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METHOD AND APPARATUS FOR OBTAINING SPECIMENS OF VIABLE BRONCHIAL EPITHELIAL CELLS

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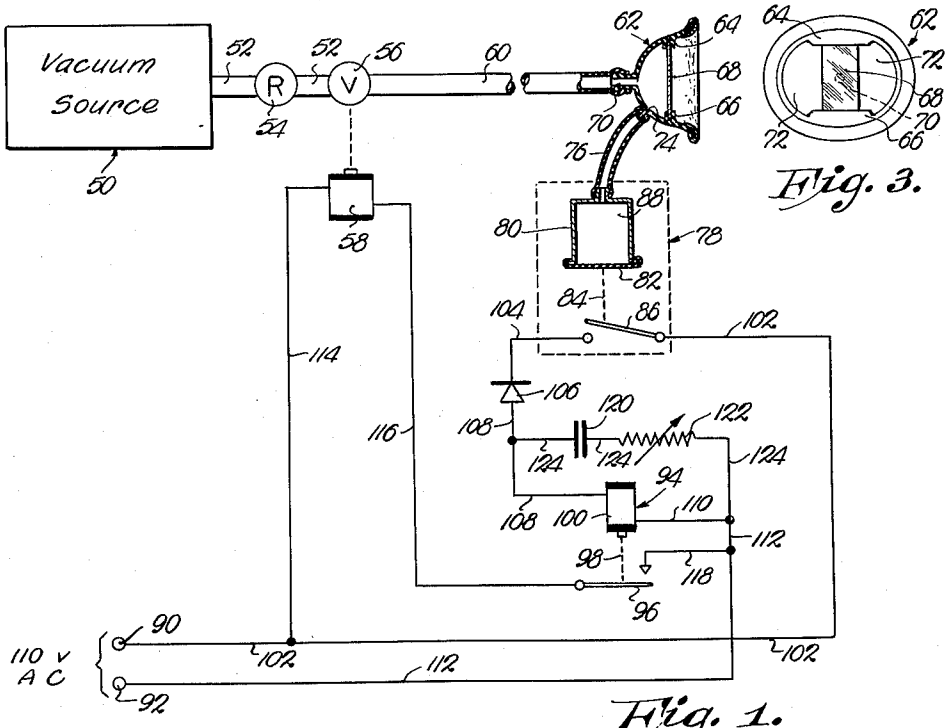


Fig. 3.

Fig. 1.

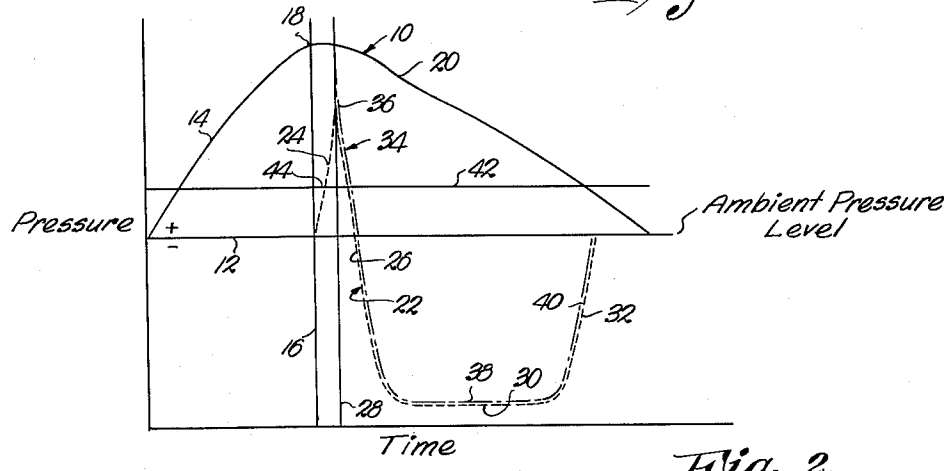


Fig. 2.

