

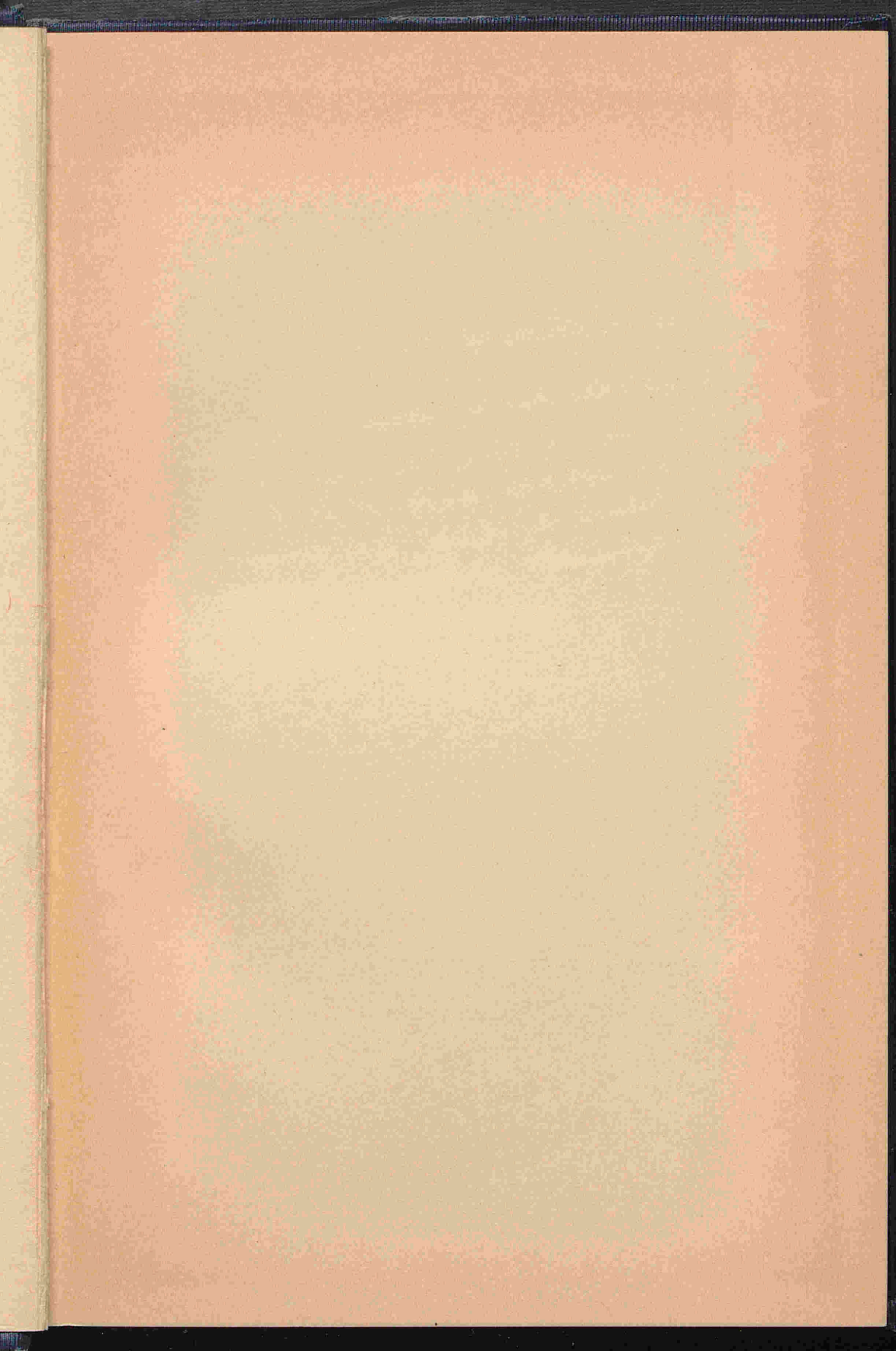
FEMALE
SEX HORMONOLOGY

WILLIAM P. GRAVES, A.B., M.D.

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FEMALE SEX HORMONOLOGY

A REVIEW

BY

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LEGADO POR
LA FAMILIA DEL
Dr. MARAÑÓN

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TO THE DISTINGUISHED MEN OF RESEARCH
WHO HAVE MADE THE BRILLIANT DISCOV-
ERIES HEREIN RELATED THIS BOOK IS GRATE-
FULLY DEDICATED.

INTRODUCTION

IN presenting a review of the advances in the knowledge of female sex physiology the author hastens to say that his part in this brilliant enterprise has been only that of an intensely interested clinical spectator. Always there has been the hope that there would issue from the achievements of the biological laboratory a new therapy capable of solving the baffling problems of functional disease in women. Expectation and disappointment have followed each other in frequent and disheartening sequence, but the startling discoveries of the past few years offer a fresh promise of success that can but stimulate the most discouraged clinician.

This review was originally undertaken to furnish a concrete picture of a complex subject for the author's personal use in the lecture room. But as the work neared completion the thought occurred that it might be of use to those members of the profession who do not have ready access to a literature much of which is scattered in technical and foreign journals.

The plan of the book has been to follow in chronological order the evolutionary steps by which a department of medicine has within thirty years risen from an insignificant position to one that may almost be dignified as a distinctive science. The book is therefore designed primarily for the student who has little previous knowledge of the subject.

The review does not pretend to be exhaustive, only such material being chosen that seems to have led, or promises to lead, to new advances. This of course is an uncertain policy for as the game proceeds the pawns will necessarily be differently placed.

A Glossary has been appended which, it is hoped, may prove to be useful to the student not only for the purposes of reference but as a means of reviewing the essentials of the subject. Under the heading "hormone," a list of some of the proprietary hormone preparations is given properly classified as to the active principle which each represents.

The choice of a bibliography has been something of a problem. A too extensive bibliography is bewildering and less useful than a small one. The question has been decided by including those articles which the author has personally read, and to these have been added a few gleaned from abstracts or book references. Doubtless some important contributions have been omitted. Each of the articles included in the list has attached to it a competent set of references so that the serious reader can without difficulty unearth the information that he wishes to find. In order to add value to the list of references the title of the paper is given in each case.

Finally it must be emphasized that the great subject of sex physiology is not at the *close* but at the *beginning* of its ultimate development. New discoveries, many of them contradictory to preconceived ideas, are appearing rapidly, and the scene is constantly shifting. Some of the most recent work, especially that which deals with the body chemistry, has been omitted since it has not yet been sufficiently coordinated with the more strictly physiologic phases to permit concrete description.

WILLIAM P. GRAVES.

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Female Sex Hormonology

CHAPTER I

EARLY HISTORY

THE ovaries have a twofold function, first, an excretory one of producing and discharging ova and, secondly, an incretory one of regulating the growth and maintaining the functions of the genital organs. Von Baer in 1827 demonstrated the mechanism of ovulation, and for long after it was believed that the stimulation of this process accounts for those phenomena that are now known to be the result of internal secretions.

The first suggestion of incretory properties in the ovaries was one of inference. In 1849 Berthold laid the cornerstone of the science of endocrinology by showing that after castration of cockerels the typical appearances of the castrate are prevented by a reimplantation of the testicle. Little attention was paid to this important observation and it was not until forty years later that the work of Brown-Séquard, who also experimented on male animals, aroused interest in a new field of research.

Proof that the Ovary is a Gland of Internal Secretion.—The present knowledge of the physiology of the female reproductive organs was initiated by Knauer who in 1896 showed in experimental animals that transplantation of ovaries prevents the usual atrophy of the uterus that fol-

lows ovarian extirpation. This experiment proved that the ovaries must produce an internal secretion which, acting through the medium of the blood, preserves the integrity of the genital organs. Knauer's conclusions were immediately verified by other investigators (Grigorieff, Ribbert, Rubinstein). In the year 1900 Halban added a new and important phase to the subject by showing that if an immature female guinea-pig is castrated and an ovary transplanted subcutaneously *normal puberty occurs*. This proved that the ovaries produce an internal secretion that governs the anatomical and physiologic *development* of genital organs.

Halban's experiments were confirmed and amplified by other researchers (Lipschutz, Steinach, Kolb, Pettinari, and others) who implanted ripe ovaries in immature animals and produced precocious growth and function of the genital organs. Implants of ovaries in senile animals to a certain extent rejuvenated them in appearance and sexual behavior.

Simon in 1904 was the first to show that the incretory function of the ovary does not depend primarily on the ova-producing mechanism as had been supposed since the time of von Baer. He found that in ovarian grafts which have "taken," the follicles degenerate whereas the interstitial tissue retains its integrity. Simon's observations were confirmed by Marshall and Jolly and others.

These early experiments proved beyond contention that *the ovary is an organ of internal secretion that governs the onset of puberty and maintains during sexual life the functions of the reproductive apparatus*.

From the first, clinical attempts at substitution therapy were made by administering ovarian extracts for all kinds

of menstrual disorders but with little success, a failure that has clouded the career of ovarian hormonology up to the present time. But the result of animal experimentation with these same extracts has been a different and remarkable story.

Jentzner and Beuttner in 1900, using simple saline decoctions and dried extracts, were unable to replace ovarian function in castrated animals as had been done by implants. Bucura a few years later reached the same negative results. Adler in 1912 was the first to produce sexual activity in ovariectomized animals by the injection of watery extracts of ovary. As Dodds in a recent lecture remarks, Adler's work marks the "turning point in the history of the search for the ovarian hormone." The interesting account of how first one and then a second hormone was identified will be resumed later on. But first it is necessary to review the studies in comparative physiology that made the discoveries possible.

CHAPTER II

THE SEXUAL CYCLE IN ANIMALS

THE necessity of using animals in the experimental search for the ovarian hormone led to intensive studies in animal sex physiology. Familiarity with this phase of the subject is essential to a clear understanding of the recent discoveries relating to the hormonology of the human female, and the student is therefore urged to read this chapter with particular care.

A universal characteristic of sexual activity throughout the animal kingdom is rhythm. Periodic sex manifestations vary widely in different species ranging in time from the daily ovulation of the hen to the flight of the seventeen-year locusts. In many animals the cycle is marked by certain outward signs that indicate the height of reproductive fertility. Darwin cites among many examples the bright coloration of birds and insects, and the odorous secretions of reptiles during the breeding season. Many of the higher mammals manifest the peak of the cycle by seasonal exhibitions of sexual excitement, for which the word *oestrus* (Greek "gadfly") is applied to females. Rut (Latin *rugire*, to roar) is properly applied only to those male animals, such as the stag or boar, that are fertile only at certain seasons. Heat and the German word *Brunst* are used synonymously with *oestrus* or rut. To cite a few examples, in female animals, the domestic pig has a three-day *oestrus* period occurring about every three weeks throughout the year; the mare and cow have a somewhat similar cycle.

Oestrus.
Rut
Brunst
Heat

The dog is in heat for about a week twice annually. The rhythm of the oestrous periods is influenced by environment. Thus the cat when in a wild state is said to have only one sexual season per year, whereas under domestication it exhibits three or four. In other animals like the deer captivity increases the frequency of the sexual cycles.

La domesticación aumenta el ciclo sexual.

The periodic cycle is not always marked by outward signs of sexual excitement. In the human species neither desire nor the act of mating occurs at any special time, but the periodicity of the sexual cycle is marked by menstruation, the same being true in certain of the higher monkeys. In some of the lower animals, like the rodents, there are no obvious external signs of a cycle in the form of sexual behavior, but, as we shall see later, there occur slight signs of periodic bleeding that seem to "adumbrate" the phenomenon of menstruation seen in man and the primates (Hartman). In 1917 Stockard and Papanicolaou studied the guinea-pig and made the momentous discovery that the ovulation period (which corresponds to oestrus), though it produces no outward signs, is accompanied by marked hypertrophic changes in the vaginal epithelium that can be easily detected by microscopical examination of smears. Other laboratory animals in which external signs of the sex changes are inconspicuous were studied and similar results obtained (rat, Long and Evans; mouse, Allen; rabbit, Pelkan). This discovery was a great step in advance for it furnished the means of measuring accurately the sex cycles of laboratory animals.

Bergman's discovery of menstruation in the rodent.

It is obvious, then, that the sex cycles of animals may according to the species be detected externally in three different ways: first, by periodic exhibitions of sexual ex-

citement (dogs, pigs, cattle); secondly, by menstruation (humans, primates); and thirdly, by vaginal changes in the epithelium (laboratory animals).

*Impressed
de la
palabra
oestrus*

At this point it is necessary to pause for a moment to explain a confusion of terms caused chiefly by the double use of the word *oestrus*. In its original sense *oestrus* means sexual desire and was first applied to those animals which manifest the sexual cycle by their outward behavior. When Stockard and Papanicolaou discovered in rodents the secretory changes of the vagina accompanying ovulation, the word *oestrus* was also applied to this histologic process, although the animals in question do not then show the outward signs of excitement which the word originally signified. Further confusion was wrought by the early idea that menstruation of the human species corresponds to *oestrus* of the lower animals, which as we shall see later is not the case. The word *oestrus* as it is most commonly used at the present time relates to the specific genital changes that can be induced in laboratory animals by the injection of certain ovarian and hypophysial substances.

The word *oestrus* is modified by numerous Greek prefixes. Thus the adjective *monoestrous* (note the "ous") is applied to those animals that mate only once a year, like the wolf and fox and some of the deer family. Animals that have more than one *oestrus* season per year are said to be *polyoestrous*. Certain animals that are monoestrous in the wild state become polyoestrous in captivity or under domestication. The *oestrous* cycle was divided by Heape into various stages. *Pro-oestrus* (also *pro-oestrum*) signifies the preliminary stage immediately preceding the active stage of *oestrus* and this is marked by definite changes in the genital tract. The period of quiet following the active *oestrus* is called *di-oestrus* in cases where *oestrus* recurs at frequent intervals as in the pig. If the interval is a long one as in the deer or fox it is called *anoestrus* (*i. e.*, no *oestrus*). The word *metoestrus* is used to describe a midperiod of regressive changes that occurs in a few animals that do not ovulate spontaneously. *Postoestrus* is a more recent term, and is used for convenience in describing the relationship between *oestrus* and menstruation.

CHAPTER III

SEX CYCLES IN THE OVARY

IN the preceding chapter we have shown that the universal sexual rhythm is expressed in certain animals by external observable signs and have intimated that there also take place morphological changes in the genital tract, periodic in character but not always outwardly apparent. We shall now review in this and the following two chapters the various *cycles* that occur in the individual organs of the reproductive tract, preparatory to correlating them with present knowledge of the sex hormones.

Ovulation.—The discovery of oestrous changes in the vagina of rodents led to an investigation of the time relationship between oestrus and the already well-known changes in the ovary described by the term "ovulation." The processes of development and ripening of the graafian follicle need not be repeated here. Suffice it to say that in the last few days of maturity preceding rupture the follicle increases rapidly, undergoing characteristic changes in the theca interna cells, and a loosening of the attachment of the ovum to the granulosa cells. The ovum itself reaches the stage of maturation. It was found in the study of several species (Robinson, Corner, Seckinger, Long and Evans) that this stage of follicle maturity is contemporaneous with pro-oestrus and that in most animals the ripe follicles rupture spontaneously during oestrus. This establishes a general law that oestrus and the culmination of ovulation are

rupture follicle
= oestrus

coincident in animals that exhibit a definite oestrus. An apparent exception to this is the fact that in three animals (ferret, rabbit, domestic cat) the follicles do not rupture and discharge their ova unless copulation occurs. In the absence of mating the follicles and ova degenerate. *The preliminary periodic development of the follicles, however, takes place exactly as in other animals.*

*the incidence of
rupture for
ovulation.*

The ovum after discharge passes through the fallopian tube into the uterine cavity where, if it is not impregnated, it degenerates. According to Corner the ovum, whether fertilized or not, reaches the uterine cavity in about three days "with singular unanimity regardless of the species and the widely variant length of the tube."

In the dog the passage of the ovum requires about a week's time. Long and Evans found that in the rat unfertilized ova do not pass beyond the last part of the fallopian tubes. In the opossum the ova reach the uterus one day after ovulation (Corner).

If impregnation does not take place the sexual cycle ends with the death of the ovum, to be resumed after the time interval typical of the individual species. Fertilization occurs in the fallopian tube. The fertilized egg reaches the uterus on the fourth day and is implanted on the prepared soil of the endometrium, the method of implantation and placentation varying widely with the species. With impregnation the whole period, including oestrus and gestation, is usually referred to as the *reproductive cycle* in contradistinction to the *sexual cycle* used when pregnancy is absent.

*cycle actually
cycle reproduction*

The Corpus Luteum.—When the graafian follicle has ruptured and discharged its ovum the walls formerly lined with rows of granulosa cells rapidly assume an entirely new structure made up of large epithelioid fat-laden cells lying

in a rich network of capillaries. This body when fully formed has a characteristic yellow color from which it derives its name *corpus luteum*, though during the first part of its growth it actually possesses a grayish hue. The histogenesis of the corpus luteum cells is still a matter of discussion and need not here be detailed. Suffice it to say that according to most authorities the greater part of the lutein tissue is evolved from an enlargement without multiplication of the granulosa cells of the graafian follicle. The exact part played by the cells of the theca interna is uncertain and probably differs in different species (Corner).

grape body
corpus luteum

If the ovum of a given follicle becomes fertilized the corpus luteum formed from that follicle grows somewhat larger and persists until the end of the pregnancy. If the ovum remains unfertilized the corpus luteum persists "at least as long as the time required for an embryo (of the particular species) to become implanted in the uterine cavity." It then begins to regress (excepting in the mouse and rat) before the occurrence of a new ovulation and hence of a new corpus luteum (Corner).

corpus luteum
it grows and
regress, it
regress and
fertilized

It is obvious that the function of the developing graafian follicle is primarily that of nourishing and discharging the egg, that is to say it is excretory in nature. It also has a secondary incretory function (to which we have already alluded and which will in due time be explained). The function of the corpus luteum, on the other hand, is purely incretory, its product being quite distinct from and antagonistic to that of the growing follicle.

Function of the Corpus Luteum.—It is now necessary to trace the steps by which our present knowledge of the function of the corpus luteum has been acquired. It started

early in this century with the far-sighted speculations of Gustav Born, who noted that in placental mammals, and in them only, a fully developed corpus luteum is always found to have reached its peak just at the time when the embryo is attached to the uterus and the placenta is beginning to form. He also observed that from the first days of pregnancy a decidual reaction begins to appear in the stroma cells of the uterine mucosa. Born was the first to suggest that these changes in the uterus are the result not of some stimulus of the ovum-mechanism but of an internal secretion of the corpus luteum which prepares the uterine mucosa for the reception and embedding of the egg. Born died in the midst of these speculations and the work of proving them experimentally was turned over to his pupil, Fraenkel.

Fraenkel selected rabbits for his experiments since it was known that in them placentation is of the decidual type and that it begins about six days from the time of ovulation. Moreover, the time of ovulation could be accurately determined since it was known that rabbits ovulate only on coition. Fraenkel reasoned that if Born was right in believing that placentation depends on an inner secretion of the corpus luteum it would be prevented if during the six days after coitus (*i. e.*, ovulation) the ovaries should be extirpated or the corpora lutea destroyed. Accordingly, during the critical six-day period he removed both ovaries in some animals, using as controls animals with only one ovary removed. In others he cauterized the corpora lutea alone, controlling these by cases in which he traumatized only the ovarian tissue without injuring the corpora. A large series of animals was observed and the results uniformly confirmed

humans
max. in
del corpus
luteo

Born 1
Fraenkel

See description
of corpus
luteum, in -
p. 100. See
modification
of dec. during the
six days after
coitus. 1.
pro the female
to provide

Born's hypothesis, for all the control animals became pregnant whereas those in which the corpora lutea were extirpated or destroyed failed of pregnancy. Fraenkel's work was amply verified by others and constitutes one of the cornerstones on which modern ovarian hormonology rests.

Another classical experiment always mentioned in giving proofs of the internal secretory function of the corpus luteum was that of Leo Loeb, published in 1907. He showed that the endometrium having been sensitized by the corpus luteum is stimulated to decidual growth (*i. e.*, maternal placenta) by the irritating effect of the embryos in the uterine cavity. Using guinea-pigs, after unfertilized ovulation (copulation with vasectomized bucks), he inserted in the uterus a foreign object, like a piece of glass, on the day on which the embryo would have been attached if the animal had been pregnant. In each case there grew at the site of trauma a tumor made up of decidual cells, which rapidly receded. At no other time of the sexual cycle was he able to produce such a deciduoma (or placentoma) nor could it be accomplished at that time if the ovaries were removed or the corpora lutea cauterized. This experiment again proved that the corpus luteum secretes a hormone which prepares the endometrium for nidation of the egg. Loeb's work was repeatedly confirmed in other animals that exhibit a decidual placentation (Frank, Corner and Warren, Long and Evans, Gasbarrini, Biedl, Peters and Hofstätter, Hammond). Fraenkel and his followers concluded from these observations that the corpus luteum produces "the" essential hormone of the ovary. How this theory was changed will be told in Chapter V.

from the
decidua
corpus luteum
secretes
hormone
which
prepares
the endometrium
for nidation.

