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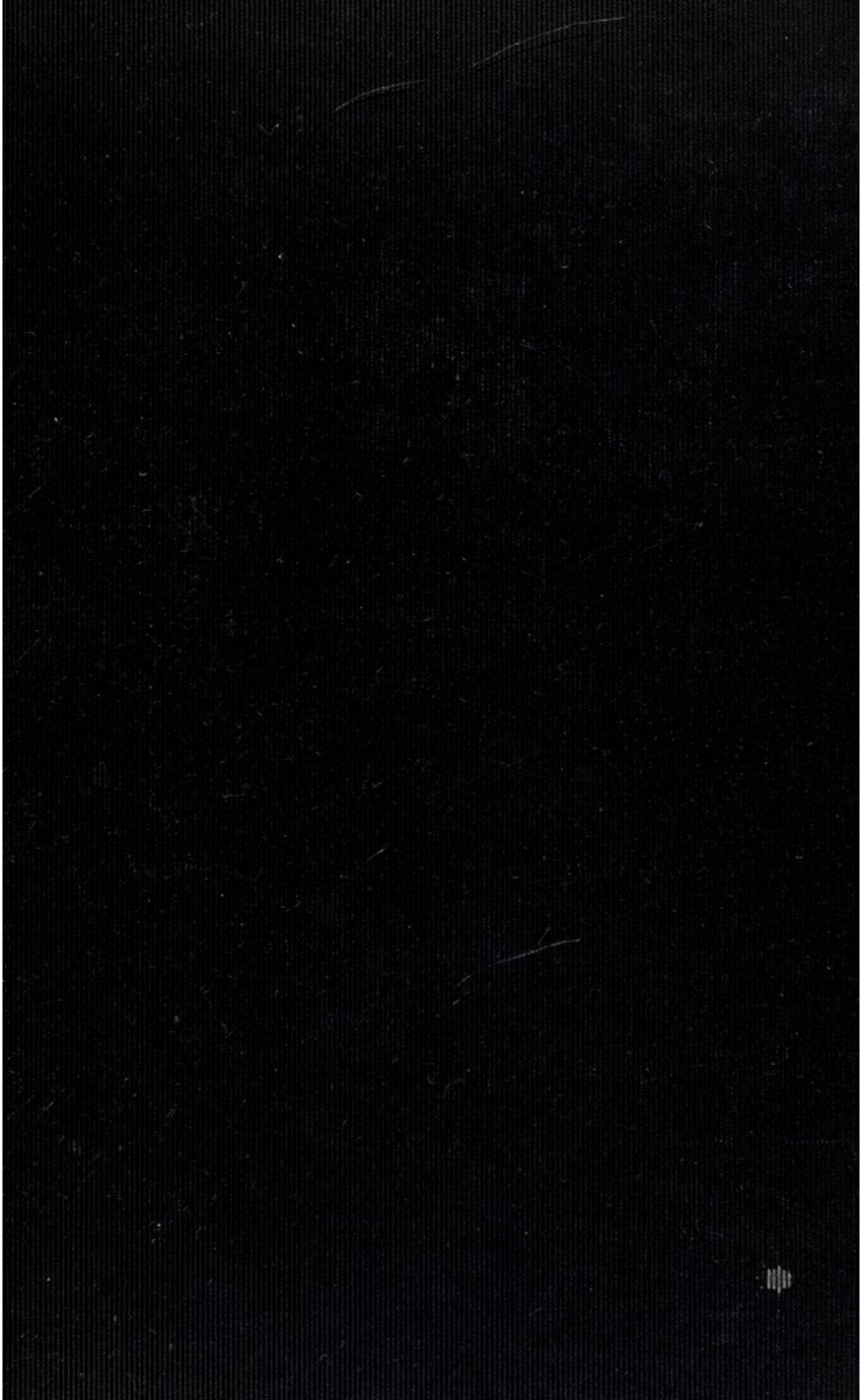https://wellcomecollection.org/works/xzvfbg4u

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THE SEX COMPLEX

A STUDY OF THE RELATIONSHIPS
OF THE INTERNAL SECRETIONS TO
THE FEMALE CHARACTERISTICS AND
FUNCTIONS IN HEALTH AND DISEASE

BY

W. BLAIR BELL

B.S., M.D., Lond.

EXAMINER IN GYNÆCOLOGY AND OBSTETRICS TO THE UNIVERSITY OF BELFAST, AND
TO THE ROYAL COLLEGE OF SURGEONS, ENGLAND; HUNTERIAN PROFESSOR
ROYAL COLLEGE OF SURGEONS, ENGLAND; GYNÆCOLOGICAL SURGEON
TO THE ROYAL INFIRMARY, LIVERPOOL. SOMETIME
ARRIS AND GALE LECTURER, ROYAL COLLEGE
OF SURGEONS, ENGLAND, AND EXAMINER
TO THE UNIVERSITY OF DURHAM

PRINTED IN GREAT BRITAIN

TO

MY FELLOW-MEMBERS

OF THE

GYNÆCOLOGICAL VISITING SOCIETY

OF GREAT BRITAIN

" Propter secretiones internas totas mulier est quod est."

Arris and Gale Lectures, 1913.

PREFACE

THIS small monograph is based on the subject matter
of several previous communications—the Arris and
Gale Lectures, delivered before the Royal College of
Surgeons, England, in 1913; the paper with which a
discussion was opened at the Royal Society of Medicine
in the same year, and other contributions bearing on this
subject, including, by the kind permission of the Editors
and Messrs. Macmillan & Co., a small portion of the
articles on 'The Disorders of Function' written for the
New System of Gynæcology.

In the Arris and Gale Lectures probably the first
definite attempt was made to demonstrate that the
reproductive functions are directed and controlled by all
the organs of internal secretion acting in conjunction,
rather than by the gonads alone, as formerly thought.
Earlier investigators had adduced evidence, it is true,
of a connexion between the genital organs and some of
the distant endocritic glands; but the observations
made do not appear to have led to the conclusion that
the association is not incidental, but, rather, that it
indicates the existence of a definite *genital system*, in
which probably all the internal secretions play a part.

This correlation of the internal secretions in regard to
the sex functions—the ' sex complex ', as we may call
it—appears already to be accepted by all physio-
logists and clinicians, except, perhaps, those few who
still deny the inter-relationship of the internal secretions.

Indeed, the views which I originally expressed are now put forward, often without acknowledgment and sometimes by those who previously opposed them, as accepted and well-recognized facts.

There are, of course, still differences of opinion concerning the details ; and it is for this reason, as well as because of the intense importance of the subject to physiology and to practical gynæcology[1], that the investigations and communications referred to—welded together, amplified and largely rewritten—are submitted for consideration in book form, in the hope that further interest may be stimulated, fresh facts noted and recorded, and existing opinions corrected or confirmed.

The outbreak of war prevented the completion of the work which had been planned in connexion with the parathyroids, pineal and thymus, of whose relations to the genital system we know so little, with the age-changes in the endocritic organs and with other equally important questions. It is improbable that I shall find time in the future for further researches, so it has not been thought worth while to delay the issue of this work, which is already long overdue owing to the causes mentioned.

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[1] In this work the author is chiefly concerned with the female characteristics and functions; nevertheless, the internal secretions are as closely connected with the genital functions of the opposite sex, in relation to which they must, therefore, occasionally be discussed for the sake of contrast or comparison.

The illustrations other than the photographs have been drawn by my laboratory assistant, Walter Plevin; and my secretary Miss Miriam Alderson has helped me in many ways.

I am indebted to Dr. Hubert Armstrong for much assistance in the revision of the proofs, and for making the index; also to my Publishers for the generous way in which my requirements have been met, especially with regard to the colour plates which have been reproduced from original colour photomicrographs.

W. B. B.

38, Rodney Street,
    Liverpool,
        January, 1916.

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INTRODUCTION

In the following pages our subject will be Woman, and I shall endeavour to make clear, so far as our knowledge allows, the difficult problem of the female sex complex in all its ramifications. To do this I shall be obliged to draw upon the facts of general biology, both in argument and experiment; but we must always remember that details which are true of one species are not necessarily so of another. We must, therefore, endeavour to go forward along the highways of the general principles, holding only to those particulars which point the way.

Our disquisition resolves itself into two sub-divisions:

    (1) A consideration of the factors which lead to the production and maintenance of the normal characteristics and functions of Woman; that is to say, of the individual with feminine attributes, primary and secondary, both of the mind and body.

    (2) A discussion of the morphological and physiological derangements of the sex complex.

At the very outset of the first enquiry we bring ourselves to the threshold of lively controversy—controversy concerning the differences between Man and Woman which has rarely been conducted on unbiassed and scientific lines. So much of this has come within

my personal experience, that I feel it best at once clearly
to emphasize the impossibility of taking sentiment
into account in a discussion of femininity and its causes,
and in my statements concerning the psychical attributes
which cannot be ignored in a consideration of this subject.
Moreover, no pretence is made of overlooking the facts
that certain social and legal questions depend closely
on the scientific aspects of sex, and that they are now
pressing for consideration, elucidation and determination.
With national and international struggles going on
around us, and with the claims of posterity meeting us
at every turn, no one can fail to recognize that the
problems of sex and reproduction are urgent and that
it is the duty of those working at this subject not only
to determine, if possible, the causes of sex and of sex
characteristics, but also to specify the relations and
functions of the two sexes under changing circumstances
and environments.

This is the twentieth century ; and, however much we
regret it, we must confess that science admits of no
sentimentality or romance. When the veil overhanging
the mystery of sex is completely torn aside, no doubt
many cherished illusions will be taken from us. Yet
somehow we survive unspoilt the ravages of science,
and quite impersonally we are able to discuss the cold,
hard facts related to our daily life in no uncertain
manner; for, whatever our knowledge of life, death and
sex may be, our mental detachment is such that these
things apply to all others rather than to ourselves and to
those dear to us. Because no longer we believe that the
heart is really the seat of the affections—because we
do not order analgesics for ' heart-ache '—are we any less
affectionate or immune to jealousy ? So, too, we may
believe that, however much we unmask the physical

attributes of sex and demonstrate the material qualities of the differences in sex psychology, and however much we dissect the complexity of sex, we shall not disturb the sex instincts of a single normal individual.

