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HORMONES AND PREGNANCY*

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The gonads and the anterior lobe of the pituitary have of recent years been shown to produce certain hormones which bear an intimate relation to the development of sexual characteristics and to the performance of sexual and reproductive functions. During gestation the products of conception also are probably capable of secreting some of these hormones. Many of these substances have now been isolated in a pure crystalline form, and even partially synthesized, whilst others are still being subjected to further purification and analysis. In particular, the hormones produced by the gonads have yielded more readily to chemical analysis, while those elaborated in the pituitary body are of a more complex nature and have not yet been isolated in a pure form.

Hormones Acting on the Secondary Sex Organs

The gonadic hormones can be divided into two classes—namely: (1) those substances which have been shown to affect essentially the male secondary sex organs; and (2) those responsible for the development and physiological changes in the female secondary sex organs. Both these groups contain several substances, closely related chemically, each of which is capable of bringing about in different doses certain end-effects.

It is, moreover, possible that, even under physiological conditions, more than one substance in a given group may be responsible for alterations in the sex organs. Thus, for example, there are quite a number of chemically closely related substances (to which the general term oestrin is applied) capable of bringing about oestrous changes in the rodent test animal, and there is no doubt that some, if not all, of these forms of oestrin can produce physiological alterations in the uterus when administered to the human subject. Similarly, work at present in progress is showing that more than one substance can produce effects on the male secondary sex organs (Butenandt, 1935; Ruzicka and Wettstein, 1935).

Although the general names of male and female hormones have been given to those hormones which appear to affect essentially the male and female secondary sex organs respectively, it must not be assumed that the secretion of these hormones is limited to one sex. On the contrary, both of these types of hormones seem to be produced, or at least excreted, in the male and in the female. Thus a male hormone can be recovered from the urine of women as well as of men, and in approximately equal amounts (Siebke, 1934); oestrin may also be present in quite appreciable quantities in the urine of men. Indeed, in the species *equus* extremely large

amounts of oestrin are excreted in the urine of the male animal (Haeussler, 1934). The hormone is probably produced by the testes, from which it can be extracted (Zondek, 1934; Courier, 1934).

Although the male hormone is excreted in the female subject, it has not so far been shown to produce any direct effects on the female sex organs.* On the other hand; the recent work of Lacassagne, Burrows, and others has demonstrated quite clearly that certain alterations in the male secondary sex organs (vesiculae seminalis and prostate) are due to the action of the oestrous hormone.

In addition to oestrin (and probably a male hormone) the ovary also produces at certain stages of its activity other hormones—namely, the hormones of the corpus luteum. Again, two active substances which can produce the typical effects have been isolated from extracts of the corpus luteum and have been also partly synthesized (Wintersteiner and Allen, 1934; Butenandt, Westphal, and Hohlweg, 1934; Slotta, Ruschig, and Fels, 1934). These hormones are secreted during certain stages of the menstrual cycle and during pregnancy, but nevertheless they have not so far been recovered from the blood. They can be extracted from the corpora lutea of various species, and an active substance has also been obtained from the placenta.

Hormones Acting on the Gonads

The hormones so far mentioned exert their effect directly on the secondary sex organs, and have no direct action on the gonads themselves. The anterior pituitary gonadotropic hormones, on the other hand, control the activity of the male and female gonads, but have no direct action on the secondary sex organs. The gonadotropic hormones are responsible for the growth of the gonads and for the production of the changes associated with sexual activity; hence they control follicular maturation, ovulation, and formation of the corpus luteum in the female, and descent of the testes and spermatogenesis in the male. They also control the secretion of oestrin, corpus luteum hormone, and the male hormone. There seem to be at least two gonadotropic hormones of the pituitary, one of which (prolan A) causes follicular maturation and the secretion of oestrin, while the other (prolan B) controls the formation and secretory activity of luteal tissue.

During pregnancy large quantities of gonadotropic hormones are excreted in the urine of the human subject.

