantable sensor may be implanted beneath the surface of the skin to measure interstitial fluid or in the peritoneal space to measure peritoneal fluid. Appx00040-00041 (3:33-42; 6:58-67).

Thus, the glucose monitor does not have to be in direct contact (*i.e.,* touching) as erroneously required by the District Court.

A review of the claims of the ’225 patent also illustrate the same point and lead to the same result. Claim 1 uses the term “contact” in two different ways. Appx00045 (claim 1). The first usage of the term “contact” is in the context of the instant term, “in contact with.” *Id.* The second instance is where the claim states: “a water immiscible oxygen dissolving substance emulsified into intimate contact with the enzyme to provide oxygen.” *Id.* (emphasis added). In this second usage, the term “contact” is modified by the word “intimate.” *Id.* There is a difference between “intimate contact” and “contact,” as used in claim 1. A person having ordinary skill in the art would have understood “in contact with” to include several different types of contact, including at least “intimate contact” as used in claim 1, “directly in contact” as used in the ’225 patent specification, and indirect or diffusional contact as provided above in the context of the ’225 patent specification. Appx01761-01763, Appx01818-01859, Appx02125-02127.

In sum, nothing in the ’225 patent mandates that the phrase “in contact with” be narrowly construed as “touching.” The word “touching” appears nowhere in the intrinsic record. Appx00028-00046. Rather, the intrinsic evidence supports a broader definition of the term in line with Arbmetrics’ proposal – *i.e.,* “in direct, indirect, or diffusional communication with.” Appx00040-00041 (3:33-42; 6:58-

67), Appx00045 (claim 1). As such, the District Court's construction should be reversed and Arbmetrics' proposed construction should be adopted.

B. The District Court's Construction of "in contact with" is Inconsistent with Its Construction of "intimate contact."

In addition to construing the term "in contact with" to mean "touching," the District Court also construed the term "intimate contact" to mean "very close contact." Appx00023-00024, Appx00027. When the District Court's "contact" definition is applied, the construction for "intimate contact" becomes "very close touching." Appx00027. This is nonsensical. There is no such thing as "very close touching." If two things are touching they are touching.

The District Court attempted to explain this by holding that "both 'intimate contact' and 'contact' can describe touching to different degrees. For example, a tap on the shoulder and a hug both involve 'contact' that constitutes touching, even though a hug might be described as 'intimate contact' while the tap is not." Appx00019. Notably the District Court cites no support for this conclusion. This is because none exists. In addition, the District Court stated that its construction of "intimate contact" as "very close contact" was meant to describe "how close the components are." Appx00023. However, "touching" and "very close touching" share the same degree of closeness – *i.e.,* touching.

C. The District Court's Construction of "in contact with" is Not Required by the Extrinsic Evidence.

As a threshold matter, the intrinsic evidence makes clear that the District Court's construction of "in contact with" is incorrect and must be reversed. As such, turning to extrinsic evidence is not necessary to determine that reversal is appropriate. Setting this aside, in evaluating the extrinsic evidence the District Court held that "the extrinsic evidence supports the construction proposed by Defendant," contending that "all of the dictionaries cited by Plaintiff include a definition consistent with the plain meaning, touching." Appx00019-00020. First, the fact that some of the extrinsic evidence supports Dexcom's proposed construction does not mandate adopting a construction in direct contravention of the '225 patent specification. *Phillips*, 415 F.3d at 1321 (noting that any usage of a dictionary definitions must be done in the context of the patent specification). Second, the District Court's conclusion ignores all of the extrinsic evidence that supports Arbmetrics' position. Appx00019-00020, Appx01761-01763, Appx01818-01859, Appx02125-02127. This failure to even consider the extrinsic evidence that supports Arbmetrics' proposed construction constitutes clear error. *Advanced Magnetic Closures*, 607 F.3d at 831.

When considered, it is clear that the extrinsic evidence also supports Arbmetrics' proposed construction. Arbmetrics' expert, Dr. Smith, has testified that a person having ordinary skill in the art at the time of invention would have

understood the term "in contact with" as "in direct, indirect, or diffusional communication with" in the context of the '225 patent. Appx01761-01763 (Smith Decl., at ¶¶ 51-60). In addition, several dictionaries offer definitions of "contact" based on "communication," not direct contact or touching. Appx01818-01840. "Communication" is the correct definition in this case because communication of an analyte (or a surrogate analyte, such as hydrogen peroxide) is required between the claimed enzyme emulsion and the conductive material (*e.g.*, the "electrode") for the sensor to generate the desired electrochemical reaction and operate as intended. Appx00039-00040 (2:43-3:4). A person having ordinary skill in the art at the time of invention would have understood this electrochemical process in the context of the claimed sensor. Appx01761-01763. For example, a person having ordinary skill in the art would have understood that the measurement of glucose is through a two-step process, where glucose is first converted to an equivalent amount of hydrogen peroxide, and the hydrogen peroxide is then measured electrochemically, where the hydrogen peroxide produced in the previous step is oxidized back to oxygen at an electrode after diffusing to the electrode surface. Appx00039-00040 (2:43-3:4), Appx01761-01763, Appx02125-02128.

What is important to this electrochemical process is the communication of hydrogen peroxide from the claimed "enzyme emulsion" to the conductive material (*e.g.*, the "electrode") through direct, indirect, or diffusional means. There is no

requirement that these elements be physically "touching" as found by the District Court. As such, the District Court's construction should be reversed and Arbmetrics' proposed construction should be adopted.

V. The District Court Erred in Its Construction of "electrode."

The District Court incorrectly construed the term "electrode" to mean "a solid electric conductor through which an electric current enters or leaves a substance." Appx00024-00025, Appx00027. In reaching this erroneous construction the District Court incorrectly framed the issue as "whether the term 'electrode' includes a membrane, or whether membrane and electrode are separate terms." Appx00024-00025. Arbmetrics never argued that the term "electrode" should be construed to include a membrane. Appx00024, Appx01723. Rather, Arbmetrics proposed that the term be construed to mean: "a conductive material, optionally including a membrane." *Id.* (emphasis added). Via this construction, Arbmetrics merely wanted to make clear that the claimed "electrode" could, not must, include a membrane or coating. Appx01723-01725.[9]

In its Claim Construction Order, the District Court actually agreed with Arbmetrics' position, agreeing that "there is nothing in the prosecution history …,

[9] Dexcom argued that the claimed "electrode" cannot include a membrane or coating. Appx02327-02330. The District Court, via its adoption of Dexcom's construction, arguably tacitly adopted Dexcom's position that the claimed "electrode" cannot include a membrane or coating. This conclusion is improper and directly contradicted by the intrinsic and extrinsic evidence.

the specification, or the claims that precludes the presence of a membrane or coating on the claim [*sic*] electrode." Appx00025. Despite this, the District Court held that the claimed "electrode" cannot include a membrane or other form of coating. Appx00024-00025, Appx00027. In reaching its erroneous construction the District Court appears to have simply misread Arbmetrics' proposal, holding that "there is zero evidence in the claims or the specification that supports Plaintiff's construction that an optional membrane *must* be included in the term's construction, which would effectively combine the two terms." Appx00024-00025 (emphasis in original). Arbmetrics' never argued that the term "electrode" should be construed to require or preclude a membrane or coating. Appx00024, Appx01723-01725. Arbmetrics merely proposed a construction that would allow for this, not require it (*e.g.,* could, not must). As discussed in this section, this construction is consistent with the intrinsic and extrinsic evidence, as well as the proper framework for claim construction. As such, Arbmetrics' proposed construction for the term "electrode" – "a conductive material, optionally including a membrane" – should be adopted.

A. The District Court's Construction is Contrary to the Intrinsic Evidence.

As acknowledged by the District Court, "there is nothing in the prosecution history …, the specification, or the claims that precludes the presence of a membrane or coating on the claimed electrode." Appx00025. Despite this, the District Court

held that the claimed "electrode" could not include a membrane or coating, which is contrary to the intrinsic evidence. Appx00024-00025, Appx00027.

The specification of the '225 patent specifically states that the electrode "can conveniently be made from platinum although a variety of other conductive materials are also useable." Appx00041 (6:44-46). This indicates that there is no limitation on the types of materials that may be used for the electrode, so long as the resultant structure is "conductive." *Id.* There is nothing in the prosecution history of the '225 patent, the specification, or the claims that precludes the presence of a membrane or coating on the claimed "electrode." Therefore, all conductive materials may comprise the claimed electrode, including materials with coatings or membranes.

In addition, U.S. Patent No. 4,680,268 ("the '268 patent"), which is incorporated by reference into the '225 patent, states: "[a]lthough not shown in the Figs., it should be appreciated to those in the art that the sensors of the present invention may include a 'third' membrane placed over anode 8 to separate enzyme 7 from anode 8." Appx01868 (7:1-4); Appx00040 (4:36-39).[10]

The '268 patent goes on to state:

> [f]irst, such a membrane allows selective diffusion of the enzyme generated product, such as hydrogen peroxide, to the anode where the peroxide is oxidized resulting in the current which

[10] The '268 patent was identified and relied on by Dexcom as part of the intrinsic record. Appx00893-00895.

> functions as a measure of the enzyme substrate, e.g., glucose or lactate. Secondly, since there can be several potentially interfering substances, such as ascorbic acid and phenolic compounds like acetaminophen, present in the body, the employment of the 'third' membrane provides a barrier to such interfering substances reducing the possibility of inaccurate or incorrect measurements.

Appx01868 (7:15-26). In other words, the '268 patent, which is part of the intrinsic record, clearly discloses the use of an electrode (*i.e.,* anode 8) having a membrane or coating. *Id.* (7:1-4, 7:15-26).

The District Court's conclusion that under Arbmetrics' proposed construction "dependent Claim 2 would encompass the same scope as independent Claim 1 and become superfluous" is also incorrect. Appx00025. Dependent claim 2 states:

> 2. The implantable sensor of claim 1 further comprising a semipermeable membrane covering the electrode with the enzyme emulsion sandwiched between the membrane and the electrode.

Appx00045 (claim 2). In other words, claim 2 discloses an electrode covered with a semipermeable membrane. *Id.* First, contrary to the District Court's conclusion, claim 2 supports Arbmetrics' proposed construction (*i.e.,* the electrode can, but is not required to include, a membrane or coating). *Id.* Second, contrary to the District Court's conclusion, adopting Arbmetrics' proposed construction does not render claim 2 superfluous. Arbmetrics' proposed construction allows for the claimed "electrode" to have an optional membrane/coating. Appx00024, Appx01723. Claim 2 requires the presence of a "semipermeable membrane" and that the claimed *enzyme*

emulsion be sandwiched between this semipermeable membrane and the electrode. Appx00045 (claim 2). On the other hand, the electrode's optional membrane/coating would be a different layer *sandwiched between the enzyme emulsion and the electrode*. This is clearly distinct from claim 2's "semipermeable membrane." As such, when the term "electrode" is properly construed, in accord with Arbmetrics' proposed construction, claim 2 remains narrower in scope and no part of it is rendered superfluous.[11]

This Court has repeatedly held that courts may not import limitations from embodiments disclosed in the specification in order to limit or otherwise vary the meaning of the claim language. *See e.g., Liebel-Flarsheim*, 358 F.3d at 905-06; *Teleflex,* 299 F.3d at 1327-28; *Inverness Med.*, 309 F.3d at 1379. The District Court's construction improperly narrows the scope of the claims to exclude such an embodiment, which is improper. As such, the same must be reversed.

[11] The District Court relied on *Power Mosfet Techs., L.L.C. v. Siemens AG,* 378 F.3d 1396, 1410 (Fed. Cir. 2004) for the legal principle that "interpretations that render some portion of the claim language superfluous are disfavored." Appx00025. First, for the reasons stated in this section Arbmetrics' proposed construction does not render any portion of claim 2 superfluous. Second, this Court's decision in *Power Mosfet* also recognized that "the rule is not inflexible." *Power Mosfet*, 378 F.3d at 1410.

B. The District Court's Construction is Contrary to the Extrinsic Evidence.

The District Court's construction is also inconsistent with the extrinsic evidence. Despite adopting Dexcom's proposed construction, which was based almost entirely on extrinsic evidence, the Claim Construction Order does not even consider the extrinsic evidence presented by Arbmetrics. Appx00024-00025. This arguably constitutes error. *See Advanced Magnetic Closures,* 607 F.3d at 831 (noting that a district court is required to "consider all the evidence").

Abmetrics' expert, Dr. Smith, testified that a person having ordinary skill in the art at the time of invention would have understood the term "electrode" as "a conductive material, optionally including a membrane." Appx01764-01766 (Smith Decl., at ¶¶ 61-67). Dr. Smith testified that a person having ordinary skill in the art would have known that there were many different types of electrodes that include a coating or membrane. *Id*. Perhaps the most ubiquitous electrode having such a coating/membrane is referred to as the "silver chloride electrode" or "AgCl electrode." Appx01764. This electrode has been used for a wide array of applications since at least the 1970's, including but not limited to pH meters, electrocardiography (ECG), and electroencephalography (EEG). *Id*. A silver chloride electrode is formed by taking a silver wire or surface (a conductive material) and coating it with silver chloride (a coating or membrane). *Id*. Therefore, a construction to the term "electrode" that precludes such an interpretation is

inconsistent with the plain and ordinary meaning of the term.

Additional extrinsic evidence further supports Arbmetrics' proposal for this term. Appx01841-01859. For instance, one widely-used dictionary in the field of biochemistry defines "electrode" as "***any conductor***, such as a piece of metal, ***metal covered with*** one of its salts, carbon, or a thin glass ***or other membrane***, used to establish electric contact with a solution or other nonmetallic part of an electric circuit." Appx01841-01850 (emphasis added). Another exemplary contemporaneous dictionary definition is consistent with this definition. Appx01851-01859 (defining electrode as, "A conductor through which an electric current enters or leaves a substance (or a vacuum) whose electrical characteristics are being measured, used, manipulated."). The evidence shows that a person of ordinary skill in the art at the time of invention of the '225 patent would have understood the term "electrode" as "a conductive material, optionally including a membrane."

In holding that the claimed "electrode" cannot include a membrane or coating, the District Court improperly narrowed the scope of the term "electrode" absent lexicography or disavowal in contravention of this Court's long-standing precedent. *Hill-Rom,* 755 F.3d at 1371-72. As such, the same must be reversed and Arbmetrics' proposed construction should be adopted.

VI. The District Court Erred in Its Construction of "hydrocarbon oils or solids."

The District Court construed the phrase "hydrocarbon oils or solids" to mean "oil or solids composed only of carbon and hydrogen." Appx00025-00027. In reaching this conclusion, the District Court correctly framed the issue as "whether 'hydrocarbon oils and solids' must be composed of only hydrogen and carbon, as Defendant proposes, or whether they can be any oil or solid that includes a hydrogen and carbon side chain, as Plaintiff proposes." Appx00025. The District Court simply decided the issue incorrectly.

The '225 patent provides examples of substances that may be utilized as an "oxygen dissolving substance" of the claimed invention. Appx00042 (8:12-16), Appx00045 (claim 5). The '225 patent states that these substances may include "hydrocarbon drugs (e.g., cortical steroids) silicones, silanes, cyclic silanes, siloxanes, fluorinated silicones and other similar organo-silicon compounds." Appx00042 (8:12-16). In this passage, which includes the only occurrence of the word "hydrocarbon" in the '225 patent specification, the patentee clearly refers to cortical steroids as "hydrocarbon drugs." *Id*. Cortical steroids include cortisone, which has the formula $C_{21}H_{28}O_5$, with five oxygen atoms included. Appx01777 (Smith Decl., at ¶ 104). This compound is not composed of only carbon and hydrogen, but instead includes a chemical group or side chain composed of hydrogen and carbon only, which is in line with how a person of ordinary skill in the art would

have understood this term at the time of invention, as described by Dr. Smith. Appx01776-01778. Thus, any interpretation of this phrase that precludes compounds or substances that are not composed solely of hydrogen and carbon – *i.e.,* the District Court's construction - is contrary to the '225 patent specification.

It is well established that it is improper to limit the scope of the claims absent (1) lexicography, or (2) disavowal of claim scope. *Hill-Rom Servs.,* 755 F.3d at 1371-72. In the instant case, the District Court not only limited the scope of the phrase "hydrocarbon oils or solids" absent lexicography or disavowal but adopted a construction that is explicitly contradicted by the '225 patent specification. This construction cannot stand and must be reversed.

In contrast, Arbmetrics proposed that the phrase should be construed to mean: "oils or solids including a chemical group or side chain composed of hydrogen and carbon only." Appx00025, Appx01733-01734. This construction is consistent with the intrinsic evidence, which clearly states that the phrase is not limited to "oil or solids composed only of carbon and hydrogen," but rather includes other compounds provided they have a chemical group or side chain composed of hydrogen and carbon only. Appx00042 (8:12-16)

In addition, Arbmetrics' proposed construction is also consistent with and supported by the extrinsic evidence. Appx01776-01778, Appx01841-01850, Appx02112. For instance, one widely-used dictionary in the field of biochemistry

provides the following two definitions of "hydrocarbon": (1) "any organic compound composed exclusively of hydrogen and carbon." and (2) "of, pertaining to, or being a hydrocarbon (def. 1) or ***a chemical group or side chain composed of hydrogen and carbon only***." Appx01841-01850 (emphasis added). This extrinsic evidence shows that patentee's use of the term "hydrocarbon oils or solids" is intended to encompass a broader definition of "hydrocarbon," to describe an oil or solid that includes a chemical group or side chain composed of hydrogen and carbon only – not the narrow range of compounds argued by Dexcom and adopted by the District Court.

In support of its erroneous construction the District Court merely quoted Dexcom's brief, stating that "'under Plaintiff's interpretation, hydrocarbon would include the claimed silicone oils, flourosilicone oils, carotenoids, and steroids" listed in Claim 5 'because these chemical classes include a chemical group or side chain composed of hydrogen and carbon only." Appx00026. First, this argument does not make sense. "Hydrocarbon" does not necessarily include all oils and steroids identified in claim 5.

Second, the fact that the claimed classes of oils and steroids could include an oil or solid that includes a chemical group or side chain composed of hydrogen and carbon only does not mandate that the term "hydrocarbon oils and solids" be construed in a manner contrary to the '225 patent specification, which dictates that

the phrase be afforded its full breadth. *See e.g., Eli Lilly and Company v. Teva Parenteral Medicines, Inc.,* 845 F.3d 1357, 1371-72 (Fed. Cir. 2017); Manual of Patent Examining Procedures § 2173.05(h).

Lastly, even if the doctrine of claim differentiation applied to this scenario, which it does not, as argued by Dexcom "the doctrine of claim differentiation is not a hard and fast rule." Appx03621 (quoting *Regents of Univ. of Cal. V. Dakocytomation Cal., Inc.,* 517 F.3d 1364, 1375 (Fed. Cir. 2008)). It is "merely 'a rule of thumb that does not trump the clear import of the specification," which clearly indicates that the phrase "hydrocarbon oils and solids" is not limited to "oil or solids composed only of carbon and hydrogen." Appx03621-03622 (quoting *Cardsoft, LLC v. Verifone, Inc.*, 807 F.3d 1346, 1352 (Fed. Cir. 2015); *see also* Appx00042 (8:12-16).

