The Journal of Obstetrics and Gynæcology of the British Empire

VOL. XXIII. MAY, 1913. No. 5.

Ovarian Secretion. A Review.

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SINCE the publication in this Journal for 1904 of the valuable review on the internal secretion of the ovary by Dr. Russell Andrews, much work has been done upon the subject, but it is impossible in a limited paper of this scope to do more than mention the results of investigations upon the still uncertain chemical properties of this secretion. The ovary, in common with the other so-called ductless glands, has a controlling or regulating influence upon the activity of the various organs of the body. The gonads or sex glands are most important of all the organs concerned in the production of an internal secretion in that they have in addition a direct and specialised reproductive function. From the time of the earliest differentiation of the ovum the sex cells are distinct from the somatic cells, and have an influence upon the latter. During the early phases of development of the embryo the male and female cell characters are indistinguishable from one another, and it is only later that sex becomes apparent.

It is not proposed in this paper to enter into the relationships between the ovary and the other internal secretory organs, but references will be confined to the function of the ovary alone. The gonads are closely bound up with the physiological and pathological processes of the bodily functions as a whole. The secretion of the ovary is said to contain a hormone or hormones (Starling) which influence the reproductive and somatic tissues. The term hormone may have its disadvantages as there is still doubt as to whether the ovary produces not only a secretion which stimulates but one which also inhibits. It is here that the difficulty of the problem lies. What portion of the ovary is inhibitory in action and what is excitatory? From the mass of contradictory experimental evidence

at our disposal it is almost impossible to formulate conclusions, and we are driven to accept only those results in which the majority agree.

Other organs of internal secretion such as thyroid, or pituitary, may assume the secretory function of reproductive glands, and thus confusion arises as to the specific function of each gland or chain of glands.

Much of our knowledge about ovarian secretion is derived from experimentalists and little from clinicians, but it is to the latter that we specially look for information, the records of ovarian function in the human female being of the greatest value. There is no doubt that observations upon the various species of animals, while agreeing in the main, must differ somewhat in detail when we are concerned with the investigation of ovarian secretion, which is closely associated with the sympathetic nervous mechanism and its manifestations. It is obvious that the complexities of the nervous system and the psychic phenomena dependent upon the reproductive functions must make for a considerable difference between the ovarian function of the human species and that of the lower mammals or birds. For many years the ovary was looked upon as an organ having only one function, viz., that of reproduction, but it is now admitted that it has a marked influence upon the nutrition of the other generative organs and the secondary sexual characters of the individual. Much of our information as to the physiological influence of the ovary is gained by observations upon the changes which take place after oöphorectomy or after transplantation of ovarian tissue to sites other than the normal. That the male and female reproductive organs have a common influence upon development is evidenced by the skeletal changes which occur at puberty, and that there is a differentiation in the character of the secretion at this period is shown by the variation in the secondary sexual characters of the individual, along with the different phenomena which can be demonstrated as peculiar to each sex.

It is difficult to separate the various physiological functions of the internal secretory organs as they have a marked influence upon one another, some having an inhibitory or antagonistic action which has full play when the opposing gland has been removed. As an example of this influence we have the persistence of the thymus after castration in young animals (Noël Paton).

It is impossible until much more work has been done upon the subject to formulate an opinion as to where the secretory action of a particular gland begins and where it ends, or how the function of an extirpated gland has been assumed by the other glands. This is of special interest in connection with metabolism, the processes of which are to a great extent regulated by these internal secretory organs. When the physiological functions are interfered with or changed by

pathological lesions the problem of the chemical correlationships that exist between these various secretory organs becomes increasingly difficult. Whether the secretion of one organ is diminished or increased as the result of some disturbance taking place in another organ it is often impossible to arrive at a conclusion as to the origin of the effects which are produced clinically or experimentally.

Influence of ovarian secretion upon development.

That the ovary has a marked influence upon the development of the individual is evidenced by the changes which take place at puberty. In the human female at puberty the secondary sexual characters of the feminine type are developed, viz., the rounding of the curves of the body, the enlargement of the mammæ, the growth of hair in the axillary and pubic regions, the increased growth of the genital organs together with the onset of menstruation and its accompanying phenomena. All these changes are associated with psychic manifestations characteristic of the female sex. Changes take place in the ossifying centres of the bones. Enlargement occurs in some of the other internal secretory organs such as the thyroid and pituitary glands, although regressive changes are observed in the thymus. The effects of suppression of ovarian secretion before the onset of puberty in the human female have not been recorded owing to the extreme rarity of the operation of oöphorectomy in young girls. The records of operations among uncivilised people for removal of the external genitals are not to be taken as evidence of the interference with ovarian function. In some cases information is obtained from the examination of women in whom the ovaries are either congenitally absent or deficient in physiological function. In such cases we frequently find maldevelopment of the external genitals and mammæ with absence of menstruation, although the development of the individual as a whole may be unaffected. Cases, however, are met with where the secondary sexual characters of the female are present but where the ovaries and uterus are absent, or where the internal secretory glands show the presence of testicular tissue when examined under the microscope. Such cases are still unexplained. Biedl states that after castration in males, as in eunuchs, there is delayed ossification of the lower bones and that it is most probable that a similar delay takes place in the human female.

Our knowledge about the effects of removal of the ovaries in animals before the onset of sexual maturity is fairly extensive, and the majority of workers are in agreement as to the suppression of the secondary sexual characters following castration. Castration in young animals causes an arrest of development in the genital organs and mammæ with subsequent atrophy. This is now no longer a matter of controversy. Marshall suggests that the female would

take on the male characters which are normally latent in each individual but that the presence of ovarian secretion has an inhibitory action upon the development. He adduces as proof of his argument the records of cases in which female fowl and deer have taken on male appearances after castration or when ovarian secretion is defective. Carmichael and Marshall have shown that castration of young rodents does not affect the growth and general nutrition of the animal. It is still, however, a matter of doubt whether the normal sexual instinct of the animal has been affected by the removal of the reproductive glands in early life.

Removal of the ovaries after puberty.