* Recent work with synthetic crystalline substances has shown that a number of male hormones, including testosterone, possess an oestrogenic action in the mouse (Butenandt and Kudzusz, 1935; Deansley and Parkes, 1936; Wolfe and Ginglinger, 1936).

* A British Medical Association Lecture to the Glasgow and West of Scotland Branch, November, 1935.

These hormones are very similar to those present in the anterior lobe of the pituitary, and they possess many of the properties of the hypophyseal hormones. Nevertheless the pituitary and the urinary gonadotropic hormones are not identical, as can be readily demonstrated by certain of their actions on the ovaries of rodents. This difference is further emphasized by a consideration of the action of these hormones on the ovaries of primates (Engle, 1934). Experimental investigation has shown that the hypophyseal gonadotropic hormones can bring about many of the normal changes witnessed in the ovary during the menstrual cycle. On the other hand, the urinary hormones have little stimulating action on the ovary of primates, and appear even to cause an inhibition of the morphological development. Such findings need, of course, careful consideration when the question of using these hormones therapeutically arises.

In addition to the gonadotropic hormones, the anterior pituitary lobe also secretes another substance, prolactin, which is intimately associated with the activity of the mammary glands. The growth of these organs during pregnancy is due to some extent to the action of oestrin and progesterin, but prolactin probably also takes a part in the control of the mammary development; moreover, the maintenance of lactation appears to be dependent on the action of this hypophyseal hormone.

Hormone Production in the Pregnant Woman

It is a remarkable fact that the concentration of the sex hormones in tissues and fluids during pregnancy shows very marked variations in different species. This makes the evaluation of the functional significance of these hormones in gestation of great difficulty. At the present stage of knowledge it is only possible to give the data for the various species and to draw a few general deductions.

In the woman the oestrin excretion in the urine, which is low during the menstrual cycle, undergoes a gradual increase following conception. It reaches a maximum shortly before parturition and then falls somewhat. After expulsion of the uterine contents the fall in the oestrin excretion is very rapid. Some remarkable findings on the nature of the oestrin excreted during pregnancy have recently been obtained by Marrian and his co-workers (1934 and 1935), for they have shown that the oestrin present is in two forms—namely, (1) a comparatively physiological inactive form; and (2) an active form of the hormone. The inactive form can be converted into the active hormone by hydrolysis.

Now, although the total amount of oestrin rises markedly during pregnancy, the amount of physiologically active hormone excreted in the urine remains quite low during the whole duration of gestation, but rises suddenly and markedly immediately preceding parturition. The amount of oestrin present in the blood also rises gradually during pregnancy, reaching a maximum about the time of parturition. Unfortunately no investigations have yet been performed on the state in which oestrin is present in the blood.

In addition to its presence in the urine and in the blood, large amounts of oestrin are also found in the placenta at various stages of pregnancy. Since the placenta (and the urine) also contain oestrin in subjects who have been ovariectomized during gestation, it seems probable that this organ is capable of elaborating the oestrous hormone. Large amounts of oestrin are also found in the faeces during pregnancy.

Immediately following conception there is a very marked increase in the excretion of gonadotropic hormones in the urine. This excretion rapidly reaches a maximum but falls somewhat in the later stages of pregnancy and

towards the time of parturition. After parturition the gonadotropic hormone excretion falls very rapidly, reaching the level observed during the normal menstrual cycle within a week or less.

Conception is also followed by a very marked increase in the gonadotropic hormone content of the blood. This content rises during pregnancy, and continues to rise right up to the later stages of gestation, thus differing from the excretion in the urine, which falls after reaching its maximum early in gestation. The placenta also contains large amounts of gonadotropic hormones during the whole period of gestation and at parturition. There is no direct evidence whether this organ actually produces gonadotropic hormones, but this question will be discussed more fully later.

