SECTION I

ORIGINAL ARTICLES

The way I went About Timing Ovulation and Conception

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In the autumn 1924 I had the privilege of going to England for 15 months as a Rockefeller-Fellow to work there in the Department of Pharmacology of University College, London, under Prof. A. J. CLARK who inspired me to study the conduction of contractions in the rat's uterine muscle at the different stages of the oestrous cycle and during pregnancy. For this purpose the uterus was fixed to cork by pins and leads were taken from three points of the uterus and attached to very light levers, and the movements of these levers were recorded optically on bromide paper (Fig. 1). Using this new method of recording the contractions of the horizontally placed uterus I have found that in the dioestrus there is a slow conduction between the ovarian and the middle part of the uterus, and that the vaginal part contracts independently of the other two, which turned out to be the type of uterine movement which demonstrates the inhibitory action of the corpus luteum hormone upon the uterine muscle. A remarkable change takes place under the action of pituitary (Fig. 2). All three parts of the muscle now contract practically simultaneously. It seems that pituitary has induced the same effect in the uterus at the dioestrous period as that which occurs naturally at oestrus and during pregnancy.

Approximately at the same time DIXON and MARSHALL, both of whom became my teachers in Cambridge in April 1925, have shown the existence of a relation between the cyclic activity of the ovary and the pituitary gland. They state that the pituitary gland secretes into the

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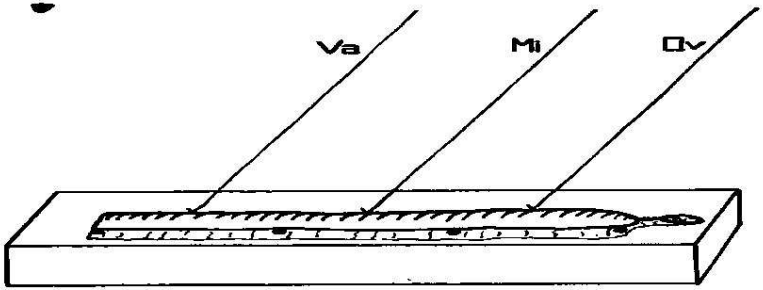

Fig. 1. Diagram showing the method of recording contractions of the uterus from three leads simultaneously.

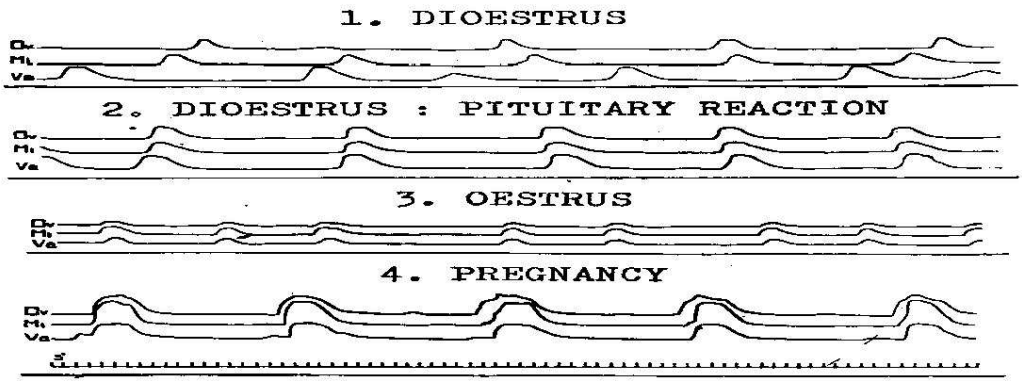

Fig. 2. In all 4 cases simultaneous records were taken of the movements of the ovarian, the middle and the vaginal part of the uterus. 1. Uterus during dioestrus. The ovarian and middle part contract in sequence, while the vaginal part moves independently. 2. The same uterus under pituitary action which causes a short wave of contraction to travel rapidly down the whole uterus. 3. Uterus in destrus. Contractions pass down the whole uterus as under pituitary. 4. Uterus in second week of pregnancy. Strong contractions pass quickly down the whole uterus.

upon whether corpora lutea are absent or present, that is to say, the secretion of the ovary in the absence of fully formed corpora lutea has a specific stimulating effect in promoting pituitary secretion. Finally, they came to the conclusion that, as the corpus luteum is supposed to undergo retrogression shortly before the close of pregnancy, the revival of the ovarian secretion causes a sudden increase of pituitary secretion, which by its action on the more sensitive uterine muscle brings about labour. Thus, it is the increase of the pituitary secretion that was looked upon as an important factor in starting parturition.