In sum, the District Court's construction of "hydrocarbon oils and solids" is contrary to the evidence and must be reversed. Arbmetrics' proposed construction, which is consistent with the evidence, should be adopted.

CONCLUSION AND RELIEF SOUGHT

For the foregoing reasons, Appellant respectfully requests that this Court reverse the District Court's claim construction findings discussed herein, vacate the District Court's final judgment, and remand this case for further proceedings consistent with this Court's mandate.

Respectfully submitted,

/s/ *Timothy E. Grochocinski*
Timothy E. Grochocinski
Joseph P. Oldaker
NELSON BUMGARDNER ALBRITTON P.C.
15020 South Ravinia Avenue, Suite 29
Orland Park, Illinois 60462
Telephone: (708) 675-1974

Counsel for Plaintiff-Appellant
Arbmetrics, LLC

ADDENDUM

ADDENDUM

Document	Appendix Range
Stipulation Reserving Right to Appeal and For Entry of Final Judgment of Non-Infringement Under the Court's Claim Construction (Dkt. No. 86)	Appx00001-00006
Order Entering Final Judgment (Dkt. No. 87)	Appx00007-00008
Order on Claim Construction (Dkt. No. 81)	Appx00009-00027
United States Patent No. 6,343,225	Appx00028-00046

Timothy E. Grochocinski
Illinois Bar No. 6295055
Joseph P. Oldaker
Illinois Bar No. 6295319
NELSON BUMGARDNER ALBRITTON PC
15020 S. Ravinia Avenue, Suite 29
Orland Park, Illinois 60462
Tel: 708.675.1975

Brandon C. Fernald (SBN 222429)
FERNALD LAW GROUP
510 West Sixth Street, Suite 700
Los Angeles, CA 90014
Tel: 323.410.0320
Fax: 232.410.0330

Edward R. Nelson, III
Texas Bar No. 00797142
Brent Bumgardner
Texas Bar No. 00795272
NELSON BUMGARDNER ALBRITTON PC
3131 West Seventh Street, Suite 300
Fort Worth, Texas 76107
Tel: 817.377.9111

Attorneys for Plaintiff
Arbmetrics, LLC

Richard Mulloy (SBN 199278)
richard.mulloy@dlapiper.com
Catherine Huang (SBN 299696)
catherine.huang@dlapiper.com
DLA Piper LLP (US)
401 B Street, Suite 1700
San Diego, California 92101-4297
Tel: 619.699.2700
Fax: 619.699.2701

Stuart E. Pollack
stuart.pollack@dlapiper.com
DLA Piper LLP (US)
1251 Avenue of the Americas
New York, New York 10020
Tel: 212.335.4964
Fax: 212.884.8464

Amy Walters (SBN 286022)
amy.walters@dlapiper.com
DLA Piper LLP (US)
2000 University Avenue
East Palo Alto, California 94303-2214
Tel: 650.833.2000
Fax: 650.833.2001

Attorneys for Defendant
Dexcom, Inc.

IN THE UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF CALIFORNIA

ARBMETRICS, LLC, an Ohio limited liability company,

Plaintiff,

v.

DEXCOM INC., a Delaware corporation,

Defendant.

Case No. 3:18-cv-00134-JLS-MSB

STIPULATION RESERVING RIGHT TO APPEAL AND FOR ENTRY OF FINAL JUDGMENT OF NON-INFRINGEMENT UNDER THE COURT'S CLAIM CONSTRUCTION

WHEREAS, Plaintiff Arbmetrics, LLC ("Arbmetrics") filed the above styled action on January 19, 2018 (Dkt. 1) asserting that Dexcom Inc. ("Dexcom") infringes claims 1, 2, 5, 7, and 8 of U.S. Patent No. 6,343,225 ("the '225 patent");

WHEREAS, Dexcom denies that the '225 patent is valid or infringed, and has filed a declaratory judgment counterclaim that the '225 patent is not infringed;

WHEREAS, the terms "emulsion" and "oxygen dissolving substance" are elements of each asserted claim of the '225 patent;

WHEREAS, in its Order on Claim Construction (Dkt. 81), issued on December 30, 2019, the Court construed the term "emulsion" to mean: "a mixture of two or more immiscible liquids, in which one liquid is dispersed in another liquid";

WHEREAS, in its Order on Claim Construction (Dkt. 81), the Court construed the term "oxygen dissolving substance" to mean: "a substance in which oxygen is preferentially soluble in comparison to water";

WHEREAS, Arbmetrics and Dexcom agree that all of Dexcom's accused products do not meet either the "emulsion" or the "oxygen dissolving substance" limitations of all asserted claims of the '225 patent as construed by the Court;

WHEREAS, to avoid the expense and time associated with briefing and resolving a motion by Dexcom for summary judgment of non-infringement, Arbmetrics consents to entry of a Final Judgment of Non-Infringement by Dexcom of the '225 patent.

THEREFORE, Arbmetrics and Dexcom stipulate as follows:

1. On the basis of: (i) the Court's construction of the terms "emulsion" and, separately, the Court's construction of "oxygen dissolving substance"; and (ii) the stipulation above that Dexcom's accused products do not practice the asserted claims in view of each of the Court's constructions of "emulsion" and "oxygen dissolving substance," either literally or under the doctrine of equivalents, the Court should enter a final judgment of non-infringement in favor of Dexcom as to the '225 patent, both with respect to Arbmetrics' offensive claims of infringement and with respect to Dexcom's counterclaim for declaratory judgment of non-infringement. Other issues, including construction of other claim terms of the '225 patent, do not form a basis for the judgment.

2. The stipulation is without prejudice to Arbmetrics' right, if any, to re-assert its claims against Dexcom should the United States Court of Appeals for the Federal Circuit reverse or modify, in whole or in part, the Court's Order on Claim Construction, including the Court's constructions of "emulsion" and "oxygen dissolving substance."

3. The parties recognize that Dexcom believes there are additional grounds for summary judgment of non-infringement, including but not limited to grounds based on claim constructions other than the terms "emulsion" and "oxygen dissolving substance." The parties agree that to the extent the final judgment is not affirmed on appeal and the case is remanded, Dexcom has the right to assert these grounds in the future and Arbmetrics has the right to dispute those grounds.

4. The foregoing is without prejudice to the rights of Arbmetrics and Dexcom to raise on appeal any other issue that may properly be raised.

5. The parties further stipulate that each side shall bear its own fees and costs incurred in this matter.

WHEREFORE, based on the foregoing, Arbmetrics and Dexcom respectfully request that the Court enter final judgment in the form attached hereto as Final Judgment of Non-Infringement.

IT IS SO STIPULATED.

Dated: January 24, 2020

/s/ Timothy E. Grochocinski
Timothy E. Grochocinski
Illinois Bar No. 6295055
Joseph P. Oldaker
Illinois Bar No. 6295319
NELSON BUMGARDNER ALBRITTON PC
15020 S. Ravinia Avenue, Suite 29
Orland Park, Illinois 60462
Tel: 708.675.1975

Brandon C. Fernald (SBN 222429)
FERNALD LAW GROUP
510 West Sixth Street, Suite 700
Los Angeles, CA 90014
Tel: 323.410.0320
Fax: 232.410.0330

Edward R. Nelson, III
Texas Bar No. 00797142
Brent Bumgardner
Texas Bar No. 00795272
NELSON BUMGARDNER ALBRITTON PC
3131 West Seventh Street, Suite 300
Fort Worth, Texas 76107
Tel: 817.377.9111

Attorneys for Plaintiff
Arbmetrics, LLC

/s/ Catherine Huang
Richard Mulloy (SBN 199278)
richard.mulloy@dlapiper.com
Catherine Huang (SBN 299696)
catherine.huang@dlapiper.com
DLA Piper LLP (US)
401 B Street, Suite 1700
San Diego, California 92101-4297
Tel: 619.699.2700
Fax: 619.699.2701

Stuart E. Pollack
stuart.pollack@dlapiper.com
DLA Piper LLP (US)
1251 Avenue of the Americas
New York, New York 10020
Tel: 212.335.4964
Fax: 212.884.8464

Amy Walters (SBN 286022)
amy.walters@dlapiper.com
DLA Piper LLP (US)
2000 University Avenue
East Palo Alto, California 94303-2214
Tel: 650.833.2000
Fax: 650.833.2001

Attorneys for Defendant
Dexcom, Inc.

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing was served on all counsel of record via email on January 24, 2020.

/s/ Timothy E. Grochocinski

Attorney for Arbmetrics, LLC

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

ARBMETRICS, LLC, an Ohio limited liability company, Plaintiff, v. DEXCOM, INC., a Delaware corporation, Defendant.	Case No.: 18-CV-134 JLS (KSC) **ORDER ENTERING FINAL JUDGMENT OF NON-INFRINGEMENT**

Presently before the Court is the Parties' Joint Motion and Stipulation to Enter Final Judgment of Non-Infringement. Based on the Parties' Stipulation Reserving Right to Appeal and for Entry of Final Judgment of Non-Infringement Under the Court's Claim Construction ("Stipulation"), the Court finds, and it is **HEREBY ORDERED**, that:

1. Dexcom does not directly or indirectly infringe, and has not directly or indirectly infringed, either literally or under the doctrine of equivalents, any claim of U.S. Patent No. 6,343,225 (the "'225 patent") under each of the Court's constructions of the terms "emulsion" and "oxygen dissolving substance."

2. Judgment is, therefore, entered in favor of Dexcom, both with respect to Arbmetrics' claims of infringement and Dexcom's counterclaim for declaratory judgment of non-infringement of the '225 patent.

3. Arbmetrics' claims of infringement under the '225 patent are hereby **DISMISSED WITH PREJUDICE**, and Arbmetrics shall take nothing from Dexcom with respect to its allegations of infringement.

4. Each party shall bear its own fees and costs.

This Final Judgment resolves the issue of non-infringement based on the Court's construction of the terms "emulsion" and "oxygen dissolving substance." Other issues, including construction of other claim terms of the '225 patent, do not form a basis for this Judgment. The Clerk of Court shall close the file.

IT IS SO ORDERED.

Dated: January 28, 2020

Janis L. Sammartino
Hon. Janis L. Sammartino
United States District Judge

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

ARBMETRICS, LLC, an Ohio limited liability company, Plaintiff, v. DEXCOM, INC., a Delaware corporation, Defendant.	Case No.: 18-CV-134 JLS (KSC) **ORDER ON CLAIM CONSTRUCTION**

Presently before the Court are Plaintiff Arbmetrics, LLC's ("Pl.'s Br.," ECF No. 66) and Defendant Dexcom, Inc.'s ("Def.'s Br.," ECF No. 123) Opening Claim Construction Briefs, as well as each Party's response to the other's Opening Brief ("Def.'s Resp.," ECF No. 68; "Pl.'s Resp.," ECF No. 69). The parties dispute the meaning of seven terms claimed by U.S. Patent No. 6,343,225 (the "'225 Patent"). The Court heard oral argument, including tutorials from the Parties, on October 31, 2019. *See* ECF No. 77. Having carefully considered the Parties' arguments, the evidence, and the law, the Court rules as follows.

LEGAL STANDARD

"A determination of infringement involves a two-step analysis. 'First, the claim must be properly construed to determine its scope and meaning. Second, the claim as

properly construed must be compared to the accused device or process.'" *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1320 (Fed. Cir. 2003) (citing *Carroll Touch, Inc. v. Electro Mech. Sys., Inc.*, 15 F.3d 1573, 1576 (Fed. Cir. 1993)).

The first step, commonly known as claim construction, is presently before the Court. Claim construction is a matter of law for the Court's determination. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388 (1996) ("[J]udges, not juries, are the better suited to find the acquired meaning of patent terms.").

Words of a claim are "generally given their ordinary and customary meaning." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). Because the inquiry into the meaning of claim terms is an objective one, "a court looks to those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004). "Those sources include the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art."[1] *Id.* (citing, *inter alia*, *Vitronics*, 90 F.3d at 1582–83).

Claim construction begins with an analysis of the words of the claims themselves. *See Scanner Techs. Corp. v. ICOS Vision Sys. Corp.*, 365 F.3d 1299, 1303 (Fed. Cir. 2004) (holding that claim construction "begins and ends" with claim's actual words). "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves

[1] The first three sources are considered "intrinsic evidence" of claim meaning. *See generally Phillips*, 415 F.3d at 1314–17.

little more than the application of the widely accepted meaning of commonly understood words." *Phillips*, 415 F.3d at 1314. The meaning of a claim term, however, as understood by ordinarily skilled artisans often is not immediately apparent. *Id.* In those situations, the court looks to "sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean." *Id.* Or, when a patentee "chooses to be his own lexicographer and use terms in a manner other than their ordinary meaning," the court can use the patentee's meaning "as long as the special definition of the term is clearly stated in the patent specification or file history." *Vitronics*, 90 F.3d at 1582.

In examining the claims themselves, "the context in which a term is used can be highly instructive." *Phillips*, 415 F.3d at 1314. Moreover, "[o]ther claims of the patent in question, both asserted and unasserted can . . . be valuable sources of enlightenment as to the meaning of a claim term." *Id.* (citing *Vitronics*, 90 F.3d at 1582). "Because claim terms are normally used consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same term in other claims." *Id.* Conversely, under the doctrine of claim differentiation, "'different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope.'" *Andersen Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1369 (Fed. Cir. 2007) (quoting *Karlin Tech., Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 971–72 (Fed. Cir. 1999)).

"Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Phillips*, 415 F.3d at 1313. "The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines them by implication." *Vitronics*, 90 F.3d at 1582. "In addition to providing contemporaneous technological context for defining claim terms, the patent applicant may also define a claim term in the specification 'in a manner inconsistent with its ordinary meaning.'" *Metabolite Labs., Inc. v. Lab. Corp. of Am.*, 370 F.3d 1354, 1360 (Fed. Cir. 2004). "Usually, [the specification] is dispositive; it is the single best guide to the meaning of a disputed term." *Vitronics*, 90 F.3d at 1582; *accord Phillips*, 415 F.3d at

1317 ("It is . . . entirely appropriate for a court, when conducting claim construction, to rely heavily on the written description for guidance as to the meaning of the claims.").

Patent claims should ordinarily be construed to encompass the preferred embodiments described in the specification, for "[a] claim construction that excludes a preferred embodiment . . . 'is rarely, if ever, correct.'" *SanDisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1285 (Fed. Cir. 2005) (quoting *Vitronics*, 90 F.3d at 1583). A court should not, however, import limitations from the specification into the claims, *Phillips*, 415 F.3d at 1323 ("[A]lthough the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments."), absent a specific reference in the claims themselves. *Reinshaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998) ("[A] party wishing to use statements in the written description to confine or otherwise affect a patent's scope must, at the very least, point to a term or terms in the claim with which to draw in those statements.").

The patent's prosecution history, if in evidence, may also shed light on claim construction. *Vitronics*, 90 F.3d at 1582. "This history contains the complete record of all proceedings before the Patent and Trademark Office [("PTO")], including any express representations made by the applicant regarding scope of the claims." *Id.* "Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent." *Phillips*, 415 F.3d at 1317. Although the prosecution history "often lacks the clarity of the specification," it is nevertheless useful to show "how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.*

"In most situations, an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term. In such circumstances, it is improper to rely on extrinsic evidence." *Vitronics*, 90 F.3d at 1583. Thus, expert testimony on the proper construction of disputed claim terms "may only be relied upon if the patent documents, taken as a whole, are insufficient to enable the court to construe disputed claim terms."

Vitronics, 90 F.3d at 1585. But, *Vitronics* does not state a rule of admissibility, nor does it "prohibit courts from examining extrinsic evidence, even where the patent document is itself clear." *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308 (Fed. Cir. 1999). As the Federal Circuit has made clear:

> [B]ecause extrinsic evidence can help educate the court regarding the field of the invention and can help the court determine what a person of ordinary skill in the art would understand claim terms to mean, it is permissible for the district court in its sound discretion to admit and use such evidence.

Phillips, 415 F.3d at 1319; *accord Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 716 (Fed. Cir. 1998) ("[T]rial courts generally can hear expert testimony for background and education on the technology implicated by the presented claim construction issues, and trial courts have broad discretion in this regard."). The court is not "barred from considering any particular sources or required to analyze sources in any specific sequence, as long as those sources are not used to contradict claim meaning that is unambiguous in light of the intrinsic evidence." *Phillips*, 415 F.3d at 1324 (emphasis added); *see also Biagro W. Sales, Inc. v. Grow More, Inc.*, 423 F.3d 1296, 1302 (Fed. Cir. 2005) ("Extrinsic evidence, such as expert testimony, may be useful in claim construction, but it should be considered in the context of the intrinsic evidence.").

ANALYSIS

The parties dispute the meaning of seven claim terms in the '225 Patent. A brief description of the '225 patent is provided below, followed by an analysis of the claim terms.

I. The '225 Patent

The '225 Patent is directed to the creation of an implantable glucose sensor for use by patients with diabetes. The glucose sensor measures the amount of glucose present in the blood through an electrochemical reaction. The reaction is sparked by an enzyme that causes glucose to react with oxygen, the end product of the reaction being hydrogen peroxide. The amount of hydrogen peroxide created by the reaction is a direct measure of the glucose concentration in the sample. The hydrogen peroxide is then oxidized back to

oxygen, which transfers electrons to an electrode, creating an electric current that can be measured. The electric current measured is directly proportional to the glucose concentration in the sample.

A problem found in many implantable glucose monitors is the high glucose-to-oxygen ratios often found in human tissue. This ratio creates problems because a surplus of glucose and a shortage of oxygen will lead to a limited number of reactions with the enzyme, which lowers the electric current produced and results in inaccurate readings. To solve this problem, the present invention attempts to increase the amount of oxygen that reaches the enzyme. To do this, the invention teaches to create an enzyme emulsion to spark the reaction described above. The emulsion is comprised of, among other things, a substance in which oxygen is extremely soluble. The oxygen soluble substance increases the oxygen available to the enzyme by creating oxygen reservoirs, from which the enzyme can pull to continue the chemical reactions.

The disputed terms are found in Claims 1 and 5 of the '225 Patent. Claim 1 describes the present invention as follows:

> An implantable sensor for sensing a concentration of an organic substrate, the sensor comprising:
>
> a conductive electrode; and
>
> a stabilized enzyme emulsion in contact with the electrode, the enzyme emulsion comprising:
>
> an oxidase enzyme that quantitatively oxidizes the organic substrate;
>
> a water immiscible oxygen dissolving substance emulsified into intimate contact with the enzyme to provide oxygen; and
>
> a protein crosslinking agent to crosslink and insolubilize the enzyme forming a stabilized gel comprising crosslinked protein and particles of said oxygen dissolving substance.

'225 Patent at 14:16–29.