The effects of the removal of the ovaries after puberty has been reached are not so marked as in cases of removal before puberty since the sex characters in the former case have become established. It is generally accepted by experimentalists that atrophy of the uterus, mammæ and other genital organs takes place (Carmichael and Marshall, Marshall and Jolly). On microscopic examination the uterus shows degenerative changes resembling the condition known as fibrosis, the glands are reduced in size and number and eventually disappear—the degree of degeneration depending upon the length of time the animal has been kept after operation. The blood vessels are diminished in size and number. The lining epithelium of the mucosa is the most persistent tissue and is the last to disappear. Procœstrum or œstrus do not occur. Clinically it has been found that removal of the ovaries is followed by the cessation of menstruation, and degenerative changes occur in the genital organs, although the majority of workers agree as to the cessation of menstruation a few still question this statement and bring forward evidence of the recurrence of menstruation after oöphorectomy (Alban Doran). Such cases cannot be proved by experiment in any species of animal, and are doubtless to be explained by the presence of a small piece of ovarian tissue which has been overlooked in removal, or by the existence of a supernumerary ovary or piece of an ovary in some other situation. In the examination of such cases a clear distinction must be drawn between menstruation and uterine hæmorrhage due to some existing pathological condition of the cervix or uterus.

Some authors think the atrophic changes in the uterus are due to the cutting off of the vascular or nervous supply at the time of operation (Hofmier, Sokoloff).

Removal of one ovary has no physiological effect as the remaining organ assumes the function of both and in the majority of cases becomes hypertrophied (Carmichael and Marshall). Bond found that this compensation took place only when pregnancy or œstrus had occurred, and concludes that bilateral ovaries function as one

gland with regard to their internal secretion. That this compensatory hypertrophy takes place irrespective of pregnancy or œstrus is evidenced by the experiments of Carmichael and Marshall, who found hypertrophy of ovarian tissue even when only a small portion of one organ was left behind and when the animals (rabbits) were isolated, assuming that ovulation in the rabbit only takes place on copulation (Heape). The work of these authors was supported by my own experiments upon rabbits.

During early pregnancy if one ovary is removed abortion does not necessarily take place, although on removal of both ovaries there is interference with the embedding and development of the ovum in the uterus. Evidence of the effect of cessation of ovarian function is to be found in the phenomena which take place at the time of the menopause when the ovaries show atrophic degenerative changes—menstruation ceases, atrophy of the uterus and mammæ takes place, and various nervous and vascular phenomena occur. In the surgical menopause the symptoms as a rule are more marked owing to the sudden removal of the ovarian secretion before the individual has become accustomed to the changes in the adjustment of the equilibrium of the internal secretory organs such as take place gradually under normal conditions.

The conclusions as to the effect of castration are, that before puberty there is an arrest in the development of the genital organs and mammæ. After puberty there is an atrophy of these organs with cessation of pro-œstrum and œstrus. The growth and development of the young animals are said to be unaffected (Marshall, Grigorieff, Halban, Carmichael). The majority of clinicians agree as to the occurrence of degenerative changes, cessation of menstruation and menopausal symptoms. Pozzi, however, records a case of menstruation occurring after double oöphorectomy in which there was development of a fibroid tumour in the uterus subsequent to the operation. In such cases the question of uterine hæmorrhage apart from menstruation has to be carefully considered.

The influence of ovarian secretion upon menstruation.

That menstruation or pro-œstrum depends upon ovarian secretion is proved by the fact of its onset at puberty or sexual maturity, and by its cessation on removal of both ovaries. Should a small piece of ovary be left in position or transplanted to another situation menstruation occurs. In cases of amenorrhœa after double oöphorectomy menstruation has been known to recur on subsequent grafting of a piece of an ovary from another individual.

The changes which occur in the uterus during reproductive life are cyclic in character, and correspond to certain changes which take place in the ovaries. The same phenomena occur throughout the whole mammalian species, but differ somewhat in their periodicity

and duration. It is now admitted by most authorities that menstruation corresponds to the pro-œstrous period in mammals, and is of the nature of a preparatory process on the part of the uterus for the reception of a fertilised ovum. The subsequent or œstrous period being that period when fertilisation is most likely to take place. The recurrence of this cyclic process among animals is influenced by seasonal and nutritional changes. The whole reproductive cycle comprises a resting or an œstrous period, this is followed by congestion of the pelvic tissues and changes in the other internal secretory organs. A hæmorrhagic discharge occurs in the uterine and tubal mucosæ in the human female and in the majority of mammals, and constitutes the pro-œstrum or menstruation. There is thickening of the mucosa at the same time and the discharge consists of blood, mucus and exfoliated epithelial cells. After the cessation of the discharge there is a proliferation of the cells of the mucosa. If fertilisation does not take place the pelvic organs gradually return to their original condition of physiological quiescence. In some of the lower mammals there is no hæmorrhagic discharge but merely a flow of mucus. In the rabbit there is no evidence of the presence of heat apart from copulation with the male. The chemical nature of the uterine discharge during menstruation is still unknown although a considerable amount of work has been done with regard to the presence of calcium salts (Blair Bell). But our knowledge is incomplete as far as concerns the nature of the chemical substances or ferments which are present as the result of ovarian secretion. Pro-œstrum can be induced to a certain extent by transplanting ovaries from an animal in the œstrous state to an animal whose pelvic organs are quiescent, or to one which has been previously castrated (Marshall and Jolly). This condition can be induced by injections of extracts from œstrous ovaries.

There is still much doubt as to the factors which influence the ætiology of menstruation and ovulation and it is difficult to separate these two phenomena. It is thought that menstruation is an expression of ovulation (Bischoff). The theory held by Pflüger has had many adherents, that the maturing follicle generates stimuli which cause a congestion of the pelvic organs, and this in turn brings about the bursting of the follicle with expulsion of the oöcyte and discharge of blood from the uterine mucosa. It is said that by raising the blood pressure in the ovary symptoms of pro-œstrum can be induced (Strassmann). There is no doubt that menstruation is dependent upon the existence of ovarian secretion as proved by the experiments in which the ovaries are removed and transplanted to different situations. The menstrual periods continue but cease later when the grafts themselves are removed (Halban, Marshall and Jolly, Kuaner). The phenomena which accompany menstruation are dependent upon the presence of ovarian secretion and not upon

