June 18, 1963 G. P. W. JORDAN 3,093,831

ARTIFICIAL GLAND

Filed Oct. 22, 1959

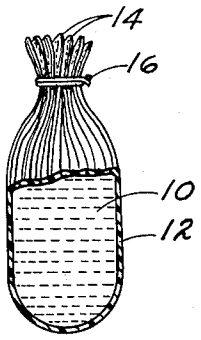

Fig. 1

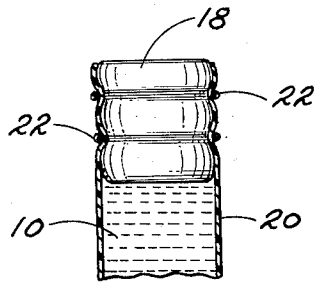

Fig. 2

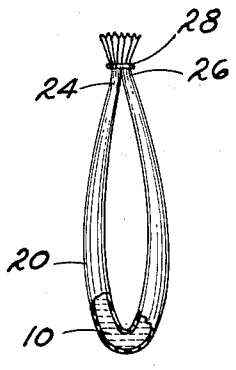

Fig. 3

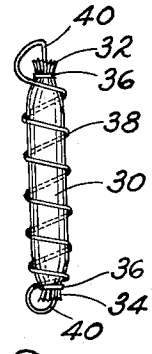

Fig. 4

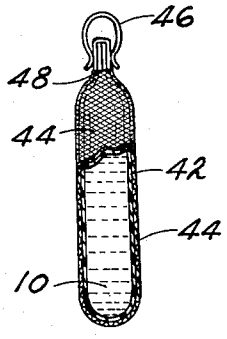

Fig. 5

INVENTOR.
GERHARD JORDAN

BY
RICHEY, McNENNY & FARRINGTON
H. F. McNenny
ATTORNEYS

United States Patent Office 3,093,831 Patented June 18, 1963

3,093,831

ARTIFICIAL GLAND

Gerhard Paul Wilhelm Jordan, San Francisco, Calif. (% Downtown Medical Center, 450 Clarkson Ave., Brooklyn 3, N.Y.)

Filed Oct. 22, 1959, Ser. No. 847,994
7 Claims. (Cl. 3—1)

This invention relates to hormone producing glands, and more particularly to a gland structure for hormone producing glands for implantation into the body of a human being or other animal.

It is well known that many diseases of the body are caused by a deficient supply of certain hormones produced by the endocrine or ductless glands. The endocrine glands are usually considered to include the thyroid, parathyroids, pituitary, adrenal, pancreas, and the gonads. These glands are called ductless glands because they secrete their hormones directly into the bloodstream through the same blood vessels which supply the nutrients to the gland. Deficiencies of these hormones are usually treated by periodic administration of the deficient hormones in a dosage determined by the extent of the deficiency. The hormones which are administered are obtained either naturally by extractions from the appropriate glands of slaughtered animals, or in some cases they are manufactured directly by synthesis. While a few of these hormones, such as thyroid extract, may be administered orally, most of these hormones are destroyed in the intestinal tract if given orally, and therefore must be administered by injection.

There are several disadvantages in administering the hormones in doses given at periodic intervals. Such administration results in the total hormone supply in the body being uneven in quantity, since it is highest directly after the administration of the hormone and decreases thereafter as the dose administered is consumed. Furthermore, because such hormones are rapidly consumed and cannot be stored in the body, the injections must be repeated continually at regular intervals.

Efforts have been made to lengthen the time required between injections by making an injection of a very large quantity of the hormone in such a manner that it is temporarily stored at the place in the body where it was injected and thereafter is released into the bloodstream in a gradual and continuous manner. Injections of these types have been called hormone deposits, or depot injections. An example of such a preparation is testosterone propionate in sesame oil, and depot-insulin. Deposits have also been made in certain cases by implanting the hormones in crystalline form directly within the body so that they are gradually dissolved. However, among other disadvantages with these methods of deposit, when the hormone is dissolved in an oil or wax to lengthen the time of absorption, with certain persons an allergic reaction may exist or may develop to the oil or wax medium. In addition, this method results in a decreasing supply as time passes and some of the hormone is assimilated, since the oil or wax medium remains constant in quantity while the decreasing amount of hormone present results in a lower concentration and hence a lower rate of assimilation.

The present invention allows deficient hormones to be supplied continually to the body at a rate which can be controlled through the action of the body metabolism and does not require continual injections or implants to maintain the hormone supply. Briefly stated, this is accomplished by enclosing live hormone producing gland tissue within a container having a wall of a semipermeable membrane. The container and gland tissue are then implanted into the body in a manner so as to be in contact with the bloodstream. In this way, the implanted

gland takes over the function of the natural gland and creates the corresponding hormone. The hormone that is produced by the gland passes out through the semipermeable membrane into the bloodstream, while nutrients for the gland tissue pass from the bloodstream through the semipermeable membrane to the gland tissue. Since this exchange of hormones and nutrients takes place in both directions through the membrane, the body itself regulates the course of the hormone production by the inter-relationship with the other hormones in the same manner as is done with the body's own natural gland.