Dependent Claim 5 describes:

> The implantable sensor of claim 1, wherein the oxygen dissolving substance is selected from the group consisting of perflourocarbons, silicone oils, flourosilicone oils, aromatic and aliphatic hydrocarbon oils or solids, carotenoids and steroids.

Id. at 14:39–43.

II. Disputed Terms

A. "emulsion" (all asserted claims of the '225 Patent)

Plaintiff would construe the term "emulsion" as "a mixture of two or more immiscible components, in which one component is dispersed in another component." Pl.'s Br. at 12. Defendant would construe the term as "a mixture of two or more immiscible liquids, in which one liquid is dispersed in another liquid." Def.'s Br. at 15. The dispute therefore centers around whether the emulsion described in Claim 1 of the '225 Patent should be limited to liquids, as Defendant contends, or whether it should include any mixtures of immiscible components, as Plaintiff contends.[2]

After reviewing the intrinsic and extrinsic evidence, the Court agrees with Defendant's proposed construction because it comports with the plain and ordinary meaning of "emulsion" as understood by a person with ordinary skill in the art. "As a general rule, the ordinary and customary meaning controls unless 'a patentee sets out a definition and acts as his own lexicographer, or . . . the patentee disavows the full scope of a claim term either in the specification or during prosecution.'" *Sumitomo Dainippon Pharma Co. v. Emcure Pharm. Ltd.*, 887 F.3d 1153, 1157 (Fed. Cir. 2018) (quoting *Thorner v. Sony Comput. Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012)). To act as its own lexicographer, the patentee must "clearly set forth a definition of the disputed

[2] The Court notes that in its Response, Plaintiff argues that the claims do not refer to emulsion in isolation and instead use the full term "enzyme emulsion," and thus the Court should construe that full term. Pl.'s Resp. at 6. Both Parties agreed at the October 31, 2019 hearing, however, that the term to be construed is "emulsion," not "enzyme emulsion."

claim term" and "clearly express an intent to define the term." *GE Lighting Sols., LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1309 (Fed. Cir. 2014). Here, both the intrinsic and extrinsic evidence leads the Court to determine that the ordinary and customary meaning is appropriate because the patentee did not clearly set forth a contrary definition to the term.

Plaintiff contends that the intrinsic evidence clearly sets forth the patentee's intent to define the term. Plaintiff points to a sentence in the specification that it contends makes explicit that the emulsion is not limited to liquids. Pl.'s Br. at 13. That sentence describes "tiny solid or liquid particles" of the oxygen dissolving substance and the enzyme that are in "insoluble form." '225 Patent at 8:56–59. This sentence, however, is not a clear indication that the patentee intended to deviate from the ordinary and customary meaning. Indeed, as Defendant notes, "the sentence seems to describe the gel formed after the emulsion is crosslinked, rather than before as in the claims." Def.'s Resp. at 11. The "tiny solid . . . particles" could therefore be formed after the gel is created and would not be present when the claimed emulsion is created.

Next, Plaintiff points to Claim 5 as evidence that the patentee did not intend for the term emulsion to be limited to liquids. Plaintiff asserts that Claim 5 "unambiguously defines the 'oxygen dissolving substance' of claim 1 as a 'solid'" and, since one of the major components of the claimed emulsion may be a solid, Defendant's attempt to limit the emulsion to liquids must be wrong. Pl.'s Br. at 13. But this evidence is not as clear as Plaintiff contends. As Defendant points out, "whenever the '225 Patent describes solids used in the emulsion, it is describing solids that have been dissolved in solution—in other words, liquid." Def.'s Br. at 18. Thus, it is not clear the patentee defined emulsion contrary to its plain meaning.

In support of its position, Defendant turns to the prosecution history. In the prosecution history, the patentee distinguishes a prior art reference, U.S. Patent 5,431,160 ("Wilkens"), because Wilkens discloses a suspension or gel—both of which may contain solids—rather than an emulsion. Def.'s Resp. at 10. The fact that the patentee distinguished the prior art on this basis shows the patentee did not intend to use the term

emulsion to capture these other types of mixtures, which Plaintiff's construction would do. By differentiating the terms, the patentee indicated that he defined the term emulsion consistent with its ordinary meaning, not contrary to it.

Defendant also points out that throughout the intrinsic evidence, the '225 Patent uses words for liquids when describing the emulsion. Def.'s Br. at 17–18; Def.'s Resp. at 10–11. For example, the prosecution history states that "droplets of the emulsion . . . serve as an oxygen reservoir . . . and because there is close contact between droplets of the oxygen dissolving substance and the enzyme, the lag due to slow oxygen diffusion through water is avoided." ECF No. 66-14 at 103. "Droplet" is a term for liquids and, as used in the prosecution history, describes the components of the emulsion as two liquids. *See* Def.'s Br. at 16.

Finally, the Court finds that the extrinsic evidence supports Defendant's construction. In fact, "all of the dictionaries and texts relied on by both parties define emulsion as a dispersion of two or more liquids." *Id.* at 15.

Based on the above, the Court adopts Defendant's construction and construes the term "emulsion" in accordance with its ordinary and customary meaning: "a mixture of two or more immiscible liquids, in which one liquid is dispersed in another liquid."

B. "in contact with" (all asserted claims of the '225 Patent)

Plaintiff would construe the term "in contact with" as "in direct, indirect, or diffusional communication with." Pl.'s Br. at16. Defendant would construe the term as "touching." Def.'s Br. at 7. Defendant argues that the term "in contact with" must be limited to physical touching, *id.* at 7–11, while Plaintiff contends that "in contact with" does not necessarily require physical touching. Pl.'s Br. at 18.

Plaintiff contends that both the intrinsic and extrinsic evidence supports its construction. Pl.'s Br. at 16. Regarding the intrinsic evidence, Plaintiff contends that the claim language mandates a broader meaning of contact that includes communication because the Patent discloses several different types of contact, all of which require more than just physical touching. *Id.* at 16–17. Plaintiff also points to extrinsic evidence that

Plaintiff contends supports its construction, including several dictionary definitions that offer definitions of "contact" meaning communication, rather than physical touching. *Id.* at 17.

Defendant argues for the plain and ordinary meaning of "contact," which it contends is "touching." Def.'s Br. at 7. Defendant contends that the intrinsic evidence, including Claims 1 and 15 and the specification, supports this meaning. *Id.* at 8–11. Defendant contends its construction is bolstered by the extrinsic evidence, asserting that every dictionary cited in the briefing—including the dictionaries cited by Plaintiff—supports its construction. *Id.* 7–8; Def.'s Resp. at 7. Defendant contends that Plaintiff's construction would render the claims indefinite and make much of the claims and specification nonsensical. Def.'s Br. at 10–11.

The Court agrees with Defendant and finds that "in contact with" means "touching." The Court begins with the language of Claim 1 itself. *Scanner Techs. Corp.*, 365 F.3d at 1303 (holding that claim construction "begins and ends" with a claim's actual words). Claim 1 uses the term in two instances, both of which use "contact" consistent with its ordinary and customary meaning of touching. First, Claim 1 describes "a stabilized enzyme emulsion in contact with the electrode." '225 Patent at 14:19–20. This language does not "clearly indicate" the patentee intended the term to embody a special meaning, such as Plaintiff's proposed construction of "indirect or diffusional communication." *See Vitronics*, 90 F.3d at 1582. Indeed, based on the specification's description of the present invention, this sentence in Claim 1 is entirely consistent with the ordinary meaning of contact, which is touching.

Second, Claim 1 describes "the enzyme emulsion, comprising: . . . a water immiscible oxygen dissolving substance emulsified into intimate contact with the enzyme to provide oxygen." '225 Patent at 14:23–25. Plaintiff contends that because the term "intimate" modifies "contact," the meaning given to "contact" as opposed to "intimate contact" must be broader and include direct, indirect, or diffusional communication. Pl's Br. at 16–17. While the Court agrees that "intimate" modifies the meaning of "contact" in

this sentence, the modification is one of degree and does not mandate Plaintiff's complete deviation from the term's ordinary and customary meaning. Defendant's construction, on the other hand, is consistent with the ordinary meaning as both "intimate contact" and "contact" can describe touching to different degrees. For example, a tap on the shoulder and a hug both involve "contact" that constitutes touching, even though a hug might be described as "intimate contact" while the tap is not. The same is true here.

The specification also supports Defendant's construction. *See Phillips*, 415 F.3d at 1315 (noting a patent's specification "is the single best guide to the meaning of a disputed term"). For example, the specification states that, "[g]enerally the device is *not directly in contact* with the circulatory system so that formation of blood clots does not interfere with operation." '225 Patent at 6:62–65 (emphasis added). Both Parties argue that this sentence supports their constructions. Plaintiff contends that, because the present invention requires the monitor to communicate with the blood, this sentence indicates that the device may be in indirect communication with the blood. Pl.'s Br. at 16. This interpretation, however, fails to take into account the entire passage. The very next sentence states that "[a]ll of the body tissues come into glucose equilibrium with the blood fairly rapidly so that placement of the device *in contact with the blood is not really required*." '225 Patent at 6:65–67 (emphasis added). If the Court construes the term as Plaintiff requests, it would mean that the glucose monitor is "not really required" to be in communication with the blood. This would make no sense because the device's purpose is to measure glucose levels of the blood. Defendant's construction, on the other hand, gives meaning to the entire passage.

Likewise, Figure 2 of the specification supports Defendant's construction. Figure 2 shows the enzyme emulsion touching the electrode. While Figure 2 cannot limit the scope of the claim, *see, e.g., Playtex Prod., Inc. v. Procter & Gamble, Co.*, 400 F.3d 901, 907 (Fed. Cir. 2005), it supports this reading in combination with the other intrinsic evidence.

Finally, the extrinsic evidence supports the construction proposed by Defendant. The Court notes that all of the dictionaries cited by Plaintiff include a definition consistent with the plain meaning, touching. *See, e.g.*, Pl.'s Br. Ex. E (Concise Oxford Dictionary

(1999) defining "contact" as "the state or condition of physical touching"); Ex. F (American Heritage Dictionary (1994) defining "contact" as "[a] coming together or touching, as of objects or surfaces"); Ex. G (Merriam-Webster's Collegiate Dictionary (1999) defining "contact" as "union or junction of surfaces").

In conclusion, the Court adopts Defendant's construction and construes the term "in contact with" to mean "touching."

C. "water immiscible" (all asserted claims of the '225 Patent)

Similar to the term "emulsion," the Parties dispute whether the term "water immiscible," should be limited to liquids. Plaintiff would construe the term to mean "will not mix with or dissolve in water." Pl.'s Br. at 20. Defendant would construe the term to mean "a liquid that will not mix with water." Def.'s Br. at 21. The Court agrees with Plaintiff and concludes that the term is not limited to liquids only.

To start, the Claim language supports Plaintiff's contention that the term does not pertain to liquids only. As used in the '225 Patent's claims, "water immiscible" describes a *characteristic* of an "oxygen dissolving substance," not what type of substance it is. This fact is supported by the claims using "water immiscible" to describe both liquids and solids. For example, Claim 5 of the '225 Patent describes the sensor of Claim 1, wherein the "oxygen dissolving substance" is selected from the group consisting of, among others, "hydrocarbon . . . solids" and "steroids," both of which are solids. *See* '225 Patent at 14:23–24. While the Court agrees that the oxygen dissolving substance is part of the emulsion, which does require liquids, *see supra* Section II.A, it is not the term "water immiscible" that mandates that the emulsion is liquids. Instead, it is the ordinary meaning of emulsion in conjunction with the specification.

The prosecution history also supports Plaintiff's construction. When distinguishing the '225 Patent from Wilkens, the patentee explicitly references solid particles as being immiscible. The patentee states that "[t]he fine particles of graphite used by Wilkins are immiscible but do not constitute an oxygen dissolving substance." *Id.* The graphite

///

materials in Wilkens are all solid, *see id.*, thus, this supports that the patentee did not limit the adjective immiscible only to liquids.

Moreover, the fact that immiscible is an adjective contradicts Defendant's construction. Defendant's proposal would improperly turn the word into a noun, describing the substance and its properties all in one. The Court finds no support for this outcome.

Based on the above, the Court adopts Plaintiff's construction and construes the term "water immiscible" to mean "will not mix with or dissolve in water."

D. "oxygen dissolving substance" (all asserted claims of the '225 Patent)

Plaintiff would construe the term "oxygen dissolving substance" to mean "a substance (a particular kind of matter with uniform properties) having a higher oxygen solubility or higher oxygen permeability than at least one of a hydrocarbonaceous polymer and an oxyhydrocarbon polymer." Pl.'s Br. at 22. Defendant would construe the term to mean "a liquid in which oxygen is preferentially soluble in comparison to water." Def.'s Br. at 23. The Parties' disagreements regarding this term focus on two characteristics: (1) whether the substance is limited to liquids; and (2) whether the substance should be preferentially soluble as compared to water or certain polymers.

Beginning with Defendant's proposal that the "oxygen dissolving substance" must be limited to liquids, the Court finds no basis for this in the evidence. The term is described as a solid in both Claim 5 and the specification. As noted above, Claim 5 describes that the oxygen dissolving substance may be "hydrocarbon . . . solids" or "steroids." '225 Patent at 14:23–24. The fact that the oxygen dissolving substance is dissolved or emulsified into a liquid when part of the claimed emulsion does not mandate that, when described in isolation, it is not a solid.

Likewise, the extrinsic evidence supports that the meaning of "substance" is not limited to liquids. As noted by Plaintiff, multiple dictionaries offer definitions that do not limit the term "substance" to liquids. *See, e.g.*, Pl.'s Br. Ex. E (Concise Oxford Dictionary (1999) defining "substance" as "a particular kind of matter with uniform properties"); Ex.

F (American Heritage Dictionary (1994) defining "substance" as "[a] material of a particular kind or constitution"); Ex. G (Merriam-Webster's Collegiate Dictionary (1999) defining "substance" as "matter of particular or definite chemical constitution"). This extrinsic evidence supports Plaintiff's construction.

Next, Plaintiff's proposed construction attempts to add permeability to the term. This finds no support in the claims or specification. Dissolving a substance is different than diffusion of the substance; consequently, permeability has no place in the construction of this term.

Turning to the solubility of the substance, both Parties agree that the construction for this term requires preferential or higher solubility. The question, therefore, is whether the substance should be preferentially soluble as compared to water or as compared to certain polymers. Plaintiff contends that "hydrocarbonaceous polymer" and "oxyhydrocarbon polymer" should be the points of comparison to the solubility of the substance. Pl.'s Br. at 24–25. These terms, however, do not come from the intrinsic record or the prior art; on the contrary, they come from two separate patents owned by Defendant that were issued *after* the '225 Patent. *See* Def.'s Br. at 25. Although Defendant owns those patents and they reference similar terms, those references are not prior art and do not overcome the fact that the terms find no support in the Patent-in-suit.

Turning to Defendant's construction, Defendant contends that the solubility of the substance should be compared to water. Def.'s Br. at 24–25. The specification describes the solubility of oxygen as compared to water multiple times. *See, e.g.*, '225 Patent at 3:33–40 ("This limits the distance that oxygen must diffuse through a poor oxygen carrier such as water."); 13:2–4 ("[A]n advantage is that steroids, like perfluorocarbons, are much better at dissolving oxygen than is water."). While the specification also describes the solubility as compared to "biological fluids," these fluids—as Defendant notes—are essentially water. Def.'s Br. at 24. And by describing the solubility as compared to water instead of biological fluids, the term avoids possible problems with ambiguity.

///

Based on the above, the Court construes the term "oxygen dissolving substance" as "a substance in which oxygen is preferentially soluble in comparison to water."

E. "oxygen dissolving substance emulsified into intimate contact with the enzyme" (all asserted claims of the '225 Patent)

Plaintiff would construe the term "oxygen dissolving substance emulsified into intimate contact with the enzyme" as "[oxygen dissolving substance as construed above] placed into close communication with the enzyme, via the emulsion." Pl.'s Br. at 26. Defendant would construe the term as "the oxygen-dissolving substance surrounds the enzyme with an emulsion-droplet reservoir of oxygen." Def.'s Br. at 26.

Both Parties focus their proposed constructions on the meaning of the term "intimate contact," with Plaintiff contending that "intimate contact" means "close communication." Pl.'s Br. at 26–27. As noted above, *see supra* Section II.B, the Court rejects Plaintiff's proposed construction of "in contact with" to mean "communication." The Court therefore rejects Plaintiff's proposal to inject "communication" into "intimate contact" for the same reason.

Plaintiff's proposed meaning for "intimate," however, captures the plain and ordinary meaning of the word. The Court agrees that a person of ordinary skill in the art at the time of the invention would have understood "intimate" as a very close connection, association, or contact. This meaning tracks with the use of "intimate" in the specification, where the word intimate is used in conjunction with both "contact" and "association." *See, e.g.*, '225 Patent at 5:23, 8:57, 8:61 (preceding contact); 10:26 (preceding association). In both instances, the specification uses "intimate" as a term of degree, describing how close the components are.

The extrinsic evidence also supports this ordinary meaning; indeed, all of the dictionaries offered by Plaintiff provide a definition of "intimate" including "close." *See* Pl.'s Br. Ex. E (Concise Oxford Dictionary defining "intimate" as "[i]nvolving very close connection"), Ex. F (American Heritage Dictionary defining "intimate" as "[m]arked by close acquaintance, association, or familiarity"), Ex. G (Merriam-Webster's Collegiate

Dictionary defining "intimate" as "marked by very close association, contact, or familiarity").

Defendant contends that "emulsified into intimate contact with the enzyme" is a coined term, not having an ordinary and customary meaning. Def.'s Br. at 26. Defendant argues that without such a definition, the term would be indefinite. *Id.* The Court does not agree and finds that the term, viewed in light of the Patent as a whole, adequately describes the proximity and relationship between the oxygen dissolving substance and the enzyme. Importantly, Defendant has failed to show that the patentee "clearly set forth a definition of the disputed claim term" and "clearly express[ed] an intent to define the term." *GE Lighting*, 750 F.3d at 1309. Without such a showing, the Court declines to find the term is a coined term and declines to deviate from the ordinary and customary meaning of the words.

As for the last remaining word in this disputed term, "emulsified," neither Party indicates any reason why the Court should deviate from the ordinary and customary meaning. *See Websidestory, Inc. v. Netratings, Inc.*, No. 06CV408WQH(AJB), 2007 WL 2019654, at *10 (S.D. Cal. July 10, 2007) (citing *Orion IP, LLC v. Staples, Inc.*, 406 F. Supp. 2d 717, 738 (E.D. Tex. 2005) ("[W]hile every word in a claim has meaning, not every word requires construction.")). The Court therefore adopts the ordinary and customary for this term as well.

Accordingly, the Court construes the phrase "oxygen dissolving substance" as defined above, *supra* Section II.E, and adopts the ordinary and customary meaning for the remainder of the term as outlines above: "oxygen dissolving substance [as defined above] emulsified into very close contact with the enzyme."