LEGEND:

——— Pressure in Bronchial System during normal Spasmatic Cough Cycle

---------- Pressure in Mask

—·—·— Pressure in Bronchial System during Cough Cycle modified by Invention

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METHOD AND APPARATUS FOR OBTAINING SPECIMENS OF VIABLE BRONCHIAL EPITHELIAL CELLS

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This invention relates to means for removing physiological specimens or materials from the human bronchial system. Although the invention could conceivably be applied for various diagnostical or therapeutic purposes, such as the removal of mucous plugs from the lower bronchi in post surgical atelechtosis, a primary utility for the contemplated method and apparatus exists in connection with the obtaining of viable bronchial epithelial cells for use as a specimen for microscopic evaluation. Accordingly, although it will be understood that the invention is contemplated to have a broader range of uses, the same will be illustrated hereinafter in terms of the application of the method and apparatus to the obtaining of such epithelial cell specimens.

The classical method of attempting diagnosis of the presence of cancerous or similar conditions in the bronchi has been to search for lesions by means of radiographic techniques. Unfortunately, however, when the condition has progressed to a point where discovery of lesions by radiographic means is possible, it is very often too late to successfully employ therapeutic or surgical procedures which might have been successful if the condition could have been discovered and such procedure followed at an earlier time. The answer to early diagnosis of the type of condition mentioned appears to lie in the microscopic examination of epithelial cell specimens from the bronchial region. However, there has heretofore existed no method or means by which reliable specimens of such type could be obtained without surgery.

Attempts to obtain specimens of viable bronchial epithelial cells by the method and apparatus incorporated in what is normally referred to as a cougholator machine, proved unsatisfactory in that suitable specimens of bronchial epithelial cells were obtained in only a very minor percent of the trials and, even in these, there was doubt as to whether the specimens included cells from the more remote regions of the bronchial system.

It may be noted that the cougholator machines referred to were actually designed for a different purpose and normally comprise a compressor cycling between positive and negative pressure which may be applied to the patient alternately by means of a motor-timed, alternating valve controlling the pressure to which a face mask or the like is subjected. It is believed that the failure of the cougholator method and machine to yield satisfactory specimens of viable bronchial epithelial cells is likely due to the normally constricted (or only slightly expanded during normal breathing) condition of the bronchial tree at the time that negative pressure (or suction) is applied by the cougholator technique in accordance with the timed operation of the valving means employed in connection therewith.

Accordingly, it is the primary object of this invention to provide an improved method and apparatus for applying a substantial negative pressure to the bronchial system at a time when the bronchial tree is in expanded condition so as to reliably obtain specimens of viable bronchial epithelial cells (or the removal from the bronchial system of other physiological matter).

It is another important object of the invention to provide such an improved method and apparatus in which the pressure conditions created by the patient during an ordinary cough spasm, and which it is known result in expansion of the various portions of the bronchial tree to a state of maximum inflation during one phase of such spasm, are utilized to control the timing of application of an externally created negative pressure necessary to withdraw the desired biological materials from even the more remote regions of the bronchial system.

Another important object of the invention is to provide such a method and apparatus in which not only the time of initiation of the application of negative pressure is controlled in predetermined fashion, but also the duration of application of the negative pressure and the magnitude thereof are controlled with a view both to assuring patient safety and optimum reliability in obtaining satisfactory specimens of the material being removed.

Still other important objects of the invention will be made clear or become apparent as the following description thereof proceeds.

In the accompanying drawing:

FIG. 1 is a schematic diagram illustrating the various structural elements utilized in a preferred embodiment of apparatus for practicing the method;

FIG. 2 is a graph showing the general relationships between certain time and pressure parameters involved in the method, no attempt being made to follow any absolute scale or proportion in connection with such graph; and

FIG. 3 is a front elevational view of the face mask which is broken away and illustrated in cross section in FIG. 1.

Referring now first to FIG. 2, the graph curve generally designated **10**, represents the internal pressure in the bronchial system of a patient during a normal spasmodic cough cycle occurring in the latter. Since the positive pressure created within a patient's bronchial system by a cough spasm is more or less superimposed upon pressures resulting from ordinary breathing, an ambient pressure level for the patient's bronchial system may be represented as by the line **12**.