A remarkable feature of the gonadotropic hormones content of tissues during gestation is their total or almost total absence from the pituitary. Several investigators have now confirmed the original findings of Zondek and Phillip that the hypophysis in the human subject contains none of these hormones during gestation, and the same applies to the organ at parturition. Whether this indicates a very rapid rate of secretion by which the hormones are sent out of the gland as soon as they are produced, or whether it indicates that the anterior hypophysis is quiescent, is difficult to decide at present. In addition to oestrin and gonadotropic hormones, male hormone is also excreted in the urine during pregnancy, but the quantities are not significantly different from those present in the urine during the menstrual cycle.

Hormone Production in the Higher Primates

The hormone production in the higher primates other than the human appears to be very similar to that observed in the pregnant woman. In the chimpanzee the urine during pregnancy contains considerable quantities of oestrin, and the same applies to the full-term placenta. The data suggest, however, that the hormone levels are rather lower than in the human (Allen, Diddle, and Elder, 1934).

The pregnant urine also contains considerable quantities of gonadotropic hormones, giving a positive Aschheim-Zondek reaction (Zuckerman, 1934). A positive Friedman test has also been reported (Snyder, 1934). The data suggest that the level of the gonadotropic hormones is rather lower than in the human, though accurate quantitative results are lacking. Zondek has also reported a positive Aschheim-Zondek reaction with the urine of the orang-outang. It is of interest to note that the urine of *Macacus rhesus* apparently shows no increase in the gonadotropic hormones excretion during pregnancy.

Hormone Production in the Equidae

Pregnancy in the *Equidae* (horse, ass, zebra) is characterized by the production and excretion of both types of hormones produced in the higher primates, but there are certain important differences in the amounts of hormone produced, and in the time at which the hormones appear and disappear in the blood and urine. The results obtained in the mare are given here, since detailed investigations have been carried out only in that animal.

Oestrin appears in the urine between the fiftieth and hundredth days of pregnancy; the gestation period is about 270 to 300 days. The amounts present may be very large, up to 30,000 mouse units per litre or more, and the hormone excretion remains at a high level for the greater part of pregnancy. Towards parturition there is quite an appreciable fall in the urine content of oestrin, and after parturition the fall is very rapid. No investigations have yet been reported on the physiological activity

of the hormone excreted. Large amounts of oestrin are also excreted in the faeces.

That the oestrin production is largely independent of the ovarian activity is shown by the fact that, after ovariectomy in the pregnant mare, there is only a temporary fall in the oestrin excretion, which maintains its normal level in the further stages of the uninterrupted gestation (Hart and Cole, 1934). Oestrin is also present in the blood of the pregnant mare, but in comparatively small quantities; even then the hormone only makes its appearance in the second half of gestation, but continues to be present up to full term.

Very little or no gonadotropic hormone is excreted in the urine of the pregnant mare, but nevertheless the hormones are present in very large quantities in the blood during certain stages of gestation, though the actual times vary somewhat in different animals. The hormones first appear in the blood about the fortieth to the fiftieth day of pregnancy, and their concentration then very rapidly increases until enormous quantities are present—100,000 units per litre or more. From about the ninetieth to the hundredth day the concentration decreases, and shortly afterwards the hormone can no longer be demonstrated in the blood. It is noteworthy that marked development of the ovaries begins at about the forty-fifth day of pregnancy. Formation of ripe follicles occurs, and this results either in ovulation and the formation of corpora lutea or in the formation of corpora lutea atretica. After the gonad-stimulating hormones have disappeared from the blood the corpora lutea regress so that by the last stages of pregnancy the ovaries contain only small follicles.

It has already been stated that the gonadotropic hormones from the pituitary and from human pregnancy urine show certain definite differences in their action on ovaries. Hamburger (1934) has investigated the properties of the gonadotropic hormones present in the serum of pregnant mares. He concluded that they were similar to those obtained from the pituitary, thus suggesting that they were hypophyseal in origin. Investigations of the hormone content of the pituitary of the mare during pregnancy offers some support for the point of view that it is at a maximum about the time when large quantities of gonadotropic hormone are present in the blood (Hellbaum, 1935, Catchpole and Lyons, 1934). In this respect the pituitary of the mare is quite different from that of the human, which contains no gonadotropic hormone during pregnancy.

