ABSTRACT
A method of, and apparatus for necrosing human tissue cells are described in which an expandable bladder filled with a fluid at a cryogenic temperature is used to subject the entire area of tissue in contact with the bladder to temperatures sufficiently low to cause coagulation necrosis, whereby the entire contacted area of tissue is simultaneously necrosed. As an example, this apparatus can be utilized to cause sterilization by necrosis of the entire functional endometrial layer of the uterus of a human female.

2 Claims, 12 Drawing Figures
CYROGENIC BLADDER FOR NECROSING TISSUE CELLS

DEFINITIONS

The following terms are used herein as having the meanings given below:

"Necrosis" means the death of the cells in a tissue.

"Functional lining" of the uterus is that portion of the inner lining of the uterus, the endometrium, to which an embryo might attach. It excludes the portions of the uterine inner lining forming the cervix, to which the embryo usually does not attach.

"Cryogenic" as an adjective is used to refer to temperatures sufficiently low to cause cell necrosis.

BACKGROUND OF THE INVENTION

The use of instruments at extremely low or cryogenic temperatures to treat the human body is referred to as "cryosurgery" within the medical profession. In cryosurgery, an instrument cooled to a very low temperature is brought into contact with body tissue and the contiguous or adjacent cells are destroyed by the cryogenic temperature, a result known also as coagulation necrosis. The destruction of a cell is usually effected by the formation of ice within a cell, which is sufficient to kill or irreversibly damage it. It can normally withstand ice formation outside the cell wall; to destroy the cell, ice must be formed inside the cell membrane.

A human cell contains both salt, most abundantly sodium chloride, and water. As the external environment of the cell is cooled, a cell protective mechanism operates to resist internal freezing of the cell. Water is expelled from within the cell through the cell membrane. The expelled water may freeze without permanent damage to the cell, but this protective mechanism results in increasing the saline concentration within the cell, lowering its freezing point and rendering it more difficult to destroy with low temperatures. This process continues, with external ice formation, until the eutectic temperature of the sodium chloride, $-21.2^\circ$C, is reached. At this temperature ice is formed within the cell and it is effectively destroyed.

Therefore, in light of the above, cryogenic destruction of a cell, or of the tissue which is formed of the cells, requires either (a) bringing the interior of the cell to a point below the eutectic temperature of sodium chloride or (b) reducing the cell temperature very quickly so that the cell protective mechanism cannot cope with the temperature change and the cell does not have time to expel sufficient water through the membrane to render its interior solution freeze resistant. In cryogenic necrosis then, the variables are the absolute temperature to which a cell is brought, the rapidity of cell temperature change, and also, not discussed above and imperfectly characterized as yet, the length of time a cell is kept at a specific temperature.

Cryosurgical techniques, utilizing cryogenic necrosis, have been used in gynecology for the treatment of chronic cervicitis and dysfunctional uterine bleeding by applying an instrument at cryogenic temperature to the affected area.

Present procedures for permanent sterilization of the human female involve major surgery to enter the abdominal cavity. The attendant disadvantages are obvious and are those of most surgical procedures: the inconvenience and cost of a hospital stay; and the high cost of services of a surgeon and other professionals.

It is the object of this invention to make available less expensive sterilization of human females by providing a sterilization procedure that may be performed more quickly than present surgical sterilization techniques and will not require the attendance of an entire surgical team or their support facilities.

The inner lining of the uterus comprises a layer of endometrium that varies in thickness from 2 to 8 millimeters, and outward from the endometrium is a layer of myometrium, or muscle tissue. After conception, the embryo attaches itself to the inner wall or surface of the uterus at some point on the functional lining and is supported and sustained by the endometrium. By substantially destroying the entire endometrial layer throughout the extent of the functional lining of the uterus by cryogenic necrosis, that layer is not capable of sustaining an embryo. An article, entitled "Destruction of the Endometrium by Cryosurgery," by W. Droegemueller, E. Makowski and R. Macsalka, appearing in the American Journal of Obstetrics and Gynecology, Vol. 110, No. 4, June 15, 1971, describes cryogenic necrosis of the uterine endometrium.