As the normal cough spasm cycle commences, air is rapidly introduced into the patient's bronchial system with resultant pressure increase in the latter as indicated by the upwardly sloped portion **14** of the curve **10**. After a short interval and at an instant of time indicated in FIG. 2 by the vertical line **16**, the internal pressure within the patient's bronchial system reaches a maximum as indicated by the point **18** on curve **10**. At such instant, the patient's bronchial tree is in a state of maximum inflation and expansion. The normal cough cycle is then continued by the patient expelling the stored air to relieve the positive pressure and accomplish the natural objectives of the cough, such period of expellation being indicated by the downwardly inclined portion **20** of curve **10**.

Reference is next made to the dotted line curve generally designated **22** in FIG. 2 and which represents the pressure that would be presented in a face mask or the like applied to the patient, if it could be arranged that a source of negative pressure of predetermined level be applied to such mask a certain interval of time after the normal cough spasm had reached its point **18** of maximum bronchial expansion at time **16**, with such source of negative pressure being uncoupled from the patient after a predetermined period. Such controlled application of negative pressure is precisely what is contemplated by the method of this invention. Thus, referring to the curve **22** again, the sharply rising portion **24** thereof represents the rapid increase of positive pressure in the mask as the patient commences to expel the pressure previously stored in his bronchial system during the portion **14** of the cough cycle; the sharply downwardly inclined portion **26** of the curve **22** representing the period of initial application to

the mask of an external negative pressure commencing at an instant of time represented by the vertical line 28, whose time of occurrence is controlled in manner hereinafter to be described; the more or less horizontal portion 30 of curve 22 representing a predetermined interval of application of the negative pressure to the mask; and the portion 32 of curve 22 inclining upwardly to ambient level representing the interval following removal of the negative pressure from the mask.

The second dotted line curve 34 in FIG. 2 represents the internal pressure within the patient's bronchial system during a cough cycle which is modified by practice of the method of this invention and in which a predetermined negative pressure is applied at time 28 to the bronchial system through the means of a mask and other structure hereinafter to be described. Since, with a sufficient capacity of the source of negative pressure, the pressure within the patient's bronchial system may be expected to closely follow the pressure within the mask during the application of such external negative pressure, the curve 34 includes a sharply downwardly inclined portion 36 running from the positive pressure region rapidly down into the negative pressure region in approximate correspondence with the portion 26 of curve 22; similarly, the modified bronchial pressure curve 34 then includes a substantially level portion 38 and a portion 40 inclining upwardly back to ambient in general correspondence with the portions 30 and 32 of the mask pressure curve 22.

Although the method will become still more clear as the description of the invention progresses, and as structure for practicing the method is explained, it may even at this point be observed that the method contemplates a modification of the normal spasmodic cough cycle, which in the absence of practice of the invention, involves only relative changes in the level of positive pressure within the bronchial system, such modification involving a rapidly applied change of polarity of the pressures acting upon the patient's bronchial system from a high positive pressure coinciding with substantially maximum expansion of the patient's bronchial tree to a substantial, but predetermined negative pressure which is applied for a predetermined period of time chosen to optimize specimen procurement without endangering patient safety.

Referring now to FIG. 1, a preferred embodiment of structure for practicing the method of the invention is schematically represented. The numeral 50 represents a vacuum source of any suitable character, which in normal installations, will be understood by those skilled in the art to involve the provision of a motor driven vacuum pump (not shown) and associated vacuum storage tank or chamber (not shown) having a line 52 coupled therewith. In order to control the maximum negative pressure of the vacuum source 50 for purposes of safety and controlling the level of negative pressure to be applied to a patient at the desired value, a vacuum relief valve 54 may be interposed in line 52. Line 52 leads to one side of a normally closed, solenoid-controlled valve 56 having associated therewith a control solenoid 58 for opening the valve 56 when the solenoid 58 is electrically energized.