CHAPTER IV

SEX CYCLE OF THE HUMAN UTERUS AND ITS CORRELATION WITH THAT OF THE OVARY

The Uterine Cycle.—Soon after the discoveries relating to the cycle and function of the corpus luteum described in the preceding chapter, Hitschmann and Adler undertook a study of the endometrium with reference to the different stages of the menstrual cycle. For this work they had plenty of material for in the earlier days of operative gynecology a curettement of the uterus was almost a routine procedure, the various thickenings of the endometrium being looked upon as a form of chronic inflammation. The observation that the uterine mucosa passes through definite phases each month had been made by Brenneke over thirty years before but little attention had been paid to it and it remained for Hitschmann and Adler to reveal one of the most important phenomena of pelvic physiology.

These investigators found that the endometrium throughout the menstrual cycle is in a constant state of change. Immediately after menstruation there is a rest stage in which the glands are small and tubular. Soon the entire mucosa begins to hypertrophy. The glands become lengthened and tortuous; the epithelial lining becomes higher; and the surface of the mucosa swollen and uneven. On account of the evident hypertrophy of all the elements of the mucosa this has been termed the *proliferative* stage. About eight days before the next menstruation the endometrium assumes a



Fig. 1.—Endometrium in the rest stage immediately following menstruation. Note the simple tubular glands, some seen in longitudinal, others in cross-section.

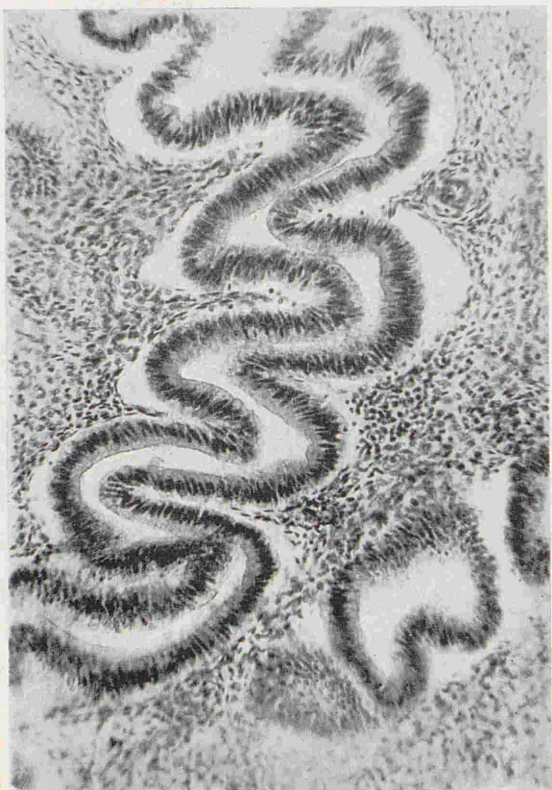


Fig. 2.—Endometrium in the proliferative stage. The whole membrane is thickened. The glands show active growth being greatly lengthened and of a tortuous snaky form.

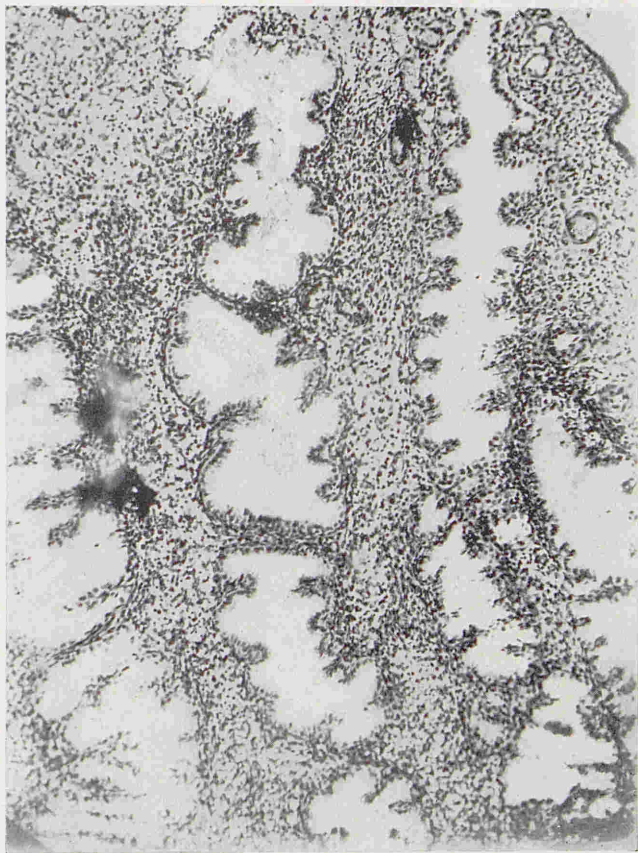


Fig. 3.—Endometrium in the premenstrual (pregravid, progestational secretory) stage. The whole membrane is still more thickened. The glands are dilated with secretion and have a typical saw-toothed, tufted appearance that is always unmistakable. The epithelium is high and of the beaker-shaped secretory variety.

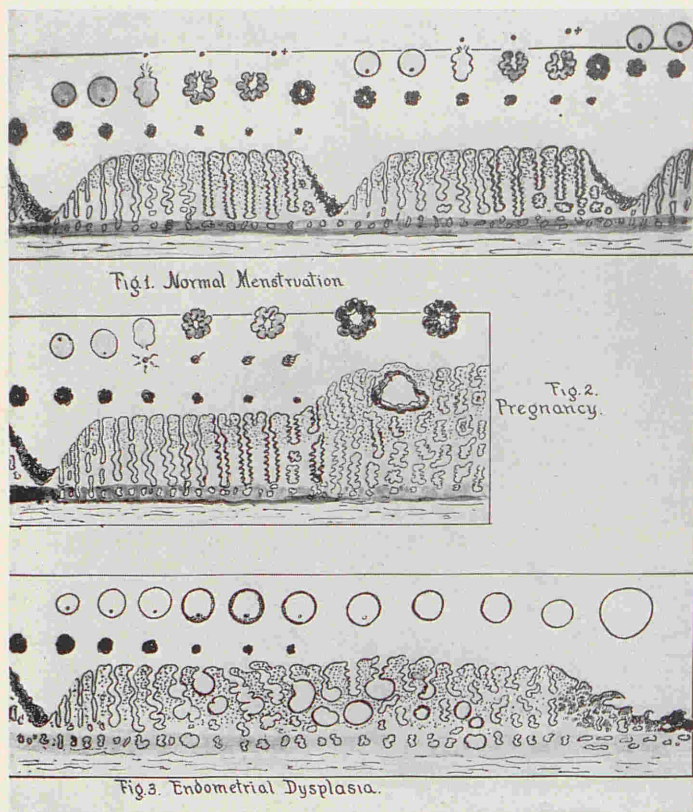


Fig. 4.—For description of this illustration see facing page.

Fig. 4.—Correlation between the ovarian and endometrial phases in normal menstruation, pregnancy, and gland dysplasia. (After Schroeder, published in *Amer. Jour. Obst. and Gynec.*, 20, 500, 1930, *Dysfunctional Uterine Bleeding*, W. P. Graves.)

1, Diagram showing the parallelism between the phases of the follicle and endometrium during a normal menstrual cycle. The middle row of diminishing figures indicates the involution of the preceding corpus luteum. The upper row of figures illustrates the development of the graafian follicle. As it develops its hormone produces characteristic growth changes in the endometrium. Near the middle of the cycle the follicle bursts, ejects the egg and becomes a corpus luteum. The corpus luteum functions up to the twenty-eighth day, inducing by means of its special hormone secretory changes in the endometrial glands. The egg, if unfertilized, dies supposedly on the twenty-eighth day. With the death of the egg the corpus luteum begins to degenerate and gradually involutes. The cyclic changes in the endometrial glands are depicted. At first simple tubular structures, the glands become hypertrophied and tortuous under the influence of the growth hormone of the developing follicle. As soon as the corpus luteum is formed, their structure is altered to that of a secretory organ. The epithelium assumes the beaker form of secreting cells, and the glands exhibit a saw-toothed (*sägeformig*) appearance. When the egg dies and the corpus luteum collapses, the endometrium disintegrates down to the basal layer, crumbles, desquamates, bleeds and rapidly regenerates (menstruation).

2, The ovarian and menstrual cycle in pregnancy. The first part of the cycle is like that of normal menstruation. If the egg is fertilized, the collapse of the corpus luteum and endometrium does not take place. The corpus luteum grows larger and continues its hormonal influence on the endometrium. The endometrium persists as a secretory organ, becoming the decidua and retaining as such the characteristics of its premenstrual stage in a more pronounced form.

3, The follicle and endometrium in a typical case of dysfunctional bleeding. The middle row of figures shows the involuting corpus luteum. The top row shows the developing follicle which at the proper time fails to burst, discharge the egg, and become a corpus luteum (ovulation). The follicle persists and continues to exert by means of its hormone a growth influence on the endometrium. The glands undergo an irregular hypertrophy (dysplasia). In the absence of a corpus luteum there is no secretory phase. In a typical case menstruation does not take place. The dysplasia of the endometrium results in localized thrombosis and necrosis, with consequent crumbling and hemorrhage. The persistent follicle or follicles become cystic, and either by their own secretion or by that of the pituitary body may maintain the dysplastic condition for an indefinite period. If the endometrium is curetted it usually regenerates in the form of dysplasia.

new and startling pattern. The glands are dilated, and the lining epithelium becomes high and columnar, like true secreting cells. The increase in the size of the epithelium causes it to become tufted, so that the inside contour of the glands has a typically saw-toothed appearance. The stroma or connective tissue cells undergo a change closely resembling the decidua of early pregnancy. In fact the entire mucosa looks singularly like that of the early maternal placenta (decidua). This was designated the *premenstrual* stage. If conception does not take place the structure breaks down on the twenty-eighth day and is swept away by the menstrual flood to be replaced quickly by a new mucosa in the simple stage of rest, the whole process occupying about five days.

On account of the close similarity of the premenstrual stage to the decidua of pregnancy Hirschmann and Adler regarded the late changes as representing a preparation of the endometrium for the reception of an egg that had *previously* been discharged and fertilized. According to them, therefore, the implantation of a fertilized egg must take place late in the premenstrual stage.

This observation was at variance with the accepted ideas of the time which placed ovulation immediately *after* menstruation. It, in fact, revolutionized the older theories and led to new researches that finally cleared up, in part at least, the inconsistencies that seemed to exist between human and animal sex physiology.

The reversal of the old preconceived notions was so important a step toward modern knowledge that we shall pause to show how it came about, using Corner as our chief authority.

Pr todo me-
menstrual,
semejante
al premen-
strual.

La implanta-
ción del huevo
de la mujer
antes de la
menstruación.

La ovulación
no ocurre, como
se creía, des-
pués de la
menstruación.

We have already mentioned pro-oestrus as the physiologic phase of the animal generative organs immediately preceding the stage of heat or oestrus, during which ovulation and, in the event of coitus, conception take place.

During the period of pro-oestrus some animals, such as the dog and mare, exhibit a mucous discharge sometimes mixed with blood. Heape, whose work had made him an authority on the subject, looked upon this discharge as the analogue of human menstruation, and he therefore stated in emphatic terms that the menstruation of the human species corresponds physiologically to the period of pro-oestrus in animals. Since ovulation takes place during oestrus, that is to say immediately following pro-oestrus, it will be seen that Hitschmann and Adler's hypothesis that ovulation *precedes* menstruation contradicted Heape. Furthermore, Marshall studying the sheep and ferret and Marshall and Jolly studying the dog, found certain changes in the endometrium during pro-oestrus which they at first interpreted as homologous to the changes in the human endometrium seen at the time of menstruation.

With this evidence against them Hitschmann and Adler's work was not at first accepted. Keller in 1909, in a study of the dog's uterus, failed to verify the findings of Marshall and Jolly regarding degenerative changes during pro-oestrus. On the other hand, he found *post-oestrous* changes of gland hypertrophy, engorgement of the stroma, etc., that simulated closely the endometrial proliferation seen by Hitschmann and Adler in the menstrual cycle of the human endometrium. This was evidence that menstruation and pro-oestrus are not homologous phenomena and

*I don't exactly
refer to
it as the
ovulation
stage as the
ovulation is
preceded by
pro-oestrus
and is not
analogous.*

that the animal uterus like that of the human passes through a secretory stage preparatory to gestation.

Further evidence of this truth was furnished by Ancel and Bouin who in 1910 studied the uterine changes of rabbits under the supposed influence of the corpus luteum. Making use of the fact that rabbits ovulate only after coitus, they mated their test animals with males that had been sterilized by vasectomy. The result was ovulation and formation of corpora lutea without pregnancy, a condition analogous to the so-called "pseudopregnancy" of the human (i. e., menstrual cycle without pregnancy).¹ Ancel and Bouin made the important observation that after this sterile ovulation and corpus luteum formation the endometrium passes through a proliferative phase much like that described by Hitschmann and Adler in the human as a preparatory stage for implantation. These changes in the rabbit's endometrium attain their maximum in about eight days (the time required for an impregnated egg to reach and nidate in the endometrium), after which the endometrium gradually retrogresses until on the twenty-fifth day it has reached a stage of rest.

Hill and O'Donoghue studying the Australian cat and Loeb studying the guinea-pig added new evidence that in the oestrous cycle of animals there ensue after oestrus (that is to say after ovulation and corpus luteum formation) progestational changes in the endometrium equivalent to the premenstrual stage of the human endometrium as demonstrated by Hitschmann and Adler.

¹ The word "pseudopregnancy" was coined by Hill and O'Donoghue in their study of the endometrial cycle of the Australian cat. Corner rightly takes exception to the expression and introduced in its place "progestation," a word that is now coming into general use.

Los cambios
pre-ovulatorios
se producen en el
animal después
del oestrus (ovu-
lución). En el
hombre, tam-
bién. Esto es
el luteo, aca-
se antes de la
menstruación. La
menstruación ha-
zlose, es, pues
post-ovulatoria: a diferencia de oestrus menstrual animal (por) que es
pre-ovulatoria (pre-oestrus). Esto se ve en los cambios de configuración.

In this way the seeming inconsistencies between human and animal uterine cycles were reconciled and properly synchronized. It is interesting to note that Marshall in a later study of dog's uteri revised his views in favor of the new theories.

To sum up, menstruation is not the homologue of pro-oestrus, preparatory to ovulation, but on the contrary is a late result of ovulation and represents a disintegration of a structure that had been built up, but not required, for the reception of a fertilized egg.

*menstruation
is as pre-ovulation
is as post-ovulation*

Other Cycles.—In pursuing our plan of leading up to the true nature and significance of the ovarian hormones it is necessary to mention briefly other cyclic changes that are apparently under the influence of the ovarian secretions. We have already spoken of the vaginal changes in rodents characteristic of oestrus. One would expect similar alterations to occur in the human species, but they are difficult to follow and so far the results of work in this field have been practically negative. Snyder and others have demonstrated a definite epithelial cycle in the fallopian tubes of the pig. Blair, Keye and Seckinger have found cyclic changes in the contraction rate of the smooth muscle of the uterus and tubes. Ancel and Bouin, Hammond and Marshall and others have shown proliferative periods in the mammary glands coincident with the development of the corpus luteum.

Correlation of the Ovarian and Uterine Cycles.—In the preceding pages, we have seen that the ovary runs a double cycle; first, that of the growing follicle up to the point of ovulation and, secondly, that of the corpus luteum which persists actively for about eight days if pregnancy is absent,

*Do not call
menstruation:
follicular
luteal*

or till the end of pregnancy if it is present. We have also seen that the human endometrium passes through a monthly cycle during which it exhibits constant phases, the last of which (preceding menstruation) imitates closely an early decidua. Further we have seen that this last or premenstrual phase corresponds in pattern to the progestational endometrium of the lower animals which follows ovulation and is coincident with the growth of the corpus luteum. In the lower animals the correlation of the ovarian and uterine cycles is simple since the time of ovulation is determined. But in the human species the time of ovulation is not accurately detectable for there is no way of observing an ovum at the time of its discharge, nor are there any outward signs (like oestrus) that indicate the event. Many attempts have been made to establish a time relationship between ovulation and menstruation or conception. The problem is greatly complicated by the fact that in the human being conception may take place during any part of the menstrual cycle though it is comparatively infrequent during the premenstrual stage. From this it must be concluded either that ovulation may occur at any time during the cycle or that the germ cells of the male may remain viable for a considerable period of time in the genital tract.

An approach to the solution of the problem was made by R. Meyer and Ruge, and later by R. Schroeder who studied specimens of ovaries and uteri removed in the operating room. They were able to follow with considerable accuracy the histologic stages in the growth of the corpus luteum and by comparing these with the concomitant picture of the endometrium to compute somewhat roughly the date of ovulation. Schroeder in his final conclusions states that rupture

Discovered
de la le
ovulation
en la espina
menstru.

of the follicles occurs about fourteen to sixteen days after the onset of menstruation, that is to say about the middle of the menstrual cycle. This estimate is generally accepted at the present time, having received new confirmation from recent observations by Corner on monkeys that have a menstrual cycle like that of woman.

*ruptura fol-
liculo, entre
14 y 16 días
del comienzo
de la regla.*

The formation of the corpus luteum is followed or rather accompanied by the characteristic premenstrual changes in the endometrium, so that there can be no doubt of an interdependence between the two, probably of a hormonal nature.

To this striking parallelism all investigators agree. The writer has repeatedly confirmed it by observing the corpus luteum and endometrium of hysterectomy specimens of large fibroids where, as is often the case, there had been no menstrual abnormality. In these cases the tumors have no influence on the ovaries and endometrium so that they may be studied in the light of perfectly normal organs.

The parallelism between the ovarian and endometrial cycles is graphically depicted in Fig. 4, adapted from Schroeder.

*una semana - Menstruación
una semana - en ovario en folículo - Menstruación. ovulación
una semana - Ovulación. Ruptura - entre premenstrual y la menstruación
una semana - Formación cuerpo amarillo - entre premenstrual y la menstruación.*

DE INVESTIGACIONES
CONSEJO SUPERIOR
CIENTÍFICAS
B. HAY
BLIOTECA

CHAPTER V

THE SEARCH FOR THE HORMONES OF THE OVARY

*For a review
actually.*

IN the foregoing chapters we have presented the chief classical facts that proved beyond contention the existence of one or more hormones in the ovary. It was clearly demonstrated that this internal secretion has many functions which are, in part (1) the prepuberal development of the primary and secondary sex characters and to some extent the normal bodily growth; (2) the onset of puberty; (3) the maintenance of the activity and integrity of the generative organs; (4) the nourishment and expulsion of the egg; (5) the preparation of the endometrium for nidation of the fertilized egg; (6) maintenance of the maternal soil for nourishment of the growing embryo; (7) preparation of the genitalia (in animals) for mating and ovulation; (8) changes in the breast necessary for lactation.

Most people conceived of the internal secretion of the ovary as a single substance but were perplexed at the multifarious and contradictory functions of which it was capable. There were many speculations as to its histologic source. Some (Tandler and Gross) reasoned that it must originate in the interstitial cells of the ovarian stroma. Others (Simon) traced its source to the lutein cells of the theca interna of the atretic follicles believing that these cells are identical with or at least derived from the interstitial cells. Some favored the granulosa cells of the follicles on the ground that an internal secretion should come from an

epithelial structure. Fraenkel and his school championed the corpus luteum cells, both from the evidence of their experiments and because the corpus luteum in its gross structure resembles other proved glands of internal secretion.

Numerous efforts were made to test the hormone by injecting into animals extracts of different parts of the ovary, but with no very definite results (Jentzner and Beuttner, Bucura, Marshall and Jolly, Adler, Schickele and Aschner, Fellner, Isovesco, and others).

Practical identification of an ovarian hormone dates from 1922 when Allen and Doisy made use of the discovery of Stockard and Papanicolaou relating to the oestrous changes in the uterine and vaginal epithelium of rodents.

Frank had tested the potency of ovarian extracts by injecting them into a spayed rat and then noting the effect on the contractions of the uterine muscle. In the quiescent stage of the sexual cycle and after castration the contractions are rapid. During oestrus they are slowed down. Frank found that under the influence of the ovarian injection the test uterus of a spayed animal is slowed down to a rhythm corresponding to that of a normal rat during oestrus. This was a complicated laboratory experiment unsuitable for practical use. Allen and Doisy injected an extract of pigs' ovaries into spayed rats, and studied the histologic changes in the uterus and vagina after autopsy. They noted the same remarkable changes described by Papanicolaou and Stockard in oestrous animals, namely, great multiplication of the epithelial layers of the vagina, and marked growth and secretory changes in the uterus. This, too, was a slow process and involved sacrificing the test animals.

These tests soon gave way to the simple one of examining vaginal smears. The vaginal smear from a rat's vagina at rest or atrophied from castration consists chiefly of leukocytes. Under the influence of natural or artificial oestrous the smear shows great numbers of non-nucleated squamous epithelium.

Having discovered the test Allen and Doisy then proceeded to standardize it by measuring the potency of the extract in rat units. The rat unit as defined by them is the "highest dilution of an extract which when given to a mature spayed rat in three injections at four-hour intervals during the first day will return a positive test (*i. e.*, cornification and desquamation of vaginal epithelium) on the morning of the third day." This standardization has been modified and corrected in more recent times (Coward and Burn) to meet the individual variations by which rats react to the stimulus.