It is, indeed, strange that such an *apologia* should be necessary in the present day, but, as already stated, I believe it to be so. And in this conviction I am supported by the following statement, written more than twenty-five years ago (1889) in that fascinating little work *The Evolution of Sex*, by Professor Geddes and Professor Thomson, and repeated in all subsequent editions :—

" A third reason why the problem of the origin of male " and female has been so much shirked, why naturalists " have beaten so much about the bush in seeking to " solve it, is that in ordinary life, for various reasons, " mainly false, it is customary to mark off the repro- " ductive and sexual functions as facts altogether *per se*. " Modesty defeats itself in pruriency and good taste " runs to the extreme of putting a premium upon " ignorance. Now this reflects itself in biology. Re- " production and sex have been fenced off as facts by " themselves; they have been disassociated from the " general physiology of the individual and the species. " Hence the origin of sex has been involved in special " mystery and difficulty, because it has not been " recognized that the variation which first gave rise to " the difference between male and female, must have " been a variation only accenting in degree what might " be traced universally."

Apparently, and unfortunately, a quarter of a century has not been a period long enough to effect a change in our outlook.

In discussing the normal factors responsible for the

production and maintenance of sex characteristics in the female, and the functions appertaining to them, I shall cover a wide field and one which, as already indicated in the preface, has never been fully attempted. Indeed, any attempt to describe the special correlated functions of the endocritic organs, or, to be more exact, of the internal secretions, appears to have been avoided by those who have worked most at the subject. Correlations have been admitted, points in support of them have been adduced, and the matter has then been dropped. In many ways this is much to be deplored, for to some extent it is accountable for the present disordered state of our knowledge. It is disappointing, for instance, to read through a work such as that of Biedl on *The Internal Secretions*, and nowhere to find an attempt to link up—if only from an analysis of the isolated results of work already done—the mysterious connexions that undoubtedly exist between the endocritic organs in regard to the specialized functions. In Marshall's excellent book on *The Physiology of Reproduction* two short pages only are set aside for the consideration of the relation of the ductless glands generally to the reproductive functions. No doubt this diffidence is due partly to the incomplete state of our knowledge ; but I think it arises more especially from the isolated way in which we usually consider most of the structures of the body : we trace the products of metabolism from organ to organ without taking into consideration the fact of what may best be described as organic harmony between various structures themselves, in spite of the suggestive lead given us by Starling in his description of the action of secretin.

It must not be inferred from these remarks that I am in any way prepared to give a complete explanation

of the interactions of the endocritic organs in regard to the genital functions and characteristics. It is necessary, however, to call attention to the fact that the genital functions in the female must be considered from a very wide standpoint in view of our accumulated knowledge concerning them. I shall deal most fully with those parts of the subject wherein I have myself worked, and shall bring forward experimental results and pathological findings to clear up many of the points at issue.

The essential fact, then, to be borne in mind in regard to this subject is that *femininity itself is dependent on all the internal secretions.* It used to be thought that a woman was a woman because of her ovaries alone. But, as we shall see later, there are many individuals with ovaries who are not women in the strict sense of the word, and many with testes who are really feminine in every other respect. This indicates a line of thought which is really the object and fundamental basis of this study—namely, that we can no longer consider that the gonads act alone in their influence on the female characteristics and genital functions, except in regard to the production of ova. We must, in fact, consider the ovaries as part of a system, to which most, if not all, the other endocritic glands belong, and in which these other organs in their relation to the reproductive functions figure with as great importance as the ovaries themselves. It must be remembered, too, that when we speak of the genital functions of the ductless or endocritic glands, we refer not only to their influence on the integrity of the uterus—anatomical and physiological—but also on the general metabolism, which is influenced to subserve the necessities of the special functions, and on the psychology of the individual.

In the second part of our subject we shall confine our attention to those pathological conditions which are probably directly dependent on derangements of the normal morphological and physiological processes concerned in the sex complex and considered in the first part of this work.

PART I

MORPHOLOGICAL, PHYSIOLOGICAL AND PSYCHOLOGICAL CONSIDERATIONS

AT the commencement it is essential that we consider how far the internal secretions are concerned in producing and maintaining the feminine characteristics, and in ensuring the full development of the genital organs. Afterwards I shall support with experimental evidence the view that the internal secretions of the ovary alone are not the sole factors in the preservation of the integrity of the genital functions, once these have been fully established.

SEX CHARACTERISTICS

PRIMARY SEX CHARACTERISTICS

It has always been considered that the primary sex characteristics are those peculiar to the genital organs, and especially to the gonads. I shall show later, however, that the primary sex characteristics cannot be limited in this way.

If we wish to seek for the origin of the primary characteristics, we are, of course, called upon to examine carefully the primary causes in the determination of sex. This question has been the subject of far more theorizing than of scientific investigation. I propose, therefore,

but briefly to review the evidence concerning the caus-
ation of sex.

The determination of sex.—In the human subject
the sexes are definitely differentiated : the species is
diœcious. In certain of the lower animals, such as
various species of worms, the sexual condition is
monœcious ; that is to say, each individual has the
genital organs of both sexes, and may be capable of
fertilizing other individuals and of being fertilized. The
term commonly employed for this condition is ' Herma-
phroditism '[1]. In bees there are three variations—
perfect females, imperfect females and males. Further,
in certain of the insects, such as the silk worm moth,
the development of an adult individual from the unfertil-
ized ovum has been observed to occur occasionally.
This is known as ' Parthenogenesis '.

It may be laid down, then, that generally speaking
the higher the species stands in the scale of evolution,
the greater is the differentiation between the primary
characteristics of the two sexes.

The various theories propounded concerning the
origin of sex emanate from three different points of view :

    (1) That sex is predetermined in the ovum and
         spermatozoon.

    (2) That sex is determined at fertilization.

    (3) That sex is regulated subsequently to fertiliza-
         tion ; that is to say, sex differentiation occurs
         during embryonic life.

(1) With regard to the hypothesis that sex is pre-
determined in the ovum and spermatozoon, it is obvious

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[1] In the sense just indicated it would be more correct to term the
condition 'Structural Hermaphroditism,' since in some worms and other
invertebrates there may even be self-fertilization—a condition which
should be known as 'Structural and Functional Hermaphroditism '.

that very little direct information can be obtained concerning the human species. Most of the evidence has, therefore, been derived from a study of insects.

The general hypothesis stated under this heading may be subdivided into the following alternatives :—(a) That sex is predetermined in the ovum (and possibly the spermatozoon) from the earliest development of the germinal cells, and that no alteration is possible ; (b) That, while the sex may be said to be predetermined in this way only for normal circumstances, altered conditions of nutrition and environment may affect the gametes, and thus influence the ultimate sex of the zygote.

As to the *unalterable primary determination of sex in the gametes* which is propounded in the first subdivision, there is evidence that in some insects and in certain snails the spermatozoa are dimorphic. For instance, Henking[1] found that some of the spermatozoa in the bug *Pyrrhocoris* possess an additional chromosome. This has been supposed to be an example of bisexuality in regard to the spermatozoa. According to Marshall[2] it is certain that the ova, also, have one more chromosome than the spermatozoa containing the lesser number. It is believed that the conjunction of ova with sperms having the greater number of chromosomes leads to the production of females, and the fusion of ova with the sperms having the lesser number to the development of males. Other investigators have shown that differences in the number of the chromosomes in the gametes are found in many species of insects, and that even in the fowl there are dimorphic spermatozoa.

Beard[3] and other observers believe that the sex

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[1] Henking, H., *Zeitsch. f. Wiss. Zool.*, 1890, vol. xlix, p. 503.

[2] Marshall, F. H. A., *The Physiology of Reproduction*, 1910, p. 623.

[3] Beard, J., *Zool. Jahrb.* 1902, vol. xvi, p. 703.

potentiality exists in the unfertilized ovum, and that when there are two kinds of spermatozoon in the same individual one variety is functionless. In this connexion it may be pointed out that it is, of course, quite an old view that in the female the ova in the right ovary produce one sex and those in the left ovary the opposite. This wild assumption, however, is directly controverted by the simple facts that in birds, and to a great extent in the mammalian *Ornithorhynchus* as I have myself found, the right ovary atrophies and the left alone remains functional, and that women and animals from whom one ovary has been removed have subsequently borne offspring of both sexes.

It has been suggested by Bateson[1] and others that primary sex determination in the gametes is purely hereditary and is subject to Mendelian laws. Even if this were so in actual fact, it would be falsified by reproductive results; for to obtain proof of this contention in regard to mammals it would be necessary to ensure the fertilization of every ovum, and that is impossible.

With regard to the proposition contained in the second subdivision, Heape[2] and many other writers hold that although *the dominant sex may be predetermined in the gamete, yet there is in each a latent* anlage *of the opposite sex which may become active and predominant before fertilization* under certain conditions of nutrition, parental vigour and general environment.

Arising from this view, which I believe is correct, so far as it goes in the life history of the individual, there have been a number of interesting studies concerning the ratio of the sexes, both in man and animals, under

[1] Bateson, W., *Report to Evolution Committee of Roy. Soc.*, rep. i, 1902, Lond.

[2] Heape, W., *Proc. Camb. Phil. Soc.*, 1907, vol. xiv, p. 121.

different conditions. From a statistical point of view the results are not satisfactory. On one hand, it has been pointed out[1] that in the aristocracy—presumably well-fed and usually vigorous—sons are more numerous than daughters; on the other, it has been believed[2] that, after the stress and indifferent nutrition which may result from a long war, male infants have been born in greater numbers than females.

It is, however, almost impossible to obtain reliable statistics regarding the influence of nutrition, environment and other indirect causes on the sex of the offspring, because the factors concerned are often mixed or conflicting, and because infantile mortality plays such a large part in the final or apparent result—that is to say, in regard to the sex ratio among adults. Be this as it may, the general opinion is held that under favourable conditions female births preponderate, and in unfavourable circumstances male.

(2) The view that *sex is determined at fertilization* is also founded on biological evidence, for it is known that male bees and the males of certain other insects are developed parthenogenetically from unfertilized ova, while the females are produced from those which have been fertilized.