the uterus or uterine secretion. These cyclic phenomena have been known to occur—with the exception of menstrual hæmorrhage which is due to the presence of the uterine mucosa—after hysterectomy when the ovaries are left behind, in cases where there is a rudimentary uterus with normal ovaries, or even when the uterus is congenitally absent. Mandl and Bürger, however, found that all cyclic changes disappear after hysterectomy alone, but there is little support elsewhere for their theories. Menstruation must be looked upon not as a hæmorrhage from the uterus and tubes, but a cyclic change which occurs in the mucosa of these organs preparatory to the reception of a fertilised ovum, the hæmorrhage being of secondary importance (Hitschmann and Adler). These changes occur in the uterine mucosa of the majority of mammals even where the accompanying hæmorrhage is very slight or absent (Keller). The view that menstruation is due to the reflex stimuli from pressure upon the follicles is to be questioned in the light of the fact that menstruation and pregnancy have been known to occur in women affected with paraplegia. The relationship between menstruation and ovulation is still unknown, but they are in close relationship one to the other. Menstruation may be taken to a certain extent as an expression of ovulation but is not necessarily an accompaniment of this phenomenon. Heape made a series of observations upon the ovaries of menstruating monkeys but did not find ripe follicles in every case. Morris records the case of onset of menstruation in an infantile uterus after grafting of an ovary from another individual. It is, however, difficult to believe that menstruation could occur with anything like normal periodicity in a congenitally small uterus. Heape believes that the occurrence of "heat" is due to the presence of a generative ferment periodically present in the blood. He believes that another substance, "gonadin," is also present and has a specific action, but what the relationship of these to one another is as yet unknown. It may be taken as accepted by the majority of observers that the ovary secretes a substance or substances whose chemical characters are unknown, the secretion being poured into the general circulation at periodic intervals. The periods vary according to the different species of mammals. This secretion has a specific action upon the uterine and tubal mucosa causing a breaking down of blood vessels, diapedesis, and exfoliation of epithelium. A hæmorrhagic discharge takes place from the mucosa containing the metabolic elements which are unnecessary for the implantation of the fertilised ovum. Menstruation is therefore a manifestation of metabolic processes and the uterus is an organ for the excretion of these products which have their origin in the ovary. This explains the general constitutional disturbances which are present in cases of scanty menstruation or when menstruation is in abeyance as in amenorrhœal conditions associated with insanity of

a toxæmic origin. The ovary gives rise to a condition of toxæmia which under normal conditions is not noticeable owing to elimination taking place by means of the uterine hæmorrhagic discharge. As menstruation is due to the internal secretion of the ovary it may be asked which part of this organ is most concerned in its production? Most authorities agree as to the corpus luteum being the most important factor. Fränkel found that after cauterization or removal of the corpus luteum the next period was missed. Marshall denies that the corpus luteum is necessary for the onset of menstruation as ovulation in most animals does not occur until œstrus or at the end of the pro-œstrous period, *i.e.*, before corpora lutea are present in the ovaries. Heape found no corpora lutea in some of the ovaries of menstruating monkeys.

Influence of ovarian secretion upon pregnancy and lactation.

Histological examination of ovaries removed during pregnancy show enlargement of the interstitial cells and development of the corpus luteum, this points to some increased functional activity on the part of these tissues. It is, however, generally believed that the ovaries are quiescent during pregnancy. Halban found as proof of this that the long bones show increase in length in young women during pregnancy. There is frequently increased deposit of fat during this period. Fränkel's experiments, however, contradict this belief and point to the activity of the corpus luteum which has a trophic influence upon the nutrition of the ovum in the early stages of pregnancy. Marshall and Jolly confirm these experiments. Loeb removed the corpora lutea in later pregnancy and found that regeneration took place in these tissues. He carried out a series of experiments upon recently fertilised rodents by mechanical stimulation of the uterine mucosa. This was followed by the appearance of decidual nodules in the uterus. If the corpora lutea were removed by cauterization or excision prior to the experiment no decidual reaction took place, thus showing the influence of the corpus luteum upon decidual formation. It may be taken as accepted that the corpus luteum is an essential factor in maintaining the raised nutrition of the uterus during early pregnancy and ultimate nutrition of the ovum (Vincent).

Clinically we find a correlation between the corpus luteum and decidual tissue in cases where lutein cysts are found in connection with syncytioma. The corpus luteum acts as a ductless gland with an internal secretion having an influence upon metabolism and upon the nutrition of the ovum in the uterus. Any interference with the trophic influence of this secretion causes separation of the ovum from its uterine attachment in the early stages of pregnancy. If fertilisation does not take place it is found that the corpus luteum degenerates and forms a scar.

Cases of repeated or so-called habitual abortion may be explained by the occurrence of some pathological changes in the corpus luteum, but this is still a matter only of theory. It is said that the application of *x*-rays to the ovaries during pregnancy does not cause abortion, and as these rays have a specific action upon the follicles of the ovary, it is still a matter of doubt how far the interstitial cells have to be considered with regard to their trophic influence upon the ovum. The persistence of the corpus luteum during pregnancy is held to be a factor in the prevention of the occurrence of ovulation and menstruation, but clinically cases of menstruation during early pregnancy are not infrequent. Also examples of superfœtation have been observed among animals. The view that the persistence of the corpus luteum prevents the onset of "heat" in animals receives support from the fact that agriculturists are able to induce "heat" by manipulating the ovary of young cows through the rectum and expelling the corpus luteum. This is followed by œstrus and fertilisation.

Lactation.

That the ovaries have an influence upon the development of the mammæ is seen from the enlargement of the breasts at puberty. These glands become enlarged frequently before the onset of and during menstruation—the period when ovarian activity is at its height. Congenital absence of the ovaries is as a rule accompanied by deficient mammary development; and castration of young animals prevents the growth of these organs. Atrophy of the mammæ takes place after oöphorectomy in adults and after the menopause. The occurrence of these changes after castration can be prevented by the transplantation of ovarian tissue to different situations. It must therefore be admitted that the ovaries have a marked influence upon the nutrition of the mammary glands by means of their internal secretion which acts irrespective of their vascular or nervous connections. The mammary glands enlarge during pregnancy and secrete milk after parturition has taken place. What this enlargement is due to is still a matter of controversy. Foges believes that the ovary causes development of the mammæ but has no influence upon the secretion of milk, this secretion taking place when the ovaries are in a quiescent state.

What is the important factor in the production of mammary secretion? This is still unproved. Lane-Clayton and Starling carried out some experiments by injecting fœtal extracts into virgin rabbits and obtained increased growth of mammary tissue. They concluded that the fœtal tissues produce a hormone which excites mammary growth and secretion. Foa found similar results with injections of fœtal tissues from one species of an animal to another. Heape found that milk secretion can take place in virgin animals,

and that it can occur apart from pregnancy without the stimulation of fœtal tissues. He supposes that the stimulation has its origin in the ovary. Vincent points to the corpus luteum as an essential factor and quotes O'Donoghue, who states that the mammæ enlarge in proportion to the growth of the corpus luteum and concludes that the corpus luteum is "intimately connected if not indeed the exciting cause of the growth of the mammary gland" (p. 85).