These two independent observations suggested that the change of the movements of the uterine muscle that occurred from the dioestrous period to oestrus might be due only to a varying decrease and increase of pituitary secretion; and in pregnancy it would be due to a steady increase, or even as DIXON and MARSHALL suggested, to a sudden increase, of pituitary secretion at the end of pregnancy, finally bringing about labour. If this should be the case, then it seemed reasonable to assume that it might be possible, by creating these conditions artificially, that is by injecting an appropriate quantity of pituitary into the body of a rabbit, to induce parturition at any time of pregnancy.

The results of this investigation carried out in the *Institute of Animal Nutrition* of the University of Cambridge under *Prof. F. H. A.* MARSHALL and *Dr. J.* HAMMOND may be divided into three groups, namely, those concerning the time from the 32nd backwards to the 29th day of pregnancy, from the 28th to the 18th day of pregnancy and from the 17th to the 1st day of pregnancy (3).

GROUP 1.

In short, it was possible to induce parturition by injecting a certain quantity of pituitary on the 32nd, 31st, 30th and 29th day of pregnancy. The minimum dose of pituitary strong enough to cause delivery on the 32nd and 31st day appeared to be equal to only 0.0075 mgrm. of moist gland per kilo rabbit, rising to 0.3 mgrm. on the 30th day, and to 0.6 mgrm. on the 29th day of pregnancy. The complete

delivery of the litter could always be induced, and this depended only on the amount of pituitary injected.

GROUP 2.

It may be said at once that this period is characterised by the fact that no quantity of pituitary was ever found sufficient to induce abortion during the day in which the experiment was carried out. As a result of this over 10 hours prolonged pituitary action, however, the foetuses were killed inside the uterus, and were cast some days afterwards. To sum up, it may be explained that the effect of pituitary action upon the pregnant uterus during this period consists of some destruction of the tissue of the spongy layer, and that this increases considerably with the advance of pregnancy and causes a corresponding amount of bleeding which finally brings about foetal death and abortion.

GROUP 3.

This group of experiments is characterised by the fact that whatever reasonable quantity of pituitary extract was injected into a rabbit in this period of gestation it was never possible to disturb pregnancy.

My own interpretation of these facts is as follows: there is no increase of pituitary secretion towards the end of pregnancy, but there is, corresponding to the growth of each muscle cell with every day, a regular rise of contractility of the muscle. The larger the muscle cell grows, the greater its ability to shorten itself. It is in consequence of this fact that the effect of pituitary extract upon the uterine muscle increases steadily the further pregnancy is advanced.

At the end of my researches in Cambridge I made an important observation which enabled me to record directly the increase of contractility of the uterine muscle during pregnancy. It was a piece of good fortune to open two rabbits and to find that they were pregnant in one horn only while the other was empty and strikingly shortened by its contraction. Under the impression of this extraordinary observa-

Fig. 3

Fig. 3. Unilateral pregnancy in the rabbit after tubal sterilisation on one horn of the uterus.

Fig. 4

Fig. 4. This picture illustrates the growth of the sterilised horn of the rabbit's uterus during an unilateral pregnancy. The increase of weight of this horn is 1:5 caused by the hormones produced in the pregnant horn.

tion I thought at once of the possibility of using these empty horns of pregnant rabbits for experiments in vitro and of studying upon them all the changes of the uterus taking place during the course of pregnancy. With this plan in my mind I returned to the clinic of gynaecology and obstetrics of the university in Graz, Austria, and built up there a new laboratory with the assistance of the Rockefeller Foundation. When this laboratory was equipped in the autumn 1926 I began to sterilize a large number of rabbits by cutting the Fallopian tube on one side and letting them become pregnant in the uterine horn of the other side (fig. 3). Shortly after I had begun to experiment on this sterilized horn which grows considerably (fig. 4) under the influence of the hormones produced by the pregnant uterus of the other side, I observed

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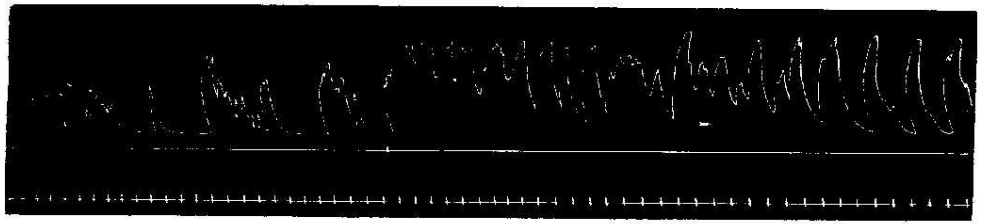

Fig. 5. Pituitary reaction 21 hours after ovulation.