Schenk[3] and others have asserted that sex determination depends on the state of the nutrition of the ovum at the time of fertilization. This view was elaborated by Schenk, who claimed that by supplying the mother with a nitrogenous diet before conception he could increase the chance of the offspring being a male. Time, however, has shattered these pretensions concerning the

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[1] Punnett, R. C., *Proc. Camb. Phil. Soc.*, 1904, vol. xii, p. 262.

[2] Geddes, P., and Thomson, J. A., *Sex*, 1914.

[3] Schenk, L., *The Determination of Sex*, Eng. Trans., 1898.

practical application of this theory, whether or not there be any substratum of truth in it.

(3) We now come to the last view; namely, that *sex is determined subsequently to fertilization.*

It has been demonstrated by Yung[1] that in tadpoles sex is not determined until late in that stage of the development of the frog; and evidence has been obtained that nutrition affects the final outcome.

Similarly it has been shown by Cuénot[2] that the differentiation of the gonads of maggots does not occur until the end of larval life. This observer found, however, that the ultimate determination of sex in these creatures was not influenced by nutrition.

For further biological details concerning the determination of sex the writings of Morgan[3], Marshall[4], Geddes and Thomson[5] and Doncaster[6], to which I am largely indebted, may be consulted.

In spite of all the information at our disposal, we must confess that the primary cause or causes of sex determination are not definitely known, and at the same time express the opinion that since it is purely a physical question observations on animals will no doubt some day lead to a complete understanding of this matter. Meanwhile, it appears that no one view alone covers all the requirements, but that truth is probably wider, and that many of the theories are correct so far as they go; and that there is some truth in most of the views for which

[1] Yung, E., *Compt. Rend. de l'acad. des Sci.*, 1881, vol. xciii, p. 562.

[2] Cuénot, L., *Bull. Sci. de France et Belg.*, 1899, vol. xxxii, p. 462.

[3] Morgan, T. H., *Experimental Zoology*, Lond., 1907, p. 363.

[4] Marshall, F. H. A., *The Physiology of Reproduction*, Lond., 1910, p. 623.

[5] Geddes, P., and Thomson, J., *The Evolution of Sex*, 1901, Revised ed

[6] Doncaster, L., *The Determination of Sex*, 1914.

there is biological evidence, but not the whole truth in any one.

At present in regard to the human species we only know, from pathological and clinical observations, that there must be a latent but predominating tendency in every fertilized ovum towards masculinity or femininity, and that every fertilized ovum is potentially bisexual. It is obvious to all that in every person there is predominating masculinity or femininity, which decides the sex denomination ; but, at the same time, it is equally obvious that latent traits of the opposite sex are always present : some men are described as being effeminate, while many a woman has the smallest possible balance of femininity in her favour. If further evidence of this bisexuality, which exists in everyone, were required, it is to be found in the embryological remains of the latent sex, which always exist in the genital ducts. These remains are invariable, and we must admit that it is in respect to the genitalia that there is the greatest difference between men and women—in some cases the only difference, according to our present standards. Unfortunately, however, the other characteristics showing less divergence have not been investigated and compared with accuracy—we have, in fact, been satisfied with observing gross differences only.

So much for the actual predisposition in the fertilized ovum towards maleness or femaleness : beyond conceiving theoretically that this is dependent on intracellular metabolism, which may possibly be subject to external interference, we know nothing definitely.

When, however, we come to a consideration of the further development of the ovum towards that point at which we can recognize sex divergence—a term which

I think best indicates the tendency of originally bisexual cells towards a predominating sex characterization—then our knowledge becomes more definite.

It appears probable that the potentiality to produce femininity, which exists in the earliest stages of segmentation of the ovum, is directed towards the future development and correlations of the endocritic organs that are subsequently to control the sexual evolution of the individual.

It may at once be stated emphatically that the ovaries alone are not responsible either for the primary or the secondary female characteristics. We have very pertinent evidence on this point, to be considered later, in the human monstrosities known as ' Hermaphrodites '. In certain of the invertebrates hermaphroditism to the fullest extent—that is with the power of fertilizing and of being fertilized—is well known, but generally speaking the higher we go in a consideration of the evolution of reproduction the greater do we find the differentiation of sex characteristics and functions.

It is probable, then—and I shall adduce much evidence on the point later—that many if not all the organs of internal secretion influence the primary genital characteristics; and that all the endocritic organs, as well as the gonads, have normally a primary tendency to produce either masculine characteristics and functions, or feminine.

It has been stated that there is no evidence that the endocritic organs, other than the gonads, differ histologically in the two sexes[1], although Kolmer[2] claims to have noted differences between the male and female

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[1] McIlroy, Louise, *Discussion. Proc. Roy. Soc. Med.*, (*Obstet. and Gyn. Sect.*) 1913, vol. vii, p. 76.

[2] Kolmer, W., *Pflüger's Arch. f. Physiol.*, 1912, vol. cxliv, p. 361.

suprarenals in rabbits, and Erdheim and Stumme[1] have demonstrated the effect of pregnancy on the pituitary. But we need not be surprised at these differences of opinion, when we remember that although the special sex elements—ova and spermatozoa—must necessarily be differentiated, the interstitial cells of the gonads, as we shall see in dealing with Hermaphroditism, do not show any special tendency to produce either male or female secondary characteristics, as has been universally presumed hitherto. But since all individuals are bisexual in varying degrees, one would expect to find in the endocritic organs—other than the generative portions of the gonads—functional, even if there were no obvious structural, differences. This is an important point that has, strangely enough, been entirely overlooked, in spite of all the evidence from the pathology of the organs of internal secretion, to which I shall call attention later.

SECONDARY SEX CHARACTERISTICS

At birth we distinguish the sex of the child by the character of the external genitalia, which in normal circumstances correspond with the internal genitalia. These genital features are generally held to constitute the primary characteristics. At the same time, as already indicated, were we able to recognize the differences, we could claim primary sex characterization, male or female, in regard to probably all the endocritic glands.

The secondary characteristics, however, constitute the *sexe-ensemble* seen not only with respect to the general

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[1] Erdheim, J., and Stumme, E., *Berl. Klin. Woch.*, 1908, vol. xlv, p. 1031.

conformation of the body and the details connected therewith, but also in connexion with the specialized functions peculiar to the sex, both physical and psychical.

No doubt the secondary characteristics appeared after the differentiation of sex was evolved, to assist sexual selection and adapt the different species to their environment and conditions of reproduction.

The secondary sex differentiations vary considerably in different classes of animal life. In some, such as the rodents among the mammalian orders, the differences in the secondary characteristics of the two sexes are slight. In others, such as the birds, they are often most pronounced.

The secondary sex characteristics are to be noted not only in the various forms of external adornment, in the reproductive differentiations and combative requirements, but also in the metabolic factors of the physiological economy.

Everyone is familiar with the ornamental feathers of the male Bird of Paradise, with the claspers of the male frog, with the antlers of the stag and with many other morphological sex differentiations too numerous to mention. But behind these morphological variations lie physiological differences in the two sexes which are undoubtedly responsible for the more obvious morphological features. It is known, for instance, that in some caterpillars the blood differs in colour in the two sexes, being green in the females and yellow or colourless in the males[1]. This, of course, indicates that the chemical composition is different in the two sexes. And differences—if less obvious than the example just mentioned—

[1] Geddes, P., and Thomson, J. A., *Sex*, 1914.

may be traced in the higher animals. Bucura[1], referring to the researches of many observers, points out that the human male uses more oxygen than the human female, and that in men the blood has a higher specific gravity, more red corpuscles and a higher percentage of hæmoglobin than in women. And these are only gross distinctions. The finer, and probably more important, have not been fully worked out, but I shall refer later to some of the differences which are dependent on the internal secretions, and are of the highest importance. Some day, perhaps, we shall be able to base our knowledge of these physiological and morphological dissimilarities on the variations to be found—both quantitative and qualitative—in the primary sex characteristics of the endocritic organs.

In the human subject the secondary characteristics of the two sexes appear to be strongly contrasted, as is shown in the following columns :—

Man	Woman
Hair on face and trunk; but in many men it tends to fall from the head about middle age.	*Hair on head is long; but is absent on face and trunk (apart from pubes and axillæ).*
Larynx large. Voice deep.	*Larynx small. Voice high.*
Muscles powerful.	*Muscles relatively weak.*
Bones heavy.	*Bones light.*
Skin coarse.	*Skin fine.*
Tendency to leanness. ('Katabolism' of Geddes and Thomson.)	*Tendency to fatness. ('Anabolism' of Geddes and Thomson).*
Psychical domination and certainty.	*Psychical dependence and hesitancy.*

[1] Bucura, C. J., *Geschlechtsundterschiede beim Menschen*, Wien and Leipzig, 1913, p. 12.

Many other minor differences—physiological, morphological and psychological—might be emphasized, were it necessary to do so. The whole subject has been fully discussed in recent years by Kammerer[1], Bucura[2], Havelock Ellis[3] and others, whose works should be consulted for further information concerning physical and psychical sex variations. It should, however, never be forgotten that Man is dimorphic, and that the prominence or otherwise of the secondary characteristics depends on the degree of masculinity or femininity present in any given individual.

It must be noted in passing that there are two stages in the development of the secondary characteristics in Man—a fact that requires special emphasis. The first stage extends from birth until puberty. During this period the development of sex characteristics is slow : in the girl the mind is often not pronouncedly feminine, although girls are supposed to, and sometimes do, show a marked liking for dolls and sewing, in contradistinction to the preference of boys for balls and fighting. So, too, in girlhood the special characteristics of mammary development and plumpness are usually absent, and the genital functions are dormant. At puberty, however, there is a remarkable change, which is not only physical but also psychical. Normally at this epoch a girl becomes shy, reserved, and essentially feminine in her pleasures and in her relations with men.

We must now briefly consider the influence the

[1] Kammerer, P., *Abderhalden's Fortschr. der naturw. Forschung,* 1912, vol. v, p. 1.

[2] Bucura, C. J., *Geschlechtsundterschiede beim Menschen,* Wien and Leipzig, 1913, p. 12.

[3] Ellis, Havelock H., *Man and Woman,* 1914, 5th ed.

endocritic glands exercise upon the pubescent develop-
ment of the female genital organs and their functions,
and upon the secondary characteristics in the normal
individual. This part of the subject is one which, in
its pathological aspect, constantly confronts us in our
clinical work.