F. "electrode" (all asserted claims of the '225 Patent)

Plaintiff would define the term "electrode" as "a conductive material, optionally including a membrane." Pl.'s Br. at 18. Defendant, on the other hand, would construe "electrode" to mean "a solid electric conductor through which an electric current enters or

///

leaves a substance." Def.'s Br. at 11. In other words, the Parties dispute whether the term "electrode" includes a membrane, or whether membrane and electrode are separate terms.

Plaintiff contends that "there is nothing in the prosecution history . . . , the specification, or the claims that precludes the presence of a membrane or coating on the claim electrode." Pl.'s Br. at 18. The Court agrees this may be true but, at the same time, there is zero evidence in the claims or the specification that supports Plaintiff's construction that an optional membrane *must* be included in the term's construction, which would effectively combine the two terms. And as Defendant points out, dependent Claim 2 describes a membrane as a separate element, describing "the sensor of Claim 1 further comprising a semipermeable membrane covering the electrode." '225 Patent at 14:30–33. If the Court were to adopt Plaintiff's construction, dependent Claim 2 would encompass the same scope as independent Claim 1 and become superfluous. *See Power Mosfet Techs., L.L.C. v. Siemens AG*, 378 F.3d 1396, 1410 (Fed. Cir. 2004) ("[I]nterpretations that render some portion of the claim language superfluous are disfavored.").

The Court therefore agrees with Defendant that membrane and electrode should be construed as two separate terms and adopts Defendant's construction of "electrode" as "a solid electric conductor through which an electric current enters or leaves a substance."

G. "hydrocarbon oils or solids" (claim 5 of the '225 Patent)

Plaintiff would construe the term "hydrocarbon oils or solids" to mean "oils or solids including a chemical group or side chain composed of hydrogen and carbon only." Pl.'s Br. at 28. Defendant would construe the term to mean "oils or solids composed only of carbon and hydrogen." Def.'s Br. at 28. The Parties' dispute boils down to whether "hydrocarbon oils and solids" must be composed of only hydrogen and carbon, as Defendant proposes, or whether they can be any oil or solid that includes a hydrogen and carbon side chain, as Plaintiff proposes.

Defendant contends that its construction is consistent with the ordinary and customary meaning of the term. Conversely, Plaintiff asks the Court to deviate from the ordinary meaning primarily based on one sentence from the specification. *See* Pl.'s Br. at

28. That sentence lists examples of substances that may be used as an "oxygen dissolving substance," stating that "[b]esides perflourocarbons hydrocarbon drugs (e.g., cortical steroids) silicones, silanes, cyclic silanes, siloxanes, fluorinated silicones and other similar organo-silicon compounds are excellent oxygen solvents and are useful in the present invention." '225 Patent at 8:13–17. Plaintiff notes that the specification refers to "hydrocarbon drugs," including cortical steroids, which are compounds that are not composed of hydrogen and carbon only and instead consist of oxygen with hydrogen and carbon as a side chain. According to Plaintiff, this precludes any interpretation of the term that limits "hydrocarbon oils and solids" to only substances composed of hydrogen and carbon. The Court cannot agree.

Under Plaintiff's interpretation, several terms in Claim 5 would become redundant or illogical. As pointed out by Defendant, "under Plaintiff's interpretation, hydrocarbon would include the claimed silicone oils, flourosilicone oils, carotenoids, and steroids" listed in Claim 5 "because these chemical classes include a chemical group or side chain composed of hydrogen and carbon only." Def.'s Br. at 29. This would render Claim 5 redundant. Because different claim terms are presumed to have different meanings, the Court declines to find that "hydrocarbon oils and solids" includes silicone oils, flourosilicone oils, carotenoids, and steroids. *See SimpleAir, Inc. v. Sony Ericsson Mobile Commc'n*, 820 F.3d 419, 431 (Fed. Cir. 2016) (quoting *Bd. of Regents of the Univ. of Tex. Sys. v. BENQ Am. Corp.*, 533 F.3d 1362, 1371 (Fed. Cir. 2008) ("Different claim terms are presumed to have different meanings.") (citation omitted)).

The Court therefore adopts Defendant's construction of "hydrocarbon oils or solids" as "oils or solids composed only of carbon and hydrogen."

///

///

///

///

///

CONCLUSION

The terms in dispute are construed as follows:

TERM	CONSTRUCTION
1. "emulsion" (all asserted claims of the '225 Patent)	"a mixture of two or more immiscible liquids, in which one liquid is dispersed in another liquid"
2. "in contact with" (all asserted claims of the '225 Patent)	"touching"
3. "water immiscible" (all asserted claims of the '225 Patent)	"will not mix with or dissolve in water"
4. "oxygen dissolving substance" (all asserted claims of the '225 Patent)	"a substance in which oxygen is preferentially soluble in comparison to water"
5. "oxygen dissolving substance emulsified into intimate contact with the enzyme" (all asserted claims of the '225 Patent)	"oxygen dissolving substance [as defined above] emulsified into very close contact with the enzyme."
6. "electrode" (all asserted claims of the '225 Patent)	"a solid electric conductor through which an electric current enters or leaves a substance"
7. "hydrocarbon oils or solids" (claim 5 of the '225 Patent)	"oils or solids composed only of carbon and hydrogen"

IT IS SO ORDERED.

Dated: December 30, 2019

Janis L. Sammartino
Hon. Janis L. Sammartino
United States District Judge

US006343225B1

(12) **United States Patent**
Clark, Jr.

(10) **Patent No.: US 6,343,225 B1**
(45) **Date of Patent: Jan. 29, 2002**

(54) **IMPLANTABLE GLUCOSE SENSOR**

(75) Inventor: **Leland C. Clark, Jr.**, Cincinnati, OH (US)

(73) Assignee: **Implanted Biosystems, Inc.**, Kettering, OH (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/395,466**

(22) Filed: **Sep. 14, 1999**

(51) **Int. Cl.**[7] **A61B 5/05**

(52) **U.S. Cl.** **600/347**; 600/365; 600/377

(58) **Field of Search** 600/309, 345, 600/347, 365, 377; 204/403, 415, 414; 435/14, 177

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,431,160 A * 7/1995 Wilkins 600/347

6,081,736 A * 6/2000 Colvin et al. ..... 600/347 X

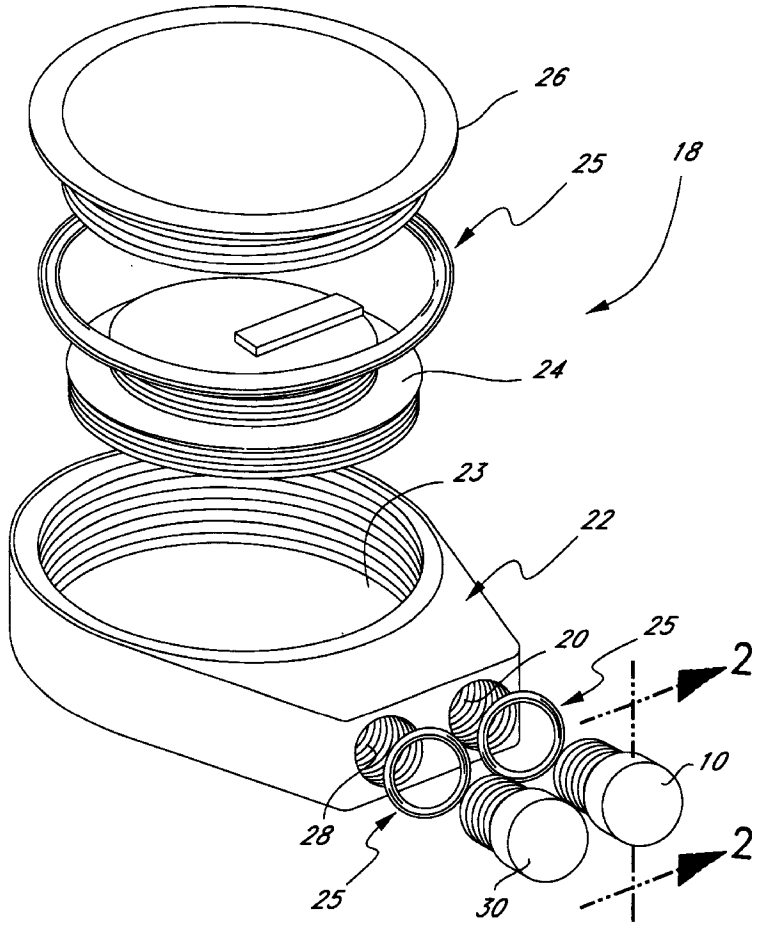
* cited by examiner

Primary Examiner—Eric F. Winakur
Assistant Examiner—Ryan Carter
(74) *Attorney, Agent, or Firm*—Crosby, Heafey, Roach & May

(57) **ABSTRACT**

The sensitivity of enzyme-based polarographic electrodes to oxygen concentration can be significantly reduced or eliminated by providing an oxygen-reservoir in intimate contact with the oxidative enzyme. This is achieved by making a stabilized emulsion between the enzyme and a compound in which oxygen is extremely soluble. An aqueous glucose oxidase solution is emulsified with a perfluorocarbon liquid, and the resulting emulsion is stabilized by chemically crosslinking the mixture to form a gel. Thin layers of the emulsion are fabricated by spreading a layer of the liquid emulsion before gelation occurs. Additional carrier proteins such as albumin may be added to the enzyne prior to crosslinking to protect enzymatic activity and enhance gel strength. Additional electron transport compounds may be added to further reduce sensitivity to oxygen concentration.

18 Claims, 10 Drawing Sheets



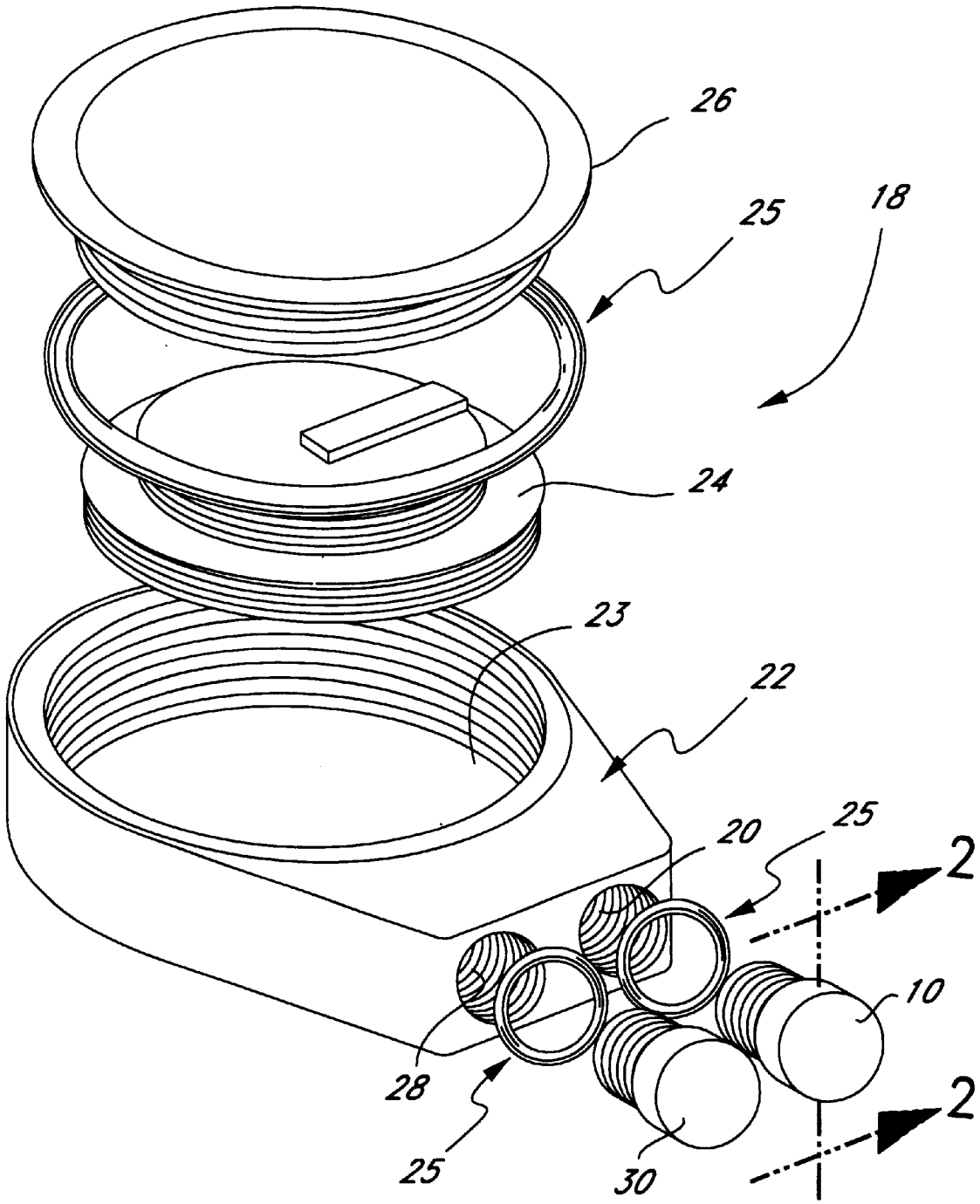
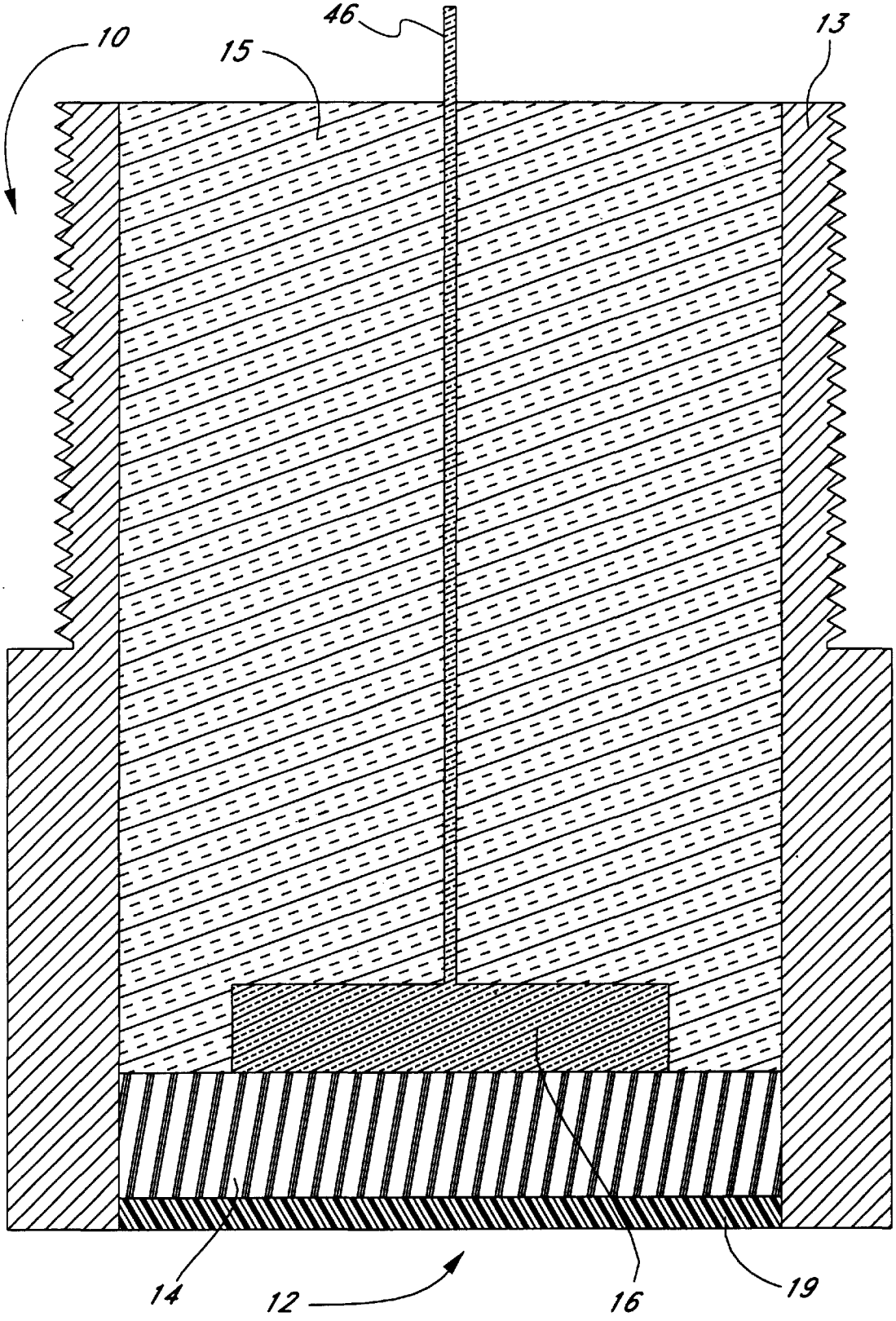


