(54) Title: ENCAPSULATED GENETICALLY PROGRAMMED LIVING ORGANISMS PRODUCING THERAPEUTIC SUBSTANCES

A device consisting of genetically programmed organisms enclosed in a variety of membraneous structures to form a therapeutic capsule. This capsule, when administered to a human subject, produces therapeutic agents and may either remain intact until excreted or removed or may dissolve its wall, thereby allowing the enclosed organisms to colonize the desired areas and in turn produce the therapeutic agents.
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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ENCAPSULATED GENETICALLY PROGRAMMED
LIVING ORGANISMS PRODUCING
THERAPEUTIC SUBSTANCES

Background of the Invention

A. Field of the Invention

The invention relates to therapeutic agents for internal administration to an animal body such as a human and to methods of their manufacture and administration.

B. Prior Art

Internally administered therapeutic agents usually encompass drugs and other non-living materials which are ingested by a user, or implanted or inserted in the user for therapeutic purposes. They are delivered to the body of the user in a variety of ways, such as in the form of capsules for oral administration or by insertion as suppositories, or in the form of liquids for oral administration or injection, among other techniques. Also, living organisms have been administered by injection e.g., small pox, vaccination, or by the oral route in the form of liquid droplets e.g., Sabin polio immunization. These agents are prepared by a variety of manufacturing processes, and are stored until their administration to the end user.

Presently, through techniques of genetic engineering, living organisms can be genetically programmed to produce therapeutic substances such as interferon, antibiotics, and insulin. These programmed organisms are subjected to a complex fermentation, extraction, and purification process.
before the therapeutic substance is administered to
the patient. Moreover, since there is uncertainty
about the potential pathogenicity of genetically
altered organisms (viruses, bacteria, or yeast for
example), elaborate safeguards have been enforced to
prevent these altered organisms from contacting or
"infecting" people. However, by deliberately
selecting non-pathogenic organisms for genetic
manipulation, or other organisms with finite
longevity, the safety precautions have been able to be
relaxed as contamination fears have lessened.

Description of the Invention

A. Objects of the Invention

Accordingly, it is an object of the invention
to provide an improved mechanism for administering
selected therapeutic agents derived from genetically
altered organism to an animal body.

Further, it is an object of my invention to
provide an improved method of generating therapeutic
agents derived from genetically altered organisms for
administration to an animal body.

B. Detailed Description of the Invention

In accordance with the invention genetically
programmed organisms which produce the desired
therapeutic agents to be administered to an animal
body such as a human are prepared in situ and enclosed
within a protective membrane providing mechanical
confinement to the organisms while they are being
administered to the animal body. The membrane may
include an inner layer containing material providing
sustenance to the enclosed bacteria for at least the
time they are outside the human body, or a nutrient material may be included in the organism section of the chamber itself. Alternatively, a microporous membrane that contains the organisms but allows passage of nutrients from a nutrient source or culture medium may be employed. The membrane and its contents (hereinafter referred to collectively as a "capsule") may be orally ingested by the human, or may be inserted as a suppository or otherwise implanted within the body. The capsule may either remain intact, exchanging its therapeutic product for nutrients until removed or excreted, or may dissolve, allowing the therapeutic organisms to colonize the target areas releasing their therapeutic products there.

In the case of bacteria, a genetically altered strain is preselected that itself produces the therapeutic agent which is to be utilized by the body. For example, altered bacteria of the type *E. Coli* produce insulin which is used to treat diseases such as diabetes. In one embodiment of my invention, the membrane dissolves within the body to a sufficient extent to release the enclosed bacteria. The bacteria then operate, within the body environment, to produce the selected therapeutic agent [e.g., insulin]. The number of bacteria are, of course, proportioned to the desired dosage of agent to be administered to the body, taking into consideration the type of bacteria, the specific portion of the body in which they were lodged, and their expected lifetime and productivity time within that body portion.

In an alternative embodiment, the therapeutic agent is generated by the bacteria within the membrane and is transferred across the membrane walls by
diffusion, the bacteria remaining within the membrane. In this embodiment, the effective pore size of the membrane is such that the bacteria are prevented from transfer across the membrane wall, while the therapeutic agent which they produce passes relatively freely across this membrane and into the body in exchange for nutrients.

In a further embodiment of the invention, a double-walled membrane is used, the bacteria being enclosed within a first or inner wall, and a layer of material providing nourishing sustenance to the bacteria being enclosed between the first wall and a second or outer wall. In this embodiment, as with the previously-described embodiments, the membrane walls may be such as to be dissolvable when ingested or inserted into the body, or may be such that the walls are relatively resistant to degradation within the body but allow passage of therapeutic products generated by the bacteria into the body. Moreover, in the case of dissolvable capsules, they may be modified to dissolve under optimal conditions for specific locality colonization and as such may be acid resistant and more soluble in an alkaline environment for intestinal colonization, or by other physical or chemical modifications designed to enhance successful colonization in their desired area. Furthermore, the capsules may be stored at cold or freezing temperatures to retard bacterial growth until administration.

The foregoing and other and further objects and features of this invention will be more readily understood on reference to the accompanying drawings showing an insertable capsule in accordance with the present invention in which:
Detailed Description of the Invention

Fig. 1 is a cross-sectional view of a therapeutic device having a single membrane wall enclosing selective therapeutic organisms on the interior thereof; and

Fig. 2 is a cross-sectional view of a therapeutic device in accordance with the invention having dual a membraneous wall enclosing the organisms.