Although the genitalia may be normal morphologic-
ally at birth (fœtal development), yet, as indicated
already, they only become functionally active at puberty
(complete development) if the whole endocritic system
is in perfect harmony, and is acting efficiently and
normally in regard to its sexual functions. Thus,
thyroid or pituitary insufficiency may cause the genital
organs to remain infantile ; and we shall see later that
disease of these structures may cause retrogression in
the genitalia even after they have functionated normally.
Further, it is believed that the gonads and uterus remain
not fully developed until the thymus atrophies at the
time of puberty. At this period of life, owing to the
withdrawal of the thymus secretion, as some authorities
think, the genital organs begin to develop ; other in-
vestigators, however, believe that it is the development
of the gonads which causes retrogression in the thymus[1].
The probability is that both views are correct ; for
experimentally it has been found that removal of the
ovaries leads to hypertrophy of the thymus, even after
atrophy has occurred in the normal course of events[2],
and that removal of the thymus in male guinea-pigs
is followed by a rapid development of the genital glands[3].

It may be well to interpose a few words here by way of
explanation and illustration of the inner meaning of the

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[1] Biedl, A., *Innere Sekretion*, 1913, 2nd ed.

[2] Calzolari, A., *Arch. Ital. de Biol.*, 1898, vol. xxx, p. 71.

[3] Paton, Noel, *Journ. Physiol.*, 1904, vol. xxxii, p. 59.

correlations that exist between the organs of internal secretion. One organ, such as the thymus, is not normally antagonistic to another, such as the ovary, for any but specific reasons. Moreover, they probably counteract one another not only directly but also indirectly through the general metabolism.

To make the principle of this indirect effect clearer, let us go a little more fully into the illustration just given. It is believed that the thymus produces calcium retention in the tissues, and thus assists in building up the bony skeleton—in fact, animals from which the thymus had been removed were found by Basch[1] and others to suffer with softening of the bones. On the other hand, I have shown experimentally that the ovaries are katabolic in regard to the calcium salts[2]; and this is also indicated in certain pathological conditions to be mentioned later. Now the calcium metabolism, around which for the moment I am building up my argument, is differently employed, if I may so use the term, at three different periods of life. Until puberty calcium is chiefly utilized for building up the skeleton; after this epoch for reproduction; and lastly, and pathologically if the termination of life be pathological, for producing changes which are associated with senility —namely, the retention of lime salts in the tissues, especially in the arteries. There is no need to allude to the many other important parts played by the calcium salts in the human economy at all periods of life. It must not, however, be thought that the thymus and ovaries alone influence the calcium metabolism, for, as in the metabolism of other elements, all the endocritic

[1] Basch, K., *Wien. Klin. Woch.*, 1903, vol. xvi, p. 893.
[2] Bell, W. Blair, *Arris and Gale Lectures*, *Lancet*, 1913, vol. i, p. 809.

organs are concerned, either anabolically or katabolically. And the same differences in regard to metabolic conditions are found in many—perhaps all—directions at the three essential periods of life which I have just described. As a natural consequence, we find that the functions of the organs of internal secretion differ not only at different periods of life, but normally in different circumstances, such as those concerned with the inter-mittent reproductive functions of women ; and not infrequently there is a coincidental alteration in structure, such as is seen in the pituitary and thyroid during pregnancy. Further work on these normal periodic variations is urgently needed.

The reproductive functions in Woman are dependent on her specialized structures, both primary and secondary ; and I have just endeavoured in a broad way to show how structure and function are closely corre-lated in producing the *tout ensemble*.

To sum up. In early life—that is to say, before puberty—the metabolism of girls is probably not very different from that of boys : the chemical processes of both are for the most part engaged in the growth of the body. At puberty, however, a remarkable change occurs, and it is at this period of life that the male becomes most widely differentiated from the female.

As we have seen, this further development is due to the activity of the reproductive functions. In Woman the change is shown by the psychical and physical alterations which accompany the onset of menstruation. As a rule, growth ceases at puberty, for with menstruation there is a large excretion of calcium and the other sub-stances which previously were required for the growth of skeletal and other tissues, but which are now no longer wanted until pregnancy and lactation occur, when a

fresh body is built up and nourished by the maternal metabolism; consequently girls who menstruate early are often short, and *vice versa*.

The characteristic functions, then, of the female are those associated with the genital activities—menstruation, gestation and parturition, and lactation.

The menopause comes at the end of reproductive life, and marks the period at which the metabolism can no longer support the strain of reproduction.

Now, this cycle of functions is directly under the control of the endocritic organs. And it appears that although before puberty and after the menopause there is little difference between the metabolism of the male and female, yet during the reproductive period there is a considerable contrast, and this is reflected in the activities and structure of the endocritic organs[1].

The fact that the internal secretions influence the production of the fully developed genital organs with normal functions is thus indicated generally, but we must now pass on to consider the relative part played by each member of the endocritic system in the preservation of the integrity of these organs and their functions.

[1] As I have been discussing sex differentiation in normal circumstances, no mention has been made of the remarkable selection different diseases, especially of the endocritic organs, exercise in regard to sex, or of the different remote effects toxins—*e.g.* of alcohol and syphilis—may produce in men and women. These sex-selective actions of pathological processes are for the most part only effective during the reproductive period.

THE FUNCTIONS OF THE OVARIES

The ovaries have two functions—the provision of ova, and the production of the specific internal secretion or secretions.

The production of ova—a necessary process in reproduction—requires no further discussion here. The questions with which we are immediately concerned relate to the connexion of the internal secretions of the female gonads with menstruation and gestation. With regard to menstruation, there is no doubt that this function depends primarily on the normal development and subsequent integrity of the uterus, and with this the internal secretion or secretions of the ovaries are largely concerned. The relation of these internal secretions to the normal progress of gestation is, as we shall see, somewhat obscure. And, although it is well known that the corpus luteum in the ovary of the pregnant female is considerably larger than in the non-pregnant, it is not certain that this hyperplasia has any more importance than that of an epiphenomenon.

The internal secretion or secretions of the ovaries have never been isolated; indeed, it is still a matter of dispute as to how and where it is or they are produced. The only evidence that there is an internal secretion rests upon the results of extirpation, destruction and implantation experiments, and to a lesser degree on clinical observations. The atrophy of the uterus which follows

oöphorectomy is believed to indicate the loss of some secretion which normally activates this organ. Some think that there is more than one secretion; and various authorities have considered that, while different hormones are produced by the lutein cells of the corpus luteum, by the interstitial cells of the stroma of the ovary and by the membrana granulosa cells, these secretions all differ in regard to the degree of importance and the period of action to be assigned to each, and that the total effect differs in different animals. And herein lies one of the great difficulties in the study of our subject: different orders of mammals have organs of internal secretion which are structurally and functionally different, although perhaps in degree only. Individuals in the same species may vary, both in animals and in Man; consequently some of the contradictory statements made by different experimenters may be explained on the ground of these variations. It may be, for instance, that the secretion of the corpus luteum in women is much less important for the normal implantation of the ovum than it is in rabbits.

I have studied the question from a morphological standpoint, for this method of investigation seemed likely to offer some solution of many of the difficulties in regard to the corpus luteum.

The *Ornithorhynchus*, in which the young is born in an egg, and consequently is never attached to the mother, has a somewhat remarkable corpus luteum. I have not seen a very recent one, but in those in the specimens examined there is an enormous deposit of fibrous tissue around what appear to be lutein cells (fig. 1). Ultimately the whole becomes a ball of fibrous tissue (fig. 2). This arrangement does not seem at all favourable to the absorption of secretion from the lutein cells.

Fig. 1.

Section of the ovary of the ornithorhynchus, showing a corpus luteum.

$\times$ 60.
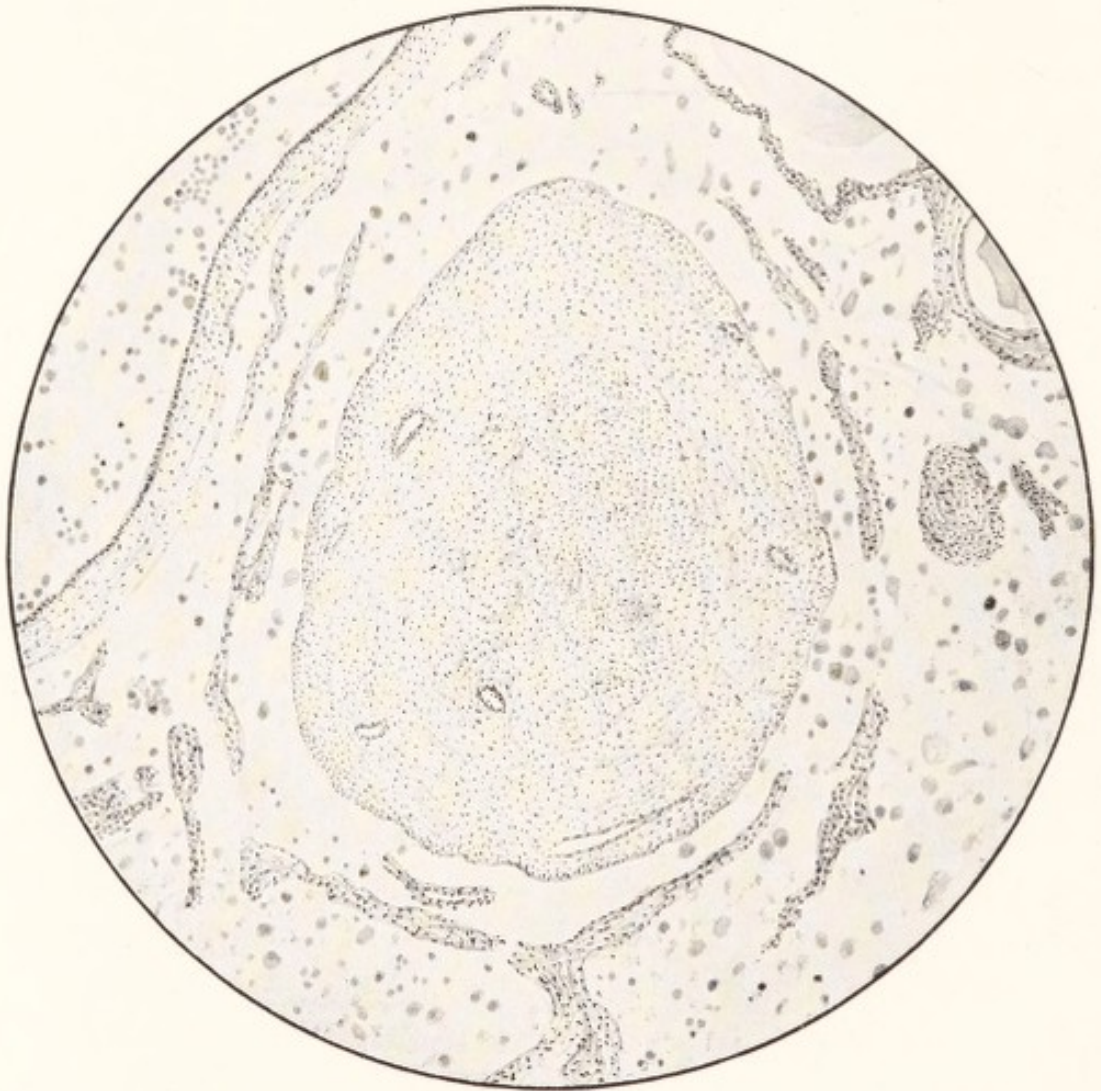
FIG. 2.