FIG. 1

FIG. 2



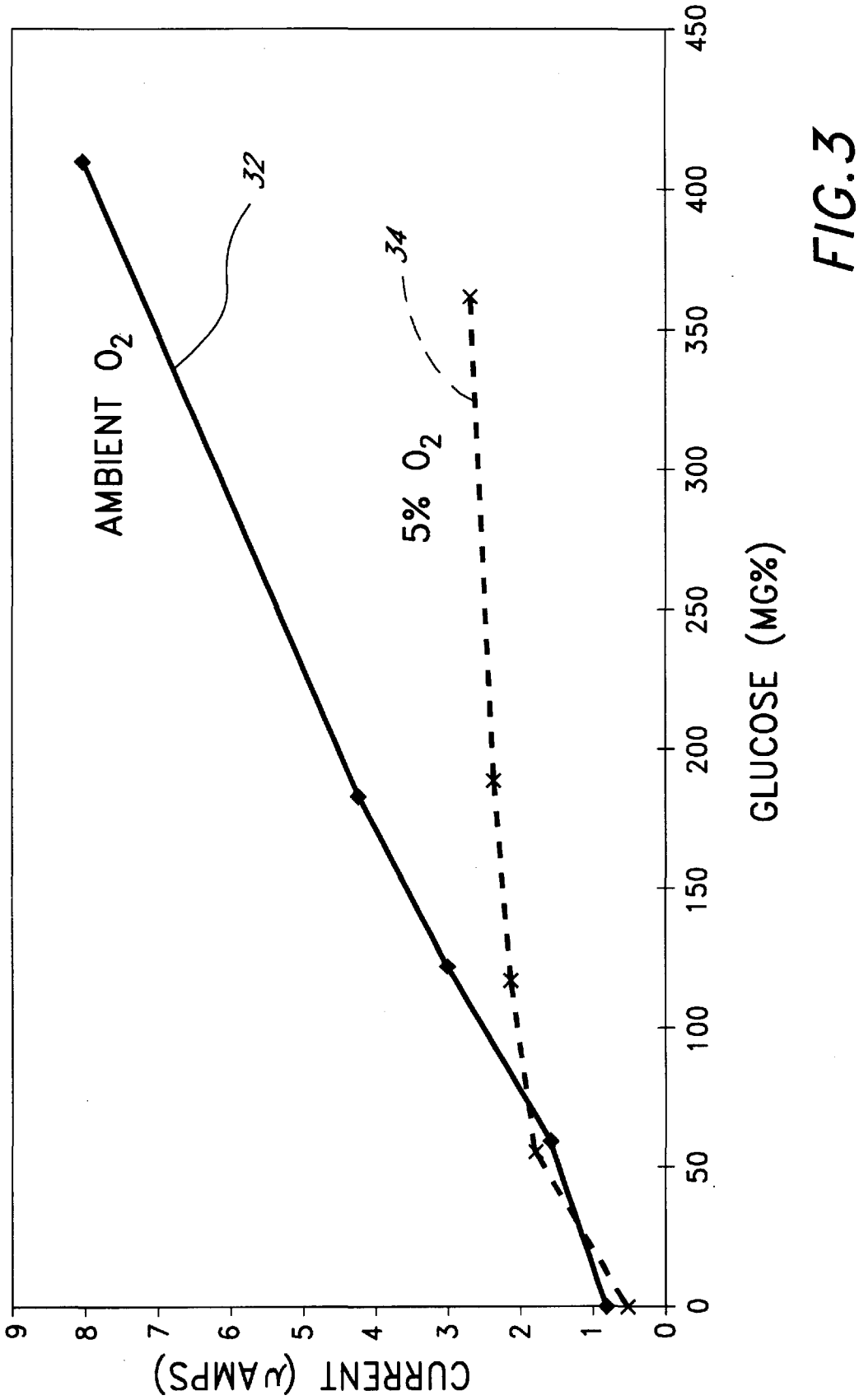

AMBIENT O_2
32
5% O_2
34
CURRENT (μAMPS)
GLUCOSE (MG%)
0
1
2
3
4
5
6
7
8
9
0
50
100
150
200
250
300
350
400
450

FIG. 3

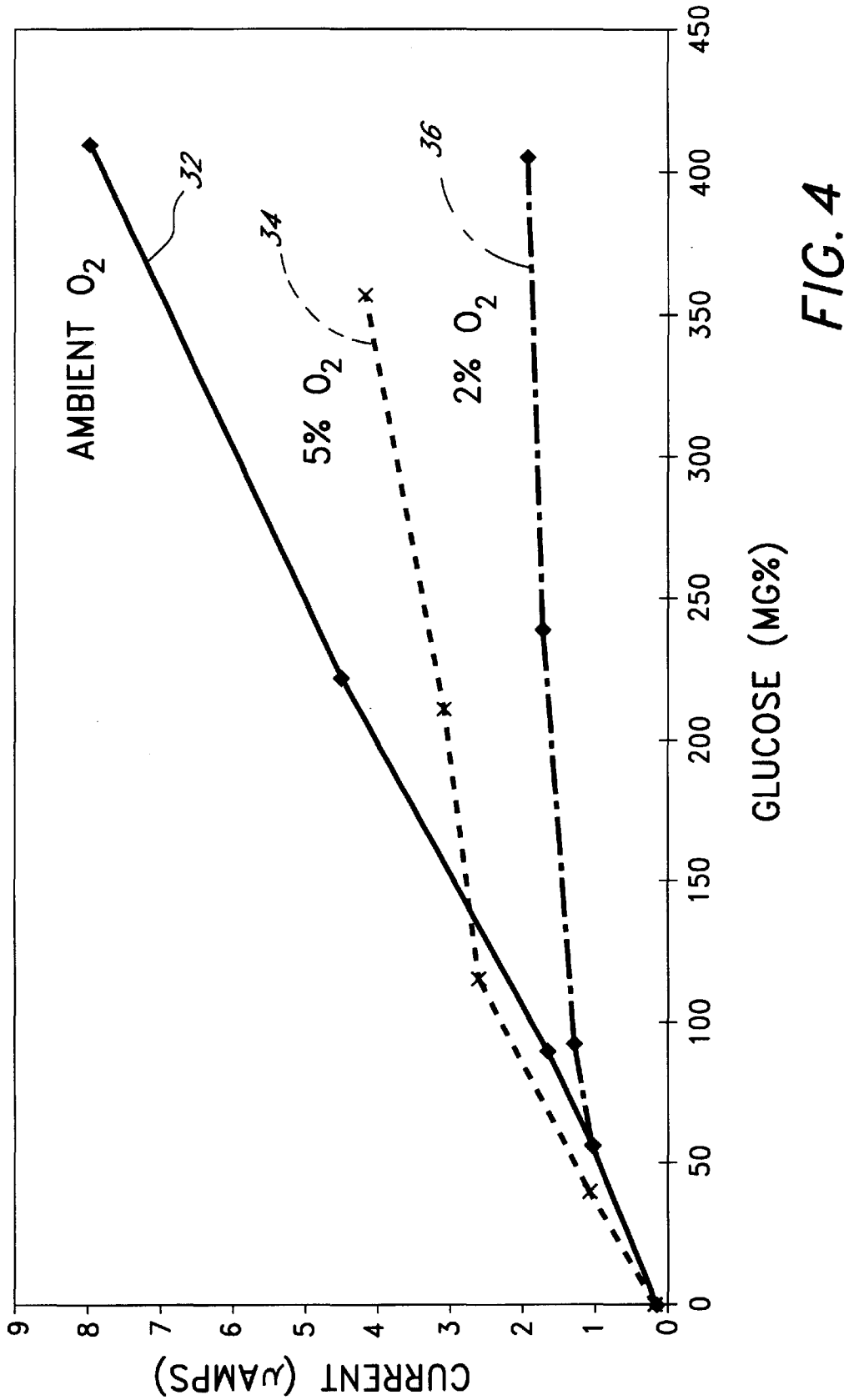

AMBIENT O_2
32
5% O_2
34
2% O_2
36
CURRENT (μAMPS)
0
1
2
3
4
5
6
7
8
9
GLUCOSE (MG%)
0
50
100
150
200
250
300
350
400
450

FIG. 4

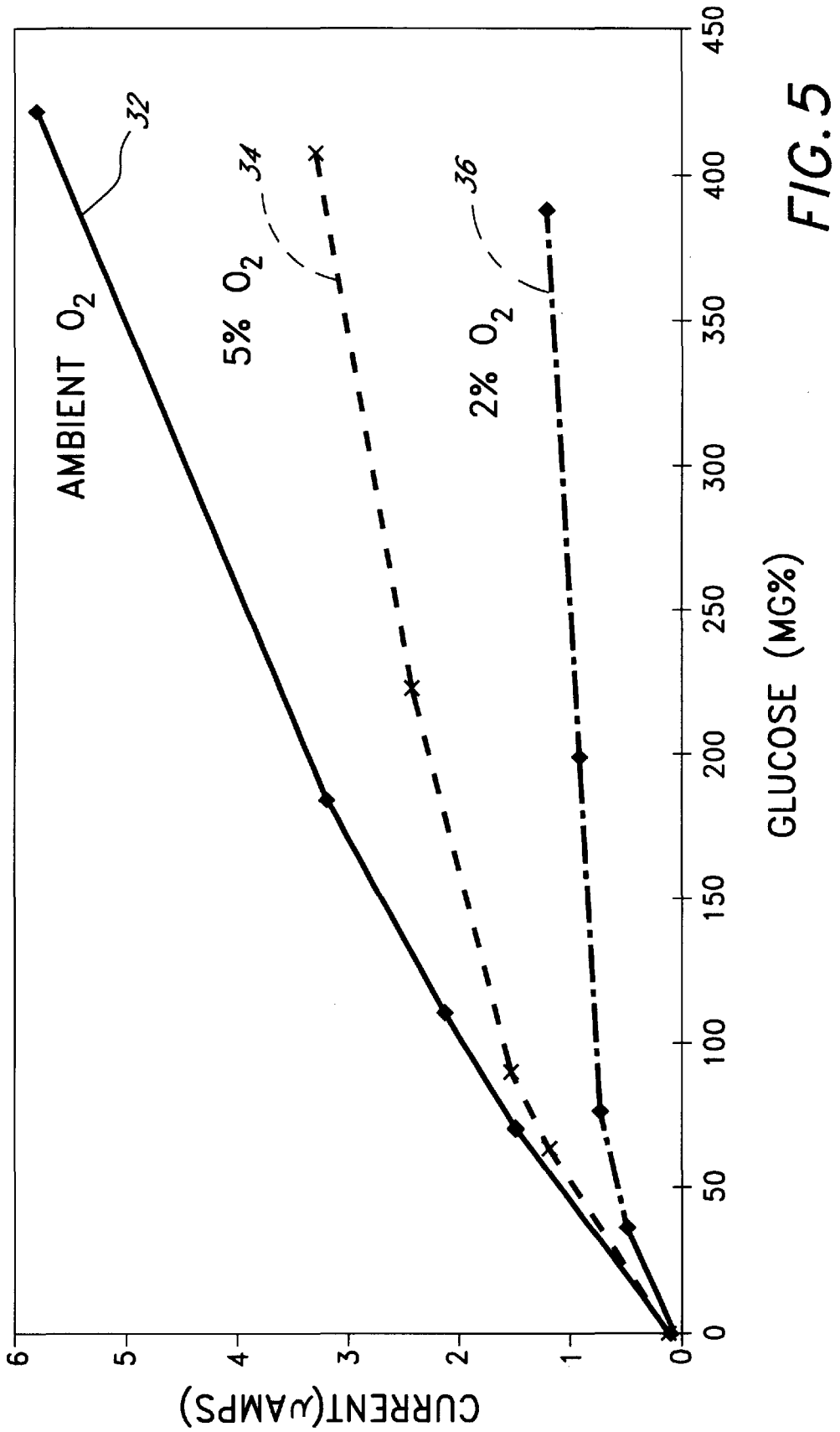

AMBIENT O_2
32
5% O_2
34
2% O_2
36
CURRENT(μAMPS)
0
1
2
3
4
5
6
GLUCOSE (MG%)
0
50
100
150
200
250
300
350
400
450

FIG. 5

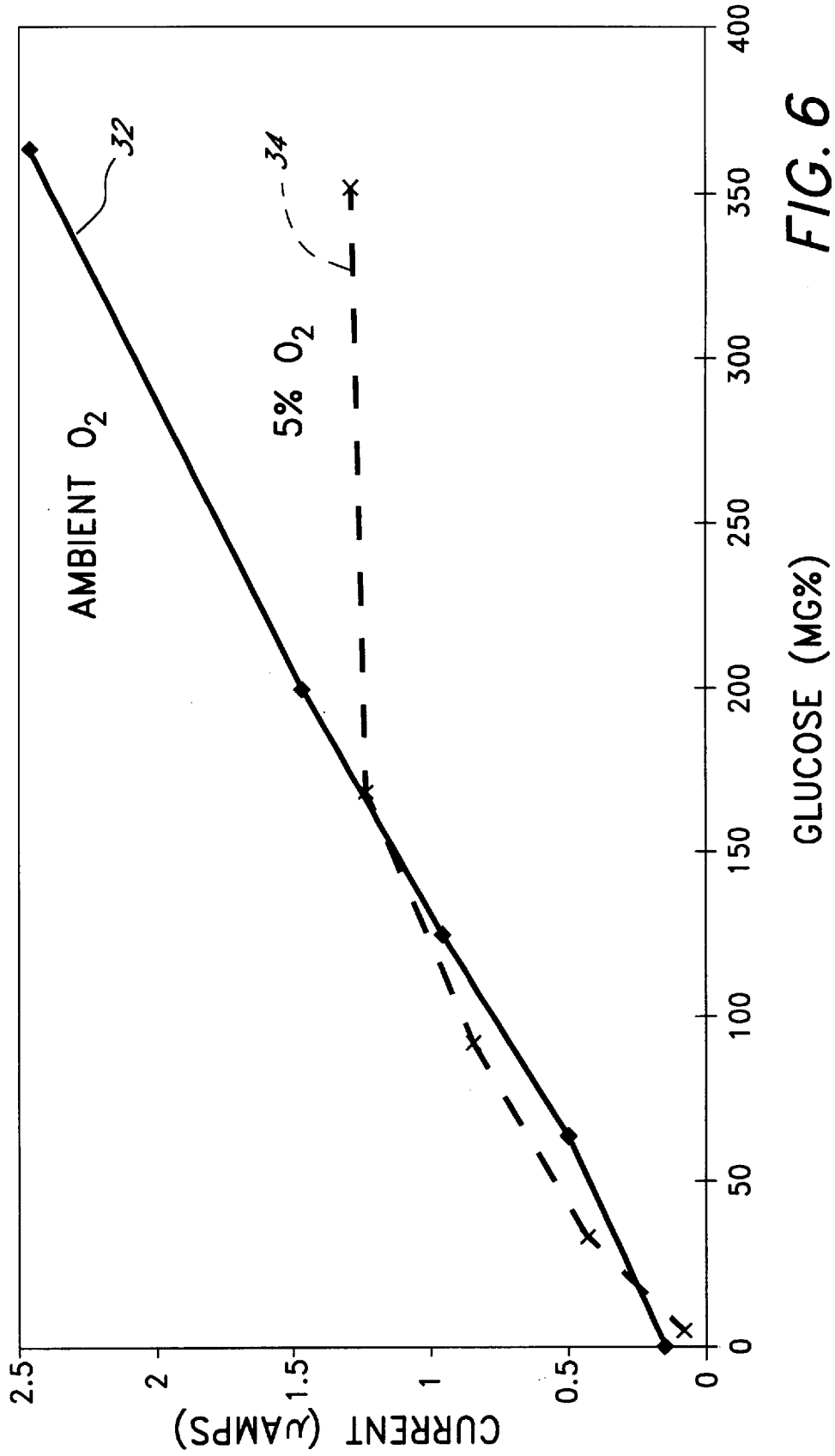

AMBIENT O_2
32
5% O_2
34
CURRENT (μAMPS)
2.5
2
1.5
1
0.5
0
0
50
100
150
200
250
300
350
400
GLUCOSE (MG%)

FIG. 6

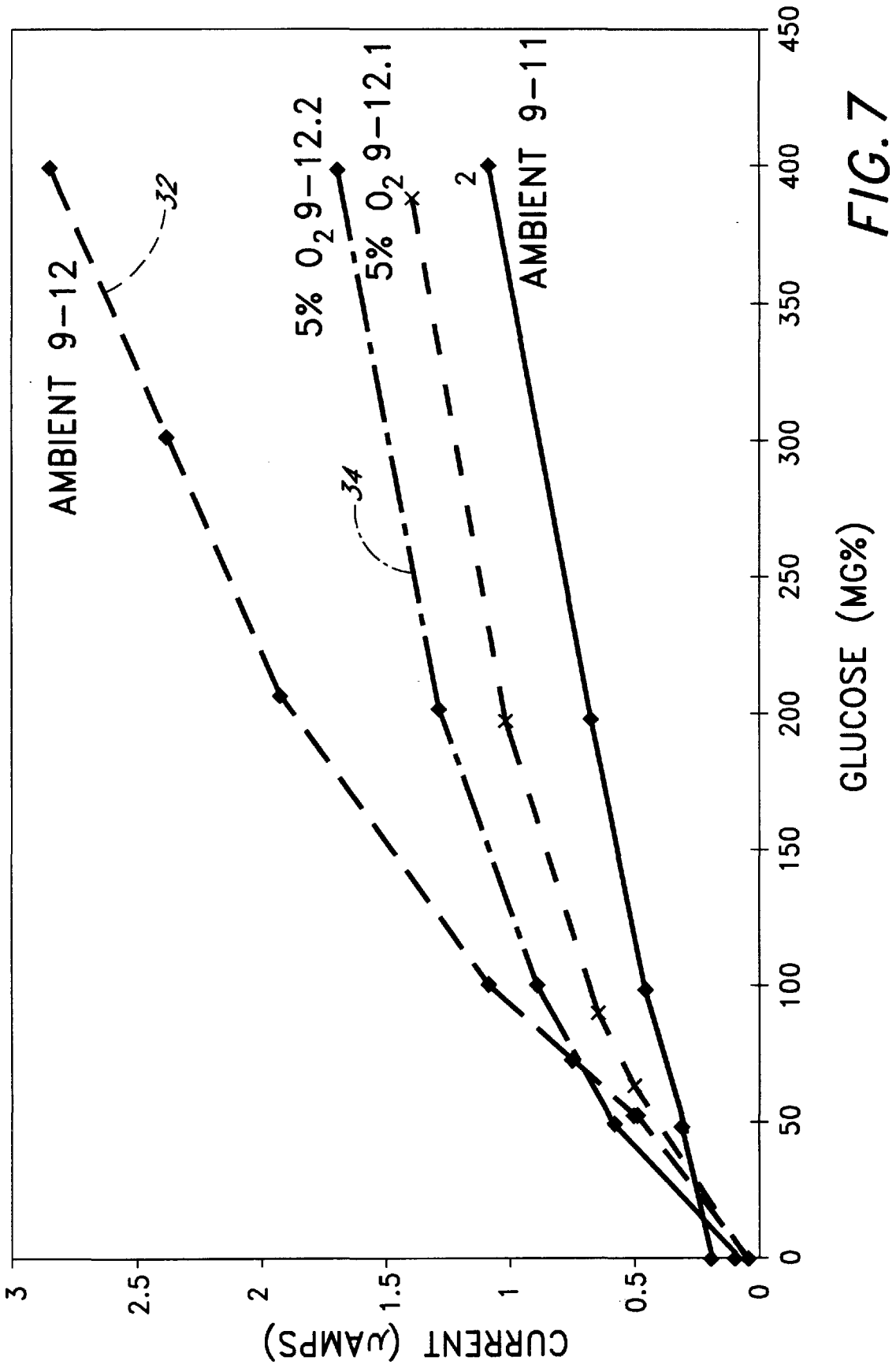

AMBIENT 9–12
32
5% O_2 9–12.2
5% O_2 9–12.1
34
AMBIENT 9–11
2
CURRENT (μAMPS)
GLUCOSE (MG%)
0
0.5
1
1.5
2
2.5
3
0
50
100
150
200
250
300
350
400
450