The method used to date, however, and described in that article, comprised use of a metal probe having a rather small operative area to successively freeze relatively small areas of the endometrium, eventually covering the entire functional lining. That process was relatively slow and laborious and considerable painstaking effort was required to insure that the entire functional lining was necrosed. The method and apparatus of this invention overcome these disadvantages by providing for cryogenic necrosis of the entire functional uterine endometrium in one application and with complete coverage. A flexible bladder is inserted into the uterus and cryogenic fluid at slightly above atmospheric pressure is circulated through the bladder, expanding it into contact with the entire inner uterine surface and at the same time removing heat from that surface so as to effect coagulation necrosis of the endometrium.

The nature of the inventive method and apparatus is set forth in greater detail in the description below taken in conjunction with the drawings, which form a part of the specification, and in which:

FIG. 1 shows in a partially schematic manner a sterilization system suitable for use with liquid nitrogen as a refrigerant;

FIG. 1a is a partial sectional view taken approximately along line 1a — 1a of FIG. 1;

FIG. 2 shows an alternative method for pressurizing the liquid nitrogen system of FIG. 1;

FIG. 3 shows schematically a sterilization system suitable for use with refrigerants that are stored at high pressure;

FIG. 4 shows an alternate arrangement for storing and supplying the high pressure refrigerant in the system of FIG. 3;

FIGS. 5a and 5b show alternative probe expansion orifices suitable for use with the high pressure refrigerant system of FIGS. 3 and 4;

FIGS. 6a through 6c show the insertion sequence of one possible probe package;

FIG. 1 shows a uterus 10 distended by an inflated bladder 11 attached to a probe generally indicated as 12. The system uses as a refrigerant liquid nitrogen 13 contained in a Dewar vessel 14 that is closed with a plug 15. The liquid nitrogen and the vaporized gaseous nitrogen that fills space 16 above the liquid in Dewar vessel 14 would normally increase in pressure due to
heat conduction through the Dewar vessel walls causing liquid nitrogen to vaporize. A vent valve 19 connected to pipe 18 is made such that when pressure in the Dewar vessel exceeds a specified value the valve opens to vent the excessive pressure. In this manner the pressure within the Dewar vessel is controlled to be lower than or equal to any preset pressure. As long as liquid nitrogen exists in the vessel, heat conduction into the liquid nitrogen will cause the vent valve 19 to slowly vent vaporized nitrogen to the atmosphere, maintaining pressure in the Dewar at the specified operating pressure. This pressure is used to force the refrigerant into probe 12. Adequate pressure is maintained in the Dewar throughout the expulsion of all of the refrigerant by causing vapor space 16 to be approximately one-half of the total Dewar volume. As refrigerant is forced from the Dewar, vapor in space 16 expands to a lower pressure until it reaches approximately one-half the original pressure that existed at the initiation of refrigerant flow. Vent valve 19 also provides conventional protection by venting any excessive pressures that should build up through some malfunction.

Pressure in excess of atmospheric applied to the surface of liquid nitrogen forces it up into vertical pipe 20, through valve 17 and flexible tubing 21 and into supply tube 22 of probe 12. In the course of passage through these tubes, the liquid nitrogen evaporates and forms gaseous nitrogen. The nitrogen fluid emerges from orifice 23 at the end of supply tube 22 and flows into bladder 11, forcing it to expand into contact with the inner surface of uterus 10. The cold nitrogen gas absorbs heat from bladder 11 and then flows through ports 24 into return tube 25 and is vented to the atmosphere at the open end 26 of tube 25. The arrows in FIG. 1 indicate the flow of nitrogen in probe 12. Supply tube 22 and return tube 25 are rigid or semi-rigid coaxial tubes. The passage of return tube 25 surrounds supply tube 22 and bladder 11 is attached to the outside surface of tube 25 by a suitable low temperature cement. The end of supply tube 22 is open to the interior of bladder 11 by virtue of orifice 23, and that end of return tube 25 is closed by being joined to the periphery of the end of tube 22. The size of orifice 23 may be quite large, in relation to the diameter of tube 22, since only low pressure gas is being fed through it and it does not act as an expansion orifice. Ports 24, comprising the only openings into return tube 25 or the inside of bladder 11, are located well back from the end of the tubes in order to force the nitrogen expelled from orifice 23 to circulate and absorb heat from bladder 11 before being vented to the atmosphere through return tube 25.