Ancel and Bouin found in rabbits that when copulation took place with a sterilized male the corpus luteum was enlarged and also the mammæ. This enlargement persisted for some days and then regression occurred, showing the dependence of mammary growth upon corpus luteum development. They believed that the corpus luteum secretion has an influence upon mammary growth but that the secretion of milk depends upon the presence of specialized glands in the uterus. Cases of mammary secretion occurring in males and in new-born children contradict the theory that the phenomenon is due to the presence of fœtal tissue secretion. That ovarian secretion is suppressed during lactation is negatived by those cases of menstruation occurring during lactation. In some such cases it is found on enquiry that during menstruation there is evidence in the child of derangements of metabolism, viz., diarrhœa and vomiting, showing that some products of ovarian secretion are in circulation in the tissues by means of the blood and that they have the mammæ as a channel of excretion in addition to that of the uterine mucosa. The corpus luteum of pregnancy is said to persist during lactation (Watson).

Maniger records a case of lactation after full term pregnancy in a patient the subject of double oöphorectomy, showing that it can occur apart from ovarian influence. Milk secretion can be augmented by the administration of various organ extracts such as infundibular extract (Mackenzie). It is doubtful, however, whether these administrations only cause a temporary stimulation of the mammary ducts by giving rise to muscular contraction. It is seen that little is known with regard to the etiology of mammary secretion and much research is wanted in order that definite conclusions may be reached.

Function of the various constituents of the ovary.

The ovary may be divided into three constituents as far as functional activity is concerned—the Graaffian follicle, the corpus luteum and the interstitial cells. Much controversy has arisen over the origin of these tissues, but it is now generally accepted by most workers on the subject that they have a common origin in the early germ cells or oögonia (Waldeyer, von Winiwarter, Skrobansky), and that the stroma is only vascular and supporting in its function. Some authors (Clark, Wendeler) maintain that the follicle cells are

connective tissue in origin. The views on the subject of this controversy are fully referred to in a paper published by me in 1910. The Graaffian follicles in the majority of mammals are present in the ovary before birth and their chief function is concerned with the production of oöcytes. These follicles develop later, rupture with extrusion of the oöcyte causing the phenomenon of ovulation to take place. The cause of rupture further than that of increased intra-follicular tension is unknown; according to Clark it is due to circulatory changes with engorgement of blood in the ovary, the increased intra-ovarian tension forcing the oöcyte to the surface. A further development of the follicle takes place by the formation of lutein tissue in its walls with hæmorrhagic infiltration—the corpus luteum. The follicle therefore is engaged in the production of the oöcyte, and the lutein tissue has a trophic effect upon the nutrition of the ovum and the metabolism of the organism as a whole. There is still uncertainty as to which part of the ovary is most concerned with the production of an internal secretion. In transplanted ovarian tissue it has been found that follicular growth in the grafts prevents the onset of atrophy of the uterus.

The *interstitial* cells are distinguished from the stroma cells by their larger size and more oval-shaped nuclei. They increase in size during pregnancy (Lane-Clayton, Wallart and Seitz) and during the œstrous season, being small in size in the anœtrous state (Regaud and Dubreuil). Wallart found the interstitial cells to be most marked between infancy and puberty; he found enlargement during pregnancy and menstruation and in association with syncytial tumours. He found that these cases were atrophied after the menopause. Cohn thinks that these cells resemble lutein cells and those of the suprarenal cortex, and that they are secretory in function. In my own experiments I confirmed those of Limon who found that the presence of interstitial cells in grafted tissue was sufficient for the maintenance of uterine nutrition. It is a matter of controversy whether these cells act in conjunction with the follicles and corpora lutea, or are antagonistic to them. It is most probable that the ovary elaborates more than one internal secretion and that the interstitial cells are responsible for part of this secretion, but the nature of such secretion or secretions is still unknown. If one ovary is removed the remaining organ becomes hypertrophied and takes on the function of both. In the microscopic examination of such an organ the interstitial cells are found to be increased in size and number. It is possible that the interstitial cells are concerned with the nutrition of the genital organs and their cyclic changes; and that the corpus luteum secretion has an effect not only upon the developing ovum but upon the metabolism as a whole. Bouin and Ancel maintain that the interstitial cells of the testes have a marked secretory function and influence the secondary sexual characters.

They injected interstitial cell tissue and modified the effect of castration upon guinea-pigs.

The *corpus luteum* is formed subsequently to rupture of the follicle. The origin of the lutein cells is still controversial. Some observers maintain that they are derived from the theca interna and are therefore of the nature of connective tissue (Kölliker, Nagel, Clark, Whitridge Williams). Others claim that they have a common origin with the oögonia (Sobotta, Marshall, Cohn, Fränkel). According to Heape the corpus luteum is formed by ingrowths of cells surrounding the follicles together with the follicular epithelium. Loeb believes that they are derived both from connective tissue and from epithelium. If fertilisation does not take place after rupture of the follicle degeneration of the corpus luteum gradually occurs. On the other hand if fertilisation does take place there is persistence of the corpus luteum and increase in size.

The corpus luteum of pregnancy is therefore a further stage in development from that occurring during menstruation. Prenant first drew attention to the corpus luteum as a ductless gland having an internal secretion, stating that it prevents ovulation during pregnancy and influences the general metabolism. In this view he is supported by Regaud and Dubreuil. The corpus luteum was formerly supposed to preserve the circulation of the ovary and thus prevent the formation of excessive scar tissue, but in view of more recent investigations upon the function of this organ it may be accepted that its function is much more complex. It is more probable that the interstitial cells have an influence over the nutrition of ovarian tissue. Fränkel's experiments showed that the corpus luteum has a secretion which controls the vascular supply of the uterus and determines the occurrence of menstruation. In addition it has an important function in causing changes to take place preparatory to the embedding of the ovum in the uterine mucosa, and the maintenance of the developing embryo until at least the formation of the placenta is completed. It therefore has a trophic influence upon the fertilised ovum. His conclusions were based upon experiments for removal of the corpus luteum by excision or cautery in rabbits at various stages of pregnancy. In early pregnancy abortion invariably took place. In women removal of the corpus luteum prevented the onset of the next menstrual period. In extra-uterine pregnancy changes occur in the uterine mucosa which must be due to some influence outside the uterus and not to the ovum alone. Pathological changes occurring in the ovum such as syncytioma are frequently accompanied by lutein cysts in the ovary. Skrobousky does not support the theory that the corpus luteum prevents ovulation from taking place during pregnancy. He is therefore in agreement with Prenant. Marshall and Jolly conclude that after ovulation which has taken place during œstrus, the