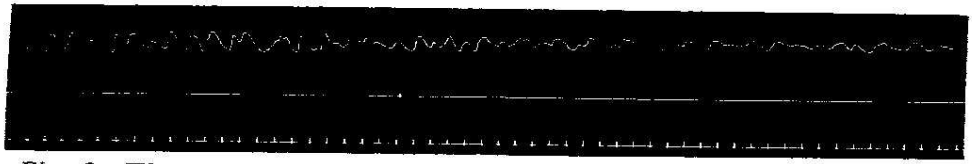

Fig. 6. The uterus shows no pituitary reaction 22 hours after ovulation.

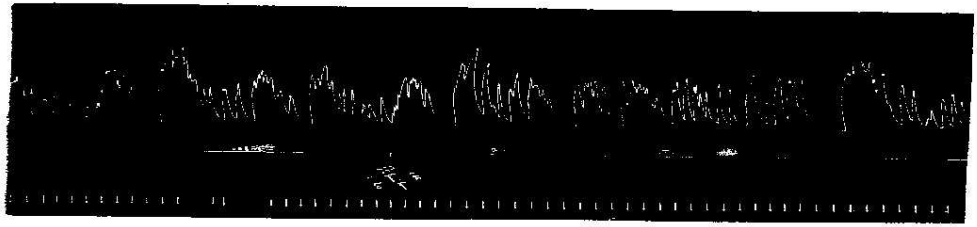

Fig. 7. The uterus does not show any influence of pituitary 9 hours after removal of the corpora lutea.

on the 31st January 1927 for the first time that the uterus did not react to pituitary. This peculiarity of the uterine muscle in early pregnancy seemed to me of particular interest and led me to discover that it was caused by the hormone of the corpus luteum. As soon as the corpus

luteum begins to act the uterus of the rabbit loses its sensitivity for pituitary within 22 hours after ovulation (Fig. 5 and 6) and regains its reactivity to pituitary 10 hours after the corpora lutea are removed (Fig. 7 and 8). All these and many other facts were found out on the uterus of the pseudopregnant rabbit which seemed particularly suited for the investigation of the function of the corpus luteum in the absence of pregnancy.

When I had completed my researches on the uterus of the pregnant and pseudopregnant rabbit I read a paper on the causes of the onset of labour before the Gynaecological Society of Berlin in May 1928 and had thereafterwards for the first time the opportunity of seeing a hysterosalpingography which was demonstrated to me by Dr. G. P. F. SCHULTZE. When I saw these strong movements of the human

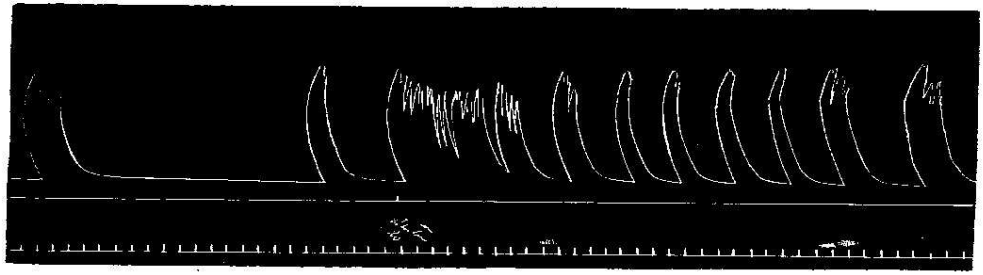

Fig. 8. The uterus begins to react to pituitary lo hours after the removal of the corpora lutea.

uterus on that day and I heard that sometimes the uterus could be seen quite motionless and sluggish I said to myself that this change of behaviour of the human uterus must also be due to the action of the corpus luteum upon the uterine muscle after ovulation. With this new experience in my mind I returned to Graz and began at once to construct an apparatus for the registration of the movements of the human uterus