It is well known that if gland tissue taken either from some other animal or a human being, not the identical twin of that person, is implanted into the body of a person, the gland tissue will quickly die because of the antigen-antibody reaction between the tissue of the gland and the body of the host. This reaction blocks up the surfaces of the implanted foreign cells which will then die from lack of their essential nutrients. The semipermeable membrane in the present invention is permeable insofar as the hormones and nutrients are concerned, but is impermeable to the much larger antigens and antibodies which are unable to pass through the membrane to interact with each other.

Additional advantages of this invention will become apparent upon reading the following detailed description of the invention of which several embodiments are shown in the accompanying drawings.

In the drawings:

FIGURE 1 is an elevational view partially in section of one construction for the gland in the form of a bag or sack closed by binding;

FIGURE 2 is a fragmentary view in section of a gland structure similar to that of FIGURE 1, but in which the end is closed by a stopper;

FIGURE 3 is an elevational view partly in section of another embodiment of the gland structure in which the container is formed by bending a tube and tying both ends together;

FIGURE 4 is an elevational view of a gland structure enclosed by a protective winding; and

FIGURE 5 is an elevational view partly in section of a gland structure similar to that shown in FIGURE 1, but having another form of protective covering and having the end closed by a metal clip.

The gland structure shown in FIGURE 1 has the specific gland tissue 10 enclosed within a suitable container, here in the form of a bag or sack 12 which is gathered together at the open end 14 which is closed and sealed by means of binding and tying with a suitable cord or filament 16. The closure made by the cord or filament 16 must be extremely tight, so as not to allow any spaces which would be greater in size than the pores or passages of the container, as will be described in greater detail hereinafter.

The gland tissue 10 may be any particular gland tissue which will secrete the desired hormone. The tissue may be of the particular gland taken from an animal or another human being, in the form of a minced glandular tissue, or of a pure culture of cell strains with normal hormone production. The gland tissue may also be made of cell strains which have a different metabolism caused by a modification or mutation such as cancer.

The sack or bag 12 may consist entirely of a semipermeable membrane, or alternatively, it may consist of a semipermeable membrane which is coated onto a rather coarsely porous material having greater structural strength than the membrane alone could possess. The nature of this semipermeable membrane is such that it has pores or passages of a diameter which allows the passage of particles with a maximum molecular weight of about 10,000 to 15,000, but prevents passage of particles having a

greater molecular weight. Pores of this size allow free passage of the steroid hormones, which have a molecular weight in the vicinity of 300, and of nutrient materials and hormones of more complex molecular structure such as insulin, which has a molecular weight of about 6,400. On the other hand, pores of this size are impervious to the complex protein molecules of antibodies, which generally have a molecular weight in the range of 160,000 to 180,000. A semipermeable membrane meeting these requirements may have a thickness on the order of 50 microns and a maximum pore size of about five millimicrons. It should also be noted that the membrane must be made of a material which is non-toxic, non-reactive, and insoluble in the bloodstream. The nature of the materials for such a membrane as well as a method of making it are set forth in greater detail hereinafter.

Because all parts of the glandular tissue must be able to receive nutrients, and the hormones produced by such cells must be carried away, it is necessary that the container for the tissue be limited in certain dimensions. This dimension limitation results from the requirement that the length of the shortest diffusion path between the interior side of the container wall and the center of the glandular tissue must not be longer on the average than two millimeters. Therefore, it is desirable that the container be tubular in form with a diameter of 4 millimeters or less. The small diffusion can be reached within a tube of a larger diameter than 4 millimeters by the introduction of a spring similar to a serpentine which expands within the tube and gives it an oval cross section. Inasmuch as the amount of tissue depends upon the nature of the tissue cells and the quantity of hormone which must be produced, the size of the gland structure must vary as required. Since there is a maximum size limit on the diameter, in some cases the quantity of gland tissue therefore requires the container to be in the form of a tubular semipermeable membrane of considerable length. The ends of the tube may be closed by a suitable stopper **18** as shown in FIGURE 2, the stopper being inserted within the end of a tube **20** and held in place by means of a binding **22**. If the necessary tube length becomes excessively long, the tube may be bent back upon itself, as shown in FIGURE 3, and both ends **24** and **26** tied together by a filament of plastic or wire **28**.

It is intended that a gland structure made under the teachings of this invention should have a useful life of at least several years in the body, and it is therefore necessary that the gland structure be protected against mechanical strains which would damage the gland cells or rupture the container and expose the gland cells to the antibodies of the host's bloodstream. This necessary protection can be accomplished by the choice of the place of the implantation, such as in the bone marrow, or by providing the gland structure with a shield of the necessary mechanical strength. One embodiment of such a shield is shown in FIGURE 4 wherein the container is shown in the form of a tube **30** having semipermeable walls and which is closed at each of the ends **32** and **34** by means of binding filaments or wires **36**. A rigid filament **38** is wound helically about the length of the tube and has the ends **40** bent over and inserted into those portions of the tube ends which extend beyond the bindings **36**.