corpus luteum is formed and that this organ elaborates an additional secretion which is responsible for the embedding and early nutrition of the ovum in the uterus. Vincent, in discussing the function of the corpus luteum, makes the observation that "heat" in animals cannot be induced by an internal secretion from the corpus luteum since ovulation in dogs and most mammals normally takes place during œstrus, and that therefore no fully formed corpora lutea are to be found in the pro-œstrous period. He concludes that "heat" is brought about by an internal secretion of the ovary and not of the corpus luteum. Loeb thinks that the corpus luteum secretes a fluid which sensitizes the uterine mucosa and is concerned in the embedding of the ovum and formation of the placenta. Rebaudi regards the corpus luteum as the most important if not the only element in the internal secretory function of the ovary. The experiments of Fränkel have been confirmed subsequently by numerous other observers (Daels, Kleinhaus and Schenk). Marshall contends that "heat" occurs in many animals at infrequent intervals, and in some animals since ovulation only takes place at the œstrous period, there are no corpora lutea in the pro-œstrous period. Fränkel's experiments with regard to menstruation are inconclusive. Records of cases in which after oöphorectomy in the early months pregnancy went on without interruption, are to be taken as doubtful, the explanation of such cases being most probably that a portion of an ovary had been left behind. Ancel and Bouin found hypertrophy in the uterine mucosa of rabbits in which ovulation had taken place without fertilisation. In Loeb's experiments for stimulation of the uterine mucosa in the presence of corpora lutea in the ovary, if a piece of the uterus was grafted elsewhere nodules appeared in the mucosa of the engrafted tissue, showing that the corpus luteum had an effect without the presence of a fertilised ovum in the uterine wall. It must be remembered in those experiments for excision or cauterisation of the corpus luteum that most probably there was some interference with the function of the interstitial cells at the same time and it is difficult to formulate conclusions as to the function of the corpus luteum alone. It has been observed that the lutein cells closely resemble those of the cells of the suprarenal cortex, and that these latter cells are subject to cyclic changes, enlarging during the sexual seasons and during pregnancy (Kolmer). That the suprarenal cortex is intimately connected with the secondary sexual characters is shown by the changes which occur in the presence of tumours of this region with precocious sex development and aberrations (Glynn).

Effect of transplantation of ovarian tissue.

It is now accepted that the ovary takes on its normal functional activity when transplanted to other situations, and that it continues

to grow and produce ova which are capable of fertilisation (Knauer). Cases of pregnancy in women following transplantation have been recorded (Morris). Halban, in young guinea-pigs previously castrated, found that ovarian grafts caused uterine and mammary development. The occurrence of atrophy after oöphorectomy has been prevented by transplanting ovarian tissue (Marshall and Jolly, Ribbert, Carmichael and Marshall, Grigorieff). Some of these authors found that ovulation occurred in the grafted tissues with formation of corpora lutea. In monkeys menstruation ceases after oöphorectomy, but it has been known to become re-established after transplantation of ovarian tissue. Œstrus takes place in rabbits in which grafts have been made (Nattrass). Most authors agree, however, that a certain amount of degeneration takes place subsequently in the grafted tissue. The presence of follicles seems to be the essential factor in the promotion of uterine activity, but it is questionable whether the interstitial cells do not play an equally important part in the maintenance of the nutrition of the other genital organs. Steinach grafted ovaries subcutaneously into young male guinea-pigs previously castrated. These animals subsequently developed female characters such as enlargement of the mammæ and changes in the skeletal structures. His results point to a specific action on the part of the secretion from the male and female gonads. Tuffier gives his clinical experience of ovarian grafting in 130 cases. He found that the grafts were of most value in the prevention of the onset of menopausal symptoms after oöphorectomy if the uterus was not removed, and he argues from this that the ovary is a link in the chain between the uterus and a toxin in the blood causing ovulation, and that elimination takes place by means of the uterine mucosa. Menopausal symptoms were more pronounced if the uterus were removed with the ovaries. In the subsequent discussion on his communication the opinion was expressed that ovarian grafts were of little value unless part at least of the uterus were left behind. This will be accepted when it is understood that the uterus is a channel for the excretion of metabolic products, and that it exercises this function when the ovarian tissue is present in the form of grafts which give rise to substances in the blood of the same nature as those which normally are to be eliminated by the uterine mucosa. Autoplastic grafts are more successful than those from another animal. Transplantation from animals more akin to each other are also more successful than non-related animals. Grafts succeed best when implanted into vascular structures such as the kidney or spleen, although in the human female it is found that the abdominal wall is the most suitable site, being easy of access for removal of the graft should any subsequent disturbance arise such as pain or suppuration. Guthrie's varied experiments upon fowls show the influence of ovarian grafts upon the offspring. It is to be concluded that the

presence of ovarian tissue in the normal situation or elsewhere causes development of the genital organs and mammæ; and that in cases of tissue transplanted after castration atrophy of these organs is prevented and their functional activity is maintained. That the ovary is an organ with an internal secretion independent of its vascular or nervous supply is proved by the physiological activity of grafted tissue. Premature menopausal symptoms occurring after oöphorectomy may be prevented by the transplantation of ovarian tissue into other regions of the body, and although these frequently degenerate later, they are of benefit in that they modify the severity of the symptoms which accompany the removal of both ovaries.

Ovarian extracts.

Since the work of Brown Séquard upon testicular and ovarian extracts, which was published in 1889, much attention has been paid to the effect of glandular extracts and their therapeutic value in disease. The results of medication by ovarian extracts are contradictory. One finds that ovarian extracts have not gained a valuable place in therapeutics when one compares the results with those given for extracts of the other internal secretory organs such as the suprarenals. Various methods of administration have been advocated, such as dried and powdered ovarian tissue as a whole, fresh tissue, fluid extracts—aqueous or alcoholic—of the ovary at various periods of functional activity, also extracts of the corpus luteum alone. Administration by the mouth, rectum, or hypodermically has been tried. Much depends upon the mode of preparation of the extract and upon the active condition of the ovaries themselves. The best results have been obtained in those cases in which the menopause has been surgically produced (Krusen). Various authors advocate ovarian extracts for menopausal symptoms, amenorrhœa or chlorosis. Obesity has been said to have improved by the administration of ovarian extract (Bucura). Fränkel is of the opinion that the corpus luteum is the only part of the ovary which has any therapeutic value, and this is confirmed by Morley's results. Numerous experiments have been performed with a view to ascertaining the physiological influence of ovarian extracts. Marshall and Jolly produced transient signs of "heat" in anœstrous animals by injections of ovaries from œstrous animals. Extracts from quiescent ovaries gave negative results.