The value of this work cannot be overestimated, marking as it does one of the chief epochs in the evolution of ovarian hormonology. It furnishes a method not only of testing a given substance, but of *measuring* its potency, an essential factor in all scientific investigations.

This simple and accurate means of assaying the ovarian secretion made possible many new discoveries. Frank was the first to demonstrate the oestrus-forming hormone in the liquid contents of the follicle—a discovery that led to the name "folliculin" to describe the active hormone. All kinds of tissues were then assayed. Frank and his collaborators found the hormone in circulating and menstrual blood, the quantity passing through a definite cycle corresponding to the menstrual rhythm. He also found it in the blood of

*History of the
folliculin.*

pregnant women and in large quantities in the placenta; also traces of it in the corpus luteum. This striking distribution of the secretion led him to dignify it with the name "the female sex hormone" and to include the places of its appearance in a general term "the gestational gland." But later investigations showed that the "female" sex hormone has a much wider distribution than the early investigators had any idea of. It is found, for example, in huge quantities in the urine of pregnant women, and to some extent in that of normal women; in the feces, bile, and liver; in the testes, blood, and other tissue fluids of males, and finally in many plants.

*David H.
Halle
Folliculin*

The final triumph of the female sex hormone (folliculin, thylokenine, oestrin) came in 1928 when Allen and Doisy in this country and a few months later Butenandt in Germany announced the isolation of the hormone in crystalline form.

The remarkable discoveries relative to the follicle hormone aroused great enthusiasm and induced many to believe that the mystery of the ovarian secretion had been solved. They saw in folliculin, the sole incretory regulator of the sex cycle, both animal and human. The almost complete absence of the hormone in the corpus luteum was regarded as the strongest proof that the ovary secretes but a single hormone.

*Tenn. da
la unio
hormone
ovaria.*

But there were also many doubters who still believed that the corpus luteum must elaborate a specific hormone entirely distinct from that of the follicle liquid. From a theoretic standpoint there was plenty of evidence to support this view. There was, for example, Fraenkel's work and Loeb's classical experiment which proved the inhibiting in-

fluence of the corpus luteum, and its power of sensitizing the uterine mucosa, even to the artificial production of a placentoma by irritation in the absence of pregnancy. The correlations between the uterine and ovarian cycles, described in detail in the preceding chapter, could not adequately be explained on the hypothesis of a single hormone. Prominent among the advocates of a dual ovarian secretion was E. Novak who in 1927 wrote: "In such animals as the rat the evidence clearly indicates that the cycle is dominated by the follicle and that the corpus luteum does not become important until after impregnation. In the human, on the other hand, the follicle is of importance in the menstrual cycle, but so is the corpus luteum, which is well-developed in the non-pregnant woman."

*Term. Analysis
Also, written.*

But scientific proof of the identity of a corpus luteum hormone was lacking. Significant experiments were performed by Loeb and Kountz, Hisaw, and Weickert. Many attempts were made to prepare corpus luteum extracts, some of them partially successful (Papanicolaou, Hisaw). But it remained for Corner in 1929 to settle the question beyond dispute. Corner's work was based on the inter-relationship between the corpus luteum phase of the ovary and the premenstrual (progestational, pregravid) stage of the endometrium, which we have shown had long been established. He first demonstrated the dependence of the uterine mucosa on the corpus luteum for the production of a progestational stage by the following experiment:

*Deuxième
de la hormone
luteale
progestative
de la mucosa
progravidie.*

The ovaries or corpora lutea were removed from rabbits fourteen to twenty hours after mating, at which time the fertilized ova are in the tubes from four to ten hours. In all cases there was complete failure of the uterine mucosa

to produce typical progestational changes seen in normally impregnated animals. None of the embryos lived after the fourth day, an indication of the dependence of the fertilized egg on a properly prepared endometrium for implantation and nourishment. These experiments were performed to confirm the work of Fraenkel and Ancel and Bouin described in Chapter IV.

Corner's next important achievement was the establishment of a test for the corpus luteum hormone similar in principle to that used for the follicle secretion. The experiment was carried out as follows:

"A doe rabbit is mated and eighteen hours later is subjected to removal of both ovaries and to the excision of a small portion of the uterus. Corpus luteum extract is administered for five days and on the sixth day after mating the animal is killed, the embryos recovered if present, and the uterus submitted to histologic examination and comparison with the specimen removed at the time of castration. Under the influence of the extract the uterus undergoes the characteristic progestational changes. To the eye and under the microscope the condition of such a uterus can in no way be distinguished from that of normal pregnancy of the fifth or sixth day except that after large doses the proliferation may be even greater than in normal pregnancy" (Corner).

In order to prove still more conclusively that the corpus luteum secretes a specific hormone that prepares the uterus for the reception of the embryo, Corner performed the same experiments but used folliculin for the injections instead of corpus luteum. The follicular fluid, though it contained large amounts of folliculin, did not in any case cause the

*La injection
de luteine
permet de
porter un
animal car-
ter de la
dépense
de l'ovule.*

*Si on injecte
folliculine,
on se forme
des ovules
mais pas de
pro-gestation.*

progestational changes produced by the corpus luteum. Corner used in his work an extract of the corpus luteum of great potency that he himself had prepared.

To prove the importance of the corpus luteum for the maintenance of pregnancy Allen and Corner removed the ovaries from pregnant rats and then administered the extract. By this substitution they were able to prolong the pregnancy to full term, whereas controls invariably aborted.

Thus the theory of a dual secretion of the ovary was unassailably established. Corner gave the name *progestin* to his new extract of corpus luteum, while the name *oestrin* became pretty generally adopted in place of a long list of terms used by various authors to denote the hormone of the follicle. Oestrin was now recognized as essentially a *growth* hormone, on account of its wide distribution in growing animals and plants, its presence in the male, and its specific influence during the proliferative stage of the menstrual cycle. Progestin appeared to be antagonistic in its action to oestrin, its specific function being to sensitize and prepare the uterine mucosa for nidation of the fertilized egg. The old idea of Fraenkel that the corpus luteum is the causative agent of menstruation was abandoned. On the contrary, menstruation was now thought to be the result of the retrogression of the corpus luteum. As Corner puts it, "If the ovum be fertilized it is assumed that the embryo causes persistence of the corpus luteum, which in turn continues its progestational effect upon the endometrium and thus postpones menstruation. Menstruation therefore (though by no means an abortion of the unfertilized ovum as it is sometimes put) is on this theory merely a violent demolition of the premenstrual uterine edifice some days after the expected

Progestina (o)
hormona (a)
tafria (a)
oestrina (o)
follicular (a)

La luteo-
no produce
la menstruación.

El cuerpo
cambiado
por la
progestina
permite la
del cuerpo
anormal.

tenant fails to arrive" (Hartman's modification of this theory is contained in Chapter VIII).

The clear-cut division of the ovarian secretion into two hormones with distinctive functions marked a new advance. It was now necessary to study more accurately the individual functions of the two hormones and to determine the nature of their interrelationship. These problems have by no means been solved, but a number of new facts have been gleaned and to these we shall now turn our attention.

The antagonism between the follicle and corpus luteum, well recognized during the speculative period, was experimentally demonstrated in many ways. If the corpus luteum is removed during the progestational period of nonpregnant animals oestrus and ovulation occur prematurely. During pregnancy/oestrus and ovulation do not usually take place, being inhibited evidently by the persisting corpus luteum. It has long been known that persistent corpora lutea in the cow cause non-ovulation and sterility, and that manual destruction of the corpora lutea is followed by fertility. Loeb by removing the corpora lutea in pregnant animals was able to produce ovulation without disturbing the course of pregnancy. The persistent corpus luteum during lactation seems to have an inhibitory effect on ovulation, which occurs infrequently during that period. Many surgeons have noted that removal of the corpus luteum during the premenstrual period leads to precocious menstruation. Johnstone states that the effect is invariable.

All this evidence, much of it well known, was amply confirmed by numerous animal experiments by which it was shown that injections of corpus luteum prevent oestrus and ovulation.

*Autogonadi
luteo-follicular.*

*Des l'incidence du
corpus luteum sur
l'ovulation, ad-
lacte ovar-
locus.*

*Persistence du
corpus luteum,
un peut ovar-
locus.*

*Les effets de
l'ablation de
l'ovaire.*

But although the products of the follicle and the corpus luteum (oestrin and progesterin) are antagonistic, they are also *synergistic*, that is to say collaborative.

un exemple
infantile (no
corpus)

This seeming paradox often seen in the endocrinological world of two secretions working both for and against one another has often been a stumbling-block to the uninitiated. The situation is, however, a perfectly simple one and exemplifies an exquisite mechanism in nature's construction. It may be explained by a homely illustration. *A* and *B* are employed to build a house. *A*, a specialist in his line, builds the foundation and turns the work of building the superstructure over to *B*, also a specialist. So far their labors are synergistic. But *A* has the inclination to keep on working at the foundation after it is finished and in so doing would either prevent or demolish the house-building of *B*. *B* therefore, in addition to his ability to build a house, must also have the special power of preventing *A* from undoing his work. In this sense they are antagonistic. *A*, however, could not build the superstructure, nor could *B* build the foundation alone. In this way they are interdependent.

The synergistic relationship between the follicle and corpus luteum has been demonstrated by a number of striking experiments.

Des choses de
menstruation
à et non si
une fois seule-
ment (si menses
utero no pre-
cedent). On
donc ovulation
lycor corpus
annuels y
menses uter-
in ne préfer-
vi dia)

Corner and Hartman working separately on the sex cycle of menstruating monkeys both found that these primates sometimes menstruate in regular course without any preceding ovulation or corpus luteum formation in the ovaries. The endometrium in such cases does not show the premenstrual changes typical of true menstruation following ovulation. They therefore concluded that in primates at least there are two types of menstruation, one where there is ovulation and a premenstrual growth of endometrium and one when these changes are absent. They then injected oestrin into castrated monkeys and produced menstruation, but without the premenstrual proliferation of the mucosa. Corner, and also Hisaw, next tried sensitizing the mucosa by injections of oestrin and then following this with a series of injections of progesterin (corpus luteum). After this double

treatment true menstruation ensued with characteristic premenstrual proliferation of the mucosa. Hisaw and Leonard produced the same progestational changes in the mucosa of spayed rabbits by the consecutive use of the two hormones. They describe the situation thus: "The function of the follicular hormone seems to be that of putting the uterus in the proper physiological condition so it can respond to the corpus luteum hormone. Neither of these substances can produce progestational proliferation in the castrate uterus when given alone. If, however, it is first brought into condition typical of oestrus through the injection of follicular hormone, and is followed immediately by corpus luteum treatment, progestational proliferation results."

Hisaw after enumerating the various results of the oestrin-progestin synergism says: "These are 'one, two' reactions in which the follicular hormone must first produce its effects before the corpus luteum hormone can act."

One of the important problems of the present day is whether the two known hormones of the ovary are themselves simple or complex. Hisaw has isolated from the extract of sows' corpora lutea a crystalline fraction which he calls A, and a noncrystalline fraction which he calls B. A has the specific property of producing in a virgin guinea-pig the relaxation of pelvic ligaments characteristic of pregnancy. B promotes the various changes that we have described as peculiar to progestin.

Producción de la mucosa premenstrual por la inyección consecutiva de los dos hormonas.

Primero el efecto de la inyección de la hormona de la ovulación, luego el efecto de la hormona de la gestación.

¿Son los dos hormonas, una simple y otra compleja?

CHAPTER VI

THE DISCOVERY OF THE HYPOPHYSIS AS AN AGENT IN THE SEXUAL AND REPRODUCTIVE CYCLES

WE come now to a new and in some ways a revolutionary stage of progress in the discovery of a profound interrelationship between the internal secretions of the ovaries and those of the hypophysis.

Knowledge that such a relationship exists dates back to 1901 when Frölich described his famous syndrome of hypopituitarism, adiposogenital dystrophy, and hyposexualism. This was followed by extirpation experiments by Crowe, Cushing, Homans, Aschner, Biedl, Blair Bell, and others, by which it was shown that removal of the greater part of the organ causes in young animals defects in body growth, metabolism, and the proper development of both primary and secondary sex characters. Fraenkel and Gellen reached similar results after x -radiation of the pituitary region in rabbits. There followed numerous feeding experiments of extracts of the anterior lobe to young animals, notably by Wulzen, Goetsch, Evans and Long, Frank, Sisson and Broyle with inconclusive, often contradictory results.

Experiments de
Ovaries: in-
jection de
extraits pitui-
taires alcali-
nés

The first definitive results were achieved by Long and Evans who injected *alkaline* extracts of beef pituitary into young rats, and produced two remarkable effects. First, the animals were stimulated to extraordinary growth involving every part of the body excepting the uterus and ovaries which remained infantile. Secondly, the maturation of the

ova was impaired or prevented but (and this is important) the follicles took on a lutein growth of the granulosa without discharging the ova (pseudocorpora lutea). The first oestrus occurred later than in the control animals.

Produit la
luteinisation
de la follicle.
y, donc, la
ovulation et
la oestrous.

The conclusion from these experiments was that the anterior lobe of the hypophysis produces a secretion which (a) promotes growth to the extent of gigantism; (b) luteinizes the follicles, and (c) inhibits ovulation and oestrus. There is a significant difference between these conclusions and those of the following experiments, and this should be noted.

The next notable series of experiments was performed by Smith and Engle working separately and together. Smith by making several transplants of whole gland, or anterior lobe only, from normal rats into immature normal female rats was able to produce all the phenomena of oestrus in about a week after the transplants were begun. This precocious sexual maturity was brought about as early as the weaning date, which is on the twenty-second day after birth. At the same time large luteinized follicles were developed in the ovaries. Thus Smith's results with transplants differ from those of Long and Evans in that he precipitated oestrus whereas the latter's extracts had delayed it.

Transplantation
de l'hypophyse:
produit l'ovulation
et la maturation
des follicles.
et luteinisation
des follicles.

Différence avec
les expériences
de Evans

The reason of the discrepancy will be explained later on.

Smith and Engle carried their method still further and secured some startling results by using heterotransplants from the rat, guinea-pig, and rabbit, in the mouse. Mice thus treated mate as early as the nineteenth day of life within forty-eight hours after the first transplant. Transplants in adult animals caused extraordinary acceleration of

Superovulation
et super
procréation par
le greffon trans-
planté

ovulation with the release of six or seven times the normal number of ova. If the animals mate at this time large numbers of embryos may be found in the uterus. To this condition of abnormal fertility Smith and Engle gave the names "superovulation" and "superpregnancy."

Next came the classical experiments of Zondek and Aschheim who elaborated the work of Smith and Engle and brought new facts to light. They employed single instead of the multiple or repeated transplants used by Smith and obtained similar though somewhat more moderate changes.

*Neurone of the
flavobulba produce
oestrus effects.*

In order to rule out every possible source of error Zondek and Aschheim transplanted into immature female mice other glands than the hypophysis to determine whether they might also stimulate the ovarian function. To this end they used extracts or transplants of thyroid, thymus, pineal, adrenal cortex and medulla and posterior lobe of the pituitary, all of which glands are thought to bear some relationship to the sexual function. None of them, however, had any influence in producing oestrus changes. The same also was true after parenteral injections of albuminous fluids like amin, serum, menstrual blood, and cyst contents.

*La madurez
precoz es
consecuencia de
el infarto de la
hipofisis.*

On the other hand, the transplantation of a fresh piece of anterior lobe in an infantile mouse (6-8 grains) invariably brought about a condition of oestrus. To quote the authors: "This condition is brought about in three or four days. The vagina opens, and the vulval epithelium is thickened. The little infantile animal acquires sex organs which correspond in size and appearance to those of mature animals. The vaginal smears are characteristic of true oestrus. The uterus is enlarged and filled with secretion. The ovaries show distinctive follicle changes (to be described later).

The infantile animal is recognized by the male as sexually ripe, and is often slain in stormy attempts at copulation."

The conclusions reached by Zondek and Aschheim were as follows:

1. The hormone of the anterior lobe of the hypophysis—and only this—sets the ovarian function in motion and brings the infantile mouse to early sexual maturity.

2. The hormone of the anterior lobe of the hypophysis which produces oestrus in the female infantile mouse is present both in the male and female gland. *Actúa en los dos sexos a pesar de su acción femenina.*

3. This hormone is still present in the female hypophysis after her own ovarian function has ceased, i. e., after the climacteric. *Permite en la hipofisis después del climacterio.*

4. The hormone of the anterior lobe that produces oestrus in virgin mice is identical in animals and humans. *Es igual en todos los especies.*

The next significant observation was a comparison between the anterior lobe hormone and the ovarian hormone (oestrin) in their effects on ovariectomized animals, and in this a far-reaching physiologic principle was established.

We have already seen that the injection of oestrin in a female castrated animal produces typical oestrous changes in the vagina and uterus (test of Stockard and Papanicolaou). Secondly, oestrin injected into a normal animal at rest produces oestrous changes in the vagina and uterus but no changes in the ovaries. *La oestrina produce cambios en la vagina y útero; pero no ovulación.*

On the other hand, anterior lobe transplantation has no effect on the vagina and uterus of an ovariectomized animal. In a normal animal it causes oestrous changes in the vagina and uterus and also ovulation and luteinization in the ovaries. *La inyección de hipofisis produce ovulación y cambios vaginales.*

From these observations Zondek and Aschheim drew the

*est vector
de la fonction
sexuelle.*

following conclusions: "The hormone of the anterior lobe is the motor of the sexual function. This hormone is pri-

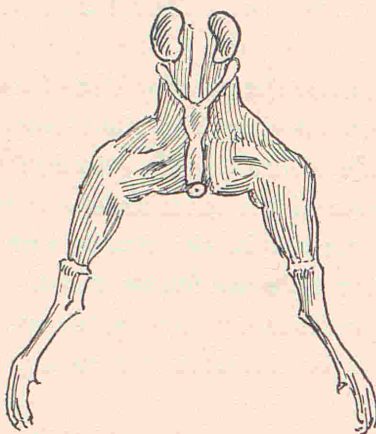


Fig. 5.—Genitals of a normal infantile mouse of 8 grains' weight. (After Zondek and Aschheim, Arch. f. Gyn., 130, 26, 1927.)

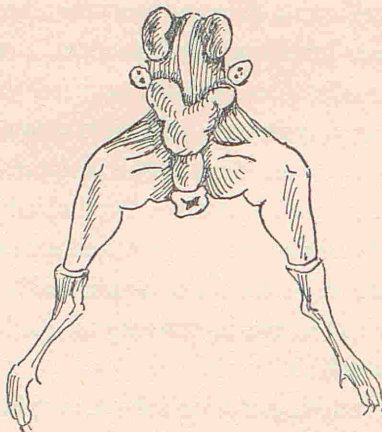


Fig. 6.—Genitals of an infantile mouse of 8 grains' weight 100 hours after implantation of a piece of anterior lobe of the hypophysis. (After Zondek and Aschheim, Arch. f. Gyn., 130, 26, 1927.)

mary, the ovarian hormone is secondary. The anterior lobe hormone brings the follicular apparatus into action, dis-

charges the follicle-ripening and mobilizes secondarily the ovarian hormone in the follicle cells."

Furthermore, the egg does not play the chief rôle in this process as formerly supposed since hormone production can take place in the follicle apparatus *without the egg*.

The theory of motor influence of the anterior lobe hormone on the uterus and ovaries is graphically shown in the accompanying diagram adapted from Zondek and Aschheim (Fig. 8).

Pregnancy Test.—With this information at hand Aschheim and Zondek were provided with a test for detecting the anterior lobe hormone as distinguished from that of the ovary. They then proceeded to put the test to practical use. They found that anterior lobe hormone is present in high concentration in the blood and urine of pregnant women. It is also present in small quantities in these and other fluids and tissues in nonpregnant women but in too small amounts to cause characteristic reactions in laboratory animals. They injected small quantities of the urine of pregnant women into the circulation of immature mice and observed constant reactions in the ovaries ninety-six hours after the first injection consisting of: (1) Maturation of the follicles and appearance of oestrus; (2) marked hyperemia and hemorrhage into the enlarged follicles. The hemorrhages are easily seen by the naked eye, and appear as brown to bluish-red points the size of a pinhead. These blood points (*Blutpunkte*) furnish the chief diagnostic sign for they can be recognized at a glance; (3) the formation of corpora lutea and the luteinization of many corpora atretica, *i. e.*, corpora lutea with imprisoned ova.

The value of this test was immediately recognized by the

*Reaction due
to pregnancy*

profession throughout the world and adopted in every clinic equipped with an experimental laboratory.

The technic of the Aschheim-Zondek test for pregnancy as originally published required the use of five immature female mice weighing between 6 and 8 gm., each animal receiving six successive injections over a period of forty-eight hours. This involved the necessity of having on hand litters of mice of the proper age, and the sacrifice of many valuable animals. In order to meet the limitations of the average laboratory various investigators (Schneider, Friedman and Lapham, Wilson, Siddall, Mathieu) devised simpler and less expensive methods for the test. The technic employed by Friedman is at the time of writing most popular. Friedman's test is based on the fact that mature rabbits do not normally ovulate excepting after copulation. But ovulation may be induced without copulation by the intravenous injection of urine from a pregnant woman, which contains the sex-stimulating hormone of the hypophysis.

