

THE RELATION OF THE ENDOCRINE SYSTEM TO
PREGNANCY*

A SUMMARY OF RECENT VIEWS

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THE purpose of this paper is to correlate certain of the phenomena of normal pregnancy with their relationship to the secretions of the ductless glands. We wish to indicate how some of the disturbances that may complicate pregnancy are either directly or indirectly dependent upon dysfunction of one or more of these glands. The great part of the science of endocrinology rests on speculation. The definitely established and proved facts concerning the action of these glands are few in number. It is only during the last few decades that the great importance of these structures on human economy is realized.

We are acquainted with the malformations that result when a baby is born with a maldeveloped thyroid gland, and of the astounding results that follow the administration of the extract of this gland. The parathyroid glands are each about the size of a pea; when three of them are removed nothing happens; when the fourth is removed there follow twitchings, spasms, paralysis, dyspnea and death. Cushing¹⁷ has demonstrated that no ill effects follow the extirpation of part of the anterior lobe of the pituitary gland (a gland only a few grams in weight) but its complete removal causes death. (More recent investigation attributes the death coincident with the removal of the pituitary gland to injury of the hypothalamus.) The romance of the glands of internal secretion and their relationship to human economy is in its very incipiency. We are cognizant of the possibilities that are forever present in that domain. With keen expectation one looks forward to the developments that the future holds in store regarding the ductless glands. The scientific, and particularly the medical, world is still vibrating to the chords of joy which the fingers of Banting and his coworkers struck. Who can foretell what tomorrow may bring?

THE FETUS AND ITS DUCTLESS GLAND SYSTEM

In order to determine the relations of internal secretions to pregnancy, it becomes necessary first to decide whether the ductless glands of the fetus itself have any influence on pregnancy. If the fetus

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elaborates internal secretions, we must ascertain whether and to what extent they, in addition to the maternal secretions, affect the course of pregnancy.

Some authors maintain that the internal secretions of the fetus itself play no part in its development and in the progress of pregnancy, and that the fetal glands of internal secretion have hardly any function during intrauterine life. Others claim that the secretions exert some influence by their admixture to the maternal blood. A little contemplation, however, will soon convince one that the internal secretory glands of the fetus are likely to wield a very powerful effect. A marked hyperemia is found in the thyroid glands of fetuses. The mammary glands of newborn boys and girls contain colostrum. The prostates of newborn boys exhibit some hyperplasia, and the uteri of newborn girls often show distinct hemorrhage. But, even if we were unaware of these findings, we could suppose that those organs which throughout life influence growth and development, would naturally function to their utmost during the period of most marked growth activity. We thus can conclude, that the fetal internal secretory glands begin to function during intrauterine life; that not only do they have a decided influence on the growth and development of the fetus per se, but that the fetal internal secretions probably pass into the maternal blood; that they are added to the maternal endocrine secretions and thus simulate a hyperactivity of the maternal glands of internal secretions.

We shall now take up the individual glands, point out their influence on pregnancy, and wherever possible mention the experimental evidence upon which the statements are based.

THE PLACENTA

That the placenta must be considered a gland of internal secretion is now almost universally accepted. The pregnancy-hyperplasia of the breasts in the mother and fetus is said to be produced by a specific hormone or ferment which proceeds from the chorionic epithelium of the placenta. Halban³ proved this by a remarkable observation. He noticed that the breasts in a pregnant woman go on developing and enlarging even if the fetus had been dead a long time if the placenta remained alive. When, however, the placenta also died, the further development of the mammary glands ceased and milk began to flow. Halban thus concluded that since the onflow of milk always coincides with the removal or death of the placenta, and is enhanced by extirpation of the ovaries, the placenta and ovaries induce the growth but inhibit the secretion of the mammary glands.

Starling and Lane-Clayton¹⁴ have regarded the fetus as the source of the mammary gland hormone. Actually, they even succeeded in inducing growth of the mammary glands by the injection of embryonal extracts into the peritoneal cavity of rabbits that had not yet been impregnated. This fact, it seems to us, does not conflict with Halban's views, for it is quite likely that the placental hormones are present in the tissues of the fetus. As just mentioned, also, the enlargement of the newborn's breasts is ascribed to this hormone.

C. M. Stimson²⁰ claims that the placental extract or hormone is not a galactagogue, and that as long as the placental hormone is in the maternal circulation, it exercises an inhibitory effect on mammary

secretion. These observations coincide with and are confirmed by the experimental results of O. Frankl²¹ on pregnant mice.