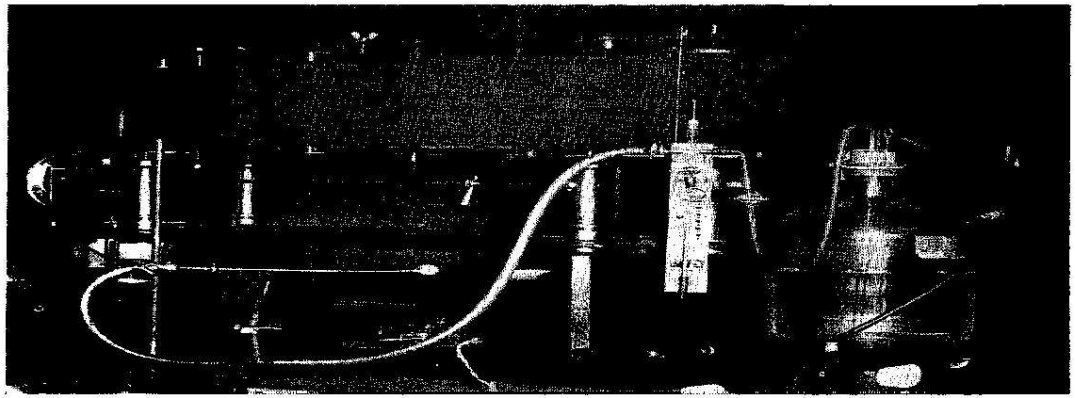

Fig. 9. The apparatus for the registration of the movements of the human uterus in situ.

in situ (Fig. 9). With this new method which was afterwards improved by introducing a small rubber-bag into the uterine cavity I examined first of all 13 normally menstruating women on different days of the menstrual cycle. After 49 examinations of this kind I had accumulated a sufficient number of facts to allow me to state that the human uterine muscle loses its sensitivity to pituitary (Fig. 10 and 11) exactly the same as the rabbit's uterus and that there exists a regular relationship between the beginning of this action of the corpus luteum upon the uterus and the following menstruation. Considering the fact that in the rabbit the action of the corpus luteum upon the uterine muscle is already detectable 22 hours after ovulation I came to the conclusion that in the woman ovulation takes place spontaneously on the 15th day before the onset of menstruation quite independently of the length of the menstrual cycle. This regularity of the relationship between ovulation and men-

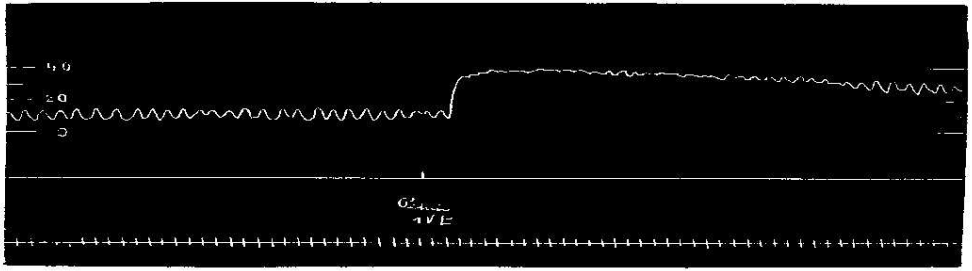

Fig. 10. The pituitary reaction of the human uterus on the day of ovulation (15th day before the onset of menstruation).

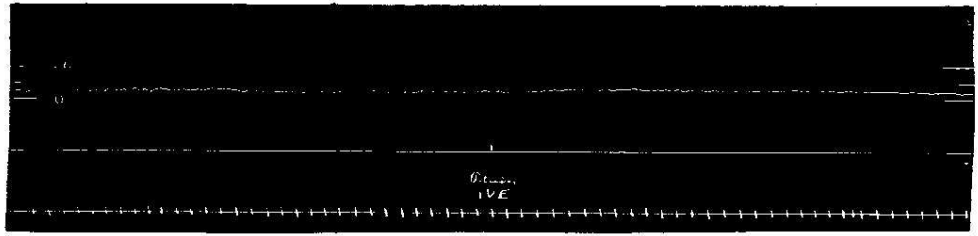

Fig. 11. No pituitary reaction of the human uterus on the 9th day before the nset of menstruation.

struation is caused by the constant duration of the function of the corpus luteum which lasts 14 days under physiological conditions.