Section of the ovary of the ornithorhynchus, showing a corpus fibrosum.

$\times$ 60.

In marsupials the attachment of the ovum is most primitive, and one would expect to find a correspondingly unimportant corpus luteum. But this expectation is not borne out by facts, although Fraenkel and Cohn[1] must have jumped to the conclusion mentioned, for they state that the corpus luteum in the marsupial is, like that seen in the monotreme (*Ornithorhynchus*), rudimentary. O'Donoghue[2], however, has carefully described the corpora lutea in several varieties of marsupials, and has shown that they are highly developed structures. That this is so will be obvious from an inspection of figure 3, in which a fully developed corpus luteum in the ovary of a marsupial (*Perameles obesula*) is seen to occupy a considerable portion of the organ and to be composed of large cells of an epithelial type.

If the importance of the corpus luteum increased with the degree of fixity of the ovum in the uterus, one would expect that the higher one went in the scale of evolution the more important would become the corpus luteum— that in Woman it would be more active than in the rabbit and other lower mammals. Evolution, however, does not necessarily entail the advancement of every structure; some atrophy, and all are dependent for their development upon the necessities of the particular species. In the human subject, in carnivora and in rodents there is an actual embedding of the ovum; but in ungulates the placental attachment is merely one of apposition, and there is no invasion of the maternal tissues as in rodents, carnivora, the primates and Man. Yet anyone who has seen the corpus luteum of an ungulate must feel impressed by its active appearance, both macroscopical (fig. 4) and microscopical (fig. 5), in

[1] Fraenkel, L., and Cohn, F., *Anat. Anz.*, 1902, vol. xx, p. 294.
[2] O'Donoghue, C. H., *Arch. f. Mikros. Anat.*, 1914, vol. lxxxiv, p. 1.

comparison with that of the human female (figs. 4 and 6).

Such facts are bewildering; so the conclusion we must draw provisionally is, that, if the corpus luteum be an organ of internal secretion which assists the implantation of the ovum, the importance of it varies with different species, and probably it has more than one function.

I have dwelt on the difficulties of an investigation into the physiology of the corpus luteum, for we encounter the same difficulties and obtain the same variability in our results throughout this subject of the Sex Complex in our search after definite information.

The interstitial cells of the ovary, also, have attracted much attention, and they, too, are believed to possess a special internal secretion. Limon[1] first called attention to *la glande interstitielle de l'ovaire*, as he termed it. Fraenkel[2] also investigated this subject carefully. He compared the ovaries of forty-five different species of mammals, and found an enormous difference in the preponderance of interstitial cells in the various ovaries. In the human ovary he could find no trace of an ' interstitial gland '.

All histologists are familiar with the structure of the human ovary (fig. 7), and the obvious scarcity of secretory cells, apart from those connected with the follicles. But if we examine the ovary of an adult rabbit or any other rodent, we see a most remarkable structure : nearly the whole of the organ is composed of a mass of cells which are epithelioid in character ; and equally striking is the appearance of the corpora lutea, the cells of which can only be distinguished, if at all, from the cells of the stroma by their larger size ; while the Graafian follicles are

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[1] Limon, M., *Arch. d. Anat. Microscop.*, 1902–3, vol. v, p. 155.
[2] Fraenkel, L., *Arch. f. Gynäk.*, 1905, vol. lxxv, p. 443.
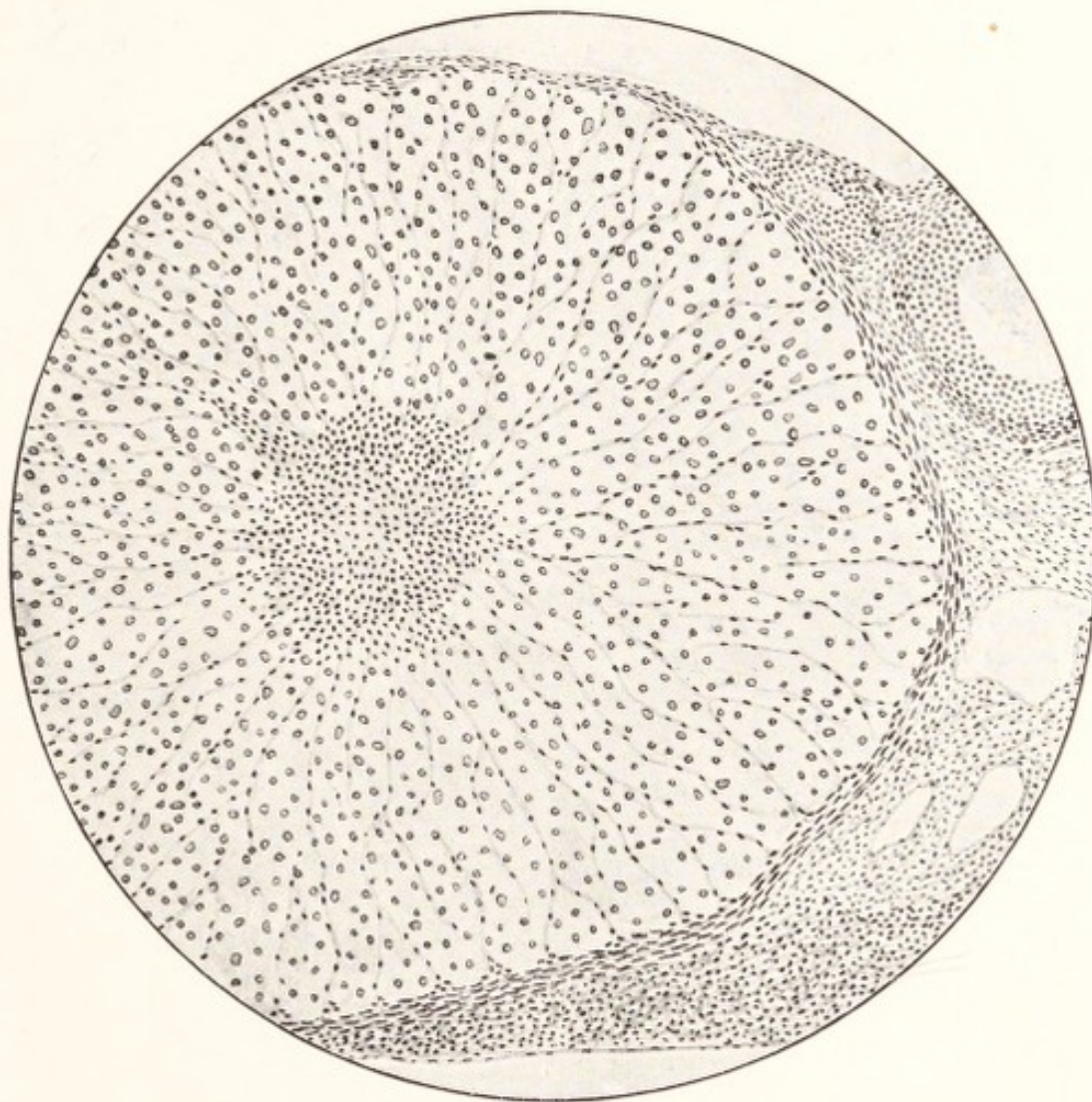
Fig. 3.

Section of the ovary of a marsupial (*Perameles obesula*), showing a fully developed corpus luteum.   (*From a section kindly lent by Dr. O'Donoghue.*)

$\times$ 60.

FIG. 4.

A.—Ovary of the cow, showing a corpus luteum associated with the oestrum.

B.—Ovary of the human subject, showing a corpus luteum associated with menstruation.

$\times \frac{1}{1}$

crowded round the periphery of the ovary as though pushed outwards (fig. 8).

What does this extraordinary appearance in rodents indicate ? From very close observation of the corpora lutea in all the stages of development I have come to the conclusion that either they do not all undergo involution in this order as in the higher mammals, but that many of them ultimately form the so-called interstitial stroma cells, or that the lutein cells are developed from interstitial stroma cells which have already become specialized.

If, however, we examine the ovary of a rabbit a few weeks old we find that it is composed entirely of primordial ova and a few follicles, scattered evenly throughout the organ, and that these are separated by bundles of connective tissue. There is an almost entire absence of definite interstitial cells (fig. 9). The absence of these cells in the very young rabbit also indicates the likelihood of their origin from the same source as—if not actually from—those of the corpora lutea in the adult, although it is probable that in the human ovary and in the ovaries of animals which contain very few interstitial cells these cells arise entirely from specialized stroma cells.

Thirdly, there are the Graafian follicles with their linings of membrana granulosa cells, to which some attribute an internal secretion. In favour of this view I shall adduce some evidence later.

My own experiments concerning the functions of the ovary have been carried out on dogs, cats and rabbits. As already stated, the ovaries of the carnivora resemble in structure the human ovary more closely than is the case with the ovaries of rodents. The methods of investigation have consisted in noting the effects of

oöphorectomy on the pregnant and non-pregnant uterus, on the other ductless glands and on the general metabolism, and of the influence of grafts in various circumstances.

