

[54] **ARTIFICIAL METHOD FOR MODIFYING
THE REPRODUCTIVE CYCLE IN ANIMALS**

[75] Inventors: **Ben W. O. Dickinson, III**, San Francisco; **Robert W. Dickinson**, San Rafael, both of Calif.; **Cecil R. Miller**, Westchester, Pa.

[73] Assignees: **Smith, Kline & French Laboratories**, Philadelphia, Pa. ; by said Miller; **Agrophysics, Inc.**, San Francisco, Calif. ; by said Ben W. O. Dickinson, III and Robert W. Dickinson

[22] Filed: **Jan. 22, 1971**

[21] Appl. No.: **108,922**

[52] U.S. Cl. **128/1 R, 128/130, 128/341**

[51] Int. Cl. **A61b 19/00**

[58] Field of Search. **128/1 R, 2 R, 3, 127, 130, 128/131, 341, 343, 345**

[56] **References Cited**

UNITED STATES PATENTS

3,192,928	7/1965	Horton.....	128/341
430,137	6/1890	Meddick.....	128/343
3,297,020	1/1967	Mathiesen.....	128/2 R
328,553	10/1885	Warmoth.....	128/127
4,825	10/1846	Merriman.....	128/127

3,502,328	3/1970	Hamilton	128/345 X
3,425,411	2/1969	Robinson.....	128/130

OTHER PUBLICATIONS

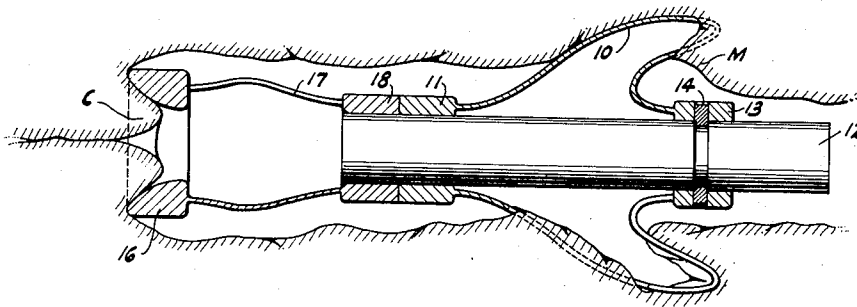
Robinson - The Control of the Ovarian Cycle in the Sheep - 1967, Sydney Univ. Press, pp. 115, 243-244 relied on

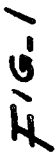
Primary Examiner—Dalton L. Truluck
Attorney, Agent, or Firm—Flehr, Hohbach, Test, Albritton & Herbert

[57] **ABSTRACT**

A method for changing and resetting the starting time of the estrus or reproductive cycle in female animals (e.g. a cow) including the steps of inserting a mechanical device therein, engaging the device with the reproductive tract wall to prevent expulsion by the animal straining and exerting pressure sufficient to alter the cross-sectional configuration of the tract wall for a substantial period of time. This pressure causes alteration or stimulation of the reproductive or estrus cycle regulatory mechanism of the animal to reset the beginning of the reproductive cycle, and under certain conditions, to cause a shortening of the cycle. A typical device includes a number of radially projecting resilient hoops.

7 Claims, 1 Drawing Figure





BEN WADE OAKES DICKINSON III
ROBERT WAYNE DICKINSON
CECIL R. MILLER
INVENTORS

BY *F. Behr, Hobbs, West,
Albion & Herbert*
ATTORNEYS

ARTIFICIAL METHOD FOR MODIFYING THE REPRODUCTIVE CYCLE IN ANIMALS

BACKGROUND OF THE INVENTION

A complex information transport network of interconnected neural and hormonal factors controls the estrus or reproductive cycle in female animals, particularly of the type having a tubular reproductive tract including an ovary (e.g. humans, cows, chickens, dogs, horses, hogs, and the like). In a cow, typical of that group, growth of an ovarian follicle begins under the influence of follicle-stimulating hormone (FSH) from the adenohypophysis. Estrogen from the developing follicle appears to be part of a neurohormonal feedback. Gonadotropin secretions in response to these neurohormonal inputs trigger the rapid growth and maturation of a follicle to reach a Graafian follicle state. Ovulation of the mature follicle appears to occur in response to the pituitary gonadotropin, luteinizing hormone (LH), which reaches a peak level just prior to ovulation. Immediately after ovulation the corpus luteum forms at the site of ovulation and produces an increased amount of progesterone which acts as a hormonal feedback. In the absence of fertilization, the corpus luteum regresses and the production of progesterone reaches minimal levels. As the progesterone output from the ovary is reduced, the output of gonadotropin from the adenohypophysis again begins to increase, the growth of another ovarian follicle will be stimulated. Thus, the time-phase combination of neural and hormonal information transports and feedbacks produces the normal estrus or reproductive cycle initiation and length of cycle regulation.