That the ovaries are not necessary for the pregnancy-hyperplasia of the mammae was proved when, in spite of castration undertaken in the early stages of pregnancy, the development of the breasts proceeded in a normal manner, and the women were able to suckle their children. In fact, it seems that removal of the ovary later exercises favorable influences on milk-production, as breeders state that castrated cows yield abundant milk.

We, therefore, infer that the enlargement of the breasts in pregnancy is chiefly the result of hormone activity, especially of placental hormones, and that secretion of milk is induced by the removal of the placenta and is enhanced by extirpation of the ovaries.

THE OVARIES

The internal secretion of the ovary is elaborated in the corpus luteum. This was demonstrated by the ingenious experiments of Frankl, in 1910 and in 1923.²¹ The functions of this secretion, as stated by Frankl, consist in a regulation of the blood-supply, of the formation of the decidua, and the implantation of the ovum. The cessation of ovulation is also ascribed to the persistence of the corpus luteum. Frankl found that when he destroyed the corpus luteum in a woman by means of a cautery, the next succeeding menstrual period failed to occur.

In the later months of pregnancy, it is the "interstitial glands" or theca cells which exert the chief ovarian influence on pregnancy. These cells in turn are stimulated to internal secretion by the products of the placental villi. This so-called "interstitial gland" consists of the hypertrophic theca cells which develop about the periphery of follicles which are undergoing atresia. These cells are particularly well developed during pregnancy. It is believed that these transient structures give rise to an internal ovarian secretion. It is quite probable, however, that the secretion of these theca cells is closely related to that produced by the corpus luteum.

That the development of the fetus subsequent to the implantation of the ovum is not dependent upon the corpus luteum was shown by Kleinhaus and Schenk.⁸ They extirpated the corpus luteum and pregnancy was not interrupted.

In concluding the discussion of the relationship of the ovarian internal secretion to pregnancy, we shall quote the words of Falta,¹³ a recognized authority on the problems involved in internal secretion. He says: "Surveying now the alterations described, which take place in the organism of pregnant women, we find that they are entirely analogous to those which occur in the premenstrual period, while, however, the phenomena of the premenstrual period proceed from the ovary, there can be no doubt at all that the similar, but potentized, manifestations of pregnancy proceed from the developed egg. It, therefore, seems to us that the conclusion lies at hand that all the manifestations of the premenstrual period are set free by the maturing follicle, which only renders intelligible the fact, that the extirpation of the ovaries during pregnancy has no influence on this phenomenon, as the maturing ovum no longer is found in the ovary, but in the uterus."

No definite evidence exists at the present time as to the etiologic relationship between corpus luteum secretions and hyperemesis gravidarum, although there have been a few cases reported that improved under the administration of the extract.

Granted that one of the functions of the corpus luteum is the imbedding and safe walling-in of the ovum after it has been fertilized, the question arises whether in women who habitually abort, we may not be able to demonstrate certain irregularities in the corpus luteum formation.

A very valuable contribution to this subject has been recently published by Allen, Pratt, and Doisy.²⁴ These investigators succeeded in extracting a lipoid hormone from ovarian follicular cysts, the corpus luteum, normal ovarian follicles, the corpus luteum of pregnancy, the human placenta, and from embryonic tissues. The authors conclude that "the corpus luteum can be excised as early as twenty days following the last menstruation without interfering with normal gestation; consequently, this endocrine function of the corpus luteum in woman during this time does not seem a necessary one."

Regarding the endocrine function of the placenta, the above mentioned authors say: "It is rather difficult to see how such large quantities of active substance (lipoid extracts of the placenta which seem to possess the same potency as the ovarian follicular hormone) could be retained in such a vascular organ as the placenta without passing freely into the maternal circulation. Since it is so well established that development of the follicles is seriously inhibited during pregnancy, it would seem to us more probable that the human placenta takes over from the ovaries the major part of the function of the secretion of this hormone, thus maintaining the maximal function of the genital tract, and initiating growth in the mammary glands during gestation. The increased amounts of this hormone in the maternal organism would seem a logical cause of the hypertrophy of other endocrine organs during pregnancy. Whether this function is borne by the embryonic tissue of the placenta or by both maternal and embryonic parts acting as a unit, is still to be determined."