EFFECTS OF OÖPHORECTOMY ON THE GENITAL FUNCTIONS AND ON THE STRUCTURE OF THE REST OF THE GENITALIA[1]

Effect of oöphorectomy on the non-pregnant uterus.—Some years ago, in conjunction with Hick, I pointed out that the first effect of oöphorectomy on the uterus was the production of atrophy in the muscular coats[2]. Figure 10 shows the normal uterus of the cat with its two muscular coats, and figure 11 that of the same cat 238 days after oöphorectomy. We concluded that the normal muscular contractions were abolished and that atrophy supervened, especially of the circular muscular coat. This has been confirmed by Marshall and others.

Effect of oöphorectomy in the pregnant uterus. —Prénant[3], and later Born and Fraenkel[4], were probably the first to call attention to the importance of the lutein cells; and the last named showed that removal of the ovaries early in pregnancy leads to abortion in pregnant rabbits. Hick and I, also, invariably

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[1] Most of the experimental investigations, not otherwise indicated, concerning the functions and interrelations of the endocritic organs detailed in Part I of this work were first described in the *Arris and Gale Lectures* in 1913, to which reference will not be made in this connexion.

[2] Bell, W. Blair, and Hick, P., *Brit. Med. Journ.*, 1909, vol. i, p. 655.

[3] Prénant, A., *Rev. Gen. de Sci.*, 1898, p. 646.

[4] Fraenkel, L., *Arch. f. Gynäk*, 1902, vol. lxviii, p. 438.
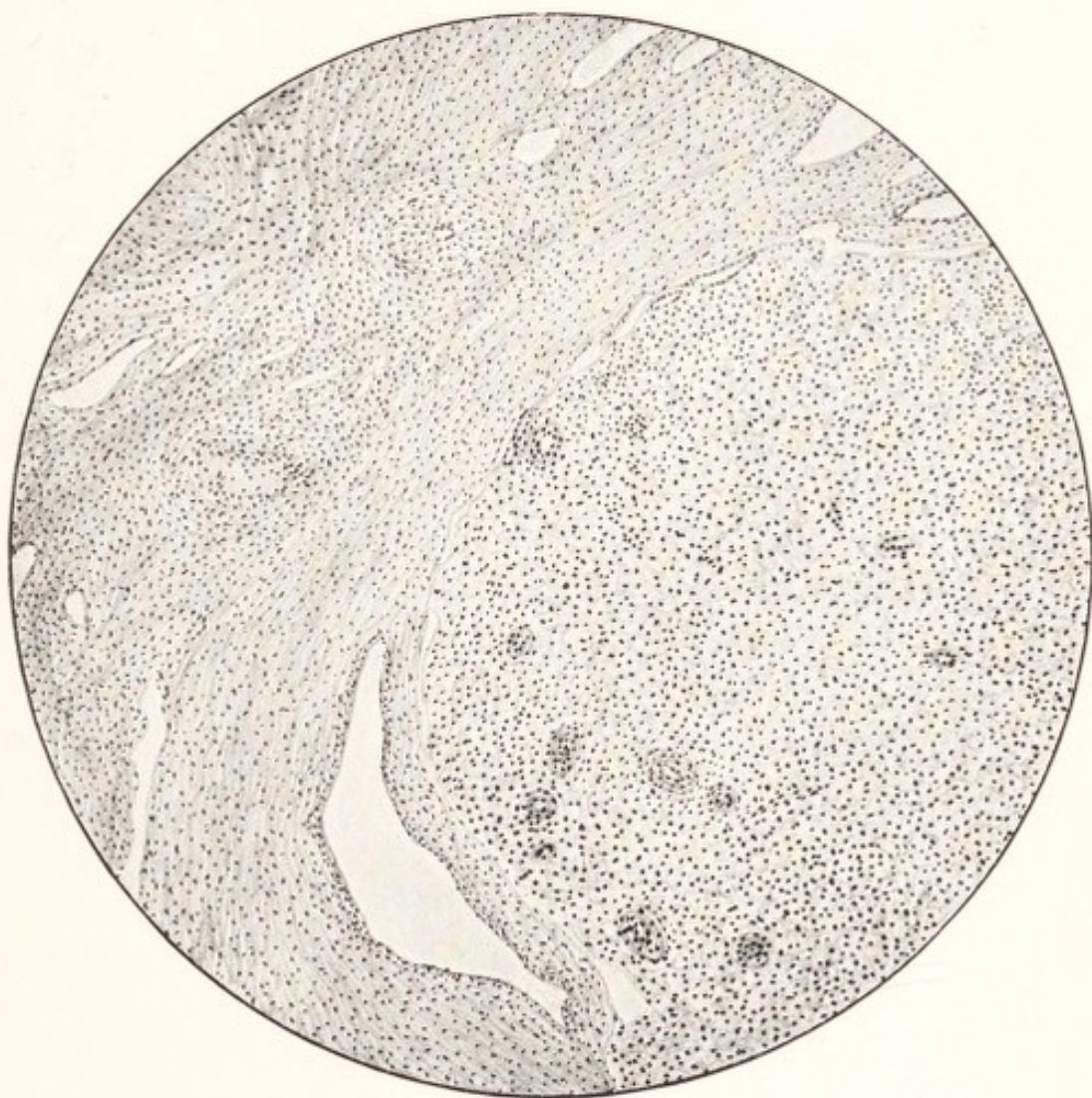
FIG. 5.

Section of the ovary of the cow, showing on the right side the cells
of the corpus luteum in which new vessels are being formed.

$\times$ 60.

Fig. 6.

Section of the human ovary, showing the lutein layer of cells.

$\times$ 60.

produced abortion by the removal of both ovaries in these animals[1], as the following experiments show :—

(a) *Control experiment.*—Black doe. Opened in the anticipation that she was a few days pregnant. Pregnancy could not be detected, but the ovaries and uterus were examined and handled, and the abdomen closed. There was no further connexion with the buck. Twenty-three days later one young one was born alive. This case was, therefore, regarded in the light of a control experiment.

(b) Grey doe. Oöphorectomy was performed on the seventh day of pregnancy. The uterus was enlarged and small nodules were visible. No abortion was seen to occur. On the thirty-third day after operation the abdomen was opened, and the uterine cornua were found to be very small. Abortion had undoubtedly occurred, and been followed by atrophy of the uterus.

(c) Black doe. Oöphorectomy was performed on the fourteenth day of pregnancy. Abortion took place on the following day. The animal was killed twenty days later when the uterus was found to be atrophied.

(d) White and grey doe. Oöphorectomy was performed on the twentieth day of pregnancy. Abortion occurred on the following day.

Other similar experiments were performed on rabbits, with the invariable result that abortion occurred in every case in which oöphorectomy was performed. Great care was taken in all cases not to expose the uterus, nor to handle it, and the operation was always completed in a few minutes.

There has been much discussion in connexion with this question since oöphorectomy was first performed experimentally during pregnancy by Fraenkel[2] at the

[1] Bell, W. Blair, and Hick, P., *Brit. Med. Journ.*, 1909, vol. i, p. 655.
[2] Fraenkel, L., *Arch. f. Gynäk*, 1902, vol. lxviii, p. 438.

suggestion of Born. Fraenkel claimed that the secretion of the corpus luteum was necessary for the implantation of the ovum. There are, however, still those who assert that the necessary operative manipulations cause the abortion which usually occurs. I am inclined to think that it is not the operative manipulation in view of our control experiments. At the same time, I do not think that a comparison can be made between rabbits and the human subject in this respect, for there are authentic cases on record in which the ovaries have been removed from women early in pregnancy—in one case, in the second week (Essen-Möller[1])—without the interruption of gestation. There could be no doubt in cases observed in women that the whole of both ovaries had been removed if parturition were followed by the artificial menopause.

It would be accurate, therefore, to say that while, on the one hand, the internal secretion of the ovary is favourable to the continuation of pregnancy, yet, on the other, this secretion is not absolutely essential in that respect—at any rate, in the human subject.

EFFECTS OF OÖPHORECTOMY ON THE GENERAL METABOLISM

I performed the following experiments to test the effect of this operation on the general metabolism.

The ovaries were removed from six cats which were kept subsequently to operation for periods ranging from 99 to 245 days. The urine was collected and fully examined at frequent intervals, both before and after operation.

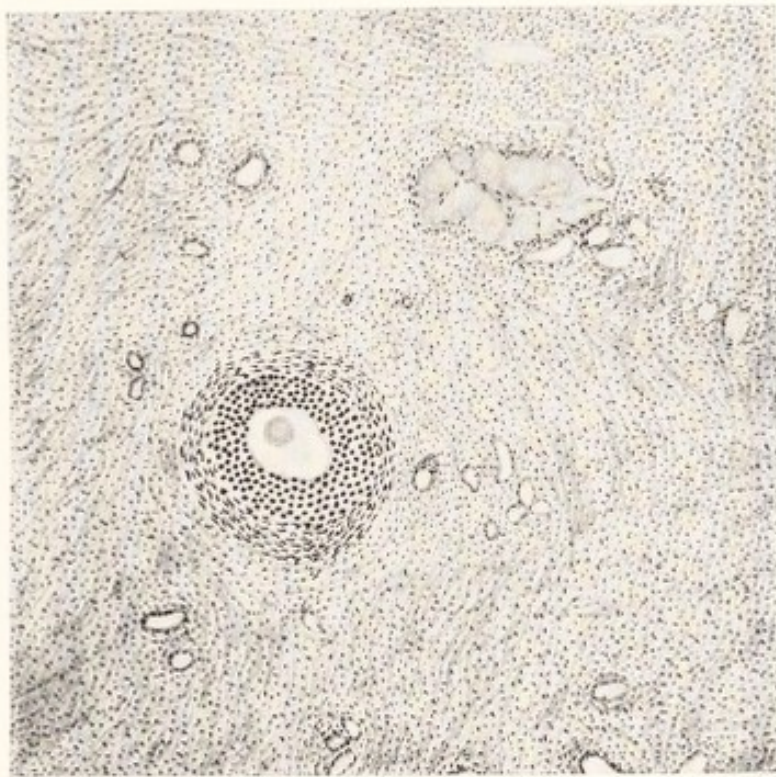[1] Essen-Möller, E., *Centralbl. f. Gynäk.*, 1904, vol. xxviii, p. 869.

FIG. 7.