Della Chiaje caused fatty degeneration of the ovaries by injecting serum from castrated animals, but his experiments seem to be complicated by other factors. Blair Bell and Hick experimented upon the degrees of contractility of the uterus after injections of fresh extracts of sheeps' ovaries. There was no effect in the quiescent uterus, but in the menstruating or pregnant uterus there was a marked result. It is said that ovarian extracts should not be

administered to pregnant women owing to their toxic effects.

The results of the administration of ovarian extracts upon metabolism are contradictory. It is said that corpus luteum extracts when given to castrated animals prevent atrophy of the genital organs but this is denied by some (Carmichael and Marshall). In spite of Bucura's results there is still some doubt as to the unfailing influence of ovarian extracts upon obesity and upon the excretion of lime salts. Ott and Scott found that corpus luteum extracts caused a fall of blood pressure which was followed by a transient rise. They also stimulated intestinal peristalsis and increased mammary secretion, but had no influence upon diuresis. According to these authors the corpus luteum has more influence than the other parts of the ovary. In some of my own experiments I found that corpus luteum extracts had an effect in raising blood pressure.

Influence of ovarian secretion upon metabolism.

That the secretion of the ovary has an effect upon the metabolism of the organism as a whole is evidenced by the constitutional disturbances which arise during menstruation and at the menopause. We are, however, still ignorant of the nature of this influence or to what extent it may act. Numerous observations have been made in regard to the changes which take place after removal of both ovaries, but the results are very contradictory and in many cases the experiments are incomplete and therefore of little value. Some information as to the influence of the ovaries has been obtained from analogous experiments upon male animals since in all the internal secretion of both types of reproductive organ has a similar influence upon metabolism.

The chief means of estimating the metabolic changes which take in an organism are by observations upon the growth and nutrition of the animal, the respiratory interchanges, the deposit of fat, and the excretion of nitrogen, calcium and phosphorus. These are best observed experimentally in their relationship to ovarian function by noting the conditions present before and after castration, before puberty and during reproductive life. Estimations upon the metabolism at puberty or the menopause are difficult to carry out owing to the length of time which these changes of condition occupy, more especially in the human female. Thus our information is mainly derived from experiments upon laboratory animals, and as these differ according to the species employed it is easily seen how records may be fallacious unless sufficient proof is brought forward of similar processes occurring in other groups of animals.

Growth of bone. In eunuchs there is increased length of the long bones due to longer persistence of the epiphyseal cartilages, verified by skiagraphs. This has been observed also in cattle, dogs, fowl (Sellheim, Launois and Roy, Tandler and Gros). No reliable

information has been obtained as to the changes which take place after oöphorectomy in girls before puberty. It is said in the human male that the secondary sexual characters are frequently undeveloped after castration before puberty and that mental deficiency is sometimes present. In women where there is early maturity of the genital organs, shortening of the long bones has been sometimes noted due to premature ossification of the epiphyseal cartilages. In delayed reproductive development in girls lengthening of the bones may be present. In view of the records given by Glynn we cannot lay stress upon the influence of the ovaries alone as so many factors connected with the secretion of the other ductless glands and their influence upon reproductive development claim consideration. This must especially be remembered when dealing with the question of osteo-malacia.

General nutrition and deposit of fat. It is stated that castration has no effect upon the growth and general nutrition of rodents (Carmichael and Marshall). Castration is largely made use of by agriculturists in the rearing of cattle and fowls for market purposes as there is increased deposit of fat. It is questionable whether the fat deposit is due to diminished oxidation of the tissue cells or to diminished energy on the part of the animal. In women obesity is frequently observed after oöphorectomy and at the menopause and also in such conditions of scanty menstruation or amenorrhœa occurring in comparatively young women where ovarian function has become diminished. It is said that after oöphorectomy or after the menopause obesity is observed in 42 to 52 per cent. of women (Biedl). Animals become fatter during pregnancy, and this fact is made use of by farmers by having their animals in better condition for market in early pregnancy than at any other time.

Respiratory quotient. van Noorden tabulates the records of observations upon gaseous interchanges, the majority of which show a diminution in castrated animals, these animals were found to be less active than the controls. Loewy and Richter found increased gaseous interchanges on feeding with ovarian substance, they diminished on withdrawal of the gland administration. After castration metabolism was reduced, the respiratory quotient being diminished 14 to 20 per cent. per kilo of body weight. They think this is due to diminished processes of oxidation. These results were not confirmed by others (Luthjé, Paechtner).

Nitrogen. van Noorden found no change in nitrogen metabolism after castration, and the results of other workers are contradictory. Schrader found retention of nitrogen immediately before and during menstruation. Lüthjé, Neumann and Vas found no change after castration.

Calcium and phosphorus. The results of observations are very inconclusive. Curàtulo and Tarulli found retention of earthy phos-

phates after castration. Neumann found slight loss P_2O_5 and Ca as increased excretion in the fæces after feeding with ovarian substance. McCrudden found no retention of mineral salts after castration. In osteo-malacia Fehling maintains that the removal of the ovaries causes a diminished excretion of lime salts. This, however, has been called in question of late years owing to the results of calcium metabolism with regard to other ductless glands. It is therefore probable that the thyroid and parathyroids may also be involved in the production of this disease. Bossi is of opinion that the adrenals are also involved. Wallart found increase in size of the interstitial cells of the ovary in osteo-malacia although all other observers have denied the existence of any apparent histological changes. In the discussion of this disease Biedl is of the opinion that there are other internal secretory organs concerned in its production. Blair Bell has found increased calcium in the blood during menstruation. As a result of examination of menstrual and hæmatocolpos fluid there is an increased calcium content when compared with systemic blood. This author affirms that a low calcium content in the blood is due to diminished genital function and he advises the therapeutic use of calcium salts in these conditions. It is highly probable that there is a relationship between the calcium metabolism and ovarian secretion but secretions of other ductless glands have also to be considered. The calcium index may be of value as indicative of the presence of ovarian ferments in the circulation.

Blood. Chlorosis has always been associated with diminished ovarian function, but as yet there is no experimental evidence in proof of this. Some workers have found diminished hæmoglobin after castration, others obtained no change. Villemin considers chlorosis to be a toxæmia due to retention of the internal secretion of the corpus luteum. It is admitted that many cases of metrorrhagia are due to derangements of the internal secretion of the ovary (Hitschmann, Adler, Blair Bell). Adler tried to determine the rate of coagulation of blood in women having menstrual disorders by Wright's method. He found retardation in cases of diminished ovarian function, coagulation being delayed for three minutes or more. In experiments on animals before and after castration, coagulation was found to be retarded after the operation. Adler concludes that ovarian secretion has a direct influence on coagulation of the blood by means of the calcium salts. Early maturity associated with small stature due to want of fixation of calcium in the organism may also have its origin in ovarian secretion.