The probe 12 and its attached bladder 11 must be sufficiently small, when the bladder is deflated and furled around tube 25, so that it can be conveniently inserted into the uterus through a partially dilated cervix. The bladder should be inflated to a pressure sufficient to insure firm contact with the tissue to be necrosed, for example, the interior uterine surface, but should preferably be maintained at about 2 or 3 p.s.i. to avoid any possible risk of internal injury to the patient. It has been found that maintaining a pressure in the Dewar of between 5–10 p.s.i. results in adequate flow of the nitrogen and the maintenance of proper bladder pressure, although the precise to be used in any case will, of course, need to be adjusted as a function of the various system parameters.

In the system described above, the liquid nitrogen vaporizes in the course of its flow from the Dewar 14 to its exit into bladder 11 at supply tube orifice 23. However, the system may alternatively be operated by permitting the nitrogen to emerge from orifice 23 as a liquid, and allowing it to vaporize in bladder 11.

Bladder 11 must be capable of withstanding cryogenic temperatures without rupturing, and should have as good heat transfer characteristics as obtainable in such materials to provide efficient freezing action. A bladder molded of a heat curing rubber bearing General Electric identification SE-5553 has been found satisfactory.

Testing conducted to date indicates that with the system shown in FIG. 1, the exterior surface of the bladder when completely enclosed in a warm liver reached -73°C within five minutes from the start of circulating the nitrogen in the bladder. Based on prior medical testing, at this temperature complete cell necrosis would occur within 2 to 4 minutes. This causes sterilization to be effected.

FIG. 2 shows alternative methods of providing the required pressurization of the Dewar in the system of FIG. 1 in which liquid nitrogen is the refrigerant. Instead of allowing the Dewar to become pressurized due to heat conduction, as shown in FIG. 1, one alternate method that may be used to pressurize the vessel 14 is an external source of pressure 52 which is connected with vertical pipe 18 through pipe 51. Pipe 18 feeds down through plug 15 and pressurizes the Dewar 14. Vent valve 19 provides conventional protection by venting the Dewar 14 to the atmosphere should excessive pressure build-up through some malfunction.

A second alternative method of providing the required pressurization of the Dewar 14 is also shown in FIG. 2. Instead of applying an external pressure to the Dewar, the vessel may be pressurized by energizing a heater coil 28 that is submerged in the liquid nitrogen 13 by means of a source of power 29 via wires 30. The heat generated by the coil causes the liquid nitrogen to vaporize and the vessel pressure accordingly increases and forces the liquid nitrogen through the pipe 20 and tubing system and into the probe 12.

FIG. 3 is a schematic diagram of another system embodiment in which slightly different type of refrigerant is used, that is, a high pressure refrigerant, rather than the liquid nitrogen of the FIG. 1 embodiment which is maintained at atmospheric pressure in a Dewar vessel as described above. The high pressure refrigerants, on the contrary, are stored at high pressure in liquid form in non-vented bottles of high strength. The liquid boils away until the vapor pressure in the bottle is equal to the saturation pressure; the refrigerant then is stored as a liquid at room temperature under its own vapor pressure, so that no Dewar vessel is necessary. Freon 13 and Freon 23, supplied by Dupont, and nitrogen oxide, are refrigerants useful for this system in the embodiment shown in FIG. 3. The Freons have a vapor pressure in the neighborhood of 500 p.s.i. and nitrogen oxide, in the neighborhood of 700 p.s.i. at room temperature. Liquid nitrogen, on the other hand, is not suitable for storage at room temperature because its vapor pressure is so high that providing storage containers of sufficient strength is impractical.

In FIG. 3 a bottle 32 is shown containing both a liquid refrigerant 33 such as Freon or nitrogen oxide and gas 34. To operate the system, outlet valve 35 is opened and the high pressure gas is forced through line 36,
3,924,628

through a three-way valve 37, and through line 38.