Section of the human ovary, showing a Graafian follicle,
a corpus fibrosum and the stroma.

$\times$ 60.

TABLE I.—*Removal of Ovaries. Averages of Metabolism Estimations of 24 hours' Specimen Urines Before and After Operation.*

Date.	Number of specimens examined.	Specific gravity.	Diacetic acid.	Acetone.	Albumin.	Sugar.	Indican.	Ca %.	Cl %.	P$_2$O$_5$ %.	Total N %.	Urea %.	NH$_3$ %.	Ammonia coefficient.		
														Urea N %.	NH$_3$ N %.	Undet. N %.
Cat No. 1.																
Commenced 3/1/12	10	1022	0	0	0	0	3 times	0·0089	0·071	0·224	1·92	3·77	0·115	90·29	5·20	4·51
Operation 24/1/12 Destroyed 2/5/12	23	1045	0	0	0	1	5 times	0·0030	0·114	0·550	4·75	9·42	0·247	92·54	4·30	3·16
Cat No. 2.																
Commenced 3/2/12	6	1029	0	0	0	Once	Twice	0·0050	0·205	0·317	2·93	5·74	0·226	90·83	7·24	1·93
Operation 13/2/12 Destroyed 5/10/12	21	1042	Once	0	0	Once	10 times	0·0026	0·148	0·527	4·43	8·79	0·287	92·82	5·21	1·97
Cat No. 3.																
Commenced 17/2/12	3	1030	0	0	0	0	0	0·0060	0·260	0·411	3·38	6·82	0·331	89·04	7·02	3·94
Operation 21/2/12 Destroyed 23/10/12	31	1034	0	Once	Once	0	7 times	0·0026	0·158	0·476	4·35	8·48	0·361	90·91	6·79	2·30
Cat No. 4																
Commenced 4/3/12	7	1053	0	0	0	0	4 times	0·0040	0·161	0·335	6·60	13·13	0·686	92·78	3·74	3·48
Operation 13/3/12 Destroyed 6/11/12	22	1047	0	0	0	0	16 times	0·0018	0·170	0·582	3·82	6·38	0·605	77·87	13·01	9·12
Cat No. 5.																
Commenced 1/4/12	5	1044	0	0	0	0	4 times	0·0016	0·216	0·433	4·10	8·16	0·295	91·62	5·96	2·42
Operation 12/4/12 Destroyed 6/11/12	23	1047	0	0	Once	0	10 times	0·0010	0·141	0·575	5·44	9·94	0·472	85·18	6·94	7·88
Cat No. 6.																
Commenced 12/4/12	9	1050	0	0	0	0	4 times	0·0015	0·131	0·602	2·05	3·94	0·207	88·72	8·24	3·04
Operation 26/4/12 Destroyed 20/11/12	19	1044	0	0	3 times	0	3 times	0·0010	0·126	0·599	4·81	9·24	0·681	89·64	5·22	5·14

TABLE II.—*Removal of Ovaries. Average of above Estimations.*
From Six Cats Before and After Removal of Ovaries

Date.	Number of specimens examined.	Specific gravity.	Diacetic acid.	Acetone.	Albumin.	Sugar.	Indican.	Ca %.	Cl %.	P$_2$O$_5$ %.	Total N %.	Urea %.	NH$_3$ %.	Ammonia coefficient.		
														Urea N %.	NH$_3$ N %.	Undet. N %.
Before operation	7 approx.	1038	0	0	0	Once	17 times	0·0045	0·174	0·387	3·49	6·92	0·310	90·54	6·23	3·22
After operation	23 approx.	1043	Once	Once	5 times	Twice	51 times	0·0021	0·142	0·551	4·60	8·70	0·442	88·16	6·91	4·92

In table I are brought together a number of records which represent the averages of the 24-hours' specimens of urine collected and examined before and after operation. The tables were worked out in this way, as it seemed the best for indicating the total results. All metabolism experiments require most careful handling, and the complete records here given show clearly why contradictory results have been obtained by various observers dealing with insufficient material. As I have already stated, there are both normal and abnormal individual variations in animals, just as there are in women under apparently similar circumstances. My animals were all kept together and fed on the same food. The urines were collected in special metabolism cages— not all on the same days, of course, owing to the number of these cages being limited.

With regard to the details to be found in this table, it will be noticed that the daily total quantities of urine collected are not stated. I have records of these, but they have been omitted because it is rarely possible in an ordinary way to make sure of collecting all the urine, and because animals, unlike women, do not pass a uniform quantity daily. I have, therefore, thought it better to give the specific gravities and deal in percentage quantities rather than total amounts. All these estimations were carried out in the Bio-chemical Laboratory in the University of Liverpool by a chemical assistant trained in this kind of work.

Since there was inevitably a slight irregularity in the individual results, and as I had a sufficient number of animals, an average estimation of all six cases was worked out (table II); and from this the conclusions were drawn.

It will be noticed that there is not a great difference

in the averages of the specific gravities before and after operation. After oöphorectomy the calcium excretion is diminished by one-half, and the chlorides are slightly diminished. The phosphorus excretion is seen to be much increased, as are the total nitrogen and urea percentages. The ammonia is found to be slightly increased : it will be observed, however, that there is no change of any importance in the ammonia coefficient. Knowing that there are considerable variations in the nitrogen metabolism in the normal animal we cannot regard the differences recorded in this respect as being abnormal. The increased phosphorus excretion might be considered somewhat curious in view of the definite decrease in the excretion of calcium by one half, but it is believed that there is no definite and certain relationship between the calcium and phosphorus excretions.

McCrudden[1], relying on what appear to be two carefully planned experiments, in which the composition of the food taken in was known and compared with the subsequent excretion in the fæces and urine, states that he found an increased calcium excretion after oöphorectomy. At first sight the experiments appear flawless ; but an examination of the tables given soon reveals figures which require considerable explanation. In the first place, it seems incredible that each animal ate to the fraction of a gramme the same amount of food in the same number of days before and after operation. Further, of the two bitches, weighing 13 lb. and 16 lb. respectively, the former excreted a total of 0·529 gramme of CaO in 20 days before operation, and 0·532 gramme in the same period after operation—a very slight increase ; while the latter excreted 6·745 grammes of CaO in 20 days before operation, and only 1·869 grammes in the

[1] McCrudden, F. H., *Journ. Biol. Chem.*, 1910, vol. vii, p. 185.
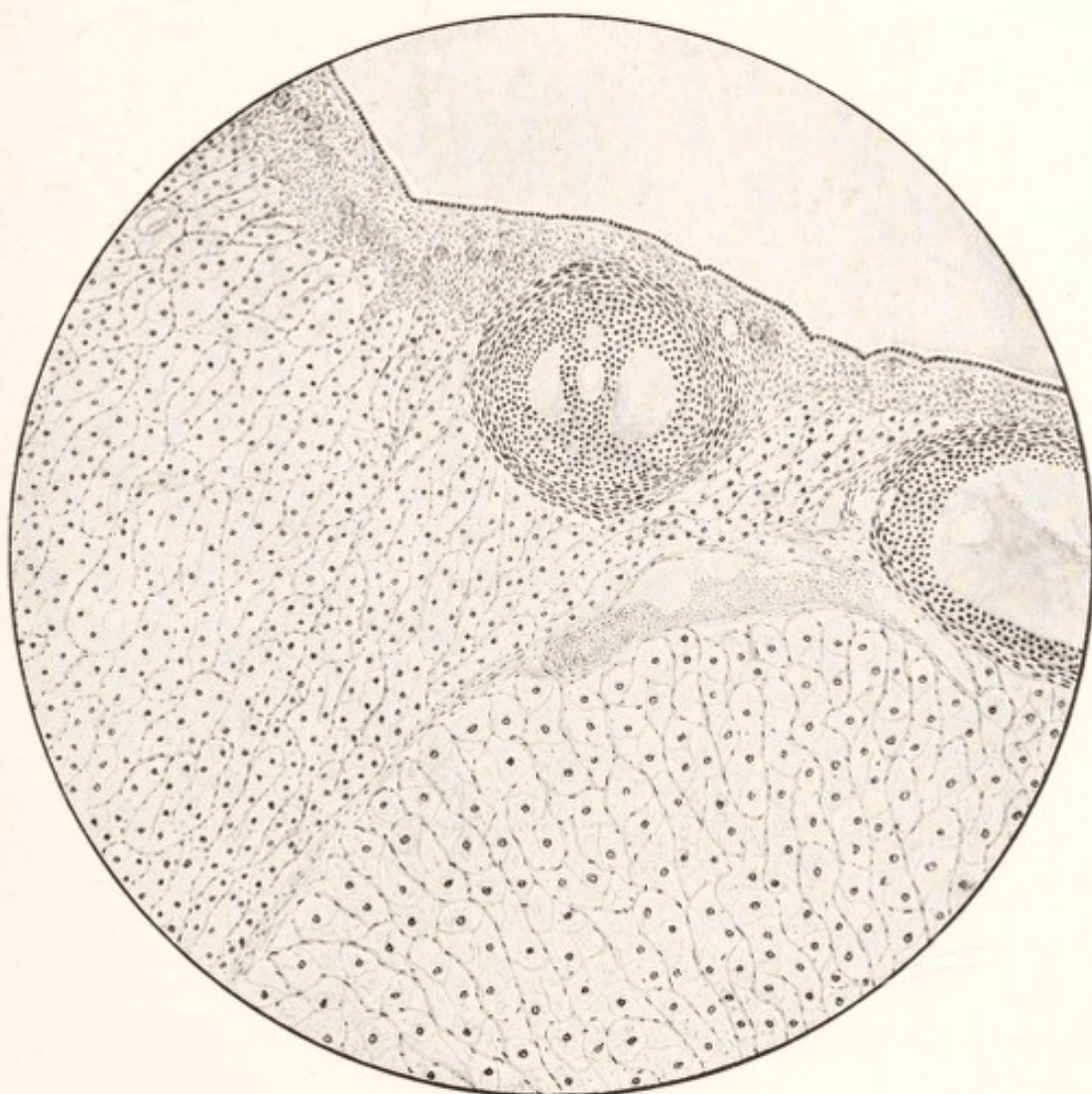
Fig. 8.