FIG. 7

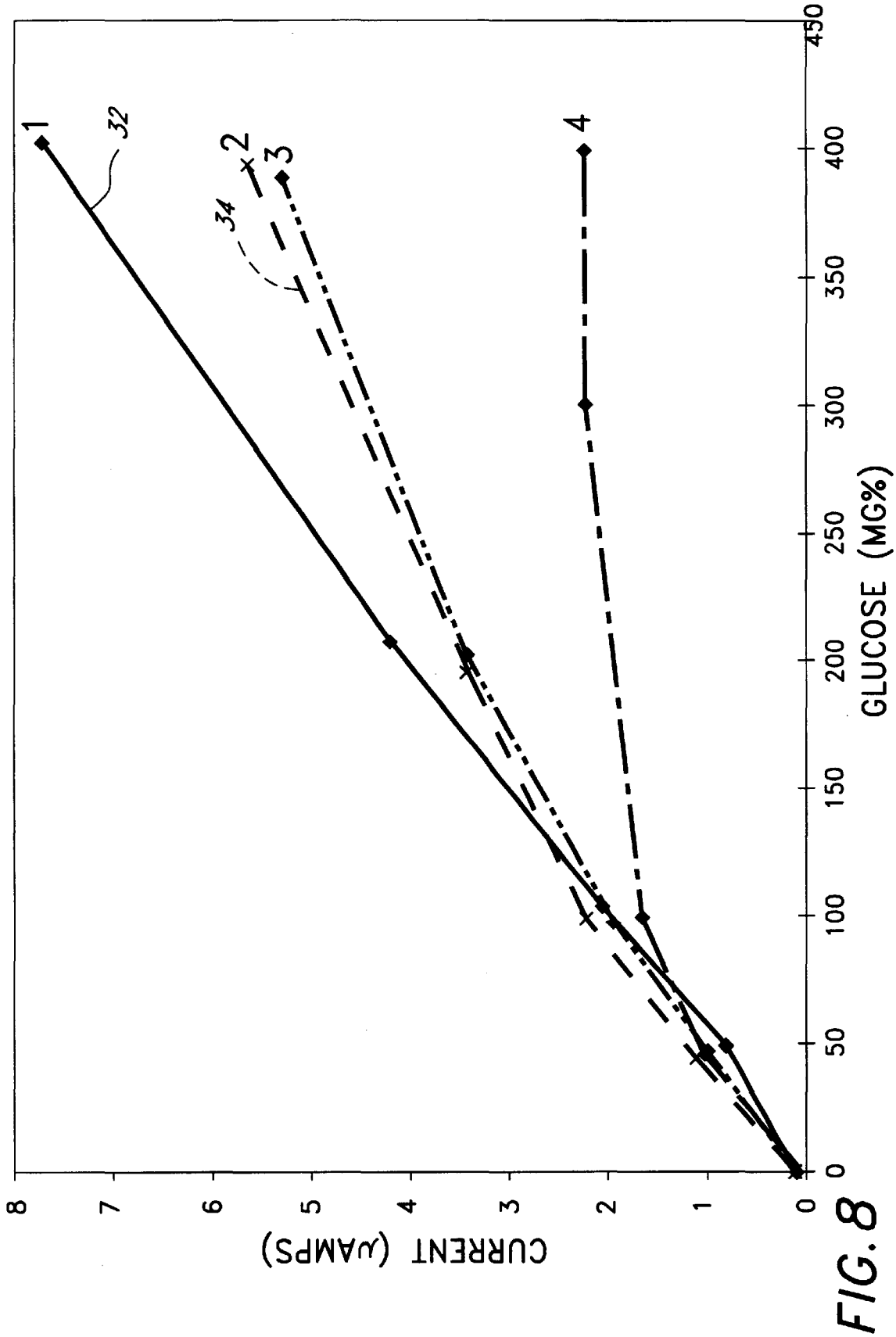

CURRENT (μAMPS)
0
1
2
3
4
5
6
7
8
GLUCOSE (MG%)
0
50
100
150
200
250
300
350
400
450
1
2
3
4
32
34

FIG. 8

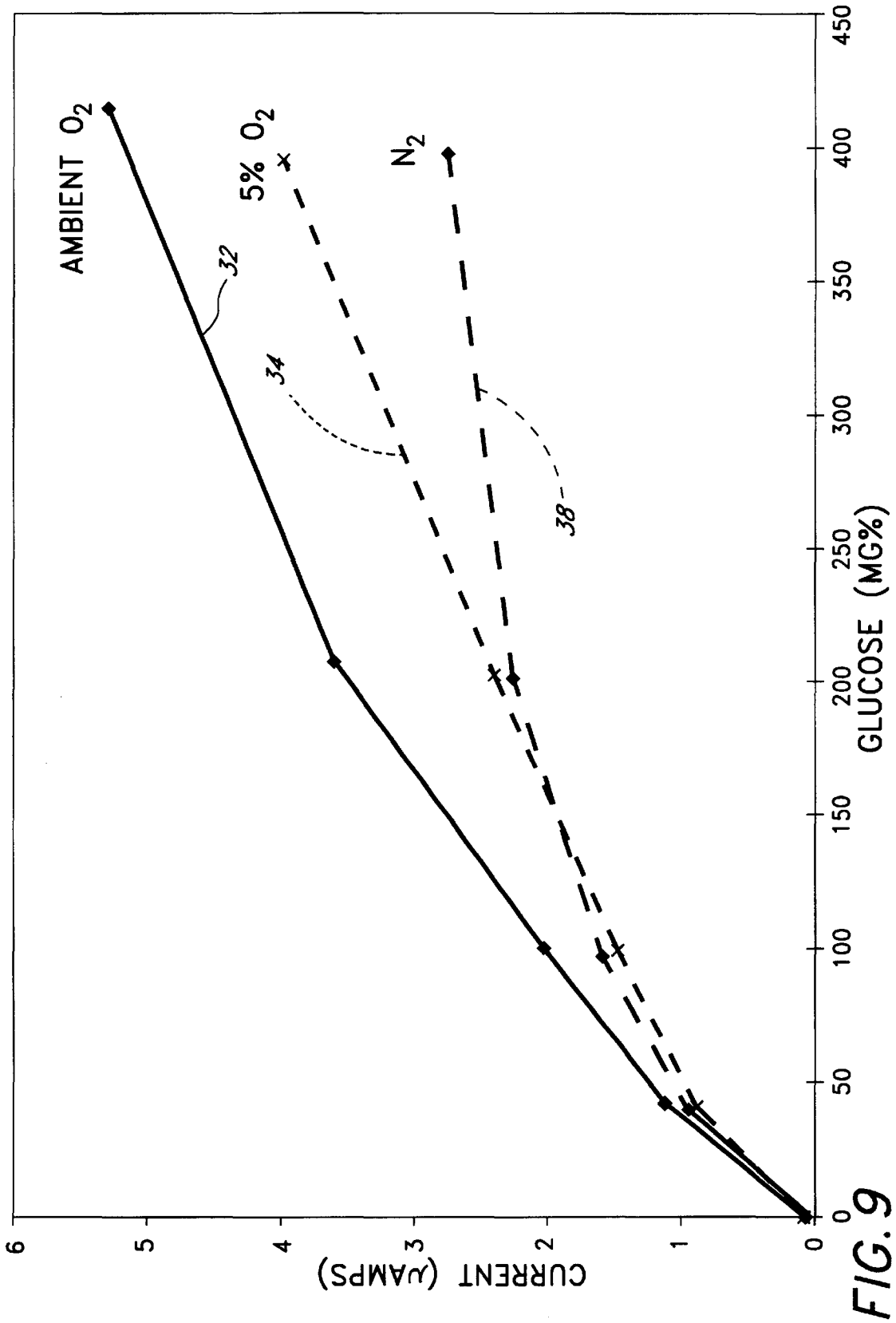

AMBIENT O_2
5% O_2
N_2
32
34
38
CURRENT (μAMPS)
GLUCOSE (MG%)
0
1
2
3
4
5
6
0
50
100
150
200
250
300
350
400
450

FIG. 9

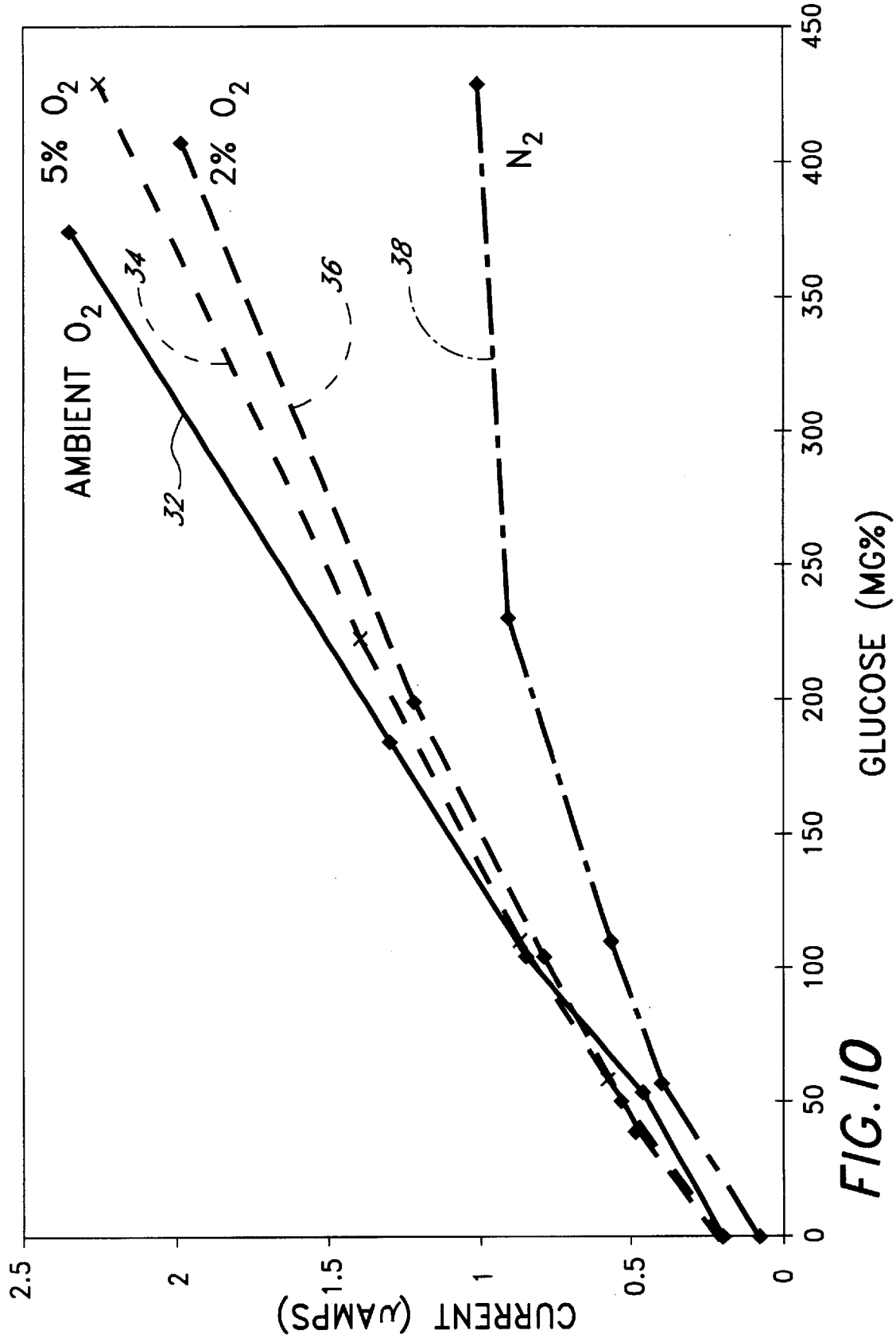

5% O_2
2% O_2
AMBIENT O_2
N_2
32
34
36
38
CURRENT (μAMPS)
GLUCOSE (MG%)
0
0.5
1
1.5
2
2.5
0
50
100
150
200
250
300
350
400
450

FIG. 10

IMPLANTABLE GLUCOSE SENSOR

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention concerns the field of electrochemical devices for detection and measurement purposes and more specifically an enzyme emulsion for use in an implantable miniature polarographic glucose sensor.

2. Description of Related Art

There is currently a considerable need for a glucose sensor that can be readily implanted into a human where it will function for a prolonged time period. The primary impetus for such a device is diabetes, a potentially devastating complex disorder of glucose metabolism, currently controllable through insulin injections, is increasing worldwide. In the United States it is estimated that over ten million persons have diabetes. The monetary cost to society is in the many billions of dollars reflecting treatment expense and loss of productivity while the human cost in impaired function, progression to blindness, limb amputations, kidney failure and heart and vascular disease is immeasurable.

It has been known for well over seventy years that this disease primarily results from inadequate secretion of the hormone insulin by the islet or Beta cells of the pancreas. When uncontrolled, this disease often leads to serious metabolic imbalances—elevated glucose levels lead to ketosis and to damaging alterations in blood pH while inadequate glucose levels lead to lethargy and coma. Diet and daily injections of insulin are now used in an attempt to control life-threatening swings in blood glucose. It is now well established that the damage is caused by excessive glucose and not directly by lack of insulin. Glucose combines with hundreds of proteins essential for normal metabolism and in that way damages the cellular machinery of the body.

Control of diabetes by insulin injection generally results in much wider swings in blood glucose level than are common in a normal individual. Occasional insulin injections (up to several per day) are unable to duplicate the strict control of blood glucose afforded by a properly functioning pancreas which continually meters out just enough insulin to maintain a stable and relatively normal blood glucose level. Extremes in blood glucose level need be avoided. Yet despite avoiding extremes in blood glucose level insulin-dependent diabetics suffer a host of other maladies, mentioned above, that decrease both the quality and length of life. Diabetics experience frequent vascular disease that often results in amputation of limbs as impaired circulation prevents adequate blood flow. Abnormal vascular growth within the eye may result in intraocular bleeding and retinal damage with progressive loss of vision. Nerve degeneration may lead to loss of sensation and other related problems.

To control the blood level of glucose by injection of insulin requires the analysis of six to eight samples of blood each day. This is usually performed by puncturing the finger tip with a small lancet and analyzing blood glucose level with a photometric "home glucose monitor." This is, of course, not a pleasant experience and requires considerable skill as well as motivation. As home glucose tests have became common, more and more data have became available demonstrating the relatively poor control of blood glucose afforded by periodic insulin injections. At the same time, a growing number of clinical studies demonstrated that strict control of blood glucose reduces many if not all of the diabetes-related diseases mentioned above. Many scientists and physicians now believe that greatly improved blood glucose control can largely eliminate the mortality and morbidity associated with diabetes.

The ultimate goal of diabetes treatment is a replacement for the patient's non-functioning pancreatic islet cells. Some scientists are seeking ways to transplant functioning islet cells into diabetic patients to provide a naturally controlled source of insulin. Other scientists are working on automatic insulin injection systems that deliver exogenously supplied insulin as needed to maintain precise blood glucose control. Most probably both of these "cures" will be needed. Although transplanted islet cells would seem to be the optimal solution, at this time anti-rejection drugs required for transplants have almost as many negative side effects as diabetes itself. In any case, a self-regulating artificial insulin source is needed to limit the damage caused by diabetes until islet transplantation is perfected. Even when transplantation is widely available, a self regulating insulin source will be needed for patient maintenance prior to transplantation, and, perhaps, for some post-transplantation support.

Many types of regulated injection systems, both implantable and external, are already available. The key problem continues to be the requirement for an accurate glucose sensor to control these injection systems. The need to continually monitor glucose levels to permit a constantly metered dispensing of insulin generally eliminates methods relying on blood samples. It is clear that an implantable glucose sensor that measures in vivo glucose levels is the real answer.

Previous to modem instrumentation the analysis for blood glucose required a venipuncture with the collection of several milliliters of blood, precipitation, filtration, treatment with a colorimetric glucose reagent and spectrophotometric determination of glucose. The invention of the first "enzyme electrode" and glucose sensor by the present inventor in the 1960's led to the production of the first commercially successful blood glucose analyzer. The Clark glucose sensor consisted of a platinum anode, a layer of glucose oxygen oxioreductase (glucose oxidase) and a cellophane or cellulose acetate membrane. A silver "reference" electrode was also incorporated into the sensor. Only 0.01 ml of blood was required and the final analysis was complete in about one minute. Since then literally billions of blood samples have been analyzed by this type of instrument.

The inventor's polarographic glucose method just mentioned is explained in U.S. Pat. No. 3,539,455. The chemical reaction most commonly used by such enzyme-coupled polarographic glucose sensors is glucose oxidase mediated catalytic oxidation of glucose by atmospheric oxygen to produce gluconolactone and hydrogen peroxide (equation 1):

$$C_6H_{12}O_6+O_2+H_2O\rightarrow C_6H_{12}O_7+H_2O_2 \quad (1)$$

In the presence of excess oxygen, the quantity of hydrogen peroxide produced will be a direct measure of the glucose concentration. The hydrogen peroxide is measured by being reoxidized by an electrode (anode) maintained at an appropriate positive potential (equation 2):

$$H_2O_2-2e^-\rightarrow O_2+2H^+ \quad (2)$$

The glucose detection process, then, is dependent upon the measurement of electrons removed from hydrogen peroxide in equation (2). The electrode is normally formed from a noble metal such as gold or platinum. The latter preferred metal although carbon, pyrolytic or glassy, graphite and other electrically conducting materials are sometimes used.

As is well known to those of ordinary skill in the art, other specific hydrogen peroxide producing oxidase enzymes can be used to produce sensors for other substances such as

cholesterol (cholesterol oxidase), amino acids (amino acid oxidase), alcohol (alcohol oxidase), lactic acid (lactate oxidase), and galactose (galactose oxidase), to name only a few.

The success of this kind of enzyme-based sensor suggested to many that a similar sensor might be implanted with a simple power source and a means for transmitting the glucose data to the outside of the body. Such a continuously reading device would not only eliminate the pain of repeatedly puncturing the finger but would also supply a constant reading of the glucose level. It is known that the glucose level in many locations in the body closely mirror the blood glucose level. Numerous attempts have been made to make such a device available to diabetics. However, experimental devices did not function a sufficiently long period of time. These failures of implanted glucose sensors were ascribed to diverse problems, many of which appeared to be without solution. For example, some believed that the hydrogen peroxide (and free radicals) generated by the oxidase reaction caused denaturation and inactivation of the oxidase enzyme. Another, more common, explanation was that the glucose sensor was "not compatible" with the human body or that the surface of the measuring tip of the electrode became coated with layers of scar-like tissue which not only impeded the diffusion of glucose but jeopardized or destroyed nearby capillaries. Others held that the platinum electrode surface became "poisoned" by body fluids. However, extensive studies of implanted platinum electrodes conducted in the inventor's laboratory over the last forty years have completely exploded the myth of the "poisoned" platinum surface. Some implanted platinum electrodes have remained functional for up to six years.

It is a goal of this invention to similarly deal with other impediments to successful implantable glucose sensors. Glucose is extremely soluble in biological fluids whereas oxygen is poorly soluble in these same fluids and must be carried by specialized biomolecules such as hemoglobin. Many tissues of the human body have an oxygen tension equivalent to between about 2–5% oxygen in nitrogen or lower. As a result, there may be a ratio of glucose to oxygen sometimes as high as 100 to 1 in subcutaneous interstitial and peritoneal fluids. This means that at the electrode surface there may be only 1% of the oxygen required for glucose oxidase to quantitatively oxidize the available glucose for measurement purposes.