*Modificación
de Friedman
en el conejo*

*Técnica
Wilson*

Wilson's modification of Friedman's technic is as follows: Fully adult female rabbits of 4 pounds' weight or over are used. The test rabbit must have been kept in strict isolation for at least one month. The test is begun at 5 P. M. by injecting into the venous circulation (usually of the ear) 5 cc. of the morning urine of the patient. Sterile precautions are not necessary. At 9 A. M., or sixteen hours after the injection, the rabbit is aseptically prepared for operation under ether anesthesia and a midline abdominal incision made. A positive reaction is revealed in the ovaries by the presence of recently ruptured graafian follicles, indicated by bright red elevations of conical form, a millimeter or two in diameter, having usually a slight depression in the center. These

must be distinguished from large unruptured follicles sometimes present, the latter being more rounded, paler and clearer in color and without the central stigma or depression. The ruptured follicles must also not be confused with certain hemorrhagic unruptured follicles more or less peculiar to the rabbit. These latter are smaller and less prominent than the ruptured follicles and are dull red to black in color.

If the findings are doubtful the test should be repeated. The abdominal wall is then closed with silk and the animal returned to isolation for subsequent use, preferably in a month's time, though it can be used earlier if necessary even within a few days (Jares). The chief advantage of Wilson's method is that the test can be made over night and in case of doubt checked again within two days.

The accuracy of the hypophysis pregnancy test is remarkable. It is especially valuable since positive results are obtained as early as eight days after the missing of a period when a bimanual examination of the uterus is quite uncertain. The test remains positive throughout pregnancy, and for about two days after parturition. Wilson finds it positive during the active stage of an extra-uterine pregnancy but negative after tubal abortion. In cases of ordinary abortion the test is positive as long as the placenta is attached and active or, as Aschheim puts it, "in biological contact with the maternal blood." From somewhat meager testimony in the literature the test seems to be positive in a certain percentage of cases of rapidly growing tumors and cancers of the genital organs. This introduces a possibility of error when in association with these growths a complication of pregnancy is suspected. Cases of functional amenorrhea, dysfunctional bleeding, and pelvic inflammation were in

Repetido

*Cyfoch tud
del metodo.*

*Causas de
error.*

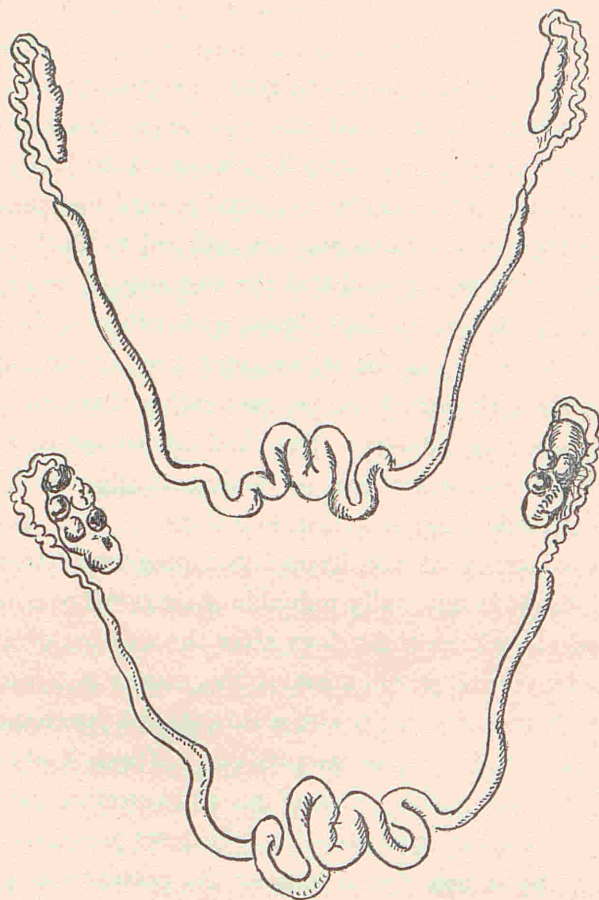


Fig. 7.—Hormone test for pregnancy, Schneider's method (pen copy of colored drawing illustrating Schneider's article in *Surg., Gynec., and Obst.*, January, 1931). Schneider uses young rabbits twelve to fourteen weeks old. The upper figure shows the bicornate uterus tubes and ovaries of a fourteen-week-old rabbit thirty hours after injection of a 7-cc. injection of urine from a nonpregnant patient, a negative result making no change in the ovaries. The lower figure shows a positive result from the urine of a patient five weeks pregnant. The ovaries are enlarged and show the presence of numerous corpora lutea and corpora hemorrhagica. It should be noted that the appearance of the ovary after a positive test in an immature rabbit differs somewhat from that in an adult rabbit described in the text under Wilson's method.

Wilson's series uniformly negative to the test, though others have reported occasional positive findings. The test is also valuable in cases of active extra-uterine pregnancy. I have seen no reports on endometriosis. The abdominal surgeon finds the test of great help in determining operative procedure in the presence of large tumors simulating pregnancy, or where a complication of tumor and pregnancy is suspected.

Especially interesting have been several reports on the Aschheim-Zondek test in cases of hydatidiform mole, and chorion epithelioma (Aschheim, Mack and Catherwood, Novak, Fanz and Gault). The response to the test in these cases seems to bear out Aschheim's dictum regarding abortion that the test is positive as long as there is a biological contact of the fetal tissues with the maternal blood.

The discovery of the luteinizing effect of the anterior lobe hormone at once drew the attention of pathologists to the strange lutein cysts that appear almost exclusively in association with hydatidiform mole and chorion epithelioma. Whereas follicle development is more or less inactive during normal pregnancy on account of the inhibitory influence of the corpus luteum, it often shows a marked, sometimes a prodigious, activity in the presence of the two chorionic diseases, especially that of mole. The follicle activity takes the form of multiple luteinized corpora atretica, which may be of a size that does not palpably enlarge the ovaries, or they may attain considerable proportions even to the size of a man's head as in a case reported by Herold. Microscopically, the cysts show a lining of highly developed theca or granulosa cells undergoing lutein transformation, the luteinization even extending to the stroma cells. The

*Uterine
chorion epithelioma.*

*Chorion & lutein-
cysts in
the uterus
chorion epitheli-
oma. In fact
are of the size
and number of
follicles seen in
ovary.*

picture of "hyperluteinization" corresponds perfectly to that seen in the ovaries of laboratory animals subjected to the action of the anterior lobe hormone. Further evidence that the processes are identical was furnished by the observation (Roessler, Zondek, Otto, Mack and Catherwood) that the amount of anterior lobe hormone secreted in cases of mole and chorion epithelioma is many times greater than during normal pregnancy.

In the comparatively few cases reported it is evident that both mole and chorion epithelioma react positively to the anterior lobe test with the same regularity as normal pregnancy. Furthermore it has been shown (Mack and Catherwood) that as long as any tissue of the two growths remains living (*i. e.*, in biological contact with the mother's blood) the test continues positive. In normal pregnancy, on the other hand, the test is negative within forty-eight hours after parturition.

The question now arose whether the increased production of anterior lobe hormone in cases of chorioma is the cause or the result of the abnormal proliferation of the chorion. Experiments in which large amounts of anterior lobe extracts were injected into pregnant animals (Teel, Zondek) though killing the fetus did not produce changes in the chorion. The view at present is that the "placenta and its elements not only serve as a storehouse for the anterior lobe hormone, but also play a part in its production" (Mack and Catherwood). According to this theory the abnormal growth of the placenta that occurs in choriomatous diseases accounts for the attendant excess of the hormone. It also explains the disappearance of response to the Aschheim-Zondek test after childbirth, and after the complete removal of chorionic tissue in choriomatous tumors.

*The placenta
produces Progesterone.*

CHAPTER VII

THE HORMONES OF THE ANTERIOR LOBE OF THE HYPOPHYSIS IDENTIFIED

THE next stage in the evolution of knowledge regarding sex physiology was the demonstration that the anterior lobe hormone contains not one but at least two, and perhaps more, active endocrine-bearing substances.

The possibility that the hormone is complex had already been suspected from certain discrepancies that had appeared in the results of different experimenters. First, the alkaline extracts of beef pituitary used by Long and Evans, when injected parenterally, produced luteinized corpora atretica (with imprisoned ova) but inhibited or delayed oestrus and normal ovulation. Second, the repeated transplants of Smith and Engle caused tremendous true ovulation with comparatively few corpora atretica coupled with growth stimulation to the degree of gigantism. Third, Zondek and Aschheim using single grafts produced a predominance of luteinized corpora atretica and hemorrhagic follicles (*Blutpunkte*). Fourth, injections of urine from pregnant women induced both ovulation and luteinization, the preponderance of which varied with the amount of urine, time of passing, the species of animal used, and other factors.

The problem of the complexity of the anterior lobe hormone was studied separately and simultaneously by Zondek and Wiesner. They arrived at identical conclusions but by somewhat different routes. By following successively the

*Protein of
the complex
had the
hormone pro-
hypo. trans*

work of these two investigators we shall be able to reach a clearer understanding of a subject that at the time of writing is generally regarded as very confusing. We shall begin with a review of Zondek's report that appeared in February, 1930.

Zondek and Aschheim, as we have described in the previous chapter, had established by grafts that the internal secretion of the anterior lobe is a "superordinated, general, specific hormone of sex" which in infantile mice produces a triad of morphological and functional reactions which they tabulated as follows:

1. Follicle ripening, ovulation, production of folliculin (oestrin) in the follicle apparatus and thereby secondary oestrus reaction.
2. Blood masses in the distended follicles (*Blutpunkte*).
3. Luteinization (production of true corpora lutea) and luteinized corpora atretica (ova imprisoned).

With this as a test they demonstrated the specific action of the hormone on the infantile animal and were thus enabled to draw conclusions as to the significance of the hormone on the general organism. Finally, they were able to isolate the hormone in chemical form, and to this substance they gave the name *prolan*.

*El prolán no
es la hormona
del crecimiento.
Es antihormona.*

They then proceeded to study the properties of prolán and first compared it with the alkaline extract used by Evans and Long which, it will be remembered, caused gigantism in immature animals but inhibited sex development. Prolán did not produce gigantism, nor did Evans and Long's extract cause the reactions of prolán tabulated above. From this it was concluded that prolán and the Evans extract are two different substances, antagonistic in their nature but both elaborated in the anterior lobe. Theoretically

prolan first exerts its influence when the growth hormone (Evans' extract) completes its function, *i. e.*, at the period of puberty. In other words, there appeared to be a special growth hormone of the anterior lobe. This hormone has not yet been isolated or named.

*le prolane
active, quand
le testicule (ou
la puberté) de
la fonction de la
hormone
del croissance*

The next step was to compare prolan with a substance from the anterior lobe shown by Kiestner and Plaut-Liebeschütz to have a regulating influence on the body metabolism and named by the authors *praephyson*. Zondek and Köhler found that praephyson does not produce the characteristic sex reactions of prolan, but that prolan causes the same metabolic chemical reactions of praephyson. Hence prolan and praephyson are not identical. The exact status of praephyson as an anterior lobe hormone has not yet been determined and is therefore recorded on the diagram (Fig. 8) with a question mark.

*le prolane,
vs. la
hormone
metabolique
(pre physon)*

Having thus eliminated the growth hormone and praephyson, the next step was to unravel the complexities of prolan itself.

Now the administration of prolan in Zondek's experiments did not always have the same reaction. Sometimes it would produce normal ripening of the follicle with rupture and deposit of the ova in the tubes, and with this process the formation of a normal corpus luteum (Reaction I). Often, however, the follicles would not rupture, the eggs would be retained and the entire cell apparatus of the follicle would become luteinized. If the potency of the extract in such a case were increased, the entire ovary would be converted into a single lutein body (*i. e.*, lutein cyst, similar to those found associated with hydatidiform mole and chorion epithelioma, *q. v.*) in which case follicle-ripening

could no longer be possible. Aschheim further showed that in testing the urines of patients, some showed Reaction I and others showed Reaction III.

*Prolan A (reaction I)
Prolan B (reaction III)* The logical conclusion from these observations that prolان contains two hormones was soon confirmed by Zondek who was able to isolate from the whole substance a product which caused when injected into immature animals only follicle ripening (Reaction I) with no luteinization (Reaction III). This product he named prolان A, the remaining luteinizing hormone being entitled prolان B.

Zondek summarizes the situation by stating that the anterior lobe of the hypophysis elaborates the following substances:

- | | | |
|--------|---|-------------------------------|
| | 1. Growth hormone. | |
| Prolan | 2. Prolan A = Follicle-ripening hormone | } Superordinated sex hormone. |
| | 3. Prolan B = Luteinizing hormone | |
| | 4. Metabolism hormone. | |

From this table it will be seen that prolان A and folliculin (oestrin) have properties in common, while prolان B and the secretion of the corpus luteum (progestin, lutin) are similar. The correlation of the four hormones will soon follow.

At this point Zondek makes some interesting comments that have a bearing on the future therapeutic application of his work. He calls attention to the fact that these hormones have not been as clearly isolated nor is our knowledge of their clinical properties as definitive as is the case of the hormones of the posterior lobe (pituitrin, oxytocin, vasopressin). He finds that prolان is chemically a very sensitive substance for it entirely loses its genital effects when fed orally to mice. On the other hand, its metabolic effect is not lost in the gastro-intestinal canal of man (Zondek and Köhler).

Moreover, the sensitivity to prolان differs greatly in different animal species. Thus he finds that the infantile rat is far more sensitive to prolان A than the mouse, whereas the mouse is more sensitive to prolان B.

Zondek mentions other uncertain factors that are well worth recording since they are sure to crop up as new discoveries are made. For example, the

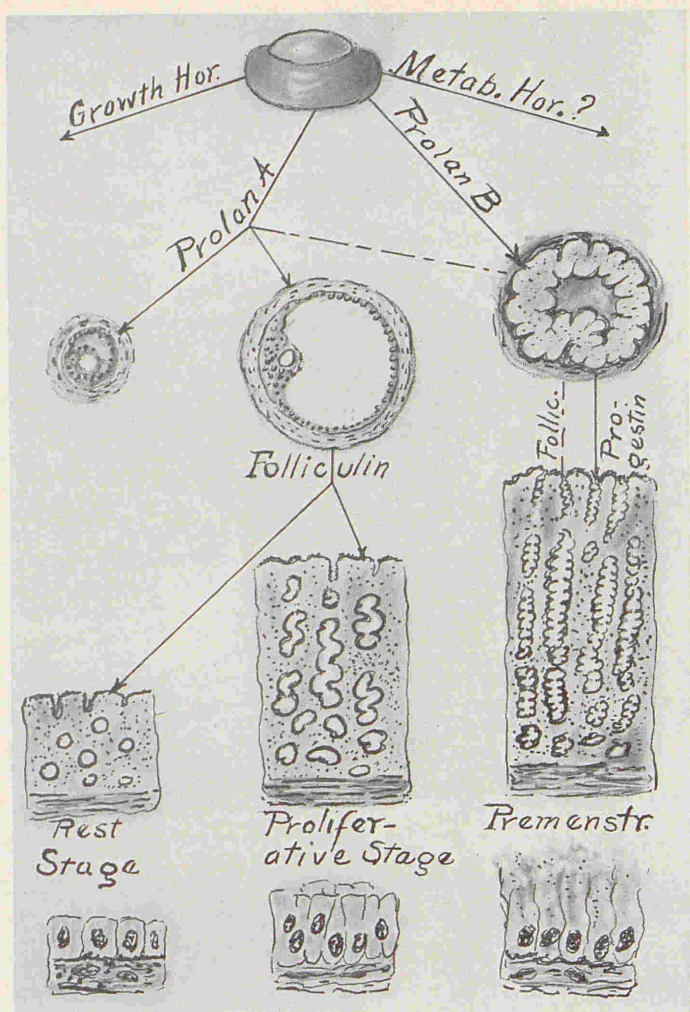


Fig. 8.—Correlation of the hormones of the hypophysis and the ovary (after Zondek, *Klin. Woch.*, 9, 1, 247, 1930). Prolan A starting from the hypophysis stimulates the growing follicle to the production of folliculin which in turn stimulates the proliferative stage of the endometrium. A small amount of folliculin is excited in the corpus luteum as indicated by the broken line. Prolan B stimulates the lutein cells of the corpus luteum to the production of progestin (called by Zondek "lutin") which changes the endometrium to the premenstrual (progestational) stage. The hypophysis also elaborates the special growth hormone and a probable metabolic hormone. Other hypothetical hormones (uterine bleeding, lactation?) are not shown in the diagram. The probable "reciprocal" relationship between the hypophysis and ovary described in more recent theories is not indicated.

blood points or hemorrhagic follicles of mice subjected to the Zondek-Aschheim pregnancy test are more or less peculiar to that species and, as we have seen, are not useful in making the diagnosis with rabbits. This seems to be a specific reaction that Zondek has not yet been able to explain. Nor has he been able to determine the hormonal or other cause of follicle rupture which is less constant than the other reactions.

Another important species difference exists in the production of folliculin, which was shown to be produced from the theca cells under the stimulus of the anterior lobe. Aschheim found that in the *human* folliculin is also produced in the corpus luteum in increasing amounts up to the time of menstruation. This had also been observed by Frank and other earlier workers. On the other hand, folliculin is not produced in the corpora lutea of laboratory animals. Since the elaboration of folliculin is under the direction of prolان A, Zondek infers that in man prolان A production is continuously going on. Only after follicle rupture does the production of prolان B occur, and it is possible that in man this rupture stimulates the hypophysis to yield prolان B, as far as man is concerned. In animals the process is different. Prolان A and B are produced one after the other. Thus prolان A mobilizes folliculin which in animals brings on oestrus, while prolان B only after oestrus creates the characteristic pregravid changes in the uterus and vagina through the agency of the corpus luteum.

*in all mammals
the folliculin
is formed from
the theca cells
of the corpus luteum.*

Correlation of Prolان A and B with the Ovarian Hormones.—If now we assemble the work of Zondek and Aschheim on the anterior lobe hormone and Zondek's division of the hormone into two constituents, at the same time recalling the morphological events of the ovarian and endometrial cycles we are ready for Zondek's final summation.

1. The female sexual function manifests itself in the following way: The anterior lobe of the hypophysis is the motor of the sexual function and the hormones of the anterior lobe are the superordinated specific hormones of sex.

*According to Zondek
the anterior lobe
of the hypophysis
controls the sex.*

2. Prolان A sets off follicle ripening and incites the theca cells of the follicle to the production of folliculin which in turn induces the proliferative phase of the endometrium.

*According to Zondek
Prolان A.*

3. Prolان B effects the change of the granulosa and theca cells to lutein cells and incites in them the production of progesterin (lutin) which changes the proliferative phase of

*According to Zondek
Prolان B.*

the endometrium to one of secretion (premenstrual, pregravid, pregestational stage).

Wiesner's Contribution.—Turning now to the work of Wiesner we encounter a somewhat different terminology which, however, should give no trouble. He designated the oestrous stage of the ovarian cycle as the alpha phase and the hormone that governs it (oestrin, folliculin) as the alpha factor. The second stage which we have been calling the pregravid (in animals) and premenstrual (in primates) he named the beta phase. To the governing hormone of this phase which we have been calling progesterin or corpus luteum hormone he gave the name "beta factor." In reviewing Wiesner's work we shall employ his language since it appears frequently in the literature and it is therefore useful to become familiar with it.

the beta phase
produces oestrogen
in the vagina
(mucification)

It will be remembered that the definitive test in animals of the alpha phase (oestrus) is the hypertrophy and cornification of the vaginal epithelium (Allen and Doisy's test), while the test of the beta phase (pregravid) is the secretory or decidual change in the uterine mucosa (Corner's test for progesterin). Wiesner and Patel discovered that the beta phase may be detected in the vagina also by the epithelium which instead of being cornified as in the alpha phase forms a layer of high mucous cells, a condition which they called *mucification*. The test requires microscopical examination of a bit of excised tissue.

With the help of this test they were able to detect the beta phase with almost as much facility as they could the alpha phase by the Allen and Doisy test (vaginal smears).

Now the ovary produces in succession two hormones (alpha and beta) which *usually* coincide, respectively, with

two phases, namely, the oestrous with vaginal cornification and the lutein with vaginal mucification. But in certain animals this exact coincidence does not invariably take place, for though the animal may ovulate and thereby have a corpus luteum the beta (*i. e.*, pregravid) phase of the vagina and uterus does not follow unless the animal mates—as was proved by the mucification test (Wiesner and Crew). This shows that the corpus luteum does not always “luteinize” unless it receives some stimulus to activate its specific hormone (progestin). Wiesner then proceeded to demonstrate that this stimulus emanates from a specific correlated hormone of the anterior lobe, and in so doing he followed somewhat the same trail as Zondek and reached practically the same conclusions.

*El cuerpo lúteo
no siempre
luteiniza; le
puede faltar el
estímulo del
lobulillo anterior
por la
vaginitis.*

Recall for a moment the experiments on hypophysectomized animals in which no genital phases of any kind occur. Grafts and acid extracts of anterior lobe repair this defect and even induce precocious genital development in immature animals as we have related in describing the work of Smith and Engle, Zondek and Aschheim, and others.

On the other hand it will be remembered that the alkaline extracts of anterior lobe were shown to prevent oestrus and to delay sexual maturity.