Nervous system. That ovarian secretion has a marked influence upon the sympathetic nervous system is well known. Neuroses are observed at puberty, during menstruation and at the menopause as evidenced by headache, fainting fits, etc. In some mental pathological conditions ovarian secretion has an effect in aggravating the

symptoms. In toxæmic conditions associated with menstruation reflex disturbances such as vomiting sometimes occur.

Skin. Dermatologists are well aware that many skin affections in women are aggravated at the onset of menstruation. Changes in the skin occur also at puberty, during pregnancy and at the menopause.

It is seen on a review of the work done upon metabolism and ovarian secretion that the data are very unreliable and that much work has to be done in this direction. So many statements have to be confirmed or refuted by further research, such as the calcium metabolism, also much work will have to be done upon the blood changes which take place during reproductive cycles, not only microscopically but chemical especially in regard to the serum changes which occur. In this way it may be possible to ascertain the presence of toxines or ferments generated by the ovary and circulating in the blood.

Internal secretion of the uterus.

It has been stated that many of the results of oöphorectomy are due to interference with the vascular or nervous supply of the uterus, and that it is the uterus which maintains the nutritional activity of the genital organs. This theory has not been proved by any direct experimental evidence. Zweifel and Abel maintain that if the uterus is entirely removed atrophy of the ovaries takes place and menopausal symptoms occur. If the uterine mucosa is left in position menstruation may continue, so that the functional activity of the ovaries depends upon the uterus. Doran quotes two cases of menstruation occurring after oöphorectomy. Mandl and Bürger believe that after hysterectomy the ovaries degenerate. Blair Bell asserts that menstruation and ovulation are dependent upon the internal secretion of the uterus. Bond thinks that the secretions of the uterus and ovaries are mutually antagonistic, and that removal of uterine secretion by hysterectomy causes hypertrophy of the ovaries. Carmichael and Marshall carried out a series of experiments in which they removed the uterus in rabbits but found no subsequent change in the ovaries. In their experiments upon the effect of oöphorectomy they found that uterine atrophy occurred in every case. These conclusions I confirmed by a series of experiments upon rabbits and found no change after hysterectomy, formation of follicles and corpora lutea taking place normally. Clinically it has been observed that the menopausal symptoms after oöphorectomy are less severe if the uterus or a portion of the uterus is left *in situ*, but this is explained by the theory that the uterine mucosa is the main channel for the excretion of metabolic products which owe their origin to the stimulation from the internal secretion of the ovary. That the uterus has a direct effect upon the ovaries themselves there is no evidence experimentally.

SUMMARY.

The ovary has a dual function—the production of ova, and the elaboration of an internal secretion or secretions. It is of the nature of a ductless gland, carrying out its function independently of its vascular or nervous supply.

The ovary controls the nutrition of the genital organs and mammæ. Removal of both ovaries before sexual maturity causes an arrest in the development of the genital organs and mammæ, prevents the onset of menstruation or pro-œstrum. The infantile type is maintained and the secondary sexual characters are not well marked. Retardation of the ossification of the long bones has been observed. There is no effect upon the growth and general nutrition (Carmichael and Marshall).

Removal of both ovaries after sexual maturity causes atrophy of the genital organs and mammæ, cessation of menstruation or pro-œstrum, and increased deposit of fat. Removal is frequently followed by certain nervous phenomena characteristic of the menopause.

Removal of both ovaries during early pregnancy causes abortion to take place.

Removal of one ovary causes compensatory hypertrophy in the remaining organ independent of pregnancy or œstrus. Abortion does not take place as a consequence of removal of one ovary.

The corpus luteum is concerned with the embedding and nutrition of the ovum and with metabolism. It controls the blood supply of the uterus. The interstitial cells are increased in size during pregnancy and œstrus and are concerned with the nutrition of the genital organs and the internal secretion of the ovary.

Transplantation of ovarian tissue after castration prevents the occurrence of atrophy in the genital organs and the cessation of menstruation.

Menstruation depends entirely upon the presence of ovarian tissue. It is a preparation on the part of the uterine and tubal mucosa for the reception of a fertilised ovum and corresponds to the period of pro-œstrum in animals. The menstrual discharge is the evidence of metabolic processes by means of which some unknown chemical substances are eliminated from the organism. Menstruation begins at puberty, and ceases at the menopause when the ovaries become atrophied. It ceases after removal of both ovaries, but can be made to recur by transplanting ovarian tissue into another situation. The correlationship between menstruation and ovulation is unknown.

The nutrition of the uterus is dependent upon the presence of ovarian tissue. Removal of uterine secretion has no effect upon the ovaries.

Ovarian extracts have been found of use in the treatment of

chlorosis, amenorrhœa, obesity and menopausal symptoms. Much depends upon the condition of the ovaries from which the extracts are prepared and the mode of preparation. Most clinicians agree that the extract of the corpus luteum has the most therapeutic value.

Information as to the influence of ovarian secretion upon metabolism is as yet unreliable. Ovarian secretion is said to prevent the onset of obesity, and to increase the respiratory interchanges. Most observers agree as to no change occurring after castration in the nitrogen metabolism. Several authors maintain that the ovaries have a marked influence upon the excretion of calcium (Blair Bell).

Retardation of the coagulation period of blood has been found in diminished ovarian function (Adler).

BIBLIOGRAPHY.