As I had received a thorough knowledge of the viability of the mammalian germ cells from F.H.A. MARSHALL and J. HAMMOND in Cambridge it was not difficult for me to conclude that when there is a definite time of ovulation there must be as well a definite time of conception. Therefore, I stated that a woman can only conceive during 5 days of her menstrual cycle, that is to say, during the 3 days before

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ovulation, on the day of ovulation and the day afterwards, and that the best day for conception will be the day before ovulation. In other words, a woman with a menstrual cycle of 28-30 days can become preg-

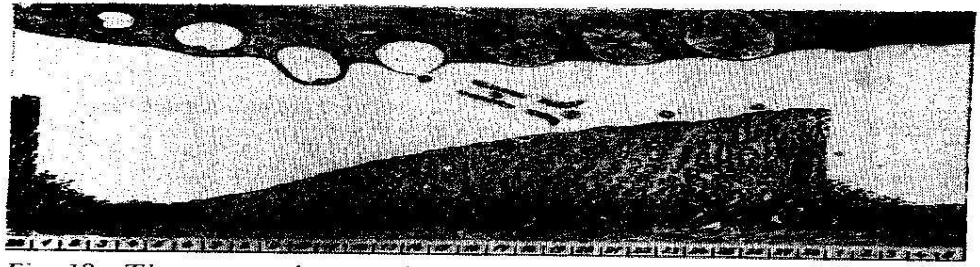

Fig. 12. The course of events in the ovary, tube and uterine cavity during the menstrual cycle of 28 days without conception.

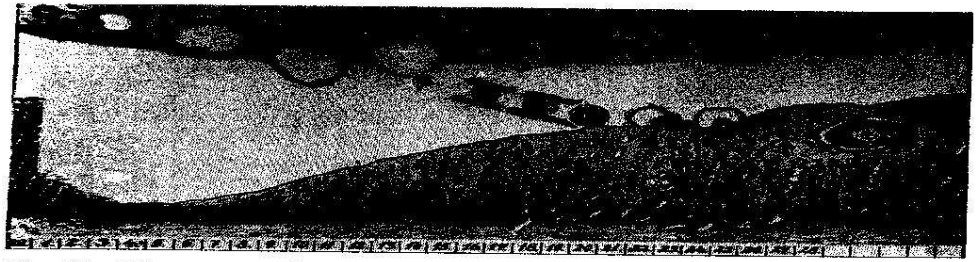

Fig. 13. The course of events in the ovary, tube and uterine cavity during the menstrual cycle of 28 days when conception occurs.

nant only in the time of the 11-17th day of this cycle; all the other days are naturally sterile. In order to explain the course of events which finally lead to pregnancy I produced two drawings (Fig. 12 and 13) which should have made it easy to understand why ovulation must

take place 14 days previous to menstruation. Considering the fact that the fertilized ovum needs at least 7-9 days to reach the stage of development when it can implant itself and produce the necessary amount of choriongonadotrophine to prevent the degeneration of the corpus luteum in order to suppress menstruation, ovulation must take place at the time indicated by the action of the corpus luteum upon the uterine muscle. In March-April 1929 I was fortunate enough to investigate a case of sterility with this new method and discovered that this woman always ovulated as late as on the 9th or 10th day before menstruation, and that this habitual delay of ovulation was the real cause of her sterility. It was the first case of corpus-luteum-insufficiency observed and realized as a cause of sterility in a 35 year old woman with a normal anatomy of her sex organs.

All these observations and conclusions published in the summer 1929 (*Münch. Med. Wschr. 1929,* 1157 and *Zbl. Gynäk. 1929,* 2193) aroused considerable attention because it was believed and taught up to that time that a fertile woman can conceive on any day of her menstrual cycle. A large number of authors took up the bag-method and repeated my researches carried out for the determination of the time of ovulation. Some of them confirmed my findings, while the others obtained entirely contrary results. These contradictory observation could be easily explained by an important difference in the technique which two groups of authors employed for their experiments. The authors who confirmed my observation that the human uterus loses its reactivity to pituitary in the premenstrual phase of the cycle used exactly the same low intrauterine pressure I recommended in the description of this new method; the other group of authors did not follow my recommendation and used an unphysiologically high intrauterine pressure which distended the uterus. Under these quite different experimental conditions they found that the uterus gives the strongest reaction to pituitary at the time when the corpus luteum is present. After I had studied the results and tracings of all the papers concerning this question I found out that there is a threshold-pressure above which the reaction of the