The other side of valve 56 is coupled by a preferably flexible conduit 60 with a face mask generally designated 62 adapted for application to a patient over the mouth of the latter. Mask 62 may be essentially of the type utilized in respiratory or anesthesia administering apparatus, but will be provided with means such as opposed pairs 64 and 66 of spaced flanges or protuberances for releasably, but securely holding the end portions of a specimen slide 68. As shown in FIG. 3, the slide 68 may be of the normal rectangular-type of heavy glass or the like as used in microscopic examination of specimens and will be centered in front of the inlet opening 70 of the mask 62 to which the line 60 is coupled, in order that viable bronchial epithelial cells being withdrawn from the patient during practice of the method, will be deposited on the slide 68. It will further be noted, however, that substantial open spaces 72 are provided within the mask on either side of the slide 68 so that the latter does not materially impede or affect the travel of air through the mask 62 toward the vacuum source 50 necessary for satisfactory maintenance of the desired negative pressure upon a patient's bronchial system.

The mask 62 is also provided with a pressure-sensing opening 74 which is coupled by a flexible tube 76 to a pressure responsive electrical switching device generally designated 78. Device 78 may be of the mercoid type having a rigid chamber defining assembly 80 provided with a flexible closure diaphragm 82 operably coupled as at 84 to a normally open, single-pole, single-throw electrical switch 86. It will be understood that the pressure sensing line 76 is coupled into communication with a chamber 88 within the assembly 80 so that, as the pressure within chamber 88 increases to a suitable level, the diaphragm 82 will be distorted to close the switch 86.

Referring again briefly to FIG. 2, it will be clear that the level at which assembly 80 of device 78 closes the switch 86, may be set to some positive pressure at a level below the peak positive pressure point 18 of the cough spasm since, during the portion 14 of the cough spasm in which internal positive pressure is being built up within the bronchial system, no substantial positive pressure will exist within the mask 62. It is thus only after the expulsion of air from the bronchial system commences at time 16, that a positive pressure is created within the mask 62. In FIG. 2, therefore, the level at which switch 86 may respond is illustrated by a horizontal line 42.

In the preferred embodiment chosen for illustrative purposes, the apparatus is adapted for operation with alternating current, and accordingly, a pair of terminals 90 and 92 represent connections with a suitable alternating current power main. There is provided a relay generally designated 94, having a normally open, single-pole, single-throw relay switch 96 operably coupled as at 98 with an operating coil 100 adapted upon energization to close the switch 96.

A potential energizing circuit for the relay coil 100 may be traced from power terminal 90 through conductive means 102 to pressure responsive switch 86, thence through conductive means 104 and any suitable type of rectifier 106 and conductive means 108 to coil 100, thence through conductive means 110 and conductive means 112 to power terminal 92. It is apparent, therefore, that the pressure responsive closing of switch 86 will control the energization of relay coil 100. Similarly, a potential energizing circuit for the valve operating solenoid 58 may be traced from power terminal 90, through conductive means 102 and 114 to the solenoid 58, thence through conductive means 116 to the relay switch 96, and thence through conductive means 118 and 112, to the power terminal 92. It is thus also evident that the energization of solenoid 58, and therefore, the opening of valve 56, will be contingent upon the closing of relay switch 96 responsive to energization of the coil 100 upon closure of the pressure responsive switch 86.

In order to provide for holding of the coil 100 in energized condition to maintain the relay switch 96 closed, the solenoid 58 energized, and the valve 56 open for a predetermined period of time during which it is desired to apply negative pressure to the patient, there is provided a resistance capacitance timing circuit comprising a capacitor 120 and a resistance 122 coupled in series with each other by conductive means 124 and in shunt with the operating coil 100 by conductive means 108 and 110. As illustrated, the resistance 122 is preferably variable in character for adjustment of the period during which negative pressure is to be applied by variation of the RC time constant of the timing circuit 120, 122, 124.