Using vaginal mucification for his test of the beta phase Wiesner found it absent after grafts and acid extracts of anterior lobe. He concluded, therefore, that grafts and acid extracts produce only the first of the two successive phases of the ovarian secretion, namely, the alpha or oestrus phase. Their action is therefore *oestrogenic*.

*El extracto de la
anterior lóbulo
produce la fase
de la ooforin
pero no la
fase de la
progestina.*

On the other hand, Wiesner found that with Evans' alkaline extract of posterior lobe he could produce the beta

phase in animals without oestrus or mating having occurred first. Therefore besides finding that the corpus luteum may exist without luteinizing changes in the vagina, he now discovered that these same changes may be induced without the corpus luteum.

These conclusions make a rift in one's conception of the sex mechanism formed up to this point and at first sight will doubtless seem confusing. However they simply mean that the corpus luteum must depend for its characteristic function on some agency higher up which can itself unaided perform the functions of the corpus luteum. This property of the anterior lobe Wiesner described as *kyogenic*. "Kyogenic" is a neologism from the Greek and signifies pregnancy-creating, in the sense of creating in the genital organs the pregravid, beta phase of structure necessary for the nidation and growth of the fertilized egg. And so Wiesner by his experiments was enabled to announce: "Two different gonadotrope (sex-gland-dominating) actions of the anterior lobe extracts have been established: (1) The *oestrogenic* (grafts, acid extracts); (2) the *kyogenic* (alkaline extracts)." Again in slightly different words: "The gonadotrope secretion of the anterior lobe, like that of the ovary, is divided into two phases—the first oestrogenic and the second kyogenic."

Wiesner named the two gonadotrope principles of the anterior lobe secretion, respectively, rho I and rho II. These correspond identically to Zondek's prolan A and prolan B.

Wiesner encountered the same interrelational peculiarities of the two substances that we have mentioned in the work of Zondek. His explanation of them is somewhat too technical to be recorded here. Suffice it to say that heat

Los cuerpos
luteos, que se
en vagina pueden
aparecer, sin
cuerpo luteo.
por lo mismo de
la hipótesis

El cuerpo luteo,
por, puede re-
cibir de un
estímulo superior;
esta puede actuar
sin intervención
del cuerpo luteo

non non

and alkali are inimical to rho I and favorable to rho II, and that in using whole extracts variations in dominance between the two principles occur depending on the amount and duration of the dosage. Thus, a specimen of whole extract in which rho I is dominant will on standing change its character to a rho II dominance. If the same extract be given in prolonged repeated doses the rho I reaction will in time be overridden by that of rho II. The problem will be cleared up when the two hormones have been isolated and purified, a work that is well under way with every prospect of success.

*¿Son dos
hormonas o
distintos com-
puestos de la
misma hor-
mona?*

CHAPTER VIII

NEW THEORIES REGARDING MENSTRUATION

THE morphological changes in the uterus and ovaries attending the human menstrual cycle have already been described in Chapter IV and should be perfectly clear in the student's mind before he attempts to master the more recent ideas. The discovery of the oestrogenic and luteinizing hormones of the hypophysis (prolan A and prolan B) did not greatly alter this picture excepting that prolan A was recognized as the motor of the proliferative phase and prolan B of the progestational phase of the ovarian secretion. It was believed that the progestational changes of the endometrium are necessarily conditioned by a previous ovulation plus the formation of a corpus luteum.

But the whole subject was thrown into confusion when Corner, Edgar Allen, Hartman and others showed that in monkeys, which have a menstrual cycle like that of woman, menstruation often takes place regularly without evidence of ovulation, and with only slight waves of growth and decline in the uterine mucosa. This is particularly true in the summer months which for monkeys is a nonbreeding season. The conclusion from these observations was that in monkeys at least (and perhaps in women) there are *two types of menstruation*—one that is preceded by ovulation and one that is not.

E. Allen and later Hartman were able to produce long flowing spells in castrated monkeys by administering oestrin (in the form of amniotin) over a period of six to eight days

As shown in
menstruation
in the monkey
(y. perianal
region) con-
tinues over

La fertilización
produce menstru-
ción en el animal
castrado

and then suddenly withdrawing it. The resultant bleeding in Hartman's cases continued eight to twenty days. He secured the same results in normal monkey adults, amenorrheic adults, and babies a year old.

Hartman's next inquiry was: Does the ovarian hormone thus administered act directly on the uterine mucosa of the spayed animal, or does it act through the hypophysis? He answered this question by first injecting amniotin (oestrin) into a hypophysectomized baby monkey, but with absolutely no macroscopical or microscopical evidence of uterine blood.

Injections of an alkaline extract of hypophysis, however, produced small amounts of blood from the uterus. Other experiments with hypophysial extracts were followed by similar results.

Hartman found also that bleeding could be induced by small doses without any of the preliminary changes in the uterus and ovaries which one is accustomed to associate with true menstruation. He therefore concluded that the stimulus for bleeding comes directly from the hypophysis and is independent of the "hyperplasia, swelling, or even congestion of the uterine mucosa." Reasoning from this he postulated a "separate anterior lobe hormone as the direct cause of bleeding, since it is here demonstrated that the bleeding is independent of the follicle stimulating effect, the luteinizing phenomenon, and the other influences attributed to the gland." This adds a new hypothetic hormone to the already crowded anterior lobe.

Hartman's final conclusion required further confirmation, but his work together with that of Corner and Allen throws new light on the clinical aspects of human menstruation.

Por su vez hay
hipofisis, etc.
de la que se produce
el efecto por
medio de la
hipofisis.

La hipofisis
actúa directamente
sobre la menstru-
ción.

Por Hartman,
esta acción
menstruante
de la hipof-
isis, se produce
el efecto por
medio de la
hipofisis.
(?)

As Novak has pointed out there is no doubt that menstruation is characteristically and probably usually preceded by ovulation and all the changes that go with it. We already know that *bleeding* can take place without ovulation, for typical dysfunctional bleeding, so common in the fifth decade, is invariably accompanied by cystic follicles and absent corpus luteum, incontestable evidence of lack of ovulation. Dysfunctional bleeding may have a certain periodicity that simulates true menstruation excepting for its abnormal duration and amount. Novak believes that the follicle (nonovulating) type of menstruation occurs in many women, especially near puberty and the climacteric, and the dysfunctional bleeding seen at those times is simply a pathologic expression of this type of menstruation. It is entirely conceivable that nonovulatory menstruation is accountable for some cases of sterility where no physical abnormality can be discovered.

Hartman's production of uterine bleeding in amenorrheic and immature animal subjects is also suggestive matter for the gynecologists. He calls attention to the fact that his experiments reveal that the "threshold for bleeding must be many times lower than that for pregravid uterine change or even change accompanying ovulation." He therefore questions how much practical good is accomplished in the mere induction of blood by administering hormones to amenorrheic women.

In a later contribution Hartman offered a brand new theory of menstruation and one that makes an immediate appeal to the imagination. In leading up to his main thesis of the true meaning of menstruation he presented a graphic tabulation showing the relationship of bleeding to the sexual

menstruación en
ovulación a los
50 años.

Algunas
menstruaciones
no ovulan.

En la menstruación
no ovulante, se
ca vómitos
de esterilidad.

Hartman
por la baja
presión de la
presión.

La hormona
hormonal, produce
una menstruación
inducida de ovu-
lación.

cycle in various animals including man. This presentation seems definitely to settle the long-debated question of where menstruation stands with reference to oestrus. It depicts so clearly the fundamental similarity between the sexual cycles of different species that an abbreviated reproduction of it is hereby given for the benefit of those who have not read the article.

Hartman, with excellent reason, assumed that so obvious and constant a phenomenon as menstruation must in the nature of things be a physiologic and not a pathologic one. As we have pointed out it had been generally accepted that menstruation represents a disintegration of the endometrium as a result of the decadence of the corpus luteum. Such a process is clearly pathologic as the proponents of the theory were forced reluctantly to admit.

Hartman, unable to accept a theory so contrary to Nature's usual practice, sought an *active* cause for menstruation by a searching study of comparative physiology. His own investigations coupled with those of Heape, van Herwerden, Halban, Corner, E. Allen, and Jaachimovits had established the identity of human menstruation and that of monkeys. The occurrence of menstruation without ovulation had been demonstrated in monkeys and inferred in the human. The time of ovulation had been established as occurring at or near oestrus in animals and halfway between menses in monkeys, and, by inference, at the same period in the human. The visible bleeding of the bitch in heat, formerly called "menstruation," was shown to be not a true menstruation at all since it coincides with the period of ovulation. A similar bleeding appears at the cotyledons of the cow at the season of heat.

La déviation
non des endo-
métrio, et un
processus patho-
logique: la
résorption et
proliferation pure.

Furthermore, it had been shown that bleeding occurs at metoestrus (between oestrus) in the guinea-pig (Stockard and Papanicolaou), the lemur *Tarsius* (van Herwerden), and in the dog. Hence metoestrus and menstruation are homologous seasons.

Hartman found the final proof of this homology in the frequent appearance in monkeys of intermenstrual bleeding at the middle of the menstrual cycle, *i. e.*, at the time of ovulation. He suggested the so-called "Mittelschmerz" as a possibly analogous condition in woman. He might also have mentioned the painless intermenstrual bleeding occasionally seen for which the gynecologist, with cancer in his mind, cures with negative findings and without cure.

The table (Fig. 9) is a slightly modified copy from Hartman. The columns M_1 and M_2 represent two successive menstrual periods typical of monkeys and man and corresponding to metoestrus in lower animals. The central broad column represents the ovulation period of lower animals and hence the season of oestrus. The upper section (1) depicts the menstrual cycle highly developed in man and monkeys and only foreshadowed in lower forms, pictured in the latter by fine lines of red that denote bleeding.

The second (middle) section (2) portrays the phenomenon of menstruation without ovulation and corpus luteum building. This is characteristic regularly of monkeys during the nonbreeding season of the summer months and occasionally during a menstrual cycle in the winter. In this section man is included for there is much clinical evidence from the operating room where not infrequently ovaries are seen quite destitute of corpora lutea in women whose catamenia are regular both before and after operation. The non-

		M ₁	Ovulation	M ₂	
	Dog	—	— •	—	
	Cow		— •		
	Guinea Pig	—	•	—	
1	Tarsius		— •		
	Monkey	■	— •	■	
	Man	■	— •	■	
2	Monkey	■	No ovulation	■	
	Man	■	No ovulation	■	
	Monkey	■	Pregnancy •	—	
	Man	■	•	—	
3	Rat		•	—	
	Guinea Pig		•	—	
	Rabbit		•	—	
	Vivip Fishes		•	—	—

Fig. 9.—Hartman's table (abbreviated) showing the phylogenetic evolution of menstruation and the homology between the bleeding of menstruation and implantation of pregnancy. (From Hartman's article in Amer. Jour. Obst. and Gynec., April, 1930.)

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ovulation section also represents the anoestrous periods of lower animals which, as we have seen, may in some species, like the deer family, last for many months. (The anoestrus of lower animals has been omitted in this modified copy of Hartman's table.)

The lower section (3) shows the comparative relationship of the pregnancy cycle, but before interpreting this it is necessary to return to Hartman's paper for further information for herein lies the crux of the whole matter.

Attention is called to the fact that human beings, apes, and old world monkeys are the only animals that menstruate in the strict sense. They are also the only forms that have a peculiarly hemorrhagic type of implantation of the ovum. A study of the youngest human ova so far recovered (Streeter, Kleinhans, Bryce-Teacher) reveal the trophoblast at first as just beginning to tap the blood vessels, without extravasation. Slightly older embryos are found to be completely surrounded by lacunae of extravasated blood. In still later stages as the ovum bulges into the uterine cavity the lakes of blood occupy large regions under the ovum, a condition which in the monkey is present from the beginning.

In a twenty-nine-day implantation of a monkey Hartman found the dilated uterine glands under the implantation sites gorged with blood, some of it reaching the vagina and constituting what the embryologists name the "placental" or as Streeter calls it the "trophoblastic" sign.

With this evidence at hand Hartman detected a significant parallelism between the hemorrhage of menstruation and that of implantation of the ovum.

These observations were made from the highly evolutionized species, man and the primates. Hartman found further

*The hemorrhage is
seen to be
like in the
implantation of
ovum.*

evidence of his theory in lower animals which he believed "hazily foreshadow the menstrual process in the metoestrous hemorrhages or slight bleedings following pseudopregnancy," to which we have already referred. In like manner he interpreted as confirmatory of his theory the hemorrhages into the pregnant uterine cavity of the rat, guinea-pig, and rabbit and even of nondeciduates described by other observers (Long and Evans, Wislocki, Bonner, and Kolster). All these "adumbrations" of human menstruation are graphically shown in the accompanying table (Fig. 9).

Not satisfied with what he had learned from mammals Hartman pursued his phylogenetic studies into the lower realm of viviparous fishes, amphibia and placental lizards and found in the scientific literature constant reference to red blood cells filtering into the blood chamber. "Everywhere the same story: red blood cells in the blood chamber," and associated with this, "degeneration of endothelium a process favoring the leakage of free blood into the pregnant organ." This phenomenon is pictured by the dotted red line in the table opposite viviparous fishes.

*La menstruation
est une fonction
active et non
pathologique*

Thus Hartman has, with suggestive scientific evidence, assigned to menstruation an active, physiologic, reasonable cause, and has done away with the disagreeable notion that the process is a pathologic one. He has shown too that the causative or regulative factor which excites, at the rhythmic moment, the bleeding of menstruation and implantation does not reside in the ovary though this organ cooperates in maintaining the rhythm. Still further he has demonstrated clearly the position of menstruation in the phylogenetic evolution of sex physiology.

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CHAPTER IX

NEW THEORIES REGARDING PARTURITION

MUCH work is being done on the part that hormones play in parturition. At the time of writing the evidence is confused and incomplete. The following quotation from Smith and Watkins will serve as an excellent introduction to a discussion of the subject.

"Just before delivery the outstanding endocrine situation is this: folliculin has reached its highest level, the luteinizing hormone has decreased, and the corpus luteum has apparently become insignificant. We have repeated successfully the work of others (Nelson, Hofbauer) showing that the administration of progestin or the luteinizing hormone inhibits the birth mechanism. A synergistic effect of folliculin and the *oxytocic* principle of the *posterior* pituitary in stimulating uterine contractions has been demonstrated by a number of investigators (Brouha, Parkes, Bourne and Burn, Knauss, Dixon and Marshall) and in addition it has been shown (Dixon, Knauss, Fröhlinholz) that progestin can make the uterus insensitive to this combination (folliculin + oxytocin)."

La luteína
decrece. Au-
mento de
progestina.
La oxitocina
hipofisaria. Esto
dos obran si-
nergicamente.
La luteína
impide la
ocurrencia.

It is necessary now to turn our attention to the rôle played by the posterior lobe of the hypophysis in its relation to the final event of the reproductive cycle—parturition.

The problem was well stated by Michael Foster in his Text-book of Physiology (1890) in the following paragraph (quoted from Dixon and Marshall): "We may be said to

¿ Porqué el
uterus se con-
trae de pronto?

be in the dark as to why the uterus, after remaining for months subject to futile contractions is suddenly thrown into powerful and efficient action, and within, it may be, a few hours or even less, gets rid of the burden which it has borne with such tolerance for so long a time."

¿ es el factor
hipofisario i por
qué se aplica
la hipofisario?

Parturition is the climax of the mysterious rhythm that characterizes all the sexual phenomena of the female, and for which no satisfactory explanation has yet been offered. Scientists are now looking to the hypophysis for a solution and with good reason, but as Novak remarks we shall perhaps have to fall back on some innate human factor as elusive as the life principle itself.

¿ Lo pseudo pre-
gnante (mami-
tante) se
acompaña
en los ani-
males de
fenómenos
reiterables
de (i) un
vacío ma-
te rical de
efusión
de la
mamaria
reiterable?

Marshall had recognized a definite hint that birth is a function of a certain stage in the ovarian rhythm from the behavior of animals that undergo the condition of pseudopregnancy. We have already described the experiments of Ancel and Bouin and later of Hammond who induced pseudopregnancy in rabbits by sterile coitus. They showed that during this period the corpus luteum remains active together with a correlated growth of the uterus and mammae. As the corpus luteum regresses the uterus also diminishes and the mammae begin to secrete milk. It has been shown that the Australian cat, the opossum, and the dog pass through a similar phase of pseudopregnancy, though in contrast to the rabbit, spontaneously, *i. e.*, without coition. To quote Marshall: "At an advanced stage of involution which may be considered as marking the termination of pseudopregnancy these animals commonly display habits or instincts which are normally associated with the act of giving birth. Thus the bitch may prepare a bed as if for a litter of pups, the marsupial cat cleans out her pouch as if for the reception of

young, and the doe rabbit plucks her breast of fur which she uses to line a nest."

These habits appear at the end of a pseudopregnancy which has been proved to be dependent on the ovarian cycle, i. e., the corpus luteum phase. Marshall reasoned that similar habits occurring at true parturition indicate that the latter is also "correlated with ovarian changes depending upon the degree of involution of the corpus luteum and not solely upon the presence of the full-grown fetus" as was formerly supposed.

Dependen-
cia, entre
el ovario y el
cuerpo lúteo
no de la
presencia del
feto (lo
demuestra el
que pero en el
falso embarazo)

It remained, then, to find what agent stimulates the uterine muscle to contractions sufficiently powerful to expel the fetus, and attention was directed to the ovarian hormones.

The first step was to test the direct action of these hormones on the contractility of the uterine muscle. This was done by observing the contraction effects of certain extracts on a guinea-pig's uterus, isolated and suspended in Locke's fluid. Dixon and Marshall found that follicular and corpus luteum extracts act on an isolated uterus in no way differently from extracts of other tissues. This showed that the ovarian hormones have no direct influence in precipitating parturition.

Según
D. y M. los
extractos ova-
rios no
tienen acción
oxidativa.

Now it had long been known that extract of the posterior lobe of the pituitary (pituitrin) has a very marked effect on the contractility of the uterine muscle both experimentally and clinically. Burn and Dale (1922) had been able to standardize the strength of a given specimen of pituitrin, so that it can accurately be measured, as to its uterine muscle contractibility.

La parte po-
sterior de la
hipófisis.

It occurred to Dixon and Marshall that the posterior

lobe is the source of stimulus for labor, but that it is activated by some outside factor. Dixon solved the question in the following ingenious way.

Cerebrospinal fluid is tapped in an anesthetized dog, and allowed to run. Injections of the fluids to be tested are made into the dog's circulation, and the cerebrospinal fluid then tested for pituitrin on the virgin uterus of a guinea-pig, suspended in Ringer's fluid, readings being made on a drum in the usual way. Any increase in pituitrin in the cerebrospinal fluid is indicated by increased contractility of the uterine muscle, and duly recorded. The extracts of numerous tissues, such as the testis, epididymis, pancreas, etc., were tried out and found negative. Extracts of corpus luteum were also entirely negative, but extracts containing folliculin (oestrin) had a decidedly exciting effect—two important observations. It was then found that during pregnancy (while the corpus luteum is active) ovarian extracts were negative, but that at the close of pregnancy (when the corpus luteum has retrogressed) they became strongly positive. The same rule held true in tests made through the sexual cycle, namely, inactivity of follicular secretion during the corpus luteum phase.

From these experiments it was assumed that during pregnancy the follicular secretion of the ovaries so far as its influence on the posterior lobe of the pituitary is concerned is held in abeyance by the corpus luteum, and that when the corpus luteum disintegrates at the end of pregnancy the follicular secretion asserts its influence and the pituitary is excited to activity. When the threshold stimulus of the pituitary upon the uterus is reached and passed the pains of labor set in and parturition results.

Experimentos de
Dixon. Se
infecta con
el fluido de la
cabeza del perro
cervical y se
la inyecta en
el abdomen de
una guinea-pig.
No, ninguna otra
extracto.

Por lo tanto, la
folliculina que se
pasa al final del
cuerpo luteo (durante
este, está inactiva)
por el cuerpo luteo
se activa la secre-
ción de la pituitaria
y aparece
la contracción
uterina.

Moreover, Dixon found that the stimulating effect of the ovaries was most marked when they had been obtained at or about the time of labor. He suggested that the hormone which stimulates the posterior pituitary is produced in greatest abundance at this period, a conjecture that was soon substantiated when it was shown that at the time of parturition the organism is flooded with the follicular hormone.

As a result of these experiments the authors deduced the theory that the ovary in the preparturition stage produces in great amounts a hormone (oestrin) which stimulates the posterior pituitary, and this hormone in turn stimulates the uterus to expulsive contractions. This theory, however, has been modified to one that states that oestrin, instead of stimulating the pituitary, sensitizes the uterus to the contracting influence of the posterior pituitary hormone (pituitrin). This later theory postulates that the sensitivity of the uterus to the posterior pituitary influence undergoes cyclic variation in correlation with the ovarian cycle, the maximum sensitivity being reached at the time of parturition (Parkes). Clinical evidence of this cyclic correlation between ovary and uterus during pregnancy is familiar. Parturition normally occurs at what would have been a menstrual period if pregnancy had not supervened. Moreover, the pregnant patient exhibits a certain mental and physical lability at the usual catamenial dates, and is at such times peculiarly liable to abort, especially in the early months.