Section of the ovary of the adult rabbit, showing the Graafian follicles pushed to the surface by the interstitial cells among which is lying a large corpus luteum—in the lower quadrant on the right side of the field.
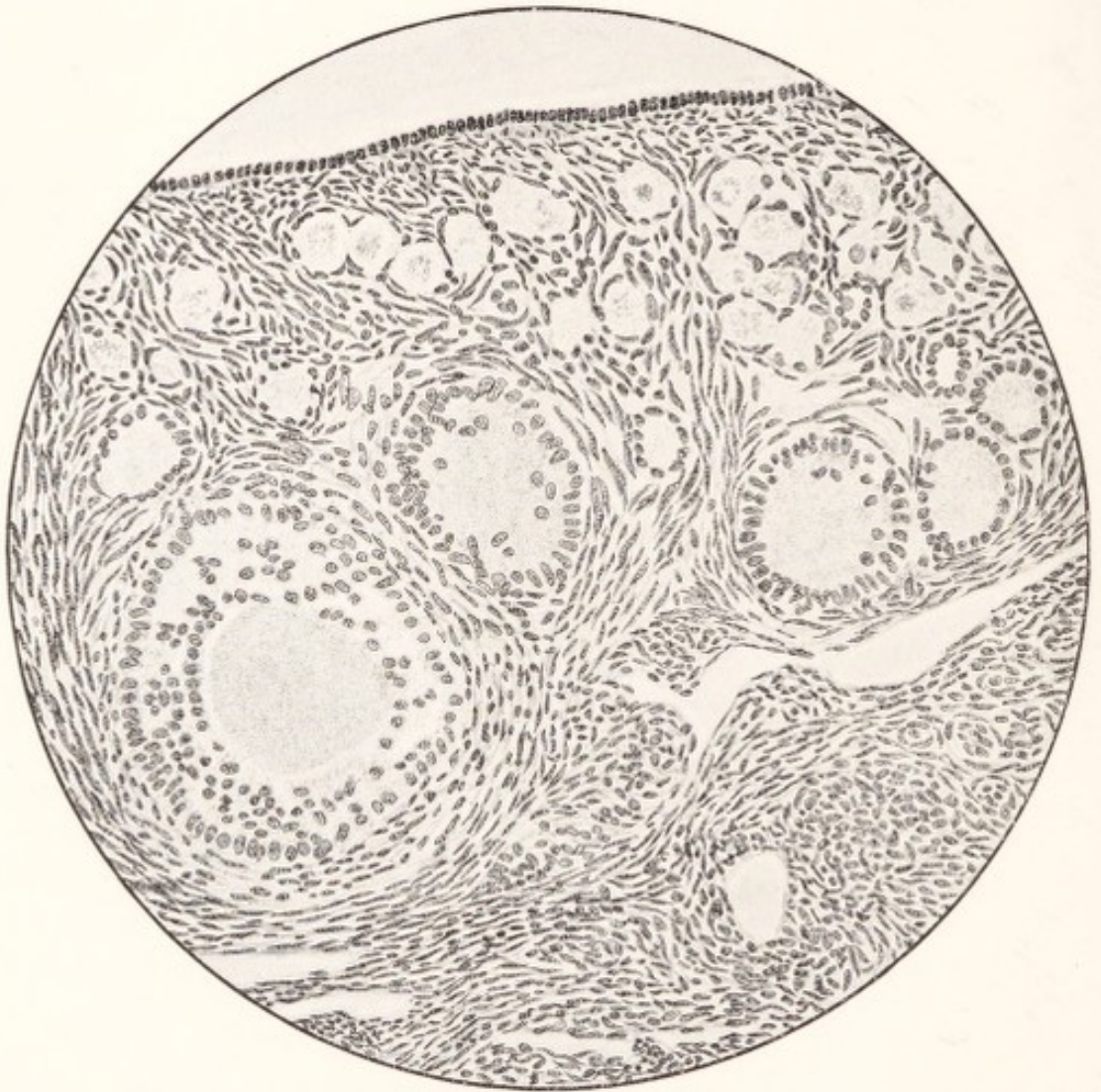
$\times$ 60.

FIG. 9.

Section of the ovary of the young rabbit, showing primordial ova and young Graafian follicles scattered throughout the organ, and separated by bundles of connective tissue cells.

$\times$ 250.

same time after operation. Surely these are extraordinary figures on which to base the conclusions at which this investigator arrived; for the last animal excreted before operation about three and a half times as much CaO as she did afterwards, and the first an infinitesimal amount more after operation than before. This is confirmatory of my figures, and diametrically opposed to McCrudden's own statements.

Louise McIlroy[1], working with a somewhat similar method on one animal only, also states that the output of calcium is increased after oöphorectomy. Her work was carried out to confirm that of McCrudden; and she gives no figures to enable us to check her conclusions.

Curatulo and Tarulli[2], also Neumann and Vas[3], found a reduction in the excretion of calcium and phosphorus after administering ovarian substance. Luthjé[4] could find no change in the metabolism after administration. Heymann, quoted by Biedl[5], found reduction in the phosphorus content of the bones of rats after oöphorectomy.

In young animals there is almost always an increase above the normal in the growth of the long bones after oöphorectomy, due to delay in the ossification of the epiphysial cartilages.

It may be of interest to call attention to a few other facts which afford evidence contributory to the view that the ovaries are concerned in promoting calcium

[1] McIlroy, Louise, *Proc. Roy. Soc. Med.*, 1912, vol. v, p. 369.

[2] Curatulo, G. E., and Tarulli, L., *Centralbl. f. Gynäk.*, 1895, vol. xiv, p. 555.

[3] Neumann, S., and Vas, B., *Monatsch. f. Geb. u. Gynäk.*, 1902, vol. xv, p. 433.

[4] Luthjé, H., *Arch. f. Exper. Pathol. u. Pharmakol.*, 1902, vol. xlviii, p. 184; 1903, vol. l, p. 268.

[5] Biedl, A., *Innere Sekretion*, 1913, 2nd ed.

excretion. During pregnancy and for at least the first few months of lactation the function of the ovaries is in abeyance in regard to menstruation, and at these times first the fœtus and then the mammary glands utilize all the available calcium ; indeed, the mother's calcareous tissues are sometimes drawn upon to her detriment. With regard to the mammary secretion, although it is so intimately connected with the genital functions, it is in reality of subsidiary importance ; that is to say, the secretion of milk is produced by a special arrangement of the general metabolism in response to various hormones connected with the necessities of the occasion. In women there is sometimes no response. Lactation is one of the side issues, and the metabolic processes connected with the production of milk are comparable with those which provide for the building up of the fœtus in the uterus. The mammary secretion will, however, be discussed at some length later. Again osteomalacia, to which, also, attention will again be directed, has often been cured by the removal of the ovaries ; and this result indicates the production of a condition of calcium retention in the tissues. My experiments are, therefore, supported by clinical observations.

The adiposity which is seen in castrated animals probably resembles that which occurs in over fifty per cent. of all women at the menopause. It has been stated that this adiposity is due, in these circumstances, not only to ovarian insufficiency but also to a coincidental reduction in the activities of the pituitary and thyroid.

Loewy and Richter[1] found that in an estimation of

[1] Loewy, A., and Richter, P. F., *Centralbl. f. Physiol.*, 1902, vol. xvi, p. 449.

FIG. 10.

Section of the cat's uterus, showing the normal muscle coats.

$\times$ 60.

FIG. 11.

Section of the cat's uterus, illustrated in figure 10, 238 days after oöphorectomy, showing atrophy of the muscle coats.

$\times$ 60.

the total metabolism, as expressed by the consumption of oxygen and excretion of CO_2, oöphorectomy caused a diminution in the proportion of 14 to 20 per cent. per kilogramme in the processes of oxidation. Biedl[1], quoting and commenting on these findings, states that strong evidence of their accuracy is to be obtained by the administration of ovarian extract, which, he asserts, will raise the lowered metabolism in castrated animals to as much as 30 to 50 per cent. above the standard obtaining before operation, an effect which cannot be produced in the case of the normal subject.

It is well known, of course, that from a casual inspection of adult animals which have undergone oöphorectomy we can detect no outward alteration except perhaps some degree of adiposity, yet apparently there is a constant depression of the total metabolism, with alterations in regard to the calcium retention and phosphorus excretion as shown by the urinary analyses. On the other hand, we know from clinical experience that easily recognizable changes may occur in women in whom an artificial menopause has been induced by oöphorectomy. At the same time, it has been a matter of very lively speculation why one woman should suffer with all manner of symptoms when her ovaries are removed, and another escape with very little or no discomfort. This is another reason why experimentation on animals has to be very carefully considered. The metabolism of women is much more easily disturbed than that of the lower animals; and psychoses and neuroses, which are not observed after oöphorectomy in animals, are often the source of the greatest distress in women.

[1] Biedl, A., *Innere Sekretion*, 1913, 2nd ed.

Recently Hoskins and Wheelon[1] have shown experimentally that in animals oöphorectomy is followed in a few weeks by increased excitability in the sympathetic nervous system. They accept the view that this is due to some disturbance in the calcium metabolism[2].

In addition to certain constant and positive results, which are always reliable in regard to the metabolism, experimentation provides us with other most useful information; and this information is just that which we cannot obtain in our clinical work, although Pathology may indicate the causal factors in many obscure phenomena. I refer to the effects produced on the other endocritic organs by removal of the ovaries.

No doubt the differences in the effects produced by oöphorectomy in women are largely dependent on the individual variations which we know exist with respect to the adjustments of the internal secretions, and which are often evident in the outward characteristics of adiposity and thinness, lethargy and brightness, and in many other physical and psychical attributes. It is clear, therefore, that if one woman be better adjusted than another against the removal of the ovarian secretion she will show less signs of the menopause. Animals do not vary to the same extent; they all seem to have remarkable powers of readjustment. But, with the higher psychical evolution of Woman it is not surprising that removal of the ovaries often causes in her a severe alteration of temperament.

It has been supposed that the changes which occur

[1] Hoskins, R. C., and Wheelon, H., *Amer. Journ. Physiol.*, 1914, vol. xxv, p. 119.

[2] Bell, W. Blair, *The Principles of Gynæcology*, 1910; *Liverp. Med. Chirur. Journ.*, 1912, vol. xxxii, p. 398.

FIG. 12.