Implanted capsules or feed additives of drugs, usually containing progestogens, the removal or stopping of which permits triggering of a rapid ovulation, are unsatisfactory because of high cost, poor synchronization, bad side-effects and poor fertility results when the ovulation retarding drug is removed or stopped.

Intrauterine devices of conventional construction are, in many instances, spontaneously expelled from the reproductive tract by the animal. Furthermore, the devices open the cervix of the cow over an extended period of time to expose the normally aseptic uterus which could potentially cause infection to the same from external sources.

SUMMARY OF THE INVENTION AND OBJECTS

It is an object of the present invention to provide a method for changing or resetting all or a combination of the follicular, luteal or ovulation phases of the estrus or reproductive cycle in animals of the type having a tubular reproductive tract with an ovary which overcomes the aforementioned disadvantages of the prior art.

It is another object of the invention to use a device for changing or resetting the follicular, luteal or ovulation phases of a female's estrus or reproductive cycle by stimulation of endogenous chemicals rather than implantation or feed addition of exogenous chemicals.

It is a further object of the invention to accomplish the above purpose utilizing only a mechanical device.

It is an additional object of the invention to provide a method for temporarily anchoring the above mechanical device in the animal's reproductive tract.

It is another object of the invention to provide a method for causing ovulation of an animal.

It is another object of the invention to provide a method for contraception by resetting the follicular, luteal or ovulation phases of the reproductive or estrus cycle.

In accordance with the above objects, a method for mechanically changing or resetting the starting time of the estrus or reproductive cycle in animals of the type having a tubular reproductive tract with an ovary is provided by a method of inserting into the animal's reproductive tract a device such as the type described in the application entitled "Device for Insertion into the Reproductive Tract and Method of Using the Same" in the names of Ben Wade Oakes Dickinson III and Robert Wayne Dickinson, Ser. No. 108,889, filed Jan. 22, 1971. A device is inserted into the animal's reproductive tract wherein it is engaged with the tract wall to retain the same within the tract for a substantial period of time by preventing expulsion of the device from the tract by the animal. It has been discovered that exerting sufficient pressure by the device to alter the cross-sectional configuration of the tract wall from the normal condition for a sufficient period of time causes adequate stimulation of the estrus or reproductive cycle neutral-hormonal regulatory mechanisms of the animal to change or reset the beginning of the reproductive cycle. For clarity of description, the following discussion will relate to the cow, which has a tubular reproductive tract including a uterus opening through a cervix into the vagina. It should be understood that, unless otherwise specified, the method may also be applied to other animals having a tubular reproductive tract including an ovary such as humans, horses, hogs, dogs and chickens. In the cow, the desirable position for tract engagement is within the vagina, anterior to the sphincter-like muscle or constriction.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a cross-sectional view of a typical mechanical stimulating device inserted into the vagina of an animal.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In order to change or reset the follicular, luteal or ovulation phases (of) the estrus or reproductive cycle, a device of the type generally described in the aforementioned application A-26130 is inserted into the tubular reproductive tract. A typical device which may be employed for the present invention, as illustrated in FIG. 1, is inserted into the vagina of a cow. This device is described as a vaginal anchor assembly in application Ser. No. 108,889 illustrated prior to insertion as FIGS. 20 and 22 and after insertion in FIG. 23 in that case. Briefly describing FIG. 1, strands 10 form an umbrella-like shape with posterior concavity of the initial rosette-like pattern as a result of partial collapse during insertion into the vagina. It is seen that the strands project into folds of the vaginal wall in intermeshing fashion. The anterior ends of strands 10 are fixedly secured to mounting ring 11 which, in turn, is carried by housing 12 as by forming the ring of a resilient material and sliding the same over the housing to form a tight fit. The posterior mounting ring 13 is slideably carried by housing 12 and is maintained in the illustrated position by means of plugs 14 extending through rings 13 and