Furthermore, the glucose oxidase in a glucose sensor must be protected from proteases and other macromolecules which might destroy or inhibit the glucose oxidase, from enzymes such as catalase which destroy hydrogen peroxide (catalase, dehydrogenases, etc.), from microbes which digest the enzymes and from soluble compounds, such as ascorbate and acetoaminophen, which interfere with the either the enzymatic or electrochemical reactions. This protection can be achieved by separating the glucose oxidase from biological fluids by a semipermeable membrane. The best known membranes that are capable of selectively excluding proteins such as catalase while allowing the entry of glucose are so-called dialysis membranes. These membranes are generally hydrophilic membranes containing "pores" that readily admit neutral molecules with molecular weights below about 5,000 Daltons. Common examples of these membranes are prepared from various regenerated celluloses such as cellophane, Spectrapore® or Cuprophan® (brands of regenerated cellulose), cellulose esters, and membranes of polycarbonate or polysulfone.

While such semipermeable membranes do a good job of excluding undesirable proteins as well as retaining the essential glucose oxidase, they also impede oxygen diffusion. Some membranes, however, such as those of polytetrafluoroethylene (Teflon® brand of perfluorocarbon resin) or of silicone rubber are permeable to oxygen, but these membranes are virtually impermeable to glucose, and hence, cannot be used to protect an oxygen requiring glucose sensor. U.S. Pat. No. 5,322,063 to Allen et al. reports a new type of polyurethane membrane said to allows some glucose permeability while favoring oxygen permeability.

Because of a superabundance of glucose and a shortage of oxygen, an implanted glucose sensor will tend to be oxygen limited and, thus, effectively measure oxygen instead of, or together with, glucose. That is, under ideal conditions when the glucose concentration is low, oxygen would be adequate so that an increase in glucose concentration would result in a concomitant and proportional increase in hydrogen peroxide and, therefore, measured current at the electrode. However, as the concentration of glucose increases, oxygen ultimately becomes insufficient causing the measured current to plateau regardless of glucose concentration. Above this plateau changes in the current reflect changes in oxygen tension (concentration) rather than in glucose concentration.

Many workers have failed to take into account the high glucose to oxygen ratio of human tissues. There are at least two ways to solve this problem: one can attempt to reduce the concentration of glucose that reaches the glucose sensor and/or one can attempt to increase the amount of oxygen available at the glucose sensor. The level of glucose can be reduced either by providing a permeability barrier to glucose or by providing additional, non-peroxide generating enzyme systems, such as dehydrogenases, besides glucose oxidase, to consume excess glucose. The polyurethane membrane mentioned above is an example of glucose restriction.

The second approach involves an attempt to increase the level of available oxygen or to maximize the availability of oxygen to the oxygen-requiring enzymes. The present inventor has previously disclosed methods for increasing the oxygen level in U.S. Pat. Nos. 4,680,268 and 4,721,677, which are hereby incorporated by reference. These patents teach the use of an oxygen-collecting chamber made of an oxygen permeable material such as silicone rubber. This chamber is separated from the oxygen-requiring enzyme by an oxygen permeable membrane. The chamber collects oxygen and delivers it by diffusion to the enzyme mixture near the measuring electrode. These patents also disclose filling the oxygen-collecting chamber with an oxygen-dissolving compound such as a perfluorocarbon liquid for speeding diffusion of oxygen to the oxygen-requiring enzyme. Alternatively, an emulsion of a perfluorocarbon liquid and the enzyme solution could be used to fill the chamber with the device configured so that the emulsion flows slowly onto the electrode, supplying oxygen and replenishing the enzyme. A recent publication (Wang and Lu, J. American Chem. Soc. 120:1048–50(1998)) adopts this liquid emulsion strategy but add graphite or carbon powder so the emulsion also functions directly as an electrode. This could cause difficulties with an implantable electrode since macrophages might react to the carbon powder.

Experiments in the inventor's laboratory have also showed that the current output from chronically implanted sensors can be used to control ascorbic acid levels in the brain using a feedback loop to an ascorbate pump and connected indwelling catheter. Further, it has been shown that polarographic anodes can be used quantitatively to measure blood flow in the vicinal capillary beds. It has been found from thousands of hours or continuous recording, that

the oxygen available to the surface of an implanted oxygen sensor, and therefore to the glucose sensor described herein, is not steady but waxes and wanes in waves of six to eight cycles per minute. In some cases the amplitude of this variation can be plus or minus 30%. Buffering such fluctuation in available oxygen would be highly desirable in an oxygen-requiring glucose sensor since the functioning of such sensors depends upon oxygen.

In glucose sensor longevity experiments in the inventor's laboratory using sensors implanted in the peritoneal space of mice it was found that some sensors retained full activity for over 400 days. Over time the activity of most sensors gradually declined. These data demonstrated that adequate longevity could be achieved but that some factor, perhaps mechanical, frequently caused loss of activity. The invention disclosed herein is designed to avoid microbial degradation of the enzyme as well as to resist attacks by free radicals, proteases and the host's immune system.

SUMMARY OF THE INVENTION

The present inventor has discovered that "oxygen sensitivity" of enzyme-based polarographic electrodes can be significantly reduced or eliminated by providing an oxygen-reservoir in intimate contact with the oxidative enzyme. This is achieved by making a stabilized emulsion of the enzyme and a compound in which oxygen is extremely soluble. For example, an aqueous glucose oxidase solution can be emulsified with a perfluorocarbon liquid and the resulting emulsion stabilized by chemically crosslinking the mixture to form a gel. Thin layers of the emulsion ideal for placing into contact with a noble metal electrode can be fabricated by spreading a layer of the emulsion prior to crosslinking. Additional carrier proteins such as albumin can be added to the oxidase prior to crosslinking to protect enzymatic activity from the crosslinking reagent.

BRIEF DESCRIPTION OF THE DRAWINGS

The objects and features of the present invention, which are believed to be novel, are set forth with particularity in the appended claims. The present invention, both as to its organization and manner of operation, together with further objects and advantages, may best be understood by reference to the following description, taken in connection with the accompanying drawings.

FIG. **1** illustrates diagrammatic view of a glucose sensor of the current invention;

FIG. **2** illustrates an cross-sectional view of a working electrode of the device of FIG. **1**;

FIG. **3** shows the response of a stabilized enzyme mixture to varying glucose concentrations with ambient or with 5% oxygen;

FIG. **4** shows the response of a stabilized enzyme emulsion containing about 7.5% Krytox brand of liquid perfluorocarbon to varying glucose concentrations with ambient or with 5% oxygen;

FIG. **5** shows the response of a stabilized enzyme emulsion containing about 15% AP200 fluorocarbon to varying glucose concentrations with ambient or with 5% oxygen;

FIG. **6** shows the response of a stabilized enzyme emulsion containing about 7% AP200 fluorocarbon to varying glucose concentrations with ambient or with 5% oxygen;

FIG. **7** shows the response of a stabilized enzyme emulsion containing about 37% AP215 fluorocarbon to varying glucose concentrations with ambient or with 5% oxygen;

FIG. **8** shows the response of a stabilized enzyme emulsion containing about 15% AP240 fluorocarbon to varying glucose concentrations with ambient or with 5% oxygen;

FIG. **9** shows the response of a stabilized enzyme emulsion containing 0.4% ferrocene to varying glucose concentrations at ambient oxygen concentrations, at 5% oxygen and at 0% oxygen (nitrogen atmosphere); and

FIG. **10** shows the response of a stabilized enzyme emulsion containing a trace of ferrocene dissolved in 15% AP215 to varying glucose concentrations at ambient oxygen concentrations, at 5% oxygen at 2% oxygen, and at 0% oxygen (nitrogen atmosphere).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following description is provided to enable any person skilled in the art to make and use the invention and sets forth the best modes contemplated by the inventor of carrying out his invention. Various modifications, however, will remain readily apparent to those skilled in the art, since the generic principles of the present invention have been defined herein specifically to provide perfluorocarbon-containing enzymes or insolubilized enzyme emulsions for use in a miniature implantable sensor based.

The present invention is directed towards a fluorocarbon-containing enzyme suspension or emulsion. Although such an emulsion can be advantageously used in a variety of implantable electrodes, it is especially useful in a miniature implantable device described in copending applications Ser. Nos. 08/769,863 and 08/779,304, which are incorporated herein by reference.

As disclosed in the above-cited copending applications, a working implantable sensor of the glucose oxidase polarographic type can be readily constructed having a volume not much greater than a United States quarter. The overall shape of such an implantable sensor **18**, as shown in FIG. **1**, may be disc shaped although many other configurations are also possible. A case **22** contains a cavity **23** holding a printed circuit board **24** and is closed by a top **26** sealed by an O-ring **25**. The case **22** also contains a first openings **28** for a reference electrode **30** and a second opening **20** for a working electrode **10**. As shown in FIG. **2**, the working electrode **10** of the device comprises an outer shell **13** with an opening **12** through which an enzyme mixture **14** along with an underlying electrode **16** contacts the body fluids. The electrode **16** can conveniently be made from platinum although a variety of other conductive materials are also useable. A conductor **46** connects the electrode **16** with the circuit board **24**. Most of the shell **13** is filled with insulating glass or plastic **15** through which the conductor **46** passes. The enzyme mixture **14** is covered by a semipermeable membrane **19** to protect the enzymes from proteases, interfering substances, and attack by microbes and/or their oxidase destroying enzymes or other products. This membrane **19** is selected to be permeable both to glucose and to oxygen. The actual working tip of this electrode could be as small al 10 μm in diameter. Generally, the area occupied by the opening **12** is small as compared to the surface area of the device **18** constituting as little as 1% of the total surface area. Preferably, the device is implanted beneath the surface of the skin with the opening **12** facing towards the underlying layer of muscle. This position allows ready access to the unit for repair or replacement. The device can also be implanted so that the opening **12** contacts the peritoneal cavity. Generally the device is not directly in contact with the circulatory system so that formation of blood clots does not interfere with operation. All of the body tissues come into glucose equilibrium with the blood fairly rapidly so that placement of the device in contact with the blood is not really required.

Many researchers working on implantable glucose sensors may not understand or appreciate the importance of in situ sensor calibration. Both the enzyme mixture and the measuring electrode may change with time. Also, the microcirculation around the sensor may change so that the effective concentration or tension of oxygen changes. Unless the enzyme mixture response has the same slope at all possible oxygen concentrations, this could significantly change the accuracy of the glucose measurements. Many common laboratory instruments are calibrated by being exposed to analytes with known concentrations after which the instrument's output is adjusted to match the known analyte amount. Unfortunately, it is not possible to easily expose an implanted sensor to a known concentration of glucose.

However, considering that the implanted sensor is measuring a body compartment that is in equilibrium with the blood, blood glucose measurements can be used to effect calibration. If the patient or technician takes a series of blood glucose measurements over time, these can be plotted against sensor output to develop a time constant for sensor response. Thereafter, manual blood glucose measurements can be used to automatically calibrate or adjust the implanted sensor. The present inventor has also disclosed methods to use a single electrode to measure both oxygen and hydrogen peroxide (see U.S. Pat. No. 5,030,333 which is incorporated herein by reference). This provides a way to automatically adjust the sensors output where the enzyme mixture response shows a varying slope depending on oxygen concentration as well as providing knowledge of oxygen availability at the electrode.

As already mentioned, oxygen is relatively poorly soluble in biological fluids, and the membrane **19** that covers the opening **12** of the glucose sensor **10** is generally not very permeable to oxygen. However, it is also true that most of the cells of the human body require oxygen to function and in health receive an adequate supply. Although oxygen is not very soluble in biological fluids, it is highly "soluble" in the red blood cells by forming weak bonds with hemoglobin. These oxygen rich cells circulate in close proximity of virtually all of the body's cells so that the necessary oxygen can diffuse across the oxygen barrier (biological fluids and cell membranes) between the red blood cell's hemoglobin and an oxygen-requiring site such as a tissue cell.

The speed of oxygen diffusion through a barrier is controlled by the thickness of the barrier and by the amount of oxygen that can dissolve in a unit thickness of the barrier. That is, making the barrier thinner, or making the barrier dissolve more oxygen will increase the rate of oxygen diffusion. Therefore, the enzyme mixture **14** and the membrane **18** should be made as thin as feasible to maximize the rate of oxygen movement into the glucose sensor **10**.

The present inventor has taken a novel approach to increasing the solubility of oxygen in the "barrier" of the glucose sensor **10**. Various perfluorochemical liquids are widely known to dissolve relatively large amounts of oxygen. The present inventor's patents (U.S. Pat. Nos. 4,105,798; 4,110,474; 4,187,252; 4,289,499; 4,443,480; RE33,451; 5,514,720; 5,635,539; 5,684,050; 5,674,913; 5,824,703; and 5,840,767) on the use of perfluorocarbon chemicals as emulsions and blood substitutes are incorporated herein by reference. There are a very large number of suitable perfluorocarbon liquids including those described in experiments below. The list comprises, but is not limited to, perfluorooctyl bromide, perfluorodichlorooctanes, perfluorodecalin, perfluoroindane, perfluorophenanthrene, perfluorotetramethylcyclohexane, perfluoropolyalkylether oil, perfluoromethyldecalin, perfluorodimethylethylcyclohexane, perfluorodimethyldecalin, perfluorotrimethyldecalin, perfluoroisopropyldecalin, perfluoropentamethyldecalin, perfluorodiisopropyldecalin, perfluorodiethyldecalin, perfluoromethyladamantane, perfluorodimethyladamantane, perfluoro-di-xylethane (mixed isomers), and perfluoro 6,7 H-undec-6-ene. Perfluorocarbon liquids are virtually insoluble in aqueous solutions, and proteins such as glucose oxidase are completely insoluble in perfluorocarbon liquids. Besides perfluorocarbons hydrocarbon drugs (e.g., cortical steroids) silicones, silanes, cyclic silanes, siloxanes, fluorinated silicones and other similar organo-silicon compounds are excellent oxygen solvents and are useful in the present invention. Besides dissolving oxygen and acting like as an oxygen reservoir, the most preferred compounds do not dissolve hydrogen peroxide. Thus, the hydrogen peroxide concentration and the responsiveness of the sensor is effectively increased. The particles of these compounds act as stepping stones for oxygen to reach the electrode surface.

However, it is known that relatively stable emulsions can be produced using perfluorocarbon liquids and aqueous solutions. When glucose oxidase, or other hydrogen peroxide-forming enzymes, are incorporated into the aqueous phase of such an emulsion, the perfluorocarbon serves as a pathway for oxygen to reach the enzyme as well as a reservoir of available oxygen. Further, it is possible to stabilize both the emulsion and the enzyme by treating the composition with a cross-linking agent such as an aldehyde similar to glutaraldehyde to chemically cross-link proteins into a gel. Tiny perfluorocarbon droplets are then enmeshed permanently by a cross-linked protein gel. Because the vapors of these perfluorocarbons are virtually insoluble in proteins or water, they are expected to remain in place for years. When amounts of enzyme below about 20% are used, the strength of this gel can be significantly increased by incorporating a relatively high concentration of additional carrier proteins into the emulsion to provide additional sites for reaction with the crosslinking reagents. Besides the aldehyde-based crosslinking agents, such as glutaraldehyde, a number of other effective protein crosslinking agents are well known in the art including carbodiimides, pyrocarbonates (i.e., diethyl pyrocarbonate), imidoesters, N-hydroxysuccinimid esters and multifunctional epoxides (i.e., polyethylene glycol diglycidyl ether).

The present invention, then, provides a greatly improved sensor by producing a cross-linked gel containing glucose oxidase or similar hydrogen peroxide-producing enzymes, an emulsified oxygen binding/permeable material, such as a perfluorocarbon, a silicone oil, a fluorosilicone oil, an aliphatic oil or organic compound such as a steroid, to carry oxygen to the enzyme, additional gelling agents, buffers and optional additives such as other enzymes and/or preservatives. Essentially, tiny solid or liquid particles of a material that readily dissolve oxygen are held in intimate contact with an oxygen utilizing enzyme which is preferably in an insoluble form.

The action of this emulsified oxygen carrier is two-fold. On one hand it holds oxygen and brings it into intimate contact with the enzyme to accept electrons from the enzyme. Because this substance is oxygen permeable it necessarily raises the effective oxygen concentration at the electrode and allows for more rapid diffusion of oxygen from a source such as the human circulatory system. At the same time the oxygen carrier effectively lowers the glucose

level because it replaces a significant aqueous volume in which glucose is very soluble with an oxygen carrying volume in which glucose is extremely poorly soluble. That is, the glucose/oxygen ratios can be adjusted by increasing the hydrophobic oxygen carrier phase at the expense of the hydrophilic glucose-dissolving phase.

It is also contemplated that the oxygen permeable particles could comprise tiny gas bubbles (trapped bubbles as in a foam) produced by incorporating relatively high vapor pressure perfluorocarbon liquid into a protein-containing gel emulsion. Over time the perfluorocarbon would vaporize to form gas bubbles which remain trapped within the gel. These bubbles would hold a considerable supply of oxygen, and gaseous diffusion within the bubbles would be more rapid than diffusion within a liquid particle of the same size.

Following is a general method for preparation of stabilized enzyme mixtures according to the present invention. If the stabilized gel is to be based on a cross-linked protein gel, a suitable soluble carrier protein, such as an albumin, i.e., bovine serum albumin (BSA), or human serum albumin (HSA), or gelatin, at about 1 to 15% by weight final concentration is dissolved in a suitable buffer such as 0.2M sodium acetate buffer (pH 5.0), and a hydrogen peroxide producing enzyme such as glucose oxidase is dissolved in the mixture at about 1% to 5% by weight final concentration. While the examples presented use relatively low levels of glucose oxidase, embodiments using concentrations of 70% or greater glucose oxidase are also effective. At such high levels it is generally unnecessary to add albumin or other proteins to aid in gel formation.

Sufficient purified glutaraldehyde as an aqueous 2.5% solution is added to dilute the protein solution to the correct final concentration. The final glutaraldehyde concentration following dilution is preferably between 0.1 and 1% and more preferably about 0.6%. This mixture is swirled briefly to mix and is then poured onto a glass plate and spread with a glass rod. Aldehyde vapors can also be used to induce crosslinking. Within a few hours a uniform layer of enzyme gel is formed. This gel can be stored at 4° C. in a humidified atmosphere to prevent dehydration of the gel.

To incorporate an oxygen dissolving substance such as a perfluorocarbon liquid, a suitable amount of the oxygen dissolving liquid (usually between about 5% and 20% by volume) is added to the protein mixture and sonicated for two 15 second intervals while being maintained on ice. After the sonication, glutaraldehyde is added and the material is treated as above. The resulting gel may be stored in an atmosphere saturated with water and perfluorocarbon vapors to prevent evaporation of the perfluorocarbon. An alternate method of preparation is to add the active glucose utilizing enzymes to the sonicated BSA-perfluorocarbon emulsion prior to the glutaraldehyde addition to avoid possible denaturation of the enzyme during sonication.

