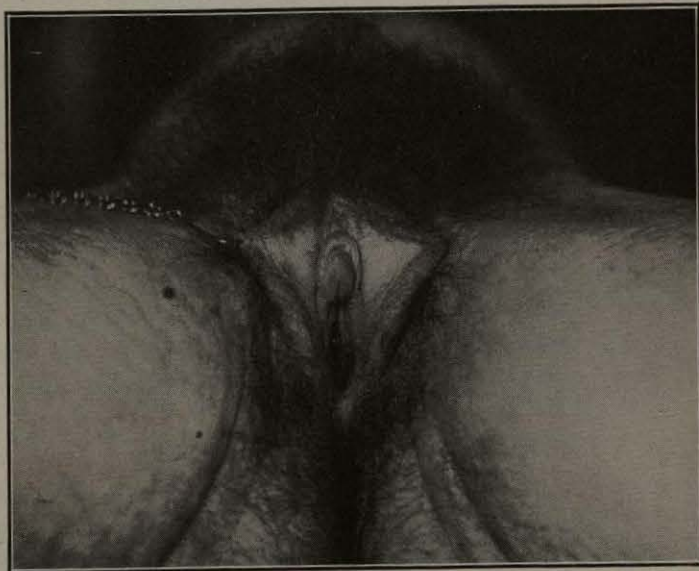


have been described in both male and female sex in which tumors of the testicle and ovary, apparently malignant in character [see page 131 of this volume for corresponding symptoms in malignant hypernephroma], occurring in children, have been accompanied by a general growth of stature and by premature appearance of secondary sexual characters such as growth of hair on the face in the male and in the armpits, and on the pubes in both sexes, development of breasts and generative



PENILE TRANSFORMATION OF CLITORIS AND ADULT HIRSUTIES DUE TO HYPERNEPHROMA IN GIRL OF SEVEN YEARS. (Jump, Beates, and Babcock.)

organs: in short, all the signs of puberty, which, on removal of the tumor, have been found to disappear."

The presence of spermin in the blood of females referred to above is an important feature of the problem as a whole, for it shows that its chemical homologue, the adrenal product, is the determining factor of sex production. Thus we have seen (page 302) that tumors of the adrenal cortex caused females to undergo changes toward male characteristics, male organs having become sufficiently developed in 10 of the women referred to by Apert as to cause them to live as men. This transformation is well shown in the above cut, illustrating the

case described on page 301, reported by Jump, Beates, and Wayne Babcock. Suggestive also in this connection are the experiments of Allen J. Smith and W. J. Crocker,⁹⁸ who found that by injecting a salt-solution extract of a cock's testis into hens these animals showed many indications of assuming male characteristics. The comb in most cases increased in size and brightened, the wattles likewise. In some of the hens the neck feathers became somewhat more brilliant, the same peculiarity applying to the small feathers at the base of the tail. In one hen a slight but distinct growth of spurs was recognized. Some of the hens became combative, and several times they attempted to cover other hens after the manner of the cock.

On the whole it seems clear that *it is to the secretion of adrenal tissues, wherever situated, that the male characteristics are due.* This phenomenon finds a ready explanation in my view that the adrenal secretion supplies the blood the oxidizing ferment which as a catalyzer endows living tissues with their vital dynamism.

Dixon,⁹⁹ after using orchitic injections, concludes that the effects observed were due to its nucleo-albumin. Orchitic extracts are known to contain nuclein, a ferrinuclein according to Cavazzani,¹⁰⁰ in the proportion of about 2.4 per cent. But this applies to semen, in which spermatozoa and other substances containing nuclein are present. Still, absence of functional testes being known to produce abnormalities of the bones, it is probable that the thymus is involved in the process. This is further suggested by the fact that Hatai¹⁰¹ found that in white rats removal of the sex glands caused the thymus to increase to almost twice its size. This feature of the process belongs to the generative sperm-cells, and not to the interstitial cells of Leydig.

With the so-called internal secretion of the testicle identified as a product of adrenal rests in this organ, and recalling the action of the adrenal product upon oxidation, metabolism, the vascular tension, etc., we can understand the morbid effects of masturbation and excessive venery—particularly the debility,

⁹⁸ Smith and Crocker: *New York Med. Jour.*, July 5, 1913.