The placenta contains also comparatively large quantities of gonadotropic hormone. The hormone has been demonstrated in the chorion at very early stages of pregnancy, and it maintains its concentration in the chorion for some time after a decrease in the occurrence in the blood (Catchpole and Lyons, 1934).

Hormone Production in Other Animals

Thus in the higher primates and in the *Equidae* there is direct evidence that large quantities of oestrin and gonadotropic hormone are produced during pregnancy. In some other animals the production of oestrin alone can be definitely demonstrated. Comparatively large amounts of this hormone have been recovered from the urine of pregnant cows and sows (Struck, 1935), and it has also been recovered from the placenta of the cow and sheep. In cows the concentration of the hormone in the urine increases right up to the last stages of gestation (Anderson, 1934; Barrie, Patterson, and Underhill, 1935).

Investigations on other animals have yielded very little direct evidence for an increased production of the sex hormones during pregnancy. Nevertheless, the alterations in the properties of the uterus of these animals offer

indirect evidence that oestrin is produced in comparatively large quantities.

As regards the gonadotropic hormone content of the pituitary, the position of the human subject is quite exceptional. In no other genus has an appreciable decrease been noted. Indeed in the mare, as already stated, and in the rabbit (Hill, 1934) there is an increased content at some stages of pregnancy.

Functional Significance of Hormones in Pregnancy

It will thus be seen from all the above data that the concentration of the sex hormones in body tissues and fluids during pregnancy shows very marked differences in various species. To some extent these differences may be dependent upon variations in the renal activity, which probably plays an important part in controlling selectively the rate of excretion. This can be readily seen from a consideration of the results for the pregnant mare, in which large concentrations of gonadotropic hormones are present in the blood yet little or none is excreted in the urine, whereas a low oestrin concentration in the blood is seen at a time when very large amounts of oestrin are eliminated in the urine. It appears, moreover, possible that the renal function may show variations in a particular species at different times in pregnancy, since it would be difficult to explain otherwise the fact that in the human the gonadotropic hormone concentration in the blood rises up to the later stages of gestation while the concentration in the urine falls somewhat after the marked initial rise.

The metabolic destruction of the hormone probably also varies in different species, though this problem has as yet received very little attention. That oestrin may be very rapidly destroyed has, however, been demonstrated both in the human subject (Robson, MacGregor, *et al.*, 1934), and in the rat (Zondek, 1934), while Catchpole, Cole, and Pearson (1935) have shown that the concentration of gonadotropic hormones injected into the blood stream of the rabbit and the gelding is rapidly reduced, the hormones being probably destroyed. Similar evidence has also been advanced by Lipschutz, Alba, and Vivaldi (1935).

Even allowing for the renal and metabolic factors, there appears little doubt that the actual production of the hormones must show marked differences in the various species. From this it would seem that the hormonal control of pregnancy cannot be identical in all types of animals. It is possible, however, that there are certain essential common factors controlling the course of pregnancy, but that variations on this common theme occur in different species and are responsible for the various results obtained for hormonal concentrations. A consideration of the known evidence regarding the action of the sex hormones during pregnancy may bring to light these essential common factors, and thus help to elucidate the factors operating in the human subject.

Function of Oestrin during Pregnancy

It appears likely that oestrin plays a part in controlling the alterations in the uterus during pregnancy in a large number of species. In the higher primates the evidence derived from hormone examination of the blood and urine is, of course, quite convincing, when taken in conjunction with the known changes in the uterus, but studies of the changes occurring in the uterus of lower animals strongly suggest the view that in these also the oestrous hormone is concerned in the control of the uterine alterations during gestation (see Robson, 1934, for discussion of these changes and their significance). It may be added that Phillip has actually demonstrated the presence of appreciable quantities of oestrin in the blood of the rabbit during the later stages of pregnancy.