Lines 36 and 38 preferably include sections of flexible hose. When the high pressure refrigerant gas reaches probe 39 it is emitted from a small expansion orifice or nozzle and the resulting gaseous expansion causes the cooling. Probe 39, which is merely indicated schematically in FIG. 3, is similar to the probe described in connection with the embodiment of FIG. 1 including the bladder, except that it is provided with expansion orifices, as shown in FIGS. 5a and 5b, rather than with the rather large supply tube orifice 23 shown in FIG. 1. This is necessary because the nitrogen of the FIG. 1 embodiment is already at cryogenic temperature since it is stored at cryogenic temperature, and orifices lose any heat through expansion on going from high to low pressure, since it is already at a low (substantially atmospheric) pressure. The high pressure refrigerants of the FIG. 3 embodiment, however, since they are stored at room temperature, must obtain their cooling from the expansion of the gas as it is emitted from a high pressure line through a small expansion orifice into the low pressure interior of bladder 11.

FIG. 5a shows a single small expansion orifice 41 located in the end of supply tube 22 and suitable for use in the probe 39 of the high pressure embodiment of FIG. 3. Instead of the single orifice of FIG. 5a, multiple expansion orifices 42, as shown in FIG. 5b, may alternatively be used. As examples of the sizes of orifices suitable for the systems described, an orifice 23 of 0.070 inch has been found suitable for the liquid nitrogen system of FIG. 1. In the high pressure system of FIG. 3, the single expansion orifice (41 of FIG. 5a) of 0.0135 inch has been used for both nitrous oxide and Freon 13 and Freon 23. Two 0.0135 inch expansion orifices (42 of FIG. 5b) or, alternatively, a single orifice (41 of FIG. 6a) of 0.024 inch have been used with both Freons.

The three-way valve 37 is used in connection with the warming of the bladder 11 after the cryogenic necrosis has been effected and prior to removal of the instrument from the uterus. Human tissue is in large part water and when it is in contact with any object at a temperature below the freezing point of water it sticks to the object by freezing to it, and will tend to tear if the object is pulled away. For this reason, after the cryogenic or freezing cycle of probe 12, in both the embodiments of FIGS. 1 and 3, bladder 11, which is configured to contact substantially the entire area of tissue to be necrosed, must be warmed before it can be removed, so that the contacted tissue is not torn.

In the liquid nitrogen embodiment of FIG. 1 the warming is accomplished by stopping the flow or circulation of cryogenic nitrogen into probe 12 and permitting the heat of the patient’s body to bring the bladder temperature up. In the high pressure embodiment of FIG. 3, the action of body heat in warming bladder 11 is assisted by circulating room temperature gas through the bladder. This is accomplished by moving the three-way valve 37. The valve, as shown schematically in FIG. 3, is in a position to pass the refrigerant gas from line 36 directly to line 38. By rotating the valve 37 one quarter turn in the counter-clockwise direction as shown in FIG. 3, the gas from line 36 will be diverted by valve 37 down into a regulator 43, which may be a Norrgren Company Model 11-010-084. Regulator 43 reduces the pressure of the gas to about 50 p.s.i. and then feeds it on through line 38 to probe 39. The gas flows through expansion orifices 41 or 42, but since it is already at a very low pressure, there is hardly any expansion or cooling, and the relatively warm gas flowing through the interior of bladder 11 hastens its warming.

FIG. 4 illustrates an alternative refrigerant feed arrangement for the high pressure embodiment of FIG. 3 wherein some additional cooling capacity is obtained. A high pressure storage bottle 44 is shown in an inverted position, so that its outlet, and the associated outlet valve 45, are located at the bottom of the bottle. In this embodiment liquid refrigerant, rather than gas, is fed from the bottle. This change of state from liquid to gas provides some additional cooling to that obtained by the gaseous expansion during emission from the probe expansion orifices.

The bladder material SE-5553 supplied by General Electric and found satisfactory for the embodiment of FIG. 1 is also satisfactory for the FIG. 3 embodiment, where the refrigerant temperature are not nearly as low: nitrogen boils at −320.4°F; nitrous oxide at −129.1°F; Freon 13 at −114.6°F and Freon 23 at −115.7°F. In addition a dispersion coating rubber supplied by Dow Corning to their number 92-009 has been found satisfactory for use with the high pressure (and higher temperature) refrigerants of the FIG. 3 embodiment. Bladders of approximately 0.020 inch thickness have been found satisfactory. Various methods of fabricating the bladder may be employed, but one method found satisfactory has been to lay up the bladder in successive thin layers upon a mandrel. This method of fabrication also facilitates placing one or more thermocouples 50 (FIG. 1a) in the bladder. The thermocouples 50 and their leads may be placed between successive layers as the bladder is formed. Such thermocouples are connected to appropriate instrumentation for monitoring bladder temperature.