In Fig. 1, a therapeutic device in the form of a capsule comprises a membraneous wall 10 enclosing, on the interior thereof, selected organisms 12 for manufacture of therapeutic agents to be internally administered to a human body. Wall 10 may comprise a material such as gelatin which is essentially impermeable both to the organism and to the therapeutic agents formed thereby, but which is broken down by the body on ingestion or insertion of the device into it or, alternatively, may comprise a material such as a microporous membrane which has a pore size sufficient to allow passage of the therapeutic agents formed by the organisms through the membrane wall and into the body on ingestion or insertion therein, while blocking escape of the organism therethrough, and which is relatively inert to degradation by the body when ingested or inserted. In the first case, the therapeutic agent is formed within the body largely outside the membraneous wall, while in the second case the therapeutic agent is formed within the membraneous enclosure.

Turning now to Fig. 2, a further alternative version of my invention is shown. A first or inner membraneous wall 20 encloses organisms 22 therein. A second or outer membraneous wall 24 encloses a layer
of nutrient 26 which provides sustenance to the
organism. Alternatively, the inner and outer chamber
may be reversed. This embodiment of the invention is
expected to be useful in cases where extended periods
of time are expected to elapse between the preparation
of the device and its ultimate utilization. As was
the case with the embodiments of Fig. 1, the
membranous walls 20 and 24 may be selected to allow
escape of the enclosed organism 22 into the body
following ingestion or insertion, or may be resistant
to degradation by the body but sufficiently permeable
to the organism that the therapeutic agent generated
by the organism escape through these walls, and
through the nutrient layer 26. In the latter case,
the layer 26 may also, in addition to, or instead of,
providing nutrient to the organism 22, provide an
absorptive layer which selectively absorbs
constituents generated by the organism which it is
desired to preclude from passage into the body.

Conclusion

From the foregoing it will be seen that I have
provided an improved therapeutic device incorporating
live genetically programmed organisms producing
therapeutic agents to a body such as a human body. In
some cases, a single dosage will be sufficient to
produce a desired agent for extended periods of time.
Alternatively, the removal of an intact capsule or
the administration of the appropriate antibiotic in
the case of the colonized alternative will discontinue
the administration of the therapeutic agent.
Moreover, complex and costly manufacturing steps
including fermentation, extraction, and purification
may be avoided altogether. This device also avoids
many of the problems associated with degradation of therapeutic agent during shipment or storage. It accommodates itself to generation and administration of a variety of therapeutic agents, and is expected to be simple, yet effective in use.

Having illustrated and described my invention, I claim:
1. A therapeutic device for insertion into an animal body comprising genetically altered living organisms enclosed within a membraneous wall.

2. A therapeutic device according to claim 1 in which said wall is formed of a material selected to degrade in the body to thereby discharge the enclosed genetically altered living organisms into said body.

3. A therapeutic device according to claim 1 in which said wall is formed of a material that is relatively inert to degradation by said body on insertion therein and has a permeability sufficient to confine said organisms while facilitating the passage therethrough of therapeutic agents generated by said organisms.

4. A therapeutic device according to claim 1 including a second membraneous wall surrounding said first wall and forming therewith a chamber enclosing a nutrient material for said organisms.

5. A therapeutic device according to claim 1 including a second membraneous wall surrounding said first wall and forming therewith a chamber enclosing a filtration layer for blocking the passage of selected products of said organisms while facilitating the passage of products forming therapeutic agents.

6. A therapeutic device for administration to a human for treatment of a disease, comprising genetically altered living organisms for producing a therapeutic agent specific to said disease and a wall confining said organisms at least until ingestion or insertion of the device into a human.
7. A therapeutic device according to claim 6 in which said wall comprises a membrane permeable to said therapeutic agent for passage of said agent therethrough while said device is within the human body.

8. A therapeutic device according to claim 6 in which said wall comprises a material degradable by the human body after ingestion or insertion therein to release the enclosed organisms.

9. A method of treating a human for a specific illness, comprising administering to said human genetically altered living organisms selected to produce a therapeutic agent specific to the illness for relief thereof, said agent being enclosed within a wall preventing release of said organisms prior to administration to the human and allowing passage of at least the organism-produced therapeutic agent therethrough within the human body after administration thereto.
INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 3
According to International Patent Classification (IPC) or to both National Classification and IPC 3
A61K 9/48, 9/50, 35/68, 39/02

II. FIELDS SEARCHED

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<td>424/19, 38, 93</td>
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Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 4

III. DOCUMENTS CONSIDERED TO BE RELEVANT 14

<table>
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<tr>
<th>Category</th>
<th>Citation of Document, 16 with indication, where appropriate, of the relevant passages 17</th>
<th>Relevant to Claim No. 18</th>
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<td>Y US, A, 4,235,871, published 25 November 1980 Papahadjopoulos et al., see column 6, line 40+, column 13, line 52+.</td>
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<td>Y US, A, 4,322,790, published 1 June 1982 Sozzi et al.</td>
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<tr>
<td>X US, A, 3,823,228, published 9 July 1974 Ferris et al.</td>
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* Special categories of cited documents: 16
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"F" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search 2
7 December 1983

Date of Mailing of this International Search Report 2
13 Dec 1983

International Searching Authority 1
ISA/US

Signature of Authorized Officer 19
[Signature]

Form PCT/ISA/210 (second sheet) (October 1981)