An alternative method of protection is shown in FIGURE 5 in which the semipermeable membrane **42** is enclosed within an open mesh sack or bag **44**. This figure also shows another alternative method of closing the end of the sack or tube, in this case by means of a **C**-clip **46** which grips on a flexible plastic shield **48** covering the gathered end of the sack to prevent cutting or tearing of the sack. It is most important that the protective shielding not impair the diffusion of fluid between the gland and the body of the host.

In order to permit ready detection of the implanted gland in case it should be necessary to remove or replace it, it is desirable that the gland structure be furnished with a material that is visible under X-ray examination. This is most readily done by making any of the various bindings **16**, **22**, **28**, and **38** out of a metal which is highly opaque to X-rays. Alternatively, the **C**-clip **46** can be made of such a metal, in which case the size of the clip is advantageous inasmuch as it results in a larger opaque area than would be possible with a wire. Of course it is necessary that the metal used be inert to chemical reaction with the body and non-toxic.

As has been stated before, the semipermeable membrane must have a certain minimum mechanical strength and have pores of such a size that molecules of a weight of 10,000 to 15,000 may pass through, but molecules having a larger molecular weight find the membrane to be impermeable. Such membranes may consist of such materials as celluloses, cellulose hydrate or any of the various cellulose esters such as cellulose nitrate and cellulose acetate, although other plastic materials may be used. One method of preparing such a membrane is to dissolve cellulose nitrate or collodion in an ether-alcohol solvent and form a film by spreading the dissolved material onto a mercury pool or glass plate. The solvent is then allowed to evaporate until the film reaches the gel stage, after which it is removed from the mercury pool or glass plate and placed in water where the ether and alcohol are free to diffuse out into the water to leave pores of the necessary size in the cellulose nitrate film.

In some cases it may be desirable that the semipermeable membrane should have pores which are larger than those pores which allow the passage of molecules with the molecular weight of 10,000 to 15,000 because the actual size of the pores can be reduced by such means as the precipitation of antigens and antibodies as well as by adhesions to the membrane caused particularly by proteins or by electrostatic forces.

Although several forms of the invention have been shown in the drawings and described above, it is understood that many other modifications and embodiments can be produced within the scope of the invention. Other structural forms than those shown may be used to provide the container for the gland tissue providing it has a semipermeable membrane of the properties described. In addition, other materials may be used for the semipermeable membrane so long as they have a pore size which allows free passage of the hormones and nutrients, but prevents passage of antigens and antibodies. These and other modifications and arrangements will be within the scope of the invention which is defined by the following claims.

Having thus described my invention, I claim:

1. An implantable gland comprising living hormone-producing tissue completely enclosed in a container, at least a portion of the walls of said container being formed of a semipermeable membrane having pores extending therethrough with a maximum pore size of about 5 millimicrons.

2. An implantable gland comprising living hormone-producing tissue completely enclosed by a flexible semipermeable membrane having pores allowing passage of hormones and nutrients having a molecular weight less than 15,000 but impermeable to antigens and antibodies having a molecular weight greater than 15,000, said pores having a maximum dimension of about 5 millimicrons, said tissue being distributed within said membrane so that the minimum diffusion path between any cell of said tissue and said membrane is less than 2 millimeters.

3. An implantable gland comprising living hormone-producing tissue completely enclosed in a container, said container being formed of a flexible semipermeable membrane having pores of a maximum size of about 5 millimicrons, and a self-sustaining permeable protective shield extending over the outside of said container.

4. An implantable gland as set forth in claim 3 wherein said shield comprises a filament wound helically about the body of said container.

5. An implantable gland as set forth in claim 3 wherein said shield comprises a web of mesh material extending over the outer surface of said container.

6. An implantable gland comprising living hormone-producing tissue completely enclosed in a container, at least a portion of the walls of said container being formed of a semipermeable membrane, said semipermeable membrane having pores with a maximum size of about 5 millimicrons and being made from a material selected from the group consisting of cellulose, cellulose hydrate, and cellulose esters.

7. An implantable gland comprising living hormone-producing tissue completely enclosed in a container, at least a portion of the walls of said container being formed of a semipermeable membrane having pores of a maximum size of about 5 millimicrons, said tissue being distributed within said container so that the minimum diffusion path between any cell of said tissue and said semipermeable membrane is less than two millimeters in length.

References Cited in the file of this patent

UNITED STATES PATENTS

2,517,513	Vaernet	Aug. 1, 1950
2,658,021	Earle et al.	Nov. 3, 1953
2,734,015	Wettstein et al.	Feb. 7, 1956