THE EPIPHYSIS (PINEAL GLAND)

We must refrain from a discussion of the importance of the pineal body, because our knowledge concerning its function and especially its relation to pregnancy is practically nil.

THE PANCREAS (ISLANDS OF LANGERHANS)

Not much had been known, heretofore, concerning the internal secretion of the pancreas and, therefore, concerning its relation to pregnancy. With the advent of insulin and our increased information concerning the activity of the cells of Langerhans, we may hope in the future to learn more about their specific rôle during pregnancy.

THE THYMUS GLAND

The thymus gland ordinarily atrophies with the approach of puberty and, therefore, does not often exert any influence upon pregnancy. Bompiani, however, has shown that in cases of abnormal persistence of the organ it undergoes diminution in size during pregnancy and

enlarges again after delivery. Its physiologic atrophy is generally ascribed to an inhibitory effect of the ovary on the thymus.

The persistence of the thymus may also give rise to a picture simulating Basedow's disease. More likely, however, this is the result of actual hyperthyroidism, for it is now recognized that in most cases of enlarged thyroid there also exists an accompanying hyperplastic thymus gland.

THE THYROID GLAND

The fact that the thyroid gland is enlarged during pregnancy, was known even in antiquity. There is no doubt that this increased volume is associated with an increased function.

Lang,¹ in a series of 133 cases of pregnancy, found the thyroid enlarged in 108, the organ beginning to enlarge definitely about the fifth month. The increase ceased, however, if thyroid extract was administered, and began again when the extract was withdrawn.

H. W. Freund, in 1882, first made a systematic study of the thyroid gland in pregnancy. It is enlarged in 65 to 90 per cent of the cases, and gradually diminishes in the latter part of the puerperal period. The enlargement is due to a hypertrophy and hyperplasia of the tissues. The changes in the glandular epithelium and the marked increase of fresh colloid point to an increased secretory activity of the organ.

It appears that the thyroid gland is influenced greatly by the activity of the sexual organs. During puberty and during the menstrual period it is the ovarian secretion, and during pregnancy it is the placental materials which lead to a hypertrophy of the gland.

In some pregnant patients definite evidence of hyperthyroidism exists, such as marked nervousness, irritability, emotionalism, tachycardia, tremors and an enlarged thyroid gland. Daly and Strouse²³ studied twenty-five cases of this sort. They treated them with no other medication than three to five drops of Lugol's solution, three times a day, and all the patients became free from symptoms, usually within seventy-two hours.

Some authors are inclined to attribute the phenomena of eclampsia, hyperemesis and puerperal psychoses to a thyrogenous influence, but there is, as yet, no experimental evidence to support this claim.

The reason for the thyroid gland hypertrophy during pregnancy evidently is the demand for increased metabolic activity required by the hypertrophy of maternal tissues and the additional life within the uterus.

THE PARATHYROID GLANDS

These glands undergo considerable hypertrophy during pregnancy, and their secretion apparently is essential to a normal progress of gestation. To a great extent they act through the calcium metabolism.

The typical parturient tetany is a rare malady. Studies upon cases that have come to autopsy, and animal experiments go to show that the tetany occurring during pregnancy results from an insufficiency of the parathyroids.

Pregnancy makes increased demands on the parathyroids, a fact quite obvious from the increased amount of calcium to be metabolized for deposit in the fetus. Quite often are found disturbances of other endocrine glands in cases of tetany of pregnancy.

The tetany of pregnancy is a particularly severe form of tetany on account of the involvement of the respiratory muscles. Published results show that 7 per cent of patients died during this affection, even though pregnancy was terminated.

Vassale, Pepere, and Zanfognini showed lesions of these organs after death from eclampsia. They also showed that experimental parathyroid insufficiency beginning during the last three months of pregnancy caused grave eclampsia. In two of the three dogs in which the parathyroids had been removed, Vassale was able to prevent eclampsia by giving large doses of parathyroid extract orally.