There are apparently three sites of production of oestrin: (1) the ovarian substance and the follicular apparatus in all animals studied; (2) the corpus luteum, which probably takes a part in the secretion of the hormone, at least in the higher primates, and contains considerable quantities of oestrin during the menstrual cycle and also during the earlier stages of pregnancy; and (3) the placenta, in which there is very strong evidence of the production of large quantities of the hormone. Removal of the ovaries, both in the human subject (Brindeau, Hinglais, and Hinglais, 1934) and in the mare (Hart and Cole, 1934), does not interrupt its production. In lower animals also (rabbit, mouse) a study of the changes occurring after ovariectomy and hypophysectomy suggests that oestrin production from the uterine contents may occur (Robson, 1931).

Oestrin plays an important part in the control of the marked growth process occurring in the uterus during pregnancy. It also exerts certain effects on the physiological activity of the uterine muscle which are probably of great significance in the processes leading to the expulsion of the uterine contents.

It is well known that the uterus is quiescent during the early stages of gestation, and that it is only later when contractions begin; these increase in intensity, but it is only at parturition that the marked contractions necessary to expel the uterine contents occur. Now it has been shown experimentally that oestrin increases the reactivity of the uterine muscle to oxytocin, and also increases its spontaneous rhythmic activity. It appears very likely that these effects are responsible for the increase in activity witnessed during pregnancy. Moreover, it seems quite possible that the sudden rise in physiologically active oestrin at the time of parturition is, in part, responsible for the marked increase in uterine activity which then occurs. It is to be noted that there is an increased oestrin production during pregnancy in a large number of species that have been investigated, and thus that the relation between oestrin and uterine activity is of widespread significance. It is, however, highly desirable that the physiological activity of oestrin produced in other species besides the human at different stages of gestation should be investigated.

Function of the Corpus Luteum during Pregnancy

Although the corpus luteum has not been recovered from any body fluids, it is highly probable that it is produced in a large number of species during pregnancy. It is, of course, secreted by the corpus luteum, but, in addition, it may quite possibly also be produced in the placenta. The fact that it has been extracted from that organ is not necessarily evidence that the organ is a site of production. In a number of instances (the human being, the mare, the cat, and the guinea-pig) removal of the ovaries during pregnancy does not necessarily lead to abortion. It has been a matter of controversy for some time whether this meant that the luteal hormone was not essential for the maintenance of gestation in these species, or whether it implied that the hormone was produced elsewhere—for example, in the placenta. The evidence adduced by Courrier and Gros (1935) in their experiments on the pregnant cat seem to prove conclusively that the placenta in that species may secrete the luteal hormone. Evidence of a similar nature on the rat has also been given by Selye, Collip, and Thomson (1935).

The luteal hormone is essential for the implantation of the ovum in the endometrium, and it probably also plays an important part in the control of the nutrition of the developing embryo, and in the growth of the uterus, although further evidence on these questions is necessary. In addition, it exerts certain effects on the

physiological activity of the uterine muscle—namely: (1) it inhibits the reactivity of the uterine muscle to the oxytocic hormone of the posterior pituitary lobe; and (2) it inhibits the increase in spontaneous motility induced in the uterine muscle *in situ* by oestrin.

Unfortunately, these actions have only been satisfactorily demonstrated in the rabbit. There is some evidence that the first effect may also occur in the human uterus, but, on the other hand, it is definitely known that progesterin does not inhibit the uterine reactivity to oxytocin in lower rodents (mouse, rat, and guinea-pig). Moreover, in the guinea-pig the motility induced by oestrin is not appreciably inhibited by progesterin (Bell and Robson, unpublished data), although in this animal the removal of the ovaries during pregnancy does not necessarily lead to abortion. It will thus be seen that these actions of progesterin on the uterine muscle are still of doubtful significance in the control of pregnancy in animals other than the rabbit, and possibly the human being, though further investigations on the action of progesterin on the uterine muscle, especially of primates, are highly desirable.