seated in accommodating recesses of housing 12. Plug 14 may be formed of a slowly disintegrable material such as water soluble cross-linked polyethylene oxide or slowly vaporizable paradichlorobenzene as described in application A-26130. It is noted that the periphery of the umbrella abuts against the posterior side of the sphincter-like constriction or muscle in the vagina denoted as M. It is an important aspect of the present invention that the anchoring portion of the device which engages the vaginal wall of the cow remains to the anterior of the sphincter-like constriction or muscle to provide the anchor with a backing for a secure position. Furthermore, if the anchor projects into the vestibule of the vagina to the posterior of the sphincter-like muscle, because the animal is particularly sensitive to foreign bodies in this region, she would begin a natural straining movement which would urge the assembly posteriorly for expulsion.

Referring again to FIG. 1, the anterior portion of the device includes a clamping ring 16 which slides over and compresses against the projecting annulus of the cow's cervix, denoted as C. Clamping ring 16 is connected to housing 12 in a flexible manner by a series of spaced apart elongated strands 17 fixedly secured at one end to the clamping ring and at the other end to mounting ring 18 which, in turn, is fixedly secured to and carried by housing 12. Strands 17 perform the function of a flexible cervical follower which allows for relative movement of the device with respect to the cervix to accommodate movement of the reproductive tract and particularly the cervix as during defecation. In addition, strands 17 are under a certain amount of compression so that the vagina is stretched axially between the cervix and muscle M.

The above device may be removed manually after it has been inserted for the desired amount of time or the device may be provided with a self-actuating removal mechanism which provides for an automatic change in shape or characteristics which engenders removal of the device. In the former or manual technique, the above-described device may be removed by manually withdrawing it without alteration or by sliding ring 13 anteriorly to collapse loops 10 so that the outward projection of the anchor is reduced or eliminated. In the automatic technique, the plug 14 may disintegrate after a predetermined period of time. Thereafter, the spring-like compression of strands 10 in a hoop-like configuration will urge ring 14 posteriorly to project into the sensitive vestibule on the posterior side of the sphincter-like muscle. This rearward movement causes the collapse of the outward projection of the anchor as with the manual assembly except that the animal's natural straining movement to eject a foreign body will urge the anchor assembly, along with the remainder of the device, to be expelled from the animal.

In accordance with the invention, radial pressure sufficient to alter the cross-sectional configuration of the tract wall from the normal condition is exerted by the above anchor assembly or other assemblies illustrated in application Ser. No. 108,889 or any other device which performs that function. Additional or axial stimulation is provided by the compressed follower strands 17. It should be understood that the latter type of stimulation normally is not essential to perform the desired results.

An effective anchor may be formed in which the primary stimulation is axial rather than radial. For exam-

ple, the anchor may include a cervical follower retained at the anterior of the device by a cervical ring in combination with an element which projects from the anchor into a recess which exists in the aforementioned vaginal sphincter-like constriction to retain the posterior side of the anchor.

For ready insertion of the device into the cow's vagina, strands 10 may be compressed into the closed hand of a technician or into a speculum as in the form of a hollow tube, not shown, which is withdrawn after insertion of the device for subsequent outward projection of strands 10. In mature animals, a device within a speculum of 2.5-3.5 inches diameter can readily be passed between the pin bones into the vulva and through the posterior vaginal sphincter-like constriction into the vagina of the cow. After the device is to the anterior side of constriction M, it can expand radially within the vagina of a mature animal without causing undue stress or related behavioral patterns because the animal, such as a cow, is not highly sensitive to the presence of a foreign object in this region of the vagina. By extending the anchor for engagement with the folds of the vagina as illustrated in FIG. 1, the device may be retained within the tract for a substantial period of time since it is engaged without local irritation to the epithelium in portions of the vaginal wall in a manner to inhibit spontaneous expulsion.

In animals of the type having a uterus opening through a cervix into a vagina which require extensive stimulation, the aforementioned vaginal stimulation may be augmented by cervical or uterine stimulation such as by means illustrated in FIG. 2. The cervical stimulator is illustrated in the form of a helical or other shaped element 20 mounted at one generally straight end in a retaining sleeve 21 which, in turn, is retained within a cervical ring 22 by means of radial spokes 23 to permit bypass of the spokes by fluids emitted from the cervix. The other end of element 20 is attached to the uterine stimulator illustrated as an enlarged helical or other shaped element 23 by means of a generally straight connecting link 24 which does not disturb the normally tight posterior os, denoted O, of the cervix. It should be understood that neither the uterine nor cervical stimulator is capable of being anchored in place for substantial periods of time to prevent spontaneous expulsion in the absence of the anchoring device described herein or of the alternative ones described in application A-26130. It is noted that the uterine and cervical stimulators distend the uterus and the cervix, respectively, to provide the desired amount of stimulation. These stimulators are only required in those exceptional cases where more stimulation than can be provided by the vaginal anchor is desired for a particular purpose.