⁹⁹ Dixon: *British Med. Jour.*, Sept. 21, 1907.

¹⁰⁰ Cavazzani: *Gazzetta d. Osp. e d. Clinische*, June 28, 1903.

¹⁰¹ Hatai: *Jour. of Exper. Zoölogy*, Jan., 1915.

languor, mental torpor, and deficient growth in boys addicted to these habits. These symptoms coincide with those which, we have seen, follow castration. Bouin and Ansel¹⁰² have shown, moreover, that extracts of interstitial tissue counteracted the effects of the latter operation and tended to promote growth.

On the whole the above data seem to warrant the following conclusions:—

1. *There is no true internal secretion of the testes, the products of the epithelial (Leydig's) and seminal cells which unitedly take part in the formation of the seminal fluid, being derived mainly from adrenal rests in those cells.*

2. *When seminal fluid is not secreted during coitus, masturbation, etc., that part of it contributed by the epithelial and seminal cells is added to the asset of adrenal products in the body at large.*

OVARIES.—There is considerable analogy between the characteristic effects of castration in the male and those following removal of the ovaries in the young. What remains of the genital organs, the uterus, vagina, and vulva, and also the breasts, retain their infantile type. In developed females this operation tends to produce atrophy of the same structures and obesity (also observed in men after castration), menstruation meanwhile ceasing. The influence of the ovaries on metabolism also corresponds with that of the testicles. The dictum of Brown-Séquard,—to whose remarkable physical improvement under the influence of testicular extract I can bear witness,—that this agent is more efficient than ovarian extract in the treatment of women, suggests a kinship between these two organic substances. This is emphasized when the pharmacological action of ovarian extract is considered. It raises the blood-pressure and slows the heart, as shown by Fedoroff,¹⁰³ Jacobs,¹⁰⁴ and others. Removal of the ovaries, moreover, reduces the oxygen intake 10 per cent., as shown by Loewy and Richter,¹⁰⁵ while ovarian extract restores it; it has been, therefore, regarded as an oxidizing ferment. Neumann and Vas¹⁰⁶ noted that

¹⁰² Bouin and Ansel: C.-r. de l'Académie des Sciences, Jan., 1904.

¹⁰³ Fedoroff: La Gynécologie, Oct. 15, 1891.

¹⁰⁴ Jacobs: Dublin Jour. of the Med. Sci., Sept. 1, 1897.

¹⁰⁵ Loewy and Richter: Berlin. Klin. Woch., Bd. xxxvi, S. 1095, 1899.

¹⁰⁶ Neumann and Vas: Monats. f. Geburtsh. u. Gyn., Bd. xv, S. 433, 1902.

ovarian extract enhanced metabolism; Senator observed that ovarian preparations increased diuresis and the excretion of urea and phosphoric acid. Its physiological effects are those of adrenal preparations, therefore, in every respect.

Its effects on oxidation are so striking, in fact, that they have been clearly recognized by many clinicians. "We are authorized to classify ovarian organotherapy among the oxidizing agents," write Dalché and Lépinos.¹⁰⁷ "This conclusion, it must be admitted, is that reached by several authors. Curatello and Tarulli believe that the internal secretion of the ovaries favors the oxidation of phosphorized organic substances, hydrocarbons, and fats. According to Gomes, it enhances oxidation and hydrolysis and favors the elimination of phosphates. . . . Albert Robin and Maurice Binet have shown that there is during menstruation an increase of the respiratory exchange. Keller, studying the general exchanges, found that there was increased nitrogen oxidation. We have ourselves found that menstruation, in itself, enhances vital functions and particularly the great function of general oxidation." Sauvé¹⁰⁸ states that ovarian extract increases the hæmoglobin content of the blood.

To which of the ovarian tissues, the Graafian follicles, the corpora lutea, or the interstitial cells, must this pharmacological action be attributed?