A considerable number of experiments have now been performed on the experimental production of abortion by the injection of oestrin in animals during the later stages of pregnancy. In certain species interruption of pregnancy can be brought about fairly early by the administration of crystalline oestrin (Marrian and Newton, 1935; Robson, 1935). The uterine reactivity in these animals is markedly increased, and in mice, as was originally shown by Parkes, the injection of oxytocin following a short period of oestrin administration results in the expulsion of live foetuses.

It is still a question to what extent these results can be applied to the human subject. Robinson and his co-workers (1935) have been able to increase the uterine activity in women during the later stages of pregnancy by the injection of large doses of oestrin; the most favourable effects were obtained in cases of uterine inertia. Bourne (1934) was unable to produce any effect in five cases investigated. Since the approximate amount of physiologically active oestrin excreted by the parturient woman is now known (Cohen, Marrian, and Watson, 1935) it seems desirable to determine whether the doses of oestrin injected are sufficient to cause an increase in the excretion of the physiologically active hormone similar to that observed at parturition, and to correlate the increase in excretion with the clinical effects produced.

Function of Gonadotropic Hormones during Pregnancy

The question of the function of the gonadotropic hormones during pregnancy is at present one of the unsolved problems in the physiology of the sex hormones. It has indeed been suggested, on the basis of experiments performed on the rabbit, that they may inhibit the motility of the uterine muscle in a manner similar to that of progesterin. Investigations on the guinea-pig fail to demonstrate any such direct action on the uterine muscle (Bell and Robson, unpublished data), even with large doses of the gonadotropic hormones, so that it is doubtful whether this effect is of any wide significance.

The problem is further complicated by our lack of knowledge as to whether these hormones may be produced by the placenta as well as by the anterior pituitary lobe. In the human subject, in whom the urinary gonadotropic hormones, excreted throughout pregnancy, possess properties somewhat different from the hormones present in the pituitary, the latter organ contains little or no gonad-stimulating hormone during pregnancy. In the mare, in which the serum gonadotropic hormones are similar in properties to the hypophyseal ones (Hamburger, 1934), the hormone content of the anterior pituitary is

increased about the time (fiftieth to the hundredth day) when these hormones are present in the blood in large concentrations. In animals other than the higher primates and *Equidae* no increase in gonadotropic hormone production can be demonstrated during pregnancy, but there is good evidence that in some of them the hypophyseal activity is essential during pregnancy; thus in the rabbit removal of the pituitary is followed by abortion, and in that animal the gonad-stimulating hormone content of the pituitary is appreciably increased during some stages of pregnancy (Hill, 1934).

All these data suggest that in the human being the placenta may secrete the gonadotropic hormones, but that in other species they are produced only in the anterior pituitary lobe. It must be emphasized, however, that these conclusions are hypothetical, and are chiefly given to illustrate directions in which research is proceeding. It is possible that, ultimately, convincing evidence will be obtained by experiments on hypophysectomized pregnant primates and mares.

Whatever their site of origin, the gonadotropic hormones must play an important part in controlling the ovarian, and especially the luteal, activity during pregnancy. It is surely of some significance that in the human being, in whom the gonadotropic hormones are produced during the whole of gestation, the corpus luteum remains active throughout a great part of that period, whilst in the mare the cessation of gonadotropic hormone production is followed shortly afterwards by degeneration of the corpus luteum and inactivity of the ovary. It is important, moreover, that in the rabbit the maximum gonadotropic hormone content of the pituitary and the period of continued luteal activity during pregnancy occur at about the same time (Hill, 1934).

It is indeed of interest to consider the relation of the hypophyseal and luteal functions in various species to the maintenance of gestation. At least three types of relationships are observed; these are exhibited by the following.