In a recent editorial in the *Journal of the American Medical Association*²² we read: "Dragstedt and his coworkers at the Northwestern University Medical School have indicated the close relationship between eclampsia and the toxemia occurring during pregnancy in the parathyroidectomized dog. Both in the latter and in man there is evidence for the existence of a toxemia arising from the pregnant uterus and caused by toxic protein derivatives. Both diseases are characterized by the appearance of tonic and clonic convulsions, usually during the latter part of pregnancy or immediately after delivery. Both disorders are relieved by emptying the uterus. Some critics might aver that it is a far cry from parathyroid tetany to eclampsia, but the Northwestern University physiologists have found that in the dog, through removal of the parathyroids, a toxemia develops that most often produces tetany but which may in many cases cause profound depression, a gradual cachexia associated with anorexia and diarrhea, or a marked ataxia and stupor without tetany. It is, therefore, not logical, they add, to say that eclampsia does not represent a functional parathyroid deficiency simply because it is possible to differentiate by clinical signs, eclampsia from tetany. A relative or absolute parathyroid deficiency in the dog renders it liable to toxemia during pregnancy, which usually manifests itself as tetany but may produce other nervous or constitutional symptoms."

The treatment of parathyroid insufficiency, aside from the general and symptomatic management, consists in the administration of parathyroidin and calcium salts.

THE HYPOPHYSIS (PITUITARY GLAND)

The hypophysis undergoes a marked hypertrophy during pregnancy. Its weight can rise to two and a half times as much as normal. Enlargement of the anterior lobe is exclusively responsible for this increase in weight. The anterior lobe becomes more juicy, softer, and heavier. This enlargement is chiefly due to an increase in the number and size of the "chief cells," and their ultimate transformation into the so-called "pregnancy cells." In the later stages of pregnancy more than four-fifths of the organ may consist of the newly-formed cells.

It was L. Comte, Moulon and Launois who first pointed out this enlargement of the pituitary. Launois and Moulon⁵ confirmed this in two instances, one of the parturients having died from eclampsia. They found a marked increase of the cellular elements. In a more recent work, Launois reiterates his previous conclusion that in pregnancy the anterior lobe is in a state of marked "hyperactivity."

Cushing¹⁷ has found that repeated pregnancies may so enlarge the

pituitary gland as to cause transient bitemporal hemianopsia due to pressure of the gland on the optic commissure. Enlargement of the pituitary gland before or during menstruation, or a disturbed secretion, may frequently be the cause of the so-called menstrual headaches.

Enlargement of the hypophysis during pregnancy is sometimes so considerable as to give rise to cerebral manifestations. In rare cases even a pressure action on the chiasma seems to be possible. V. Reuss¹⁶ described repeated temporary blindness during pregnancy, while Bellinzona and Tritondani reported bilateral narrowing of the visual field. Certain manifestations point to an increased hypophyseal function during pregnancy, such as increased growth of the pelvis and osteophytic formations on the internal surface of the skull. Tandler and Grosz¹⁵ emphasize that in gravid women there is a coarseness of the facial features, especially of the soft parts of the nose and lips, and moreover, that a thickening of the hands is not rare,—manifestations that remind one of a slight grade of acromegaly. These acromegaloid changes of the hands, feet, and sometimes of the face, are directly attributable to the oversecretion of the anterior lobe of the pituitary body.

In the usual cases of acromegaly in women, we often find amenorrhea and sterility. As far as present reports go, pregnancy is not disturbed and runs to a successful termination in women suffering with acromegaly.

Whether the posterior lobe adds any additional secretion during labor to stimulate uterine contractions is not known; but we are all aware of the potency of the extract of the posterior lobe of the pituitary gland upon uterine contractions when administered to a pregnant woman.

The glycosuria of pregnancy is also due to a stimulating effect of pregnancy on the pituitary gland. Some direct experimental evidence for this assumption can be found in the work of Diton, who has shown that injections of ovarian extract stimulate the secretion of pituitrin. J. H. Burn found that pituitrin, though it did not in itself cause hyperglycemia, was, nevertheless, able to inhibit the fall of blood sugar which would otherwise have followed the injection of insulin. I think, therefore, the statement is justified that the glycosuria of pregnancy is due to the stimulating effect of the pregnancy on the pituitary gland which then directly inhibits the internal secretion of the pancreas. It may well be that in its inception this process is physiologic, diverting the stream of sugar from storage in the maternal tissues to the use of the fetus.

THE ADRENAL GLANDS

Experimental evidence fully sustains the view that the mother's autoprotective resources are developed coincidentally with the growth of the fetus through a corresponding augmentation of the functional activity of the adrenal system. The following observations on the changes of the adrenals during pregnancy are definitely established: (1) The cortex of the adrenal undergoes hypertrophy during pregnancy, especially in the zona fasciculata and the zona reticularis. (2) There is an appearance of vacuoles in the cells of the zona reticularis and a marked pigmentary accumulation which must be looked upon as a sign of increased secretory activity. (3) During pregnancy the

cholesterin content is increased in the cortex of the adrenal gland. The lipoidemia, i.e., the increase of fat in the blood seen in normal pregnancy is largely the result of the increased cholesterin formation in the cortex of the suprarenal gland.