According to Mulon¹⁰⁹ (1904), the *corpus luteum* presents all the morphological characteristics of an aggregate of chromaffin cells, to which class the cells of the adrenal medulla also belong. Indeed, Prenant¹¹⁰ found that, both in origin and histological structure, the corpus luteum, which remains after elimination of the ovum, shows all the characteristics of an internal secretion gland. Schaefer states that its extreme vascularity suggests that its product passes into the blood. This would explain its influence upon distant organs such as the mammary glands; Ancel and Bouin¹¹¹ having shown that the development of the latter coincided with that of the corpora lutea, and that destruction of these bodies arrested the develop-

¹⁰⁷ Dalché and Lépinos: Bull. Génér. de Thérap., Jan. 8, 1902.

¹⁰⁸ Sauvé: Paris Médical, April 1, 1911.

¹⁰⁹ Mulon: C.-r. de la Soc. de Biol., vol. lvi, p. 113, 1904.

¹¹⁰ Prenant: Revue Générale des Sciences, 1898.

¹¹¹ Ancel and Bouin: C.-r. de la Soc. de Biol., vol. lxxvii, p. 466, 1909.

ment of the mammary gland. The corpora lutea are endowed, however, with other important functions. According to Bandler, it assists not only in the preparation of the uterine mucosa for the formation of the uterine deciduum and in the reception and fixation of the ovum, but also, as first shown by Prenant,¹¹² and in common with the ovary proper, it serves to protect the maternal organism against the destructive local activities of the parasitic ovum and its placental secretion. When impregnation does not take place, the proliferation of the lutein cells occurs only during the few days which the menstrual cycle lasts.

The corpora lutea are formed, as is well known, after the discharge of the ovum, in the *Graafian follicles*, the lining of which forms folds and becomes permeated with blood-channels. When pregnancy occurs, the epithelium of the Graafian follicles proliferates, its cells increase in size and become filled with yellowish granules: the corpora lutea. The follicles have been credited with the power to promote the nutrition of the uterine mucosa and to initiate the premenstrual congestion of the latter. From my viewpoint all these functions are to be attributed to the corpora lutea of the Graafian follicles; though by "function" here I mean only the part the former play as chromaffin cells (of which, we have seen, they possess all the morphological characteristics) in reactions with other agencies. What is the nature of these bodies?

A suggestive fact is that the structure described by Bouin¹¹³ as the *interstitial gland* is known to fulfill various functions attributed also to the corpora lutea. It becomes enlarged during menstruation as well as during pregnancy, thus sustaining sexual life up to the menopause. It attains its highest development during the pregnant state, beginning with the nidation of the fertilized ovum in the uterus. Located in the ovarian stroma, interstitial cells have been found to maintain the nutrition and integrity of the uterus, through some process as yet undetermined.

From my viewpoint, this process is explained through various facts brought out in the course of our analysis of testicular internal secretions, and the conclusion submitted that adrenal

¹¹² Prenant: *Loc. cit.*

¹¹³ Bouin: *Revue médicale de l'Est.*, vol. of 1902.

rests, medullary and cortical, constitute the so-called internal secretions of these organs. Thus, Limon,¹¹⁴ quoted by Biedl,¹¹⁵ found that "the interstitial tissue of the ovary is composed of epithelial cells, the protoplasm of which is filled with granules resembling fat which stain black with osmium. These cells are differently placed in different animals; they are sometimes arranged in compact masses and cords." Now, this description applies precisely to the cortical portion of the adrenals. Indeed, this similarity had been noted by others than myself in respect to the ovaries. "That the interstitial stroma cells possess a secretory function is suggested," also writes Biedl, "by the presence of fat granules and other secretory enclosures, as well as by certain resemblance, commented upon by many (Mulon, Wallart), to the cells of the suprarenal cortex."

Although Bouin gave the ovarian cells of this type the name of "interstitial," they do not correspond with the interstitial or Leydig cells of the testicle, which, as Schaefer states, "show, when present, many analogies with the cells of the corpora lutea." This physiologist also expresses the opinion that the corpora lutea appear not to be concerned with the secondary sex phenomena. Interesting in this connection is what has been termed, "a remarkable instance of the correlation of the corpus luteum with the secondary sex characters" described by Pearl and Surface,¹¹⁶ of the Maine Agricultural Experiment Station. A cow which had produced three calves and given an abundant flow of milk suddenly ceased to produce the secretion from the mammary gland. The udder rapidly shrank to a small size and the animal began to show the external characteristics of a bull. After a lapse of eight months the assumption of the male characters in various regions of the body was complete and perfect. A necropsy showed, as the only gross abnormality, a simple cystic condition of the ovaries. Histologically and cytologically these organs differed from the normal cow's ovary in only one essential respect, namely, that they had no corpora lutea, thus leaving the interstitial cells intact. If *absence* of corpora lutea played any rôle in the process it could only be a passive one

¹¹⁴ Limon: *Archives d'anat. microscop.*, vol. v, fasc. ii, Sept., 1902.