That the stimulation of the uterus is not due to a direct action of the posterior pituitary has been confirmed by interesting experiments in producing abortion in pregnant

La acción
"pituitaria"
de la "del
ovario es
mayor cuando
se da el parto
es de un tipo
que produce el
parto. En otros
casos, como en
zobros, puede
producirse en
el infante
crisis melancólicas

Resumen. 1º
hipofisario. 2º
hipofisario.
3º hipofisario
uterino

La pituitaria
es la que
regula el
ritmo de
la vida
reproductiva

El parto, esto es, la
expulsión del
feto, ocurre
por eso, al
parto, porque
cuando el
feto está en
el útero, y
se acerca al
parto, se
produce un
estado de
aborto.

Dois hormônios
retirados da
parte posterior
do hipotálamo
(oxtocina
e vasopressina).

laboratory animals with ovarian secretion (oestrin) and posterior lobe secretion (pituitrin) singly and in combination. The success of these studies was made possible by the work of Kamm, Aldrich, Grote, and Rowe who in 1928 separated two extracts from the posterior lobe of the pituitary body, one having the *oxytotic* property of stimulating the musculature of the uterus, and one having a *vasopressor* effect.

To the first they gave the name *oxytocin*, and to the second *vasopressin*. The two outstanding properties of the posterior lobe have long been known to the profession in their use of pituitrin (an extract of the whole gland), for assisting the uterine contractions of childbirth and for the relief of postoperative intestinal stasis.

Os efeitos sobre
o útero são
específicos de
cada hormônio.

Kamm and Aldrich and their co-workers demonstrated the specific effect of oxytocin on the isolated uteri of guinea-pigs. Bourne and Burn went further and by using a special recording apparatus were able to test the effect of the hormone on the human pregnant uterus. Their results entirely confirmed the work of Kamm and Aldrich in that oxytocin "had a powerful stimulant action on the uterine musculature, whereas vasopressin even in large doses had little effect of any kind on the uterus in labor." They also found that oxytocin is a safer drug to use during labor than pituitrin since it avoids certain dangers such as shock, evidently due to the presence of vasopressin in the whole extract.

A ação comparada
da de pituitrina,
oxtocina
e vasopressina.

Parkes in an experimental study of the physiologic mechanism of labor compared the effects of pituitrin, oxytocin and vasopressin on pregnant mice.

First, he found that pituitrin regularly caused abortion, but that in each case the abortion was characterized by the

birth of dead fetuses from one to three days later. This showed that the abortion "was not a real simulation of a parturition mechanism," but was the result of something that first caused the death of the fetus.

parturition, here
abortion precedes
matured of
fetus (more
e vero!)

Second, he tested oxytocin alone and found that even in large doses (*i. e.*, twice the normal clinical dose) pregnancy was not interrupted.

oxytocin, in
interupte el
embarazo.

Third, he tried the effect of vasopressin alone, and found that it acted just like pituitrin in that it produced the abortion of dead fetuses from one to three days later, evidently the result of "some vascular disturbance in the placenta sufficient to cause fetal death and subsequent evacuation of the uterus."

Vaso-pressin,
o alone causes
la parturition:
(a aborts por
feto muerto por
mucosa vascular).

Fourth, he next repeated the experiments of others who had shown that pregnancy is interrupted by injections of oestrin, using the newer purified preparations of the hormone. Single large doses, and moderate repeated doses, failed for the most part to produce abortion, but large doses repeated frequently over thirty-six hours usually caused a "regular" but "delayed" abortion forty-eight hours after the last injection.

Repetidos dosis
repetidos de
feto muerto,
produce un
a aborto regu-
lar y tardio.

Fifth, the final step was to compare these results with a series in which a repeated dosage of oestrin that had proved incapable of causing abortion alone, was followed immediately by an injection of oxytocin. This combination caused immediate "regular" abortion in the majority of tests as contrasted with no abortions from oxytocin alone, and delayed abortion only after repeated large doses of oestrin alone. It therefore appeared that oxytocin exerts its expulsive influence on the uterus only when its musculature has first been sensitized by oestrin.

Oxytocin causing
parturition en
segunda dosis.
Se tarda al
a aborto regular,
normal.

Si mujer es insensible a la oxtocina

In this way Parkes established the principle of a synergism between oestrin and oxytocin.

Durante el embarazo, la luteína (progestina) impide de la mujer sensible a la oxtocina.

But, it will be asked, if this principle is true, why is it that abortion does not take place at any time during the course of pregnancy since oestrin is continually being elaborated? The answer is that progesterin, the hormone of the corpus luteum, probably makes or at least is a factor in making the uterus *insensitive* to the combined effect of oestrin and oxytocin. Oestrin is produced in increasing quantities up to the time of delivery, when it is found in large amounts in the urine, blood, and placenta. As oestrin increases, its antagonist, progesterin, after a period of activity decreases as the corpus luteum gradually disintegrates, so that just before delivery oestrin is at its highest, and progesterin at its lowest level. Oestrin then dominates the situation, and sensitizes the uterus to oxytocin, which in turn stimulates the uterus to expulsive contractions.

Al final del embarazo, aumento de la luteína y disminución de la oxtocina.

Por eso, la administración de luteína inhibe el parto.

Causa del parto retrasado.

A significant confirmation of this theory is found in the experiments of Teel, Nelson, Piffner and Haterius, and Smith and Watkins, which show that the administration of progesterin or of the luteinizing hormone of the anterior lobe *inhibits* the mechanism of birth. Thus one can imagine that delayed parturition may be the result of the abnormal persistence of a corpus luteum that is out of tempo with the clocklike regularity of the reproductive cycle.

El ovario es un regulador; el útero es la ejecutora.

Of course this rather simple explanation of the mechanism of parturition even if it turns out to be fundamentally true is the merest outline of what actually takes place. The theory as we have stated it seems to assign to the ovary the rôle of time-regulator, but it now appears that the ovary is only a secondary though necessary agent under

(¿por el ovario quien lo regula? a el ritmo cornico!)

the control of the hypophysis which is the real "motor" of the entire complicated apparatus. The correlation between the ovaries and hypophysis has by no means been completed. The relationship of the other glands of internal secretion, especially the adrenals, presents a tantalizing and as yet unconquered field for research. Finally, the realm of biochemistry looms large as the ultimate ground on which the secrets of parturition and all the processes that go with it and lead up to it will be revealed. For pioneer work in this field the reader is referred to the contributions of Smith and Watkins, references to which will be found in the Bibliography.

*Los hormonas
vales, no se
solo si
actúan.*

Placenta.—Mention should be made of the more recent work on the hormones of the placenta. The placenta is both a storehouse and a producer of substances necessary for the nourishment and growth of the fetus. It contains, for example, vitamins, insulin, thyroxin, folliculin, and anterior lobe hormone. It has already been proved that the placenta actually elaborates folliculin. Waldstein in 1921 was obliged to remove the ovaries of a patient thirty-four days' pregnant. Pregnancy continued to term. During the entire period of gestation the patient, though she had no ovaries, continued to show the normal amount of folliculin in the blood and urine, and at term the placenta contained the usual quantity of folliculin. In this case the folliculin could have been produced only by the placenta (Zondek).

*Es un depósito y
una fábrica de
hormonas.*

*Queda de
la fábrica
en la placenta
lo que produce
la hipófisis.*

There is at the present time a controversy as to whether the so-called "anterior lobe hormone" found in the placenta is stored there, its original source being in the hypophysis, or whether the placenta assists the hypophysis in supplying

*¿El feto o
la hipófisis:
¿lo produce
esta o la
almacena o
la hipofisi?*

the extra amount required during pregnancy, or whether the placenta alone furnishes it.

Several investigators, notably Phillip, take the last view, claiming that the anterior lobe hormone found in such quantities in the urine, especially of early pregnancy, is a product not of the hypophysis but of the placenta.

Zondek emphatically denies this claim, and holds to the supremacy of the hypophysis though he admits that if the placenta produces folliculin it is conceivable that it may also aid the hypophysis in manufacturing anterior lobe hormone.

Zondek has standardized the ALH (anterior lobe hormone) in mouse units and is thereby able to measure the quantity of the hormone in any given fluid or tissue. He does not think that the mere finding of ALH in the placenta is a proof of its having been manufactured there for it is also found in higher proportion in the blood and urine. Zondek found it in copious amounts in the contents of a large ovarian cyst removed during pregnancy. Zondek and others have shown that when the placenta contains most ALH the hypophysis contains very little or may be entirely "empty" of it. This fact has been used as evidence of the placental production of the hormone. Zondek on the other hand believes that it indicates a rapid output from the hypophysis to meet the special requirements of the organism. He also finds a great variation in the amount of ALH used in different species, even between those that have a similar method of placentation. The subject, at present much unsettled, is evidently one of great importance.

Zondek in concluding the article from which the above brief notes have been abstracted, takes the occasion to stress the "superordination" of the hypophysis in the following words:

"Without the anterior lobe and its hormone no sexual activity, no ovulation, no sexual rhythm!

"Without the anterior lobe, atrophy of the sexual organs!

"Without the anterior lobe, no conception!

"With disturbance of the anterior lobe, death of the egg!"

Papad. ca. le
hypophysis (lobules
anterior)

CHAPTER X

NEW THEORIES REGARDING LACTATION

THE marked changes that take place in the breast at puberty, during pregnancy, and at the climacteric have long suggested the probability or even certainty that the breast is influenced by the same hormones that regulate pelvic sex physiology. The supposed source of the lactation hormone has successively been sought in the fetus, placenta, follicle fluid, corpus luteum, and finally in the hypophysis. A detailed description of this search during the past quarter century is given by Corner in his well-known report on the Hormonal Control of Lactation, to which the reader is referred. The following is a brief recapitulation of the work done previous to Corner's.

*This tissue is
the source.*

Halban in 1905 concluded from clinical evidence that the chorionic ectoderm (placenta) is responsible for the proliferation and lactation of the mammary gland.

Starling and Lane-Clayton in 1906 tested experimentally the effect of aqueous extracts of ovaries, placental and uterine tissue, and fetuses. Only slight proliferative changes at the most were noted in no way equivalent to those of normal pregnancy. Similar negative results were secured by others who repeated the experiments (Biedl and Königstein, 1910; Frank and Unger, 1911; Aschner and Grigoriu, 1911, and Fellner, 1913).

Ancel and Bouin in 1911 in their famous experiment of producing pseudopregnancy by mating female rabbits with vasectomized bucks, observed a proliferation of the mammae equalling that of midpregnancy. They inferred that the first stage of mammary growth is induced by the corpus luteum, lactation being the result of some other factor, unknown.

Hammond in 1917, observing the persistence of corpora lutea in pregnant rabbits, removed the fetuses on the fifteenth day, and noted an arrest of mammary development with immediate appearance of milk in the duct. He concluded that in pregnancy the corpora lutea are made to persist through the influence of the fetuses, and that the corpora lutea in turn maintain the growth of the mammary gland. These experiments were only partially confirmed.

From 1913 to 1928 numerous experimenters tested the effect of oestrin on the breasts. They were able to produce in immature animals growth changes of the breasts equivalent to those that occur naturally at puberty, but not comparable with those of normal pregnancy. (Corner concludes from this work that the partial success of previous experimenters was due to the presence of oestrin in various organ extracts that were used.)

The most distinctive results so far obtained seemed to be those of Hammond, who referred them to the effect of corpus luteum. The problem of testing further the corpus luteum consisted now in some method by which the corpora lutea of a nonpregnant rabbit might be prolonged over a period corresponding to normal pregnancy. This was solved by Parkes in 1929 by applying the discovery of

*Es evidente
la acción
"puberal" pro-
voca "proliferación"
de la glándula
mamaria, sobre los
mamones.*

*Luteinización
del cuerpo
por el extracto
de hipófisis.*

Evans (1924) that alkaline extracts of the anterior lobe of the hypophysis induce in female animals luteinization of graafian follicles and also cause persistence of preexisting corpora lutea. Parkes first produced pseudopregnancy by the Ancel-Bouin method and then after ten days prevented retrogression of the corpora lutea by daily administration of Evans' hypophysis extract. In this way he induced mammary growth far beyond the stage of pseudopregnancy seen by Hammond. Parkes ascribed this striking effect to the endocrine action of the corpora lutea which he had kept alive with his hypophysis extract.

At about this time Corner had succeeded in producing his new and highly potent extract of progesterin. With this extract he had been able to carry to full term pregnant doe rabbits that had been deprived of their ovaries eighteen hours after conception. In all of these experiments the breasts underwent the identical changes of hypertrophy and lactation typical of normally pregnant rabbits. Corner reasoned that if these changes were due to his continued administration of corpus luteum (progesterin) the same effect should be induced with progesterin in spayed nonpregnant rabbits. He therefore made this test in several animals but did not succeed in causing the slightest alteration in the breasts.

This seemed like excellent evidence that the corpus luteum does not effect the mammary changes in pregnancy, but as Corner pointed out it was not conclusive since it had been demonstrated (Hisaw, Corner) that the corpus luteum does not exert its known effects (*e. g.*, on the endometrium) without having first been prepared by oestrin (see previous chapter on *synergism*). Spayed nonpregnant rabbits are devoid of oestrin.

En la parrilla
cía del cuerpo
luteo, se
acompañó
hipertrofia
mamaria -
(por el pro-
la hipofisi)

Con el extracto
luteo, se
puede llevar
a la unión
un cuerpo
con la ovulación
de la concep-
ción. Hay
hipertrofia
mamaria.

Por ende
hacemos un
extra de cuerpo
luteo, el extracto
de cuerpo luteo,
produce el efecto
de la mamaria.

Y es, por ende
ampliado, un
factor fabu-
loso; y el
cuerpo luteo
actúa a través
de la mamaria,
solo si esta
ha sido pre-
parada por
la foliculosa.

La foliculosa.

with hypophysis extract. They used only animals that had ovulated and had thus been exposed to the effects of corpus luteum. They inferred that the action of the hypophysis extract was due to a previous sensitization of the corpus luteum. Corner's experiments ruled out any such possibility. He admitted, however, the possibility that the hypophysis requires preparation from oestrin. After lactation is established oestrin is hostile, as shown by Smith and Watkins, who have inhibited lactation in mice by the administration of oestrin.

In sum, then, it has been demonstrated that the proliferative and lactational changes of the mammary glands during pregnancy and following parturition are due, not to a follicular or corpus luteum hormone as formerly supposed, but to the direct action of the anterior lobe of the hypophysis. Whether or not the effect is due to a special "hormone of lactation," or whether it is identical with one of the two proved hormones of the anterior lobe has not been determined (Smith and Watkins).

The part played by the body chemistry in lactation has been interestingly shown in the recent work of Orent and McCollum. They reared young rats to maturity on a manganese-free diet. The females attained sexual maturity in a normal manner and produced the normal number of young when mated at proper intervals. In 58 cases out of 59 these females failed to suckle their young. "They appeared indifferent to them and did not give them the care or opportunity to suck which is characteristic of female rats on the same dietary formula with small amounts of manganese added." The manganese-free rats exhibited the same indifference toward foster-young from stock litters. Among other important data it was found by spectroscopic test that in the offspring of manganese-free mothers manganese is absent—proof that manganese passes through the placenta if it is present in the mother's blood. The authors

Probablemente
no. lo pre-
ben los cor-
de pre-con-
tra. Pero de-
no de origen
hipofisario
La función
inhibe la
lactación.

La hormona hi-
pofisaria, lacta-
togeno, es la
misma substancia
o no?

La falta de
manganeso
impide la
lactación.

No hay mang-
neso en los
de estos ratos.

manganese
hypophysis.

have suggested a provisional hypothesis that manganese is in some way concerned with the production of a hormone by the anterior lobe of the hypophysis which is essential for the proper development and functioning of the mammary glands.

CHAPTER XI

ORGANOTHERAPY

SUBSTITUTION therapy has not kept pace with the brilliant physiologic discoveries in sex hormonology. In fact, therapeutic success has been so meager that the scoffer might well remark with sly innuendo that the mountains have labored and brought forth only a ridiculous mouse. But the outlook is by no means gloomy for the new knowledge of the mechanism of sex processes indicates clearly enough that the therapeutists of the past, working entirely in the dark, have wasted their energy in a feverish use of extracts from the *wrong organ*. In efforts at progress the discovery that one has been on the wrong trail is of considerable importance.

The history of ovarian organotherapy though covering many years can be told in comparatively few words. Substitution therapy for various pelvic disorders referable to supposed ovarian deficiency immediately followed Knauer's classical experiments in 1896, and has been pursued until recent times with gradually lessened enthusiasm. The claims of the advocates of ovarian therapy, set forth in an extensive literature, partly clinical and partly commercial, may be summed up in the conclusions of one of the first articles published in 1898 by Bestion de Camboulas (ref. Dodds), of which the following is a translation.

1. The painful symptoms of the natural menopause have disappeared or are considerably relieved by ovarian extracts without any other medication.

As varied.

As part of
the mountain.

Falsa afirm-
teropica.

funtelides
de la opo-
teropica ov-
na total
(No lo creo.
Por lo pro-
prio? Vase
Novo y
disminuye).

Anders
resultados.

2. The same results have been observed in the affections that follow ovarian castration.

3. The rapid amelioration that we have observed in amenorrhoeic and chlorotic patients has been constant.

4. The influence of ovarian extract on the mental troubles that accompany genital lesions or castration are real.

To these claims there were later added relief from all forms of abnormal uterine bleeding and cure of sterility. Many clinicians, however, were unable to attain these results and the literature was full of conflicting reports. The controversy subsided when Frank, Novak and others demonstrated the very small amount of potent substance in the commercial extracts and its rapid destruction in the gastrointestinal canal. The isolation of folliculin and its discovery in large amounts in the placenta and amniotic fluids roused new hopes. But the newer and more potent extracts produced results little better than the older preparations. However, there still remained the scientific fact that these same preparations exert a profound influence on the genital processes of laboratory animals and the mystery of their failure in human application was greater than ever.

Amenorrhoea.—The discovery of the part played by the hormones of the anterior lobe in throwing new light on the physiologic mechanism of sex processes served to explain in part at least the failure of ovarian extracts as a therapeutic measure especially for amenorrhoea. The experiments leading up to this explanation have already been described and we shall now refer to them again following in a measure the argument presented by Novak in recent papers.

1. Hartman and his co-workers were unable to produce oestrus in hypophysectomized monkeys whether normal or

*Recherches
d'Anders.*

*La fabrication
des hormones
par les ovaires
et les
gonades.*

*La régulation
de la reproduction
par les hormones
de la hypophyse
et les ovaires.*

castrated even with very large amounts of ovarian follicular hormone. They concluded, therefore, not only that the ovarian hormone is dependent for its effectiveness on the anterior lobe but that it is itself an activator of the anterior lobe. This reciprocal synergistic behavior of two correlated hormones appears so often that it need no longer be a matter of confusion. In this case the companionate hormones are folliculin and prolan A. This at once suggests a reason why the direct administration of folliculin in humans is ineffective.

2. The human is a much bulkier, more complex and less sensitive animal than the mouse. Should we therefore expect similar quantitative reactions in the two organisms? Marrian and Parkes have taken the wind out of the sails of folliculin preparations by showing that the "hundreds of mouse units" that they represent is no great dose even for a mouse. They showed that the amount of oestrin unit sufficient to produce Allen and Doisy's vaginal-smear test for oestrus is two hundred times less than that required to produce the full oestrous changes in the uterus necessary for mating and pregnancy. In other words, the untreated mouse must itself produce 200 units to reach full genital oestrus. Marrian and Parkes came to the following conclusion, one that should be of interest to the clinician: "On a weight-for-weight basis a woman would require about 2000 times as much as a mouse. Since an ovariectomized mouse requires 200 units to induce complete oestrus, an ovariectomized woman might be expected to require 400,000 units to induce analogous symptoms. Attempts to give oestrin to women by mouth, by which route 50 to 100 units are required to produce an effect equal to

En un caso de hipofisitis, una activación de la pituitaria.
A un caso de pituitarismo, etc. - En el Prolan A.

No se puede esperar que el humano sea tan sensible como el animal.

Las unidades comerciales son insuficientes, aun para los ratos.

La unidad comercial es 200 veces menor que la necesaria (en el mismo ratón).

Es decir, que una mujer con insuficiencia ovariana necesitaría 400,000 / (cuando nubladas o unidades). - Es. pues, 400.000. cantidad de dosis.

1 unit given subcutaneously, would thus appear to be fantastic."

*Adelson, la
menstruación
por la ooforectomía
no es
verdadera
menstruación*

3. But supposing the administration of folliculin does induce a flow of blood in an amenorrheic woman, is it a true menstruation? This question has already been answered in the account of experiments on monkeys in which it was shown that the induction of bleeding by this method is not accompanied by the uterine and ovarian changes characteristic of the normal menstrual cycle. Hartman has shown that the "threshold of uterine bleeding is low." Many of us have noted occasionally the occurrence of bleeding after the administration of ovarian extracts in amenorrheic women—conceivably the effect of the hormone; but the rare cases in which the normal menstrual rhythm is restored would seem to be a spontaneous change rather than the result of our feeble drug.