Protective measures are desirable in accordance with the present invention. Exerted pressure should be insufficient to cause extensive cutting or irritation of the tract wall or pressure necrosis in the area of the engaged tract wall or to cause overstimulation of reproductive cycle regulatory mechanisms to thereby prevent undesirable side effects. Furthermore, reproductive tract fluids should be channelled past the area of engagement to minimize fluid stagnation and resultant irritation or infection evolving from growth of microorganisms in the stagnant retained fluid. This is accomplished in the bypass of the spaced-apart hoops 10. In addition, housing 12 may be hollow and open-ended to

provide an open passageway for fluids. Also, strands 10 should be no more rigid than necessary to provide adequate stimulation and to prevent expulsion by animal straining or natural movement. Nylon or plastic strands of 1/16-3/32 inch OD have been found to have the proper amount of flexibility for this purpose. Nylon, polyethylene and other plastics which are biologically compatible materials may be used to construct the device for extended retention in the vaginal lumen without causing irritation.

By way of example, in the cow an anchor of the type illustrated in FIG. 1 having an outer diameter of seven inches and with 12 to 16 plastic strands has been found to be sufficient stimulator and retainer for purposes of the present invention. Of course, the addition of the anterior anchor portion which provides axial stimulation would provide additional stimulating effects, if desired.

It has been found that insertion of devices of the foregoing type into the vagina of a cow engages the vaginal wall for retention in the tract by preventing expulsion by the animal. Furthermore, the radial pressure exerted, which is sufficient to alter the cross-sectional configuration of the tract wall from the normal condition, if applied for a sufficient period of time, causes adequate stimulation of the estrus or reproductive cycle regulatory mechanisms of the animal to change or reset initiation of follicular, luteal or ovulation phases of the animal's reproductive or estrus cycle. When the device is in place for a period greater than about one-half hour, cervical mucus flows and opening of the cervix almost immediately follows. This effect is inferred to be generally associated with an increase in estrogen which is normally precursive of behavioral estrus during a normal non-artificially stimulated reproductive cycle. Removal of the device after cervical mucus flow begins results in an in-phase rise in about one day of progesterone, estradiol, estrone and an LH peak in about 1 day but with a mixed FSH result. However, neither stimulated standing heat nor associated ovulation occur within one or two days after mucus flow, as would be expected in a normal estrus or reproductive cycle.

The continued vaginal implantation of the device beyond a few hours causes a soft spot or small follicle to develop on the ovary in about one to three days. This soft spot may mature into a normal follicle in about five days when the device remains in place.

Continued vaginal implantation of the device beyond two to three days produced the unexpected result that the udders of milking cows were substantially fuller at milking than they would normally be at that time in the reproductive cycle. It may be inferred from this observation that such continued implantation causes accumulation of oxytocin, possibly in the posterior pituitary, with a consequent higher continual release rate of oxytocin than without the device in place. Such high oxytocin release rate is known to result in a fuller udder.

When the device is removed, there is an immediate and dramatic increase in uterine tone which is inferred to indicate a rapid release of a pool of oxytocin, probably from the posterior pituitary.

By leaving the device implanted in the vagina for an indefinite period of time and in excess of, for example, 20 days, the beginning of the reproductive cycle has been artificially changed or reset. This regulation of the timing of the cycle may be employed for contraception

as in human beings by increasing the effectiveness of the "rhythm" method of contraception.

The frequency of this reduction in the timing of the reproductive cycle coupled with the resetting of the beginning of the cycle is an extremely effective aid in artificial or natural insemination. These long implantation time devices are generally of a lower level of stimulation, i.e. smaller in size, and provide less radial pressure than those used in the combined implantation/removal methodology.

Another effective application of the foregoing observations is to implant the device in the animal for a certain minimum time (e.g. at least six to seven days in cows). Thereafter, the device may be removed with the knowledge that at a subsequent time thereafter the animal may be inseminated.