In operation, assuming that a suitable negative pressure is established in the source 50, that electrical power

is applied to the terminals **90** and **92**, and that the mask **62** is suitably installed over the mouth of the patient from which a specimen is to be obtained, the patient is instructed to attempt to cough in the ordinary manner. At this juncture, the switch **86** will be open, the coil **100** de-energized, the relay switch **96** open, the solenoid **58** de-energized, and the valve **56** closed. As the patient commences the cough spasm, his bronchial system will be inflated by the application of positive pressure therewithin as indicated by the portion **14** of curve **10** in FIG. 2. Upon completion of such normal spasmodic inflation of the bronchial system to a peak positive pressure as at the point **18** on curve **10**, the natural effort of the patient to complete the cough cycle will at time **16** commence an expulsion of air from the bronchial system, out the mouth and into the mask **62**.

Such initial expulsion of air builds up the pressure within the mask **62** to a positive value, as indicated by the portion **24** of curve **22**, until the level **42** is exceeded. As the pressure level within the mask **62** exceeds the level **42**, such pressure is transmitted through the sensing line **76** to the chamber **88** and the switch **86** is closed as at point **44** in FIG. 2. After initial closure of the switch **86**, a very small time delay occurs during which the relay switch **96** closes responsive to the energization of coil **100** and the valve **56** opens responsive to the energization of solenoid **58**. This interval is somewhat exaggerated in FIG. 2, as will be apparent from the fact that the total interval between time **16** and time **28** at which negative pressure is applied, will normally be of the order of 15 milliseconds. After such short delay during which the valve **56** is being opened, such valve does reach an open condition applying a predetermined level of negative pressure or vacuum to the line **60**, the mask **62** and thereby, the bronchial system of the patient as represented by the portion **26** of mask pressure curve **22** and portion **36** of bronchial system pressure curve **34**. Such negative pressure is then maintained in the mask **62** and upon the bronchial system of the patient for a predetermined period of time, preferably of the order of one-half second, as represented by the portion **30** of mask pressure curve **22** and the portion **38** of bronchial system pressure curve **34**.

It will be understood that the RC timing circuit **120**, **122** and **124** functions to supply current to the coil **100** of relay **94** to maintain the latter energized and the relay switch **96** closed, even after the pressure responsive switch **86** has been opened by the influence of the negative pressure transmitted to chamber **88** from mask **62** through the sensing line **76**. The resistance **122** controls the rate of discharge of electrical energy stored within the capacitor **120**, through the relay coil **100**, so that by appropriate adjustment of the value of resistance **122**, the length of the period during which the negative pressure is applied to the patient, as at portion **38** of curve **34**, may be set to any desired value. After exhaustion of the stored energy from capacitor **120**, the relay coil **100** is de-energized, relay switch **96** re-opens, valve operating solenoid **58** is de-energized, and control valve **56** is re-closed. Thereupon, the pressures in both the mask **62** and the patient's bronchial system return to ambient level **12** as indicated by the portion **32** of mask pressure curve **22** and the portion **40** of bronchial system pressure curve **34**.

It will be understood that during the period of application of negative pressure to the patient's bronchial system, air is rapidly exhausted from the latter through the mask **62**. Since the patient's bronchial system is greatly expanded when such negative pressure is applied thereto, it will be clear that viable bronchial epithelial cells will be drawn with the exhausted air into the mask **62** and deposited in substantial quantity upon the specimen slide **68**, which may thereafter be removed from the mask **62** for microscopic examination.

The effectiveness of the method and apparatus has been

clinically verified and in one series of tests, suitable specimens of viable bronchial epithelial cells were obtained in 111 out of 114 trials. In these tests, a negative pressure of the order of three to four centimeters of water was utilized, it being noted that the positive pressure within the bronchial system at the peak point **18** of the normal cough spasm, was found to often reach a level of from 60 to 80 millimeters of mercury.