To use the gel prepared as above a small piece is placed over a platinum electrode and covered with a piece of a Cuprophan® (brand regenerated cellulose) membrane. Altematively, the gel can be divided into numerous small particles, and a slurry of these particles can be placed on the electrode surface and covered by the membrane. An additional variation is to paint the fluorocarbon-enzyme emulsion onto a membrane before the crosslinking agent has caused the mixture to "set." FIG. **3** shows the response of an ordinary stabilized enzyme mixture electrode to a range of glucose concentrations in either ambient (about 20%) or in 5% oxygen. An enzyme mixture was prepared according to the above method and contained about 2% glucose oxidase in an about 4% BSA gel stabilized with about 0.6% glutaraldehyde. Note that an ambient oxygen trace **32** shows an approximately linear response to at least a glucose concentration of 400 mg % (0.4%). On the other hand, a 5% oxygen trace **34** plateaus above about 50 mg % glucose indicating that oxygen is limiting the reaction.

It has been discovered that the concentration of BSA relative to glucose oxidase is may be important for producing higher and/or more stable signals. However, these factors do not appear to greatly affect the glucose concentration at which a sensor plateaus because of oxygen limitation. Because an implanted glucose electrode is expected to experience low oxygen tensions, the goal is to produce electrode response that is largely oxygen independent, or that at least produces a near linear response at low oxygen tensions.

FIG. **4** illustrates the effect of adding an emulsified perfluorocarbon liquid to the stabilized enzyme mixture. The mixture in this case contains about 13% BSA, about 3% glucose oxidase and about 7.5% of emulsified Krytox® (brand of perfluoropolyalkylether synthetic oil, product of du Pont de Nemours) perfluorocarbon crosslinked with about 0.6% glutaraldehyde. The intent is for the perfluorocarbon to act as an oxygen source for the enzyme reaction. Because the perfluorocarbon is emulsified into tiny particles, there is an intimate association between the oxygen carrying perfluorocarbon and the oxygen-requiring enzyme. This limits the distance that oxygen must diffuse through a poor oxygen carrier such as water. With the perfluorocarbon acting as an oxygen source adequate enzyme response can occur even at low oxygen tensions.

In FIG. **4** the ambient oxygen trace **32**, as before, is linear to at least 400 mg % glucose. However, the 5% oxygen trace **34** is now linear to at least 100 mg % glucose. Above this glucose concentration the slope of the response changes, but the electrode continues to show increasing response to over 350 mg % glucose. The electrode even shows some response at a very low oxygen concentration of 2% oxygen as is shown in a third trace **36**.

Experiments with a large range of different perfluorocarbons have indicated that the amount as well as the type of perfluorocarbon can have a significant influence on the efficacy of the stabilized enzyme-perfluorocarbon mixture. Because the perfluorocarbon dissolves neither H_2O_2 nor H_2O_2 vapor, the response to small changes is faster. Generally, mixtures containing at least 15% by volume perfluorocarbon give better results. Also, perfluorocarbons with higher boiling points (lower vapor pressures) generally appear more effective. It is likely that there is a significant evaporative loss of lower boiling point perfluorocarbons (especially those with a boiling point below about 50° C.). This loss could significantly decrease the amount of perfluorocarbon available to act as an oxygen source/conductor.

FIG. **5** shows the results of a stabilized enzyme emulsion containing about 12% BSA, 4% glucose oxidase, 15% AP200 perfluorocarbon (mixed trimethyl and/or isopropyl perfluoro-decalins) (boiling point approximately 200° C.) crosslinked with 0.6% glutaraldehyde. In this case both the ambient oxygen trace **32** and the 5% oxygen trace **34** show relatively linear responses to above 350 mg % glucose although the slopes of the responses are somewhat different. The 2% oxygen trace **36** shows a very shallow response. These results should be compared with FIG. **6** where the enzyme emulsion contains only about 7% AP200. Note that the 5% oxygen trace **34** plateaus at about 150 mg % glucose when the lower concentration of perfluorocarbon is used.

FIG. **7** illustrates the results obtained from an emulsion similar to that of FIG. **5** except that 37% perfluorophenanthrene (AP215) (boiling point approximately 215° C.) is used in place of the AP200. The results are very similar to those of FIG. **5** indicating that there is probably little benefit to greatly increasing the quantity of perfluorocarbon beyond about 15%. As the amount of perfluorocarbon is increased, the overall signal decreases.

As mentioned above, there is some indication that there is a benefit to using an even higher boiling perfluorocarbon. FIG. **8** shows the results of a stabilized enzyme emulsion containing about 15% AP240 (mixed pentamethyl and/or diisopropyl perfluoro-decalins) perfluorocarbon (boiling point approximately 240° C.), 10% BSA, 3% glucose oxidase and 0.6% glutaraldehyde. The AP240 was emulsified with the aid of 0.75% (final concentration) Pluronics F-68 brand emulsifying agent. A number of other emulsifying agents suitable for producing stable perfluorocarbon emulsions are well known in the art and can readily is used in the present invention. In addition, 0.75% glucose was added to protect the active site of glucose oxidase during cross-linking reaction. The comparison of the ambient oxygen trace **32** with the 5% oxygen trace **34** shows that this preparation is somewhat more active than the preparation illustrated in FIG. **5**.

Inspection of Equations (1) and (2) show that the sensor indicates the rate of glucose oxidation (proportional to glucose concentration) by measuring removal of electrons from hydrogen peroxide at the electrode. When the enzyme oxidizes a molecule of glucose, an electron is removed from the glucose and accepted by a cofactor within the enzyme. Reacting with oxygen, which accepts an electron from the enzyme cofactor to produce hydrogen peroxide, regenerates the enzyme. At the surface of the electrode the electron is removed from the hydrogen peroxide thus regenerating oxygen. The electron flows through the circuit and is measured as a current. Thus, the hydrogen peroxide merely acts as an electron carrier to move electrons from glucose (by way of glucose oxidase) to the electrode.

It is also possible to use alternative electron carriers to move electrons from the reduced cofactor in glucose oxidase to the electrode surface. In theory any of a number of artificial electron carriers with the correct redox (reduction/oxidation) potential can perform the role of oxygen and hydrogen peroxide, thus rendering the entire reaction oxygen insensitive. Possible electron carriers include indophenol dyes, methyl viologen dyes, and various organometallic compounds. A presently preferred electron carrier for use with glucose oxidase is ferrocene (dicyclopentadienyliron) and its derivatives in which iron acts as the actual electron carrier. In proper formulations ferrocene can carry enough electrons from glucose oxidase to the electrode surface that the glucose oxidase reaction becomes independent of oxygen (i.e., can occur anaerobically). Ferrocene is virtually insoluble in aqueous solutions, and while ferrocene is soluble in some organic solvents, these solvents are generally not suitable for use in an implantable electrode. However, ferrocene is somewhat soluble in certain perfluorocarbons.

FIG. **9** shows the results of adding 0.4% by weight ferrocene to a stabilized enzyme mixture containing about 15% by weight BSA, 3.3% by weight glucose oxidase and about 0.6% glutaraldehyde. The ferrocene is dispersed into the buffer used to dissolve the glucose oxidase but does not appreciably dissolve therein. However, the ferrocene does affect the electrode response. Both the ambient oxygen trace **32** and the 5% oxygen trace **34** show a reasonably linear response to increasing glucose concentration, albeit at different slopes. Significantly, a 0% oxygen trace **38** (experiment performed under nitrogen) also shows some response to glucose. Thus, while the reaction is more pronounced in the presence of oxygen, the ferrocene is able to carry at least some electrons from the glucose oxidase to the electrode otherwise there would be no response at 0% oxygen.

The present inventor has discovered that ferrocene (as well as certain ferrocene derivatives) is slightly soluble in perfluorocarbon liquids. Thus, it is possible to incorporate ferrocene directly into the perfluorocarbon-enzyme emulsion. FIG. **10** shows the results of incorporating ferrocene-containing perfluorocarbon into a stabilized enzyme emulsion. Here the enzyme mixture contained about 15% AP215, 12% BSA, 4% glucose oxidase and about 0.6% glutaraldehyde as a crosslinking agent. A quantity of ferrocene (less than 1% by weight) was added to the perfluorocarbon and allowed to dissolve overnight prior to sonicating the perfluorocarbon into the remaining ingredients. Enough ferrocene dissolves into the AP215 to color the liquid a light yellow. The intent is to saturate the perfluorocarbon with ferrocene.

Significantly, the ambient oxygen trace **32**, the 5% oxygen trace **34** and the 2% oxygen trace **36** all show a linear response with surprising similar slopes. The 0% (nitrogen) trace **38** shows a much flatter response slope. This indicates that while the trace amount of ferrocene incorporated in the mixture does not carry as many electrons as does hydrogen peroxide, the perfluorocarbon plus ferrocene shows an unexpected synergistic activity superior to either ferrocene or perfluorocarbon alone. In some unknown way the ferrocene potentiates the effect of the emulsified perfluorocarbon particles.

The perfluorocarbon-insoluble enzyme mixtures of the present invention also permit other modifications that enhance the long-term stability and useful life of the implanted sensors. As mentioned above, premature failure of implanted electrodes has been attributed to free radical or oxidative damage to the enzyme. Therefore, addition of antioxidants or free radical trapping agents such as Vitamin E (tochopherols) can extend electrode life. Another problem that has troubled other research on implanted sensors is rejection of or immune reaction to the implant. As mentioned above, a fibroblast capsule often develops around an implant. This is, per se, not harmful, but the body may also mount a direct immune attack on the measuring membrane **19**. This results in inflammation and proliferation of a large population of leukocytes in the vicinity of the membrane **19**. Proliferating leukocytes can result in the release of "killing oxygen" wherein oxidative damage to the stabilized enzyme can occur. These white cells may consume considerable amounts of oxygen with their own respiration.

Even though the device of the present invention is preferably implanted at a site away from direct blood circulation to avoid problems caused by formation of blood clots, leukocytes can migrate out of the circulatory system to congregate around any "foreign" body. This leukocyte accumulation may damage the membrane and/or compromise the accuracy of the glucose readings. However, this problem can be largely avoided by incorporating an effective amount of an anti-inflammatory, anti-leukocyte compound into the enzyme mixture. One example is the addition of hydrocortisone, or similar cortical steroids such as cortisone and prednisone, at about 0.1 to 1.0% by weight. These steroids gradually dissolve in the aqueous phase of the enzyme mixture and very slowly diffuse out through the

membrane 18 to keep the surrounding area free from attack by leukocytes (especially by macrophages). An advantage is that steroids, like perfluorocarbons, are much better at dissolving oxygen than is water.

In a series of experimental implants of titanium devices, similar to those of FIG. **1**, in rats it was found that devices in which the enzyme mixture contained cortical steroids showed no evidence of inflammation. On the other hand, identical devices lacking cortical steroids showed significant evidence of inflammatory response when removed from the animals after six weeks.

Other non-steroidal anti-inflammatory drugs (i.e., aspirin, ibuprofen, naproxyn, ketoprofen and the like) or anti-inflammatory lymphokines or "anti-rejection" drugs (e.g., cyclosporine) may also be advantageously incorporated into the enzyme mixture. In addition, drugs that impede cell replication (e.g., "antineoplastic" agents) often have an advantageous effect in reducing inflammation and excess tissue proliferation. Useful agents include vinca alkaloids (vincristine and vinblastine), taxol derivatives and other well-known anti-tumor drugs.

Another serious impediment to long-term sensor implants is that of microbial contamination by bacteria and fingi, etc. While microbes may directly destroy the glucose-metabolizing enzyme, it is also likely for them to disrupt the glucose measurement by consuming glucose and oxygen or by producing catalase or peroxidase or other enzymes that consume the hydrogen peroxide before it can react with the electrode surface. The present inventor has found that the incorporation of antifungals or wide spectrum antibiotics into the enzyme mixture largely prevents microbial interference. For example, gentamycin and/or penicillin, and/or other broad-spectm antibiotics and antifungals (e.g., ketaconazole) can be incorporated into the enzyme mixture to prevent microbial growth. A relatively large concentration of antibiotic can be added so that sterility of the enzyme mixture is guaranteed for a long period of time. Slow diffusion of the antibiotic through the membrane keeps the entire area around the implanted sensor free of infection. Further, the electrode constantly produces hydrogen peroxide which is a powerful anti-infective agent.

The semipermeable membrane **19** is generally believed to protect the glucose oxidase from various proteases. However, in the experiments leading to the present invention, it was discovered that stabilized glucose oxidase is not readily attacked by a common proteolytic enzyme, trypsin. Apparently the chemical cross-linking that stabilizes the enzyme destroys the trypsin sensitive sites. Therefore, trypsin may be incorporated as an anti-proteolytic enzyme to help destroy other proteolytic enzymes that might be produced by microorganisms, etc.

Stability of the enzyme mixture of the present invention can also be improved by the addition of antioxidants and/or free radical trapping agents. Vitamin E, lycopene, and carotene which are also oxygen solvents, can be incorporated into the enzyme mixture as can any of a number of "preservatives" such as various parabens, BHT (butylated hydroxy-toluene) and its analogs, and/or superoxide dismutases. Further angiogenic factors can be added to ensure capillary growth and blood circulation near the sensor. Addition of an enzyme system to generate nitric oxide from arginine can be used to monitor microcirculation near the sensor. That is, arginine is injected into the patient's circulation, and a nitric oxide response by the sensor is indicative of adequate microcirculation.

In addition to the equivalents of the claimed elements, obvious substitutions now or later known to one with ordinary skill in the art are defined to be within the scope of the defined elements. The claims are thus to be understood to include what is specifically illustrated and described above, what is conceptually equivalent, what can be obviously substituted and also what essentially incorporates the essential idea of the invention. Those skilled in the art will appreciate that various adaptations and modifications of the just-described preferred embodiment can be configured without departing from the scope and spirit of the invention. The illustrated embodiment has been set forth only for the purposes of example and that should not be taken as limiting the invention. Therefore, it is to be understood that, within the scope of the appended claims, the invention may be practiced other than as specifically described herein.

I claim:

1. An implantable sensor for sensing a concentration of an organic substrate, the sensor comprising:

a conductive electrode; and

a stabilized enzyme emulsion in contact with the electrode, the enzyme emulsion comprising:

an oxidase enzyme that quantitatively oxidizes the organic substrate;

a water immiscible oxygen dissolving substance emulsified into intimate contact with the enzyme to provide oxygen; and

a protein crosslinking agent to crosslink and insolubilize the enzyme forming a stabilized gel comprising crosslinked protein and particles of said oxygen dissolving substance.

2. The implantable sensor of claim **1** further comprising a semipermeable membrane covering the electrode with the enzyme emulsion sandwiched between the membrane and the electrode.

3. The implantable sensor of claim **1**, wherein the enzyme emulsion also contains an additional carrier protein.

4. The implantable sensor of claim **3**, wherein the additional carrier protein is selected from the group consisting of serum albumin and, gelatin.

5. The implantable sensor of claim **1**, wherein the oxygen dissolving substance is selected from the group consisting of perfluorocarbons, silicone oils, fluorosilicone oils, aromatic and aliphatic hydrocarbon oils or solids, carotenoids and steroids.

6. The implantable sensor of claim **5**, wherein the oxygen dissolving substance is a perfluorocarbon liquid selected from the group consisting of perfluorooctyl bromide, perfluorodichlorooctane, perfluorodecalin, perfluoroindane, perfluorophenanthrene, perfluorotetramethylcyclohexane, perfluoropolyalkylether oil, perfluoromethyldecalin, perfluorodimethylethylcyclohexane, perfluorodimethyldecalin, perfluorotrimethyldecalin, perfluoroisopropyldecalin, perfluoropentamethyldecalin, perfluorodiisopropyl decalin, perfluorodiethyldecalin, perfluoromethyladamantane, perfluorodimethyladamantane, perfluoro-di-xylethane, and perfluoro-6,7 H-undec-6-ene.

7. The implantable sensor of claim **1**, wherein the crosslinking agent is selected from the group consisting of aldehydes, carbodiimides, imidoesters, pyrocarbonates, epoxides and N-hydroxysuccinimid esters.

8. The implantable sensor of claim **1**, wherein the oxidase enzyme is selected from the group consisting of cholesterol oxidase, amino acid oxidase, alcohol oxidase, lactic acid oxidase, oxygen oxidoreductase, galactose oxidase, and glucose oxidase.

9. The implantable glucose sensor of claim **1** further comprising an electron transport compound dissolved in the water immiscible oxygen dissolving substance.

10. The implantable glucose sensor of claim **9**, wherein the electron transport compound comprises ferrocene.

11. The implantable sensor of claim **1**, wherein the enzyme emulsion further comprises an antioxidant.

12. The implantable sensor of claim **1**, wherein the enzyme emulsion further comprises an antimicrobial agent.

13. The implantable sensor of claim **1**, wherein the enzyme emulsion further comprises an anti-inflammatory agent selected from the group consisting of steroids, lymphokines, and non-steroidal anti-inflammatory drugs.

14. An implantable glucose sensor for sensing a concentration of glucose, the sensor comprising:

a metal electrode; and

a stabilized enzyme emulsion in contact with the electrode, the enzyme emulsion comprising:

a solution of glucose oxidase protein for oxidizing glucose to quantitatively produce hydrogen peroxide;

a perfluorocarbon liquid emulsified with the glucose oxidase; and

a crosslinking agent to crosslink covalently said protein to form a stabilized gel comprising crosslinked protein and particles of the perfluorocarbon liquid.

15. The implantable glucose sensor of claim **14** further comprising a semipermeable membrane covering the electrode with the enzyme emulsion in contact with a first surface of the membrane and sandwiched between the membrane and the electrode and with body fluids or cells in contact with a second surface of the semi-permeable membrane.

16. The implantable sensor of claim **14**, wherein the oxygen dissolving substance is a perfluorocarbon liquid selected from the group consisting of perfluorooctyl bromide, perfluorodichlorooctane, perfluorodecalin, perfluoroindane, perfluorophenanthrene, perfluorotetramethylcyclohexane, perfluoropolyalkylether oil, perfluoromethyldecalin, perfluorodimethylethylcyclohexane, perfluorodimethyldecalin, perfluorotrimethyldecalin, perfluoroisopropyldecalin, perfluoropentamethyldecalin, perfluorodiisopropyl decalin, perfluorodiethyldecalin, perfluoromethyladamantane, perfluorodimethyladamantane, perfluoro-di-xylethane, and perfluoro-6,7 H-undec-6-ene.

17. The implantable glucose sensor of claim **14** further comprising an electron transport compound dissolved in the perflurocarbon liquid.

18. The implantable glucose sensor of claim **17**, wherein the electron transport compound comprises ferrocene.

* * * * *

CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitations of Fed. Cir. R. 32(a). This brief contains 10,494 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Fed. Cir. R. 32(b). This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in fourteen (14) point Times New Roman font.

Dated: April 27, 2020

/s/ *Timothy E. Grochocinski*
Timothy E. Grochocinski
Counsel for Plaintiff-Appellant
Arbmetrics, LLC

CERTIFICATE OF SERVICE

The undersigned hereby certifies that on May 11, 2020, an electronic copy of the Brief of Appellant was filed with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the CM/ECF system. The undersigned also certifies that all participants in this case are registered CM/ECF users and that service of the Brief will be accomplished by the CM/ECF system.

/s/ *Timothy E. Grochocinski*
Timothy E. Grochocinski