*Si el ritmo
menstrual se
repara, a un
cambio es
spontáneo.*

*Terminando
el tratamiento
debe usarse:
1. folliculina
2. prolán.
Después usamos
oestron elevando
a la práctica.*

Is there then no hope for the treatment of amenorrhea, especially in those young women who, with no congenital or acquired stigma of Fröhlich's syndrome, suddenly cease menstruating after a sexually normal adolescence, or even after child-bearing? Bearing in mind the "one, two" reactions of the alpha and beta factors, one is led immediately to the idea of first administering oestrin (or prolán A if it were available) and then at the appropriate time of shifting to prolán B—certainly a logical clinical experiment. At the time of writing this treatment is being carried out doubtless by many clinicians, but it is too early for the publication of convincing reports.

Dysfunctional Bleeding.—The morphological changes in the endometrium and ovaries that accompany dysfunctional

bleeding have been made so familiar in later literature that it is necessary to mention them only in briefest outline.

In the typical case the endometrium shows evidence of intensive and prolonged follicle stimulation by a marked and irregular hypertrophy of the stroma and glandular elements. The glands exhibit only the proliferative phase of the menstrual cycle, with no evidence of those secretory changes characteristic of corpus luteum influence. The ovaries are devoid of a normal corpus luteum, but usually contain one or more cystic follicles, the fluid of which is more or less rich in folliculin. Abnormal bleeding is present from broken-down areas in the endometrium (now doubted). The absence of a corpus luteum is characteristically heralded by temporary cessation of the menses. There are many variations to this histologic picture with corresponding differences in the duration, amount, and periodicity of the abnormal flow.

At endometrio-
ectasia et
ectasia proli-
fero. At was
corpus luteum
with cor. sup-
virescent fol-
licles, in
corpus luteum
menses pro-
longed by
corpus luteum
flow.

This condition has long been recognized as the result of a functionally disturbed rhythm in the ovarian cycle, and has appeared especially appropriate for organotherapy. Obviously folliculin would not do, since the ovaries are already well charged with it and the endometrium shows evidence of an overdose. Clinicians turned naturally to the corpus luteum to supply the defect of that organ. But the commercial extracts of corpus luteum proved ineffective and it has been necessary to resort to operative or radio-logical measures to restore the patient's health and sometimes even to save her life. Such measures are exceedingly useful when employed near the menopause, but unfortunate in the treatment of younger patients.

At hypofun-
ctionem cor-
poris lutei
propter cor-
poris lutei
actionem.
At hypofun-
ctionem cor-
poris lutei
propter cor-
poris lutei
actionem.

When Corner produced his powerful extract which he called progestin there was great hope that it might solve the problem of dysfunctional bleeding, but no preparation of progestin so far has been made suitable for administration in the human.

Moreover, the corpus luteum as an independent sovereign

*Para 5 line
ante la
luteinización (pro-
gesterona) en
la hipófisis.*

has been overthrown, after the demonstration that monkeys and humans may menstruate rhythmically without a corpus luteum. Since the corpus luteum depends for its activity on its collaborator, the luteinizing hormone of the anterior lobe, there is no assurance that even if progestin could be furnished in suitable form it would be effective in treating dysfunctional bleeding.

*Capítulo del Pro-
lan B, barto
para alterar
la menstruación
normal (en forma
progestínica).*

The researches of Zondek and Wiesner, as we have shown, proved that prolan B when administered alone produces the luteinizing effects formerly attributed solely to the corpus luteum, and when an available extract of this hormone was prepared it was applied to the treatment of abnormal menstruation. Comparatively few reports have been made of this treatment at the time of writing, that of Novak and Hurd being the most important. Their results are especially significant, for almost for the first time in the history of sex organotherapy the treatment follows the line of a definitely scientific rationale. Novak says: "Our results in 51 cases, many of them of the recurring type, with often a number of previous curettements were far more satisfactory than those obtained after any other method of organotherapy with which we are familiar. Bleeding was checked in 44 cases of this series often with astonishing rapidity." Novak, however, does not believe that the blood-checking effect of prolan B is due to a luteinization of a lagging follicle, since the effect is often too rapid for such a process. There must, he thinks, be some other factor in the case as yet unknown.

*Por precedentes
efectos del
prolan B en
el tratamiento
de los hemor-
ragias.*

George V. S. Smith in a recent paper reported definite relief in eleven cases of dysfunctional bleeding treated with a luteinizing hormone prepared from the urine of pregnant

women. One case with a complicating fibroid was not relieved.¹

Smith extended the treatment to the bleeding of pregnancy, reasoning that insufficient progestin, by failing to maintain the decidua and thus impairing the vitality of the ovum, might be a factor in miscarriage. His results were partially successful but as yet too incomplete for definite conclusions.

Para evitar los abortos.

Nervous Disturbances Related to the Menstrual Cycle.—Much of the earlier organotherapy was directed to a relief of subjective symptoms that appear to be the result of a deficient or deranged ovarian function seen chiefly in dysmenorrhea, menstrual molimina, and the nervous irritability and flushes of the menopause. Many careful clinical observers encountered a sufficient number of favorable responses to the treatment to indicate that the results meant something more than a changed mental attitude of the patient. This was especially true of menopausal flushes, which are sufficiently distinctive to be of some use in empirical studies.

Afectos nerviosos de la menopausia.

This partial success contrasted sharply with the complete failure of the ovarian extracts to affect abnormal changes in the menstrual cycle. It seemed as if the unknown nervous factor in the syndrome of sex dysfunction might possibly be sensitive to even small doses of the ovarian hormone. Whether this has been a complete delusion remains to be seen.

Very little new light has been shed as yet on this important field of organotherapy. Campbell and Collip have

¹ According to G. V. Smith the successful results of the luteinizing hormone of the hypophysis in treating abnormal uterine bleeding of endocrine origin is its ability to cause the excretion of folliculin through stimulation of the corpus luteum.

Hormones
Placenta

Hypoparathyroidism
contraction

isolated several hormonal principles from the placenta with which they secured some favorable practical results especially in the treatment of dysmenorrhea, but this work as reported is too incomplete for final judgment. A significant step in the right direction is the work of Fluhmann who has studied the presence of prolactin in the blood from cases of abnormal pelvic function by the application of the Aschheim-Zondek test for pregnancy. He finds the test invariably negative in normally menstruating women whereas in abnormal cases it is frequently positive. This is markedly so in castrates, the reaction appearing some time after the operation and persisting for long periods—in one case fourteen years. Here is a definite imbalance which suggestively coincides with the well-known hypertrophy of the anterior lobe that takes place after removal of the ovaries. It is reasonable to expect that the collection of facts of this kind will ultimately lead to a more rational and perhaps successful therapy.

GLOSSARY

ALH. Used for the sake of brevity to denote the combined sex hormone of the anterior lobes of the hypophysis. Equivalent to prolan.

Allen and Doisy and Butenandt's isolation of folliculin. (Both reports published in 1928.) Folliculin extracted in pure crystalline form. *Historical landmark.*

Allen and Doisy's vaginal smear test. The microscopic study of the vaginal secretion of laboratory animals, to determine the presence and potency of oestrogenic substances. A positive test shows large numbers of cornified and desquamated epithelial cells. A negative test shows a collection of leukocytes. A positive reaction can be induced by oestrogenic substances both in spayed and immature animals. The cornified epithelium is characteristic of the vagina of a normal mature animal during the period of heat or oestrus. *Historical landmark.*

Alpha factor. Introduced by Wiesner to designate the hormone that governs the alpha or oestrous phase of the ovarian cycle.

Alpha phase. Used by Wiesner to denote the oestrous stage of the ovarian cycle.

Ancel and Bouin's experiment. (Published in 1910.) The endometrium of rabbits after sterile coitus and formation of a corpus luteum, passes through a secretory stage analogous to the premenstrual phase of the human menstrual cycle. *Historical landmark.*

Anoestrus. The long period of rest that occurs between the oestrus seasons of monoestrous animals.

Aschheim-Zondek test for pregnancy. Based on the luteinizing effect of the anterior lobe hormone found in the urine of pregnant women. See Chap. VI. *Historical landmark.*

Berthold's experiment. (Published in 1849.) Transplantation of testicles in spayed cockerels prevents characteristics of the castrate. *Historical landmark.*

Beta factor. Introduced by Wiesner to designate the hormone that governs the beta or progestational phase of the sexual cycle.

Beta phase. Used by Wiesner to denote the progestational stage of the ovarian cycle.

Bleeding hormone. Hypothetical hormone of the anterior lobe of the hypophysis, suggested by Hartman as the causative agent of uterine bleeding, independent of the two sex hormones.

Blood-points. See *Blutpunkte*.

Blutpunkte. German word meaning blood-points. Used by Aschheim and Zondek to describe the minute visible hemorrhages seen in the ovaries of mice after injection of the urine of pregnant women, a distinctive positive finding in the original Aschheim-Zondek test for pregnancy, but not useful in the test with mature rabbits.

Chorionic ectoderm. Same as *Trophoblast*.

Corner's discovery of progestin. (Published in 1929.) Isolation of the hormone of the corpus luteum progestin, proving the twofold nature of the ovarian internal secretion. *Historical landmark.*

Corner's and Hartman's discovery. (Both reports published in 1930.) Periodic menstruation may occur in primates without ovulation and corpus luteum formation. *Historical landmark.*

Cycle. Used to express the rhythmic periods of sexual activity in various species, and also the periodic changes that take place in the individual tissues of the sexual organs, both primary and secondary. The word is variously modified to include many special cyclic conditions that depend on the rhythm of sexual activity. The following are examples:

Sex Cycle. Relates specifically to the periodic genital changes when pregnancy does not supervene. Thus an oestrus period without conception is a sexual cycle. The time that elapses between the beginning of one menstruation to the beginning of the next is a sexual cycle. If conception occurs the sexual cycle is merged into and extended to a reproductive cycle.

Reproductive Cycle. Begins as a sexual cycle and when conception takes place continues through gestation and parturition.

Menstrual Cycle. Used either as a general term synonymous with the sexual cycle in humans and primates or more frequently to express the definite cyclic changes in the endometrium indicative of the stages of rest, proliferation, secretion, and disintegration.

Endometrial Cycle. Used either synonymously with menstrual cycle, or to include the entire reproductive cycle. In the latter case, it comprises the stages of menstruation, rest, proliferation, progestation (= secretion + conception), decidual reaction, placentation, deciduation.

Ovarian Cycle. The development of a graafian follicle, rupture and discharge of the egg, corpus luteum formation and regression in the absence of pregnancy. In case of conception the cycle becomes lengthened to a reproductive one, with persistence and growth of the corpus luteum followed by gradual regression to the time of parturition.

Vaginal Cycle. The periodic oestrus changes of the vaginal epithelium in laboratory animals, consisting of hypertrophy and desquamation. Made use of in the Allen and Doisy test for oestrogenic substances.

Uterine Cycle. Comprehensive term including the menstrual endometrial cycles, and that of the musculature.

Decidual reaction. The change of the stroma cells of the endometrium characteristic of the decidua of pregnancy.

Deciduoma. Same as *Placentoma* (*q.v.*).

Dioestrus. The period of quiet following oestrus in animals in which oestrus occurs at frequent intervals.

Dysfunctional bleeding of the uterus. Used by the author in place of the term "functional" bleeding in common use. See *Functional bleeding*.

Dysplasia of the endometrium. Used by the author in place of "hyperplasia" in common use (*q.v.*).

Evans' extract of the hypophysis. An alkaline extract of the anterior lobe in which the hypothetical growth hormone is dominant, in that it induces gigantism in immature animals with delay of puberty.

Excretory. Pertaining to an organ whose function is one of excretion. Used in contrast to incretory which relates to organs of internal secretion. Some organs like the ovary and pancreas are both excretory and incretory in function.

Extracts. See *Commercial extracts* under *Hormone*.

Female sex hormone. A term introduced by Frank to describe the follicular (oestrogenic) hormone found in the ovarian follicles and elsewhere in the body (blood, placenta, etc.). On account of the discovery of the hormone also in males and plants the expression though at first widely adopted is being given up in favor of the more exact term "oestrin."

Follicle. The small vesicular sac imbedded in the ovary that contains the egg-cell or ovum. The young undeveloped bodies are called *primordial follicles*. When they develop and ripen toward maturity they are called *graafian follicles*. A follicle that aborts, *i. e.*, from death of the egg, is said to be *atretic*, the process being named *follicle atresia*. The follicle is lined with one or more layers of epithelial-like cells called the *granulosa*. In the periphery of the sac outside of the granulosa is a capsule-like sheath, the *theca interna* made up of cells derived from the interstitial cells of the ovary (*q. v.*). Outside of the theca interna is another fibrous sheath, made up of pure connective tissue, the *theca externa*. The follicle contains a fluid, *liquor folliculi*, which is richly supplied with the hormone folliculin (or oestrin). When the follicle has matured and discharged its egg (ovulation) the follicle at once becomes a corpus luteum. The granulosa cells and to some extent the theca interna cells becoming hypertrophied and assuming a yellow color. This change in the follicle cells is called *luteinization*, and is supposed to be brought about by the prolan B hormone of the hypophysis. Prolan B is therefore commonly termed the *luteinizing hormone*. The corpus luteum then secretes a hormone of similar properties named

by Corner *progestin* which prepares the endometrium for nidation of the fertilized egg.

Sometimes a maturing follicle does not rupture but retains the egg imprisoned. Under these conditions the follicle may yet become luteinized, the luteinizing process taking place chiefly in the theca interna cells. A luteinized follicle of this nature is called a *pseudo-corpora-luteum*. Such a body may become cystic and is then known as a *lutein cyst*. Pathologic lutein-cyst formation is associated with hydatiform mole and chorionepithelioma, and is evidently the result of an excess of luteinizing hormone emanating from the abnormally growing placental tissue.

Folliculin. Hormone secreted by the growing follicle. Same as oestrin. See *Follicle* and *Oestrin*.

Fraenkel's discovery. (Published in 1903.) Demonstrating an internal secretory property of the corpus luteum which prepares the endometrium for the reception and imbedding of the egg. *Historical landmark.*

Functional (dysfunctional) uterine bleeding. Now generally used in place of such former terms as "metropathic," "myopathic," "nonmalignant," "idiopathic," "uterine insufficiency," etc. It relates to the abnormal hemorrhages associated with dysplasia of the endometrium (*q. v.*). Since the corpus luteum and consequently the premenstrual phase of the endometrium are lacking, the hemorrhages represent a true bleeding and not a deranged form of menstruation. The source of the bleeding is a matter of doubt. Many believe that it issues from localized areas of necrosis caused by thrombosed vessels of the endometrium. The underlying stimulus of the condition is evidently derived from the oestrogenic hormone of the ovary, possibly associated with abnormal activity of the related factor in the hypophysis.

Gestational gland. Introduced by Frank to include all the tissues in which the female sex hormone is found. The expression is now little used.

Gigantism, giantism. Excessive body growth due to abnormal activity of the growth hormone of the anterior lobe of the hypophysis.

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Gonadotrope. Means sex-gland-dominating and is applied to the two sex hormones of the anterior lobe of the hypophysis.

Granulosa. See *Follicle*.

Growth hormone. A general term indicating the influence of a given hormone on body growth and development. Thus oestrin has definite properties of stimulating and regulating growth and may properly be called a growth hormone. Evans' alkaline extract of the anterior lobe contains a hormone that produces gigantism in immature animals. This principle not yet isolated is called the growth hormone of the anterior lobe of the hypophysis.

Halban's experiment. (Published in 1900.) Implantation of ripe ovaries in immature animals induces precocious growth and function of the genital organs. *Historical landmark.*

Hemorrhagic type of placentation. Refers to the extravasation of blood in the endometrium around the chorionic villi seen in certain species including man and monkeys. Considered by Hartman the homologue of menstruation, and explaining menstruation as an active physiologic function instead of a pathologic process of disintegration.

Hitschman and Adler's rediscovery. (Published in 1908.) The distinctive phases of the endometrium during the menstrual and reproductive cycles. *Historical landmark.*

Hormone. A chemical incretory substance elaborated in an organ and carried by the blood stream to other associated organs which are thereby excited to functional activity. Synonymous with endocrine, and internal secretion.

The hormones described in this book include only those of the ovaries and the hypophysis, They are listed as follows:

OVARIES

Follicle. Oestrin. Synonyms—folliculin, female sex hormone, ovarian hormone, alpha factor, feminin, thylekenin.

Corpus Luteum.

1. Progestin. Synonyms—lutin, corpus luteum hormone, beta factor.
2. Relaxin.

HYPOPHYSIS. ANTERIOR LOBE

Prolan A. Synonyms—rho I, oestrogenic hormone, alpha factor.

Prolan B. Synonyms—rho II, luteinizing hormone.

Growth hormone.

Praephyson. Synonym—metabolism hormone.

Lactation hormone (hypothetic).

Bleeding hormone (hypothetic).

HYPOPHYSIS. POSTERIOR LOBE

Oxytocin.

Vasopressin.

COMMERCIAL PREPARATIONS OF THE OVARIES

The following is a representative though incomplete list of hormone products commercially prepared for therapeutic use.

PREPARATIONS CONTAINING THE OESTRIN PRINCIPLE

Agomensin (Ciba Company, Inc.). Nonstandardized ovarian substance. Tablets.

Amniotin (Squibb). Aqueous solution. Subcutaneous injection. Standardized. Also vaginal pessaries.

Estrogen (Parke Davis). Colloidal extract. Standardized. Hypodermic use.

Glovarian Pills (Schiefflin). Glycerin extract. Standardized. Oral use.

Menformon (Degewop, A. G.). Watery extract. Standardized. Hypodermic, intramuscular or intravenous use.

Ovarian Residue (Hynson and Westcott and others). Tablets. Ovarian substance not including corpus luteum. Nonstandardized.

Progynon (Schering). Tablets. Standardized.

Theelin (Parke Davis). Follicular hormone in crystalline form. Standardized. Hypodermic or intramuscular use. Also vaginal suppositories.

Varium (Burroughs and Wellcome). Tablets. Whole ovarian substance nonstandardized.

PREPARATIONS CONTAINING THE PROGESTIN PRINCIPLE

Lipo-lutin (Parke Davis). Emulsion. Subcutaneous and intramuscular use.

Lutein tablets (Hynson and Westcott). Oral use.

Sistomensin (Ciba Company, Inc.). Tablets. Oral use.

COMMERCIAL PREPARATIONS OF THE HYPOPHYSIS

ANTERIOR LOBE. Numerous proprietary extracts used alone and in combination with other glandular substances.

The standardized extract of the luteinizing hormone, used by Novak, Smith, Lawrence, and others with marked success in cases of dysfunctional uterine bleeding has not yet been put on the market. It will be called antuitrin.

POSTERIOR LOBE.

Pitocin (Parke Davis). Contains the oxytocic principle of the posterior lobe of the hypophysis. Standardized. Hypodermic or intranasal administration.

Pitressin (Parke Davis). Contains the vasopressin principle of the posterior lobe. Standardized. Hypodermic or intranasal administration.

Pituitrin (Parke Davis and others). Aqueous extract of posterior lobe of hypophysis. Standardized. Contains both oxytocin and vasopressin. Hypodermic administration.

Hormonology. The science relating to hormones (internal secretions, endocrines). Synonymous with endocrinology.

Hyperluteinization. Used to describe the excessive luteinization of the cystic follicles associated with hydatiform mole and chorion epithelioma. The condition is a result of abnormal amounts of the luteinizing hormone of the anterior lobe contained in and possibly manufactured by the neoplastic placental tissue. A similar condition of the follicles can be induced in animals by large doses of the luteinizing hormone.

Hyperplasia (dysplasia) of the endometrium. Used specifically to describe the appearance of the endometrium in typical cases of functional (dysfunctional) bleeding. The condition is due to a failure of the ovary to ovulate and form a corpus luteum. The influence of the corpus luteum hormone (progestin) is therefore lacking and the follicular hormone (oestrin)

from the unruptured follicle continues to exert unchecked its proliferative effect on the endometrium. This abnormal growth stimulus results in a bizarre hypertrophy and hyperplasia of the endometrial glands. Many of them grow to a large size with wide spherical or irregular openings. These holes or spaces seen in a section of the endometrium give to the picture a "Swiss cheese" appearance, an expression popularized by Novak.

Incretory. Pertaining to internal secretion. Synonymous with endocrine.

Interstitial cells of the Ovary. The characteristic strongly nucleated cells that make up the body of the ovary. It is thought that they take part in the elaboration of the oestrin hormone. From them are developed the theca interna cells of the follicle and the interstitial gland, prominent in some animals.

Knauer's experiment. (Published in 1896.) Transplantation of ovaries in spayed animals prevents genital atrophy. *Historical landmark.*

Kyogenic. Literally pregnancy-producing. Introduced by Wiesner to describe the hormone of the anterior lobe that is capable of stimulating the corpus luteum to create the beta (pro-gestation) phase of the genital organs. It is applicable to the hormone rho II (prolan B, luteinizing hormone).

Lactation hormone. Hypothetical special hormone of the anterior lobe of the hypophysis that regulates the proliferation and lactation of the breasts. Suggested by Corner.

Locke's solution. A fluid containing sodium chloride, calcium chloride, potassium chloride, sodium bicarbonate, and glucose, used in physiologic experiments usually for observing the contractions of the muscles of the heart and uterus.

Loeb's experiment. (Published in 1907.) Production by irritation of a deciduoma (placentoma) in the uterus of a rabbit after sterile coitus and the formation of a corpus luteum. *Historical landmark.*

Liquor follicle. See *Follicle*.