1. Animals in which (a) removal of the pituitary is followed by atrophy of the corpus luteum, and (b) removal of the ovaries does not necessarily cause abortion (for example, the guinea-pig). In such animals hypophysectomy may be followed by normal pregnancy and parturition.

2. Animals in which (a) removal of the pituitary is followed by atrophy of the corpus luteum, and (b) ovariectomy is followed by abortion (for example, of the rabbit). In such animals hypophysectomy is followed by expulsion of the uterine contents.

3. Animals in which removal of the pituitary is not followed by atrophy of the corpus luteum—for example, the rat and the mouse. In these animals hypophysectomy may be followed by normal pregnancy and subsequent expulsion of the uterine contents.

It will be seen that hypophysectomy leads to abortion only when the consequent degeneration of the corpus luteum has similar consequences (for example, in the rabbit). The fact that the administration of progesterin to the pregnant hypophysectomized rabbit will prevent abortion, and may be followed by a normal pregnancy and parturition (Robson, 1936), is additional evidence that in some species the essential function of the pituitary in the later stages of pregnancy is the maintenance of luteal activity. Further evidence in support of this view is the fact that both pregnancy and the luteal function can be maintained in the hypophysectomized rabbit by the administration of gonadotropic hormone (Robson, unpublished data).

It is at present difficult to dogmatize about the hormonal control in animals in which removal of the ovaries does

not lead to abortion, but the evidence presented here suggests that in these the placenta may be responsible for the continued secretion of progesterin. If such is the case, the placental activity may be quite independent in extent and duration from any hypophyseal control—for example, in the guinea-pig. A similar independence of the progesterin secretion by the corpus luteum from pituitary control may also be witnessed in species in which hypophysectomy during pregnancy does not lead to atrophy of the corpus luteum (rat, mouse).

Functions of Uterine Contents during Pregnancy

The foregoing discussion leads to the question, "What part do the uterine contents play in the control of the changes concerned in pregnancy and parturition?" It has already been noted that in some species removal of the pituitary may be followed by continued pregnancy and parturition (rat, mouse, guinea-pig), while in another (rabbit) the administration of progesterin to the hypophysectomized animal is sufficient to maintain a normal gestation leading to parturition at the usual time. Moreover, in the rabbit the state of the uterus at parturition shows that the oestrous activity normally present has also occurred under the experimental conditions.

To what extent the hypophyseal activity is necessary for the maintenance of luteal function and production of oestrin during gestation and at parturition in the mare and in the primates is at present unknown. Incidentally, the possibility that the placenta may be responsible for gonadotropic hormone production during pregnancy in the human has already been noted.

The limited evidence at present available therefore suggests that the uterine contents are, at least in the later stages of gestation, ultimately responsible for the control of the production of the hormones concerned in the maintenance of gestation and parturition. The finding of Newton (1935) that death of the foetuses in the mouse may be followed by the expulsion of normal placentae at the time of expected parturition offers additional evidence for that point of view. In so far as the production of luteal hormone is concerned, the uterine contents may act not only by controlling the extent and duration of activity of the corpus luteum, but also by the secretion of the hormone itself. In so far as oestrin is concerned, it is probable that the uterine contents may secrete this hormone, though there is at present no evidence to indicate whether the secretion of oestrin by the ovary is under the control of the uterine contents. The mechanism by which the uterine contents control the extent and duration of the luteal activity (the mechanism which, in the rabbit, appears to be exerted through the agency of the pituitary) is at present unknown; the possibility that a new hormone (or hormones) may be involved cannot be excluded.

The active changes occurring at parturition and leading to the expulsion of the foetus and placenta may take place in the absence of the pituitary (both anterior and posterior lobes), and in animals with inactive ovaries. Normal parturition may occur at a normal time in pregnancy in cases in which the activity of the pituitary can be excluded, and probably in the absence of ovarian function. It would thus appear that the mechanism of parturition and time of its occurrence may be dependent essentially on the function of the uterine contents. It must be emphasized, however, that this statement is not a general one applicable to all species, but has been derived from experiments performed in some species and may not be true for all types of animals.