Adler. *Archiv. f. Gyn.*, xcv, 1912.
Ancel and Bouin. *Compt. Rends. Soc. de Biol.*, lxv, 1908. *Journ. de Phys. et Path. gén.*, xii, 1910.
Andrews-Russell. *Journ. of Obst. and Gyn. of Brit. Emp.*, 1904.
Biedl. "Innere Sekretion," 1910.
Bischoff. Quoted by Biedl.
Blair Bell. *System of Gynæcology*, 1910. *Proc. Roy. Soc. Med.*, 1911.
Blair Bell and Hick. *Brit. Med. Journ.*, 1909.
Bond. *Brit. Med. Journ.*, 1906.
Bossi. *Brit. Med. Journ.*, 1908.
Brown Séquard. *Compt. Rends. Soc. de Biol.*, 1889.
Bucura. Quoted by Biedl.
Carmichael and Marshall. *Proc. Roy. Soc. B.*, vol. lxxix, 1907. *Journ. of Phys.*, xxxvi, 1907—1908.
Clark. *Johns Hopkins Hosp. Rep.*, vii, 1898.
Cohn. *Archiv. f. Gyn.*, lxxxvii, 1909.
Cieratulo and Tarielli. *Centralbl. f. Gyn.*, xix, 1895.
Daels. *Surg., Gyn. and Obst.*, vi, 1908.
Della Chiaje. *Rev. de Gyn. et de Chir. Abd.*, xvi, 1911.
Doran, Alban. *Trans. Lond. Obst. Soc.*, 1905. *Journ. of Obst. and Gyn. of Brit. Emp.*, 1902.
Fehling. *Archiv. f. Gyn.*, xxviii, 1890; xxix, 1891.
Fränkel. *Archiv. f. Gyn.*, lxviii, 1903; xci, 1910. *Zeitschr. f. Geb. u. Gyn.*, lxiv, 1910.
Foa. Quoted by Vincent.
Foges. *Münch. med. Wochenschr.*, liv, 1907.
Grigorieff. *Centralbl. f. Gyn.*, 1897.
Glynn. *Quart. Journ. of Med.*, v, 1912.
Guthrie. *Journ. of Exper. Med.*, Lancaster, Pa., xii, 1910. *Journ. of Exper. Zool., v*, 1908.
Halban. *Centralbl. f. Gyn.*, xxv, 1901.
Heape. *Proc. Roy. Soc.*, lxxvi, 1905. *Quart. Journ. of Microscop. Sci.*, xliv, 1900. *Phil. Trans. Roy. Soc. B.*, clxxxviii, 1897.
Hitschmann. Quoted by Adler

Hofmier *Zeitschr. f. Geb. u. Gyn.*, vol. v. Quoted by Marshall.
Keller. *Monat. f. Geb. u. Gyn.*, xxxiv, 1911.
Kleinhaus and Schenk. *Zeitschr. f. Geb. u. Gyn.*, lxvii.
Kuaner. *Centralbl. f. Gyn.*, xx, 1896. *Archviv. f. Gyn.*, lx, 1900.
Kölliker. Quoted by Biedl.
Kolmer. *Pflüger's Archiv.*, cxliv., 1912.
Krusen. *Bull. Johns Hopkins Hosp.*, xii, 1901.
Lane-Clayton. *Proc. Roy. Soc.*, lxxxvii, 1906.
Lange. *Münch. med. Wochenschr.*, 1903.
Launois and Roy. Quoted by Vincent.
Limon. *Journ. de Phys. et de Path. gén.*, vi, 1904.
Loeb. *Journ. Amer. Med. Assoc.*, 1908. *Anat. Anz.*, xxvii, 1906.
Loewy and Richter. Quoted by Van Noorden.
Luthjé. Quoted by Van Noorden.
Mandl and Bürger. Quoted by Marshall.
Marshall. " Physiology of Reproduction," 1910.
Marshall and Jolly. *Phil. Trans. Roy. Soc.*, cxcviii, 1906.
McCrudden. *Journ. Biol. Chem. Balt.*, vii, 1910.
Mackenzie. *Quart. Journ. Exp. Phys.*, iv, 1911.
McIlroy. *Proc. Roy. Soc. Edin.*, xxxi, 1910. *Proc. Roy. Soc. Med. Lond.*, v, 1912.
Morley. *Journ. Mich. Med. Soc.*, Detroit, viii, 1909. *Journ. of Obst. and Gyn. Brit. Emp.*, xvii, 1910.
Morris. *New York Med. Record*, lxix, 1906.
Nagel. *Arch. f. Mikv. Anat.*, xxxi.
Nattrass. *Report of Phys. Lab. of Melbourne Univ.*, 1910.
Neumann. *Arch. f. Gyn.*, li, 1896; xlvii, 1892.
Neumann and Vas. *Monat. f. Geb. u. Gyn.*, xv, 1902.
Noël Paton. *Journ. of Physiol.*, xxxii, 1905.
O'Donoghue. Quoted by Vincent.
Ott and Scott. *Contrib. fr. Phys. Lab. of Med. Chir. Coll. of Philadelphia*, 1912.
Paechtner. Quoted by Biedl.
Pflüger. " Ueber die Eierstöcke der Sangetiere und des Menschen," Liepzig, 1863.
Prenant. Quoted by Vincent.
Pozzi. *Ann. de Gyn. et d'Obst.*, 1905.
Rebaudi. *Centralbl. f. Gyn.*, xli.
Regaud and Policard. *Compt. Rend. de Soc. de Biol.*, liii, 1901.
Regaud and Debreuil. *Compt. Rend. de Soc. de Biol.*, lxvi, 1909.
Ribbert. Quoted by Marshall.
Schrader. *Arch. f. Gyn.*, lx, 1900.
Shrobansky. *Arch. f. mikv. Anat.*, lxii. 1903. *Münch. med. Wochenschr.*, 1913.
Schultz. *Central. f. Allg. Path. u. Path. Anat.*, xi, 1900.
Sellheim. Quoted by Biedl.
Sokoloff. *Arch. f. Gyn.*, l, 1896.
Sobotta. *Anat. Anz.*, x, 1895. *Archiv. f. mikv. Anat.*, xlvii, 1897.
Starling. " Croonian Lectures," 1905. *Proc. Roy. Soc.*, lxxxvii, 1906.
Steinach. *Pflüger's Archiv.*, cxliv, 1912.
Strassmann. *Arch. f. Gyn.*, lii.
Tandler and Gros. *Wien. klin. Woch.*, lxxxvii, 1908.
Tuffier. *Rev. de Gyn. et de Chir. Abd.*, xviii, 1912.

Van Noorden. "Metabolism and Practical Medicine," *Trans. Walker Hall*, 1907.
Vincent. "Internal Secretion and the Dualler's Glands," 1912.
Villemin. *Compt. Rend. de Soc. de Biol.*, lxiv, 1908.
von Winiwarter. *Arch. de Biol.*, xvii, 1901.
Waldeyer. "Eierstocke und Ei," 1870.
Wallart. *Zeitschr. f. Geb. u. Gyn.*, lxi, 1908.
Wallart and Seitz. Quoted by Biedl.
Watson. *Journ. of Physiol.*, xxxiv, 1906.
Wendeler. Martin's "Die Krankeiten des Eierstocks u. Nebeneierstocks," 1899.
Whitridge Williams. *Obstetrics*, 1912.
Zweifel and Abel. *Zentral. f. Gyn.*, xxiii, 1899.