Lutein. The yellow pigment or lipochrome contained in the cells of the corpus luteum.

Luteinizing, luteinization. See *Follicle*.

Maturation (ripeness). Applied here both to the graafian follicle and the ovum. It pertains to the condition just preceding ovulation.

Maturity. Relates here to the period when an animal becomes sexually ripe, *i. e.*, the age when the sexual organs become capable of reproduction. Synonymous with puberty.

Metoestrus. Meaning between oestrus. It relates specifically to certain regressive changes that take place midway between the ovulation-times (*i. e.*, oestrus) of certain animals—changes that are accompanied by a show of blood. Metoestrus in lower animals is now regarded as the homologue of menstruation in humans and primates.

Mittelschmerz. German word relating to dysmenorrheic pains that in some women occur midway between the menstrual periods. It is supposed to be contemporaneous with ovulation (Hartman).

Monoestrous. Pertaining to those animals that have only a single oestrus period each year.

Mucification. Used by Wiesner to describe the mucified changes in the vaginal epithelium of laboratory animals during the beta phase of the sexual cycle.

Nidation. Literally "nesting." Pertains to the implantation of the fertilized egg (embryo) in an endometrium that has been prepared for the event by the corpus luteum hormone (progesterin).

Nonovulational menstruation. Periodic bleeding without preceding ovulation seen in monkeys during the nonbreeding season, also in humans, most frequently near the menarche and climacteric. The abnormal bleeding of gland dysplasia is of the nonovulational type.

Oestrin. The ovarian hormone which when injected into laboratory animals produces the genital changes characteristic of oestrus. It is synonymous with folliculin and female sex

hormone and is supplanting these terms in scientific literature. Oestrin is especially appropriate since it implies its physiologic effect without begging the question of its origin. See also *hormones*.

Oestrogenic. Introduced by Wiesner to describe the principle of the anterior lobe hormone in grafts and acid extracts, that stimulates the alpha phase of the sexual cycle. It applies to the hormone rho I which is equivalent to prolan A. The word is now applied as a general term to a substance that is capable of inducing oestrus changes in laboratory animals.

Oestrous. Adjective form, pertaining to oestrus.

Oestrum. The time during which an animal is in the condition of oestrus. Often used interchangeably with oestrus.

Oestrus (also estrus). (Greek "gadfly.") Originally means sexual desire. It is used specifically to denote the sexual condition of the female animal at the mating season. It is synonymous with heat and Brunst (German) and analogous to rut in the male. The word has been extended as a general term to include the morphological changes of the genital organs of the female animal during the mating period. In its narrowest physiologic sense it corresponds to the time of ovulation, the word pro-oestrus being used to designate the preparatory genital changes such as the opening of the vagina and the hypertrophy of the vaginal epithelium in laboratory animals. On account of the secretion, sometimes bloody, that appears in certain animals at this time it was erroneously believed that pro-oestrus corresponds to the menstrual period of humans and primates. (See *Metoestrus*.)

Ontogenetic, ontogeny, ontogenesis. See *Phylogenetic*.

Ovulation. The discharge of a ripe ovum (or egg) from a graafian follicle. In the human ovulation takes place spontaneously usually midway between the menstrual periods. In rabbits ovulation occurs at the time of coitus.

Ovum, pl. ova. The female reproductive cell discovered by von Baer in 1827.

Oxytocic. Literally hastening childbirth. Used specifically to describe the hormone of the posterior lobe of the hypophysis, oxytocin, which excites the uterine musculature to expulsive contractions after it has been sensitized by folliculin.

Oxytocin. The hormone of the posterior lobe of the pituitary that excites the uterine muscle to contraction. It is the constituent of pituitrin which gives value to that drug in the practice of obstetrics. Pituitrin is an extract of the whole gland and contains besides oxytocin another hormone, vasopressin (*q. v.*). Oxytocin has been isolated and is used therapeutically in the drug pitocin put out by Parke Davis.

Phylogenetic, phylogeny, phylogenesis. Pertaining to the evolution of living species from the one-celled protozoan to man: in contradistinction to ontogenetic which relates to the evolution or development from the egg to maturity of an individual organism. The parallelism in the stages of development between phylogeny and ontogeny is one of the basic laws of the doctrine of evolution.

Pituitrin. Extract of the whole posterior lobe of the pituitary. See *Oxytocin* and *Vasopressin*.

Placental mammals. All mammals excepting the monotremes and most marsupials.

Placentation. The mode of attachment of the placenta. It has great variation in different species and to some extent in the same species. It is a matter of much importance in biological studies.

Placentoma. Localized growth of the endometrium produced by irritating the uterine mucosa of a rabbit after sterile coitus and formation of a corpus luteum (Loeb's experiment). The temporary growth is the result of the presence of a corpus luteum hormone. The word "placentoma" of course refers to the *maternal* placenta and not to the trophoblast, and is therefore misleading. Its synonym *deciduoma* is preferable.

Polyoestrous. Pertaining to animals that have more than one mating season each year.

Postoestrus. A general term signifying *after* oestrus or *after* ovulation, in contradistinction to pro-oestrus. Thus menstruation is described as a postoestrus phenomenon in that it does not immediately precede ovulation as formerly supposed, but is a sequence to it in the sexual cycle.

Potency. The quantitative power of given hormonal extracts to produce genital reactions in laboratory animals.

Praephyson. Substance extracted from the anterior lobe by Kiestner and Plaut-Liebeschutz having a regulating influence on body metabolism. It is supposed to be a special hormone of the anterior lobe.

Premenstrual stage of the endometrium. The condition of the uterine mucosa following ovulation and the formation of a corpus luteum. The mucosa under the influence of the corpus luteum hormone (progesterone) becomes a secretory organ. The glands are dilated with secretion. The lining cells are large and beaker-like, and form tufts along the sides giving to the gland the characteristic saw-tooth pattern. The stroma cells foreshadow the decidual reaction of pregnancy. The premenstrual endometrium resembles the true decidua of pregnancy in which the specific histologic characteristics are merely accentuated. The premenstrual phase is therefore analogous to the pregravid, progestational, or pseudopregnant stage used in describing the endometrium of animals under the influence of the corpus luteum hormone (progesterone).

Prepuberal. Antedating puberty.

Primary sex characters. The genital organs. These are distinguished from the secondary sex characters which include the breasts and comprise all the recognizable marks of sex such as distribution of hair, general contour, quality of skin, skeletal proportions, etc.

Primates. The highest order of mammals consisting of man, apes, monkeys, and certain suborders of the monkey. From the fact that many of the primates menstruate in a manner homologous to that of man they are of the greatest experimental importance in studying human sex physiology.

Progestation stage. Used by Corner to define the secretory phase of the endometrial cycle, immediately preceding menstruation or implantation of the embryo. It is synonymous with pregravid and premenstrual as applied to the endometrium.

Progesterone. Name given by Corner to his highly potent extract of corpus luteum by the use of which he was able to establish the identity of a corpus luteum hormone distinct in its properties from that of the follicles. Synonymous with the term "lutin" introduced by Zondek.

Prolan. Name given by Zondek and Aschheim to the undivided sex hormone of the anterior lobe of the hypophysis. When injected into immature female mice it produces a double reaction. (1) Follicle ripening with oestrus changes in the vagina, and (2) luteinization of the ovarian follicles in the form of true corpora lutea and luteinized corpora atretica. These two effects are correlated respectively with the two hormones of the ovary, oestrin and progesterin. Prolan is synonymous with "superordinated sex hormone" used to describe the "motor" capacity of the anterior lobe in stimulating and regulating sexual functions.

Prolan A. Name given by Zondek and Aschheim to the oestrus-stimulating principle of prolان. It is supposed to "motivate" the production of oestrin in the ovarian follicle.

Prolan B. Name given by Zondek and Aschheim to the luteinizing principle of prolان. It is correlated with the hormone of the corpus luteum, progesterin, which it is supposed to mobilize. Being found in large amounts in the placenta and urine of pregnant women it is thought that the placenta may assist the hypophysis in its manufacture. It has been prepared for therapeutic administration and is being used successfully in cases of dysfunctional uterine bleeding. Prolan B is the principle in the urine of pregnant women which induces the luteinizing changes in the ovaries of laboratory animals that form the basis of the Aschheim-Zondek test for pregnancy.

Proliferative stage of endometrium. The second phase of the uterine mucosa following the first stage of rest. The mucosa under the growth impulse of folliculin (oestrin) shows a marked hypertrophy of the glands and a piling up of the lining epithelium with frequent mitoses. The glands assume a characteristic snaky appearance. The proliferative stage is also called the "oestrin phase" (Burch, Williams, and Cunningham).

Pseudo-corpora luteum. See *Follicle*.

Pseudo-pregnancy. The premenstrual phase of the endometrium of humans and primates. It is so called because the premenstrual phase of the endometrium in these species simulates closely the pregnant endometrium just before implantation.

Reaction I. Used by Zondek to describe the follicle-ripening and oestrogenic effect of prolán.

Reaction II. Used by Zondek to describe the Blutpunkte induced by prolán in the ovaries of immature mice.

Reaction III. Used by Zondek to describe the luteinizing effect of prolán on the ovarian follicles of immature mice.

"Regular" abortion. One that is due to contractions of the uterine musculature induced by the oxytocic principle of the posterior pituitary after sensitization of the uterus by oestrin, a process analogous to normal parturition. Opposed to delayed abortion that represents the expulsion of a fetus that has first been killed by some toxic or traumatic agency.

Relaxin. Specific hormone isolated from the corpus luteum which relaxes the uterine ligaments of virgin laboratory animals in the manner seen during pregnancy (Hisaw).

Rest stage of the endometrium. The condition of the newly formed uterine mucosa immediately following the completion of menstruation, distinguished by simple tubular nonsecreting glands.

Rho I. Name applied by Wiesner to the oestrogenic hormone of the anterior lobe of the hypophysis. Synonymous with Zondek's prolán A.

Rho II. Name applied by Wiesner to the kyogenic hormone of the anterior lobe of the hypophysis. Synonymous with prolán B and luteinizing hormone of the hypophysis.

Ringer's fluid. A preparation similar to Locke's solution and used for the same purpose in physiologic experimentation. See *Locke's solution*.

Secondary sex characters. See *Primary sex characters*.

Sensitization. The preparation of a tissue or organ by one hormone, so that it is able to respond functionally to the action of another. It is an expression of the principle of synergism between hormones. Examples: Oestrin prepares (sensitizes) the endometrium for its reaction to progestin. Oestrin sensitizes the uterine musculature at the time of parturition for the contractile effect of oxytocin.

Stockard and Papanicolaou's discovery. (Published in 1917.) Ovulation in rodents is accompanied by cornification and desquamation of the vaginal epithelium. *Historical landmark*.

Substitution therapy. Administration of an incretory gland substance to supply the deficiency or absence of that gland in a given organism. Substitution may be carried out by the oral or subcutaneous use of extracts or by transplantation of the gland itself.

Superordinated hormone of sex. Used by Zondek and Aschheim to define the sex hormone of the anterior lobe (prolan) as the "motor" of the hormonal activity of the ovaries.

Superovulation. Used by Smith and Engle to describe the extraordinary acceleration of ovulation following heterotransplants of anterior lobe in mice. The great increase in pregnancies that followed mating of these animals was termed "superpregnancy."

Superpregnancy. See *Superovulation*.

Synergistic. Literally, working with or collaborative. Applied to two hormones which produce by combined action an effect which neither could accomplish when acting alone. The effect is often a "one, two" reaction, in which "two" must inhibit the continued activity of "one."

Tempo. Timing, rhythm. Used in describing the harmonious rhythm of sexual functions.

Theca interna. See *Follicle*.

Transplantation. A general term pertaining to the grafting of an organ of internal secretion in the tissues of the same or another individual.

Autotransplantation, planting a graft from one part of the body to another in the same individual.

Homotransplantation, grafting from one individual to another of the same species. Used also as a synonym for autotransplantation (Dorland.)

Heterotransplantation, grafting from one individual to another of a different species.

Trophoblast. The embryonic layers that line the chorionic villi of the placenta. Synonymous with chorionic ectoderm.

Trophoblastic or placental sign. Used by embryologists to describe the show of blood that may appear in the vagina as a result of the hemorrhagic type of placentation (*q. v.*).

Vasectomized animal. Usually a male rabbit from which the vasa deferentia have been extirpated. The union of such an animal with a normal female results in a "sterile coitus." Since the female rabbit ovulates only under sexual excitement, a corpus luteum may thus be induced at will. The effects of the corpus luteum hormone on the unimpregnated uterus can then be studied. This experiment has led to discoveries of great importance, notably by Loeb, Ancel and Bouin, and Corner.

Vasopressin. One of the two hormones of the posterior lobe of the pituitary, the other being oxytocin. It raises the blood pressure by stimulating the muscular tissue of the arterioles and capillaries to contraction. It also contracts the musculature of the intestine and increases peristalsis. It is besides an antidiuretic. It is now prepared as a separate product in the drug pitressin put out by Parke Davis.

Viviparous. Pertaining to most mammals, many lizards and some fishes, which produce living young from within the body. Opposed to *oviparous*, which pertains to creatures producing eggs that hatch after exclusion from the body.

Wiesner's demonstration of two sex hormones of the anterior lobe. (Published in 1930.) Rho I, the oestrogenic hormone, and rho II, the kyogenic hormone. *Historical landmark.*

Zondek's demonstration of two sex hormones of the anterior lobe. (Published in 1930.) Prolan A, the follicle-ripening hormone and prolan B, the luteinizing hormone of the anterior lobe of the hypophysis. *Historical landmark.*

Zondek and Aschheim's experiments. (Published in 1927.) Following pioneer work of Long and Evans and Smith and Engle, demonstrating the superordinated sex hormone of the anterior lobe of the hypophysis. *Historical landmark.*

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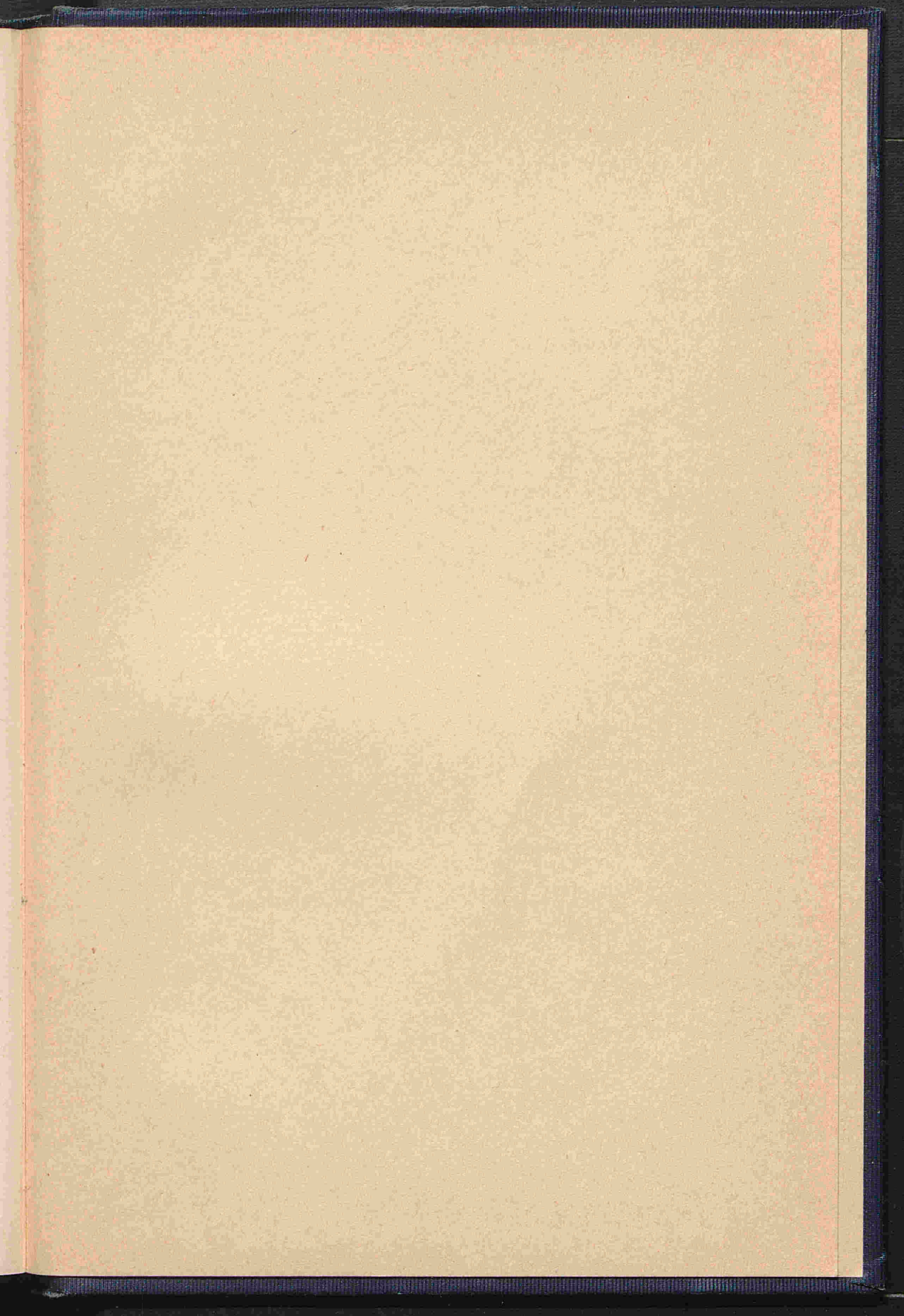
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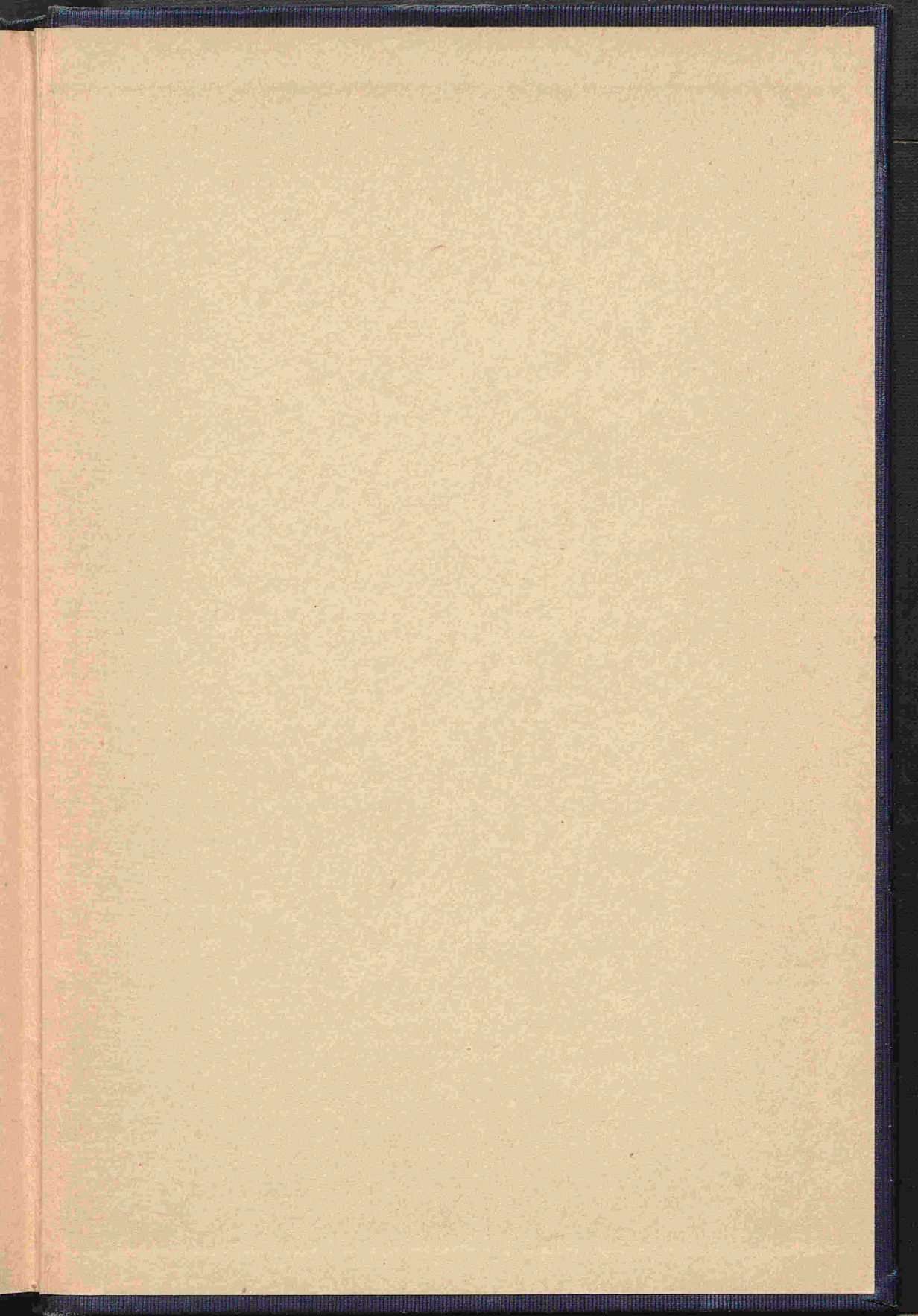
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