It will be appreciated by those familiar with the physiological factors involved, that two aspects of the functioning of the method are particularly important to its success. Firstly, the application of the negative pressure to the patient's bronchial system occurs substantially at an optimum point of the normal cough cycle reflex during which the bronchial tree is at or near its maximum physiological expansion and thereby provides maximum clarity of the pathway used for excretion of the desired viable bronchial epithelial cell specimen materials. Secondly, it is significant to the most efficient action of the method that the air being expired or withdrawn from the bronchial system during the application of the negative pressure is actually being accelerated, which further assures the securement of an optimum specimen both as to the amount of material obtained and as to the remoteness of the regions of the bronchial tree from which such specimen material may be withdrawn.

Accordingly, it is believed evident that the method and apparatus contemplated by this invention are ideally adapted for accomplishing all of the above-mentioned and other objects of the invention. It will be clear to those skilled in the art, of course, that certain minor modifications and changes of method parameters or structural details might be made without departing from the true spirit or intention of the invention. Accordingly, it is to be understood that the invention should be deemed limited only by the fair scope of the claims that follow.

Except as otherwise expressly indicated, all references hereinabove and in the claims to positive and negative pressure levels will be understood as referring to pressure levels compared with or measured from ambient atmospheric pressure, rather than absolute pressure levels.

Having thus described the invention what is claimed as new and desired to be secured by Letters Patent is:

1. The method of removing physiological specimens from the bronchial system of a human being which comprises the steps of: subjecting a human bronchial system to an ambient external pressure level; causing said bronchial system to undertake a natural cough spasm cycle; sensing the pressure condition of said bronchial system while said cough spasm cycle proceeds; detecting the attainment by said bronchial system of a predetermined elevated level of positive pressure occurring substantially at the peak of said cough spasm cycle; responding to detection of attainment of said elevated level of positive pressure by thereupon applying an external negative pressure of predetermined level to said bronchial system while said bronchial system is in a state of substantially optimum expansion and inflation prevailing at the peak of said cough spasm cycle; discontinuing the application of said negative pressure to said bronchial system after a predetermined period of time; and receiving a specimen withdrawn from said bronchial system under the influence of said negative pressure during said period.

2. The method as set forth in claim 1, wherein said predetermined negative pressure level is of the order of about two to five centimeters of water.

3. The method as set forth in claim 1, wherein said predetermined period is of the order of about three-eighths to five-eighths second.

4. The method as set forth in claim 1, wherein said negative pressure is applied at a time when the internal positive pressure within the subject's bronchial system is of the order of at least about forty millimeters of mercury.

5. The method as set forth in claim 4, wherein said negative pressure is maintained at a level of the order of

about three to four centimeters of water for a period of the order of about one-half second following initial application thereof.

6. In apparatus for removing physiological specimens from the bronchial system of a human subject, the combination of: a vacuum source for providing negative pressure of predetermined level; structure for effecting a pneumatic coupling with the bronchial system of a subject; conduit means for coupling said source with said structure; a valve coupled with said conduit means, said valve having an operated condition for communicating said negative pressure of said source to said structure through said conduit means and a stand-by condition for preventing effective communication of said negative pressure of said source to said structure through said conduit means; pressure responsive means pneumatically coupled with said structure for sensing pressure conditions within the latter and operably coupled with said valve for actuating the latter from said stand-by to said operated condition thereof when a positive pressure within said structure in excess of a predetermined value is sensed.

7. Apparatus as set forth in claim 6, wherein said valve is provided with an operating solenoid, and said pressure responsive means includes a pressure operated electrical switch, and electrical means operably coupled with said pressure operated switch and said solenoid for controllably energizing said solenoid.

8. Apparatus as set forth in claim 7, wherein said electrical means includes a relay having a relay switch and a coil for operating the latter, a coil energizing circuit having said coil and said pressure operated electrical switch coupled therein, and a solenoid energizing circuit having said solenoid and said relay switch coupled therein.

9. Apparatus as set forth in claim 8, wherein is provided a delay circuit coupled with said coil energizing circuit.

10. Apparatus as set forth in claim 9, wherein said delay circuit includes a resistive element and a reactive element coupled in series with each other and in shunt with said coil, one of said elements being adjustable.

11. Apparatus as set forth in claim 6, wherein said structure includes a face mask, a specimen receiving member, and means for releasably holding said member within said mask.

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