Indeed, a study of the physiology of the sex hormones in different species leads to the conviction that there

exists a bewildering variety in the production and mode of action of these substances. In so far as their activity during pregnancy is concerned, it appears, however, possible that the diversity of action in this respect might be partly explained by the hypothesis that the uterine contents have, to various extents for different species, taken control of, or even superseded, functions otherwise performed by endocrine structures in the host organism.

Summary

1. The properties of the hypophyseal and gonadic hormones produced during pregnancy and responsible for changes which then occur are briefly described.

2. The concentration of hormones in the urine, the blood, the placenta, and the pituitary during pregnancy is reviewed in (a) the human being, (b) certain higher primates, (c) the mare, and (d) some other animals.

3. The relation of the sex hormones to the alterations occurring during gestation in various species is discussed; an attempt is made to evaluate their significance in the processes responsible for the maintenance of pregnancy and initiation of parturition.

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A CENTRE, OR CENTRES, IN THE HYPOTHALAMUS CONTROLLING MENSTRUATION, OVULATION, PREGNANCY, AND PARTURITION

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It is only within the last few years that our conception of the menstrual cycle in man has been freed from false analogies to the oestrous cycle in other mammals. It is now generally believed that the cycle is dependent on the varying amounts of folliculin and corpus luteum hormone circulating in the blood, this ovarian activity being stimulated and controlled by a substance or substances elaborated in the anterior pituitary gland.

The purpose of this communication is to advance evidence of a clinical nature in favour of the thesis that there are one or more centres in the brain, probably in the hypothalamus, which control menstruation, ovulation, pregnancy, and parturition. It is suggested that this centre receives afferent stimuli from (a) the ovaries (hormonal in nature); (b) the external generative organ (by nervous paths); and (c) the special senses and psyche (that is, psychological). The efferent impulses operate through (a) the anterior pituitary gland, and (b) nervous impulses to the generative organs.

Hypothalamic Centres

Evolution from the unicellular forms of life to that of the mammal, and the consequent "division of labour," has necessitated the vesting of the ultimate control of every function in the central nervous system. The centres in the cerebral cortex—such as those for vision, speech, and hearing—are not, like the vasomotor and respiratory centres situated in the medulla, essential to life. It is not always realized that centres exist which either initiate or control coughing, salivation, expectoration, body temperature, and vomiting. That at least some of these activities cannot occur apart from their centres is evidenced by the fact that herbivora cannot vomit. In general, the activity of the centre is dependent on afferent stimuli which may be either nervous or chemical, specific or catholic. Likewise the efferent stimuli may be either nervous or chemical, or both nervous and chemical.

The vegetative centres, of which the carbohydrate centre may be taken as an example, are situated in the hypothalamus. Removal of the pancreas results in death from diabetic coma. If, however, the anterior pituitary gland is extirpated subsequent excision of the pancreas is compatible with life. It would seem that the anterior pituitary substance tends to raise, and the secretion of the islets of Langerhans to lower, the level of the blood sugar, and that the carbohydrate centre co-ordinates the activities of these two opposing hormones. Situated in this region of the brain are two cell masses, named the paraventricularis and the supra-opticus. Greving has shown that nerve fibres from these cell masses pass into the pituitary stalk. Not only do they receive a very rich systemic blood supply, but they are also freely bathed with blood returning from the pituitary sinusoids. Further, it is now accepted (Clark and Boggon) that the prefrontal cortex and the cortex of the gyrus cinguli are connected with the thalamus, and the mid-line nuclei of the thalamus with the hypothalamic nuclei. It may therefore be postulated that these cell masses are rendered sensitive to the difference in the hormonal content between the systemic blood and that returning from the pituitary