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uterus to pituitary is reversed: all authors like myself who used a pressure as low as possible under 30mm. Hg. obtained the same results as I described in my original paper; the other group of investigators who made their contradictory observations employed unconsciously a pressure more or less far above 30 mm. Hg. But quite independent of the level of the intrauterine pressure employed, the uterus shows a distinct change in its reactivity to pituitary before and after ovulation. A critic of my work who did not grasp the importance of this methodical detail made the following remarkable statement in the *British Journal of Obstetrics and Gynecology, April 1951:* "Indeed, it may well be that KNAUS has built a correct theory on some incorrect observations and premises".

This new method also enabled me to prove the existence of the anovulatory cycle in the woman. In the summer 1933 I had the opportunity of applying this method to a 20-year old woman 9 times during the first 3 cycles after a normal delivery. Her uterus showed in the ante and in the post-menstruum the same reactivity to pituitary and revealed by this attitude the absence of ovulation and corpus-luteum-formation during the time of lactation as confirmed on the endometrium by LASS, SMELSER and KURZROCK.

At the end of this story about the way I went to work to find the time of ovulation and conception it might be of interest to learn something of the acceptance of this provocative doctrine by the medical world. It was curious to observe that my statement that the ovum is liable to be fertilized only for a few hours after ovulation experienced no contradiction and was at once accepted. But no one would at first believe that the spermatozoa do not retain their fertilizing power in the female genital tract longer than 30-40 hours after they are deposited there. It was necessary to do much more work on this question to prove the corectness of this statement and it took 10 years until it was finally accepted. I had to publish more than 80 papers in German, English, French and Italian, dealing with many details of these researches, and I had actually to fight for more than 20 years for the acceptance of the fixed time of ovulation until so much practical experience had been accumulated that the number of sceptics, at first very large, gradually

diminished. Today, as many other methods introduced for the determination of the time of ovulation have confirmed my findings, the 15th day previous to menstruation is widely recognized as the time of ovulation. Everyone who can read German or Spanish will find all the details of this research work and the corresponding world-literature of the last 100 years (more than 2000 items) in my book: *The Physiology of Human Procreation (Die Physiologie der Zeugung des Menschen,* 4. Auflage, Wilhelm Maudrich, Wien, and *La Fisiologia de la Reproducción en el Hombre,* Segunda edición, Espasa-Calpe, Madrid).

The practical value of my doctrine is best shown by the fact that there are 20 German editions of my work: *Woman's fertile and sterile days and their accurate calculation,* meant for the general public, besides editions of this book in English, French, Italian, Spanish and Norwegian.

Summary

A short description is given of the course of the author's own researches which he began as a Rockefeller Fellow and physiologist in 1924 in England and which enabled him in summer 1929 to state that there is a "safe period" during the menstrual cycle which can be accurately calculated if the individual type of the menstrual cycle is known. This progress in the physiology of human procreation has been already widely utilized for deliberate or planned conception (artificial insemination) as well as for the natural control of conception all over the world.

Sumario

Se hace una breve descripción del curso de las investigaciones hechas por el autor, las cuales inició como miembro de la Institución Rockefeller y como fisiólogo en Inglaterra en 1924; esto le permitió establecer en el verano de 1929, que hay un "período seguro" durante el ciclo menstrual que puede ser precisamente calculado, si se conoce el tipo individual del ciclo menstrual. Este progreso en la fisiología de la procreación humana ha sido ya ampliamente utilizado en todo el mundo para la concepción deliberada o planeada (inseminación artificial), así como también para el control natural de la concepción.

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Sommaire

On donne une courte déscription du cours des investigations propres de l'auteur, lesquelles il commença comme membre de L'Institution Rockefeller, et comme physiologist en Angleterre en 1924. Tout celá lui a fait capable, á l'été de 1929, d'établir qu'il y a une "période sûre" pendant le cycle menstruel, que peut être précisement calculé, si le type individuel de cycle menstruel est connu. Cet progrès á la physiologie de la procreation humaine a eté déjà utilisé amplement, par tout le monde, por la conception deliberée ou planée (insemination artificielle), comme aussi pour le contrôle naturel de la conception.

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