It has been found that neither stimulated standing heat nor ovulation always occur while the device is still implanted. These lacking effects are believed to be the result of an improper balance of hormones.

Removal of the device after a certain minimum time of continuous stimulation may result in standing heat and ovulation but it is not clearly defined from animal to animal. The high occurrence of an apparently normal ovulation with precursor standing heat probably indicates the existence of a proper balance of hormones.

Insertion of a mechanical device of the above general type stimulates endogenous chemicals to modify the estrus or reproductive cycle produces a relatively normal condition with minimal side effects to the animal. This is in marked contrast to the substantial deleterious side effects which result in the use of exogenous chemicals as with implants or feed additives.

Although the foregoing discussion relates primarily to insertion of a device in the vagina of a cow, it should be understood that the method is applicable to animals of the type having similar stimulated response mechanisms and also having a tubular reproductive tract including ovaries. Of course, to accommodate different sizes and shapes of the animals' reproductive tracts and the different cycle times, the foregoing sizes and shapes of the device and timing for adequate stimulation would be modified.

We claim:

1. In a method for inducing early follicle growth and estrus in a prepuberal animal of the type having a vagina terminating at the posterior end in a normally closed vulva and at the anterior end at the cervix of the uterus, said vagina having an annular sphincter muscle between the anterior and posterior ends of the same, utilizing a device including mounting means with an annular surface and spaced-apart yieldable means carried by the mounting means and projecting axially of the annular surface and being disposed circumferentially about an axis generally coincident with the axis of the annular surface, said spaced-apart yieldable means being capable of being compressed to a size so that the device can be readily inserted through the vulva into the vagina, said device being of a length so that it can be disposed between the cervix and the sphincter muscle, the method comprising the steps of inserting the device through the vulva into the animal's vagina into a position anterior of said vaginal sphincter muscle while the spaced-apart yieldable means is compressed, permitting the spaced-apart yieldable means to expand into contact with the vaginal wall to expand the vaginal

wall beyond its normal condition to thereby retain the device within the vagina and preventing expulsion of the device from the vagina by the animal while permitting the vulva to remain closed and permitting said device to remain in the vagina for a period greater than one day so that pressure is exerted on the vaginal wall for said period to induce early follicle growth and estrus.

2. A method as in claim 1 in which the pressure exerted by the device on the vaginal wall is insufficient to cause extensive abrasion of the vaginal wall or pressure necrosis of the vaginal wall.

3. A method as in claim 1 wherein the device is formed to permit flow of reproductive tract fluids past the device in the vagina.

4. A method as in claim 1 in which the device is retained in the vagina for at least five days.

5. A method as in claim 1 together with the step of removing the device when estrus has commenced.

6. A method as in claim 1 in which the animal is of a type having a cervix with a lip which projects into the vagina and in which the device is positioned so that the mounting means engages said lip to assist retention of said device in the vagina and to stimulate the cervix.

7. In a method for inducing early follicle growth and estrus in a prepubertal animal in which the reproductive tract is characterized in that it is defined by a fold-containing wall forming an elongate sheath-like tubular passage with its anterior end leading from the cervix of the uterus and with its posterior end terminating in a normally closed vulva and which has an annular sphincter muscle between the anterior and posterior ends and in which the device is characterized by having mount-

ing means with the mounting means including an annular portion, spaced-apart yieldable means carried by the mounting means and projecting axially of the mounting means and also extending circumferentially about an axis generally coincident with the axis of the annular portion, said yieldable means being deformable from a normal expanded condition to a depressed condition, said yieldable means in said depressed condition being of a size so that it can be readily inserted through the vulva into the passage of the animal, said device having a dimension extending longitudinally along the passage which is such that the device can be disposed between the cervix and the sphincter muscle to permit the vulva to remain in its normally closed condition when the device is between said sphincter muscle and the cervix, the method comprising the steps of compressing the yieldable means and inserting the device through the vulva into the passage so that the device is positioned between the cervix and the sphincter muscle, permitting the yieldable means to expand into engagement with the fold-containing wall to cause expansion of the fold-containing wall beyond its normal condition so that the device will be retained within the passage to thereby inhibit expulsion of the device from the passage by the animal, and permitting said yieldable means to exert pressure against the fold-containing wall for a period of at least one day to cause stimulation of the animal in the vicinity of the fold-like wall to thereby induce early follicle growth and estrus in the animal and removing the device from said passage after estrus has been induced.

* * * * *

35

40

45

50

55

60

65