The embodiments of FIGS. 1 and 3 each have advantages and disadvantages so that neither can clearly be preferred to the other. The liquid nitrogen refrigerant of the FIG. 1 embodiment provides a much lower temperature and consequently faster tissue freezing. It, however, has the disadvantages of imposing more constraints upon the system components, especially the bladder, because of the lower temperature, and it requires the inconvenience of low temperature refrigerant storage. The high pressure refrigerants, on the other hand, useful in the FIG. 3 embodiment, are conveniently stored at room temperature, are generally more readily available than liquid nitrogen, but compare unfavorably with liquid nitrogen in having higher temperatures and consequently slower freezing.

In using the cryogenic system of either FIGS. 1 or 3 to sterilize a female, the procedure is as follows. The cervix is visualized and then grasped with a tenaculum. Then the cervix is dilated with instruments to approximately one centimeter. Then probe 12, with bladder 11 furled tightly around it, is inserted through the cervix into the uterus. The refrigerant is applied to probe 12 for a sufficient period to accomplish cryogenic necrosis of the functional endometrium. The bladder 11 is then warmed and removed.

FIGS. 6a through 6e shows in sequential steps the application of one configuration in which either of the embodiments of FIG. 1 or FIG. 3 may be packaged: a tampon-type cartridge. FIG. 6a shows the package, comprising a “handle” portion, which is comprised of supply tube 22 and return tube 25, the bladder 11 furled tightly around the end of return tube 25, and encased in a cylindrical sleeve 48 terminating in an annu-
7
lar shoulder 49. The outside diameter of the sleeve should be less than one centimeter so that it may be readily inserted into the partially dilated cervical opening.

FIG. 6b shows the sleeve 48 containing the furled probe being inserted into the opening in the cervix 55. In the next step, shown in FIG. 6c, sleeve 48 has been fully inserted into the cervix 55, being stopped by the abutment of the sleeve shoulder 49 against the outer cervical surface. Also in FIG. 6c, the probe has been advanced so that the end of the probe with the furled bladder 11 has been pushed free of sleeve 48 and is positioned inside the uterus. When the refrigerant is applied to probe 12, bladder 11 inflates and assumes the position inside the uterus shown by FIG. 6d, showing a view along a vertical plane through the body, and FIG. 6e, showing a view along a horizontal plane through the body.

The primary feature of the package of FIG. 6 is the use of the flanged sleeve 48. This sleeve, which is preferably about 2.5 centimeters in length, is used to protect the bladder from mechanical damage during storage and handling prior to use and also as an insertion aid. Since the inner uterine surface within about 2.5 centimeters of the cervix opening is not part of the functional uterine lining and should not be necrosed, the insulating effect of the sleeve will protect this portion of the uterus and prevent an unnecessary loss of cooling capacity.

While certain illustrative embodiments and details thereof have been set forth herein, various changes and modifications thereto as will occur to those skilled in the art may be made without departing from the scope of the invention, which is defined only in the appended claims. For example, although the embodiments of the invention have been described in detail in connection with the female sterilization application, it should be appreciated that by appropriately configuring the bladder, tissue other than the uterine lining tissue can be necrosed and the uterus lining or a portion thereof may be necrosed for purposes other than sterilization such as for treating dysfunctional uterine bleeding.

What is claimed is:

1. A method of effecting coagulation necrosis of the functional uterine endometrium comprising the steps of:
   a. inserting a flexible bladder in the uterus;
   b. inflating said bladder with a fluid at cryogenic temperature so that said bladder is in substantially continuous contact with the inner surface of the functional uterine lining, said fluid undergoing a phase change to extract heat from said functional uterine endometrium; and
   c. maintaining said bladder so inflated with said fluid at said cryogenic temperature for a period of time sufficient for said heat extraction to effect simultaneous coagulation necrosis of substantially all of the functional uterine endometrium.

2. A method as defined in claim 1 wherein the exterior of said bladder in contact with said lining is maintained at least −73°C for at least 2 minutes.

* * * *