Pollak could demonstrate during pregnancy a heightened glycosuric action of adrenalin. This tendency of pregnant women to alimentary glycosuria and alimentary ketonuria is well known. Many authors cite those disturbances as stigmata of a disturbance of liver function, as a result of degenerative changes. But Wilhelm Falta says that it is rather incredible that a normal physiologic process, such as pregnancy is, should regularly lead to such severe disturbances of the liver, and he would, therefore, regard the glycosuria as an increased irritability of the liver cells rather than as a degenerative process.

The occurrence of pigmentation on the face, around nipples and abdomen during pregnancy is explained in the following manner: the pigment is iron-free and, therefore, is not a derivative from the blood. It is well known that disturbed function of the adrenals will lead to the deposition of pigment. In Basedow's disease, e.g., the production of adrenalin is increased and in Addison's disease it is lessened, and in both of these conditions abnormal pigmentary deposition is frequent. Hence, it is quite possible that the regular occurrence of pigmentation, along the linea alba, navel, perineum, labia majora, areolae of nipples, and in the face (*chloasma uterinum*) is due to increased action of the adrenals.

The fact is also recognized that there is a distinct increase in growth of hair during pregnancy, due to increased activity of the suprarenal cortex. Halban demonstrated the increased-growth-tendencies of the hair in animal experiments. After shaving the abdomen of pregnant animals the hair grew faster than on the abdomen of nonpregnant animals similarly treated. There are also cases on record of women who, during each period of pregnancy, became excessively hirsute, and following labor there was a gradual loss of hair and a return to normal.

All of these facts support the assertion that there is an increased activity of the adrenals during pregnancy. It is true, that thus far it has been found impossible to demonstrate an increased adrenalin content of the blood during pregnancy. This, however, may perhaps be due to our lack of a finer laboratory technic.

Sajous¹² explains the occurrence of eclamptic seizures on the following basis: "During pregnancy the mother's blood becomes increasingly laden with waste-products, those of the developing fetus being added to her own. To protect the organism her adrenal system and thyroid apparatus become increasingly active, owing to the exciting action of the waste products on these organs. When the adrenal system does not become sufficiently active to enhance adequately the blood's antitoxic properties, the toxic wastes are allowed to accumulate in the blood in sufficient quantities to provoke convulsions. The convulsions are due to irritation by these poisons of the vasomotor and sympathetic centers. All the vessels of the body being violently contracted, a wave of blood is forced into all capillaries, including the cellular elements and neuroglia of the cerebrospinal system. The activity of the cortex being suddenly enhanced, a flood of impulses is transmitted to every portion of the spinal system and the seizure occurs."

CONCLUSION

This summarizes our present meager knowledge of the relationship between the glands of internal secretion and pregnancy. In conclusion, we wish to say a few words concerning the endocrine therapy of certain disturbances complicating pregnancy.

The pregnant condition brings with it an increase in the metabolic processes of the female organism, resulting in part from the hyperplasia of the thyroid, adrenals, and hypophysis. The increased secretion of these organs brings about an increased irritability or power of response of the sympathetic and parasympathetic systems. Some authors who maintain that the pernicious vomiting of pregnancy is due to this irritation of the sympathetic nervous system, advocate ovarian extract which is supposed to have an inhibitory action on the sympathetic system, and thus produces relief in a certain number of cases. It has also been observed that the blood of eclamptic patients has the power of vasoconstriction, due possibly to an overactivity of the hypophyseal-adrenal system. Also this vasoconstriction can be overcome by the injection of ovarian extract.

The neuropathia gravidarum, a tendency to dropsy, and the dermatoses of pregnancy are also probably expressions of excessive or perverted secretory activity of the endocrine glands.

It stands to reason, therefore, that, if future investigation delineates more clearly and definitely the exact *modus operandi* of the toxemias in relation to internal secretions, we shall then perhaps be enabled to have a rational system of endocrine therapy for these conditions. But until these means become available, strict adherence to the fundamental methods must be advised; namely, rest, hygiene, elimination, and stimulation.

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