¹¹⁵ Biedl: "Internal Secretory Glands," p. 399, 1913.

¹¹⁶ Pearl and Surface: *Science*, xli, p. 615, 1915; *Jour. Am. Med. Assoc.*, July 14, 1915.

which endowed the "interstitial organ" of the ovary with active rôle. Such being the case, and the interstitial gland corresponding, as observed by Mulon, Wallach, and myself, with the adrenal cortex, we are brought to realize that *the secondary sex characteristics are attributable, in the female, to the ovarian interstitial cells, which correspond morphologically and chemically with those of the adrenal cortex.*

On the other hand, the foregoing analysis tends to show that *the interstitial cells of the female are not the same structures as the interstitial (Leydig) cells in the male; the Leydig cells, connected functionally as they are with the sperm-cells, correspond with the Graafian follicles and their corpora lutea, as secreting structures.*

On the whole, however, and in keeping with conclusion 1 submitted in respect to the testicles: *There is no true internal secretion of the ovaries, the products of the Graafian follicles and their corpora lutea and of the interstitial stroma-cells being derived mainly from adrenal rests in those cells.*

Here, however, the physiological rôle of the testicular products cannot be reproduced, for if, as in the male, the products of the adrenal rests were absorbed when not secreted through sexual congress, masturbation, etc., the male characteristics would assert themselves in the female through the accumulation of the secretion of her interstitial cells. Hence, *to provide against the loss of female characteristics through accumulation of the secretion of the interstitial glands in the body at large, the products of the ovarian adrenal rests are eliminated periodically, i.e., during the menstrual cycle.*

It is because of this fact, as we have seen, that the loss of the testicular glands causes in the male the appearance of female characteristics, while in the female the accumulation through tumors, etc., of adrenal cells, causes the development of male characteristics.

Finally, when pregnancy occurs, all the dynamism which the adrenal rests provide through the influence of their secretion, acting mainly as catalyzer, on oxidation, become necessary for the development of the new being, lactation, etc., and the menstrual cycle ceases.

CHAPTER X.

THE POSTERIOR PITUITARY AS A GENERAL NERVE-CENTER AND AS CO-CENTER OF THE ANTERIOR PITUITARY IN SUSTAINING LIFE.

THE IDENTITY OF THE LOWER BRAIN.

IN the earlier editions of this work I urged that certain centers in the medulla oblongata were probably but subsidiary centers which received nervous impulses from the pituitary body by way of the tuber cinereum and other basal structures. I held, moreover, that "inhibition" as obtained by physiologists represented a pathological phenomenon in that it was caused by excessive constriction of the cardiac arterioles provoked by vasoconstrictors contained in the nerve stimulated, the vagus.

As is well known, it was the work of the brothers Weber (1845) which first suggested that the heart could be "inhibited" by stimulation of a definite region in the medulla. Their experiments differed from those we have reviewed in that the tissues of the base of the brain were traversed by the current, thus exciting structures in which we have seen sympathetic and other nerves pass from the pituitary to the bulb. One pole having been placed in the nasal cavity of a frog and the other on the spinal cord over the fourth or fifth vertebra, the heart's action momentarily ceased, then gradually resumed its normal activity. Approximation of the poles upon the cerebral hemispheres and stimulation of the cord produced no effect upon the heart. "Not until the medulla oblongata between the corpora quadrigemina and the lower end of the calamus scriptorius was stimulated," says William T. Porter, "did the arrest take place. Cutting away the spinal cord and the remainder of the brain did not alter the result." The level of fibers from structures below the brain is also suggested by the effects of experimental injury of the bulbar area which Flourens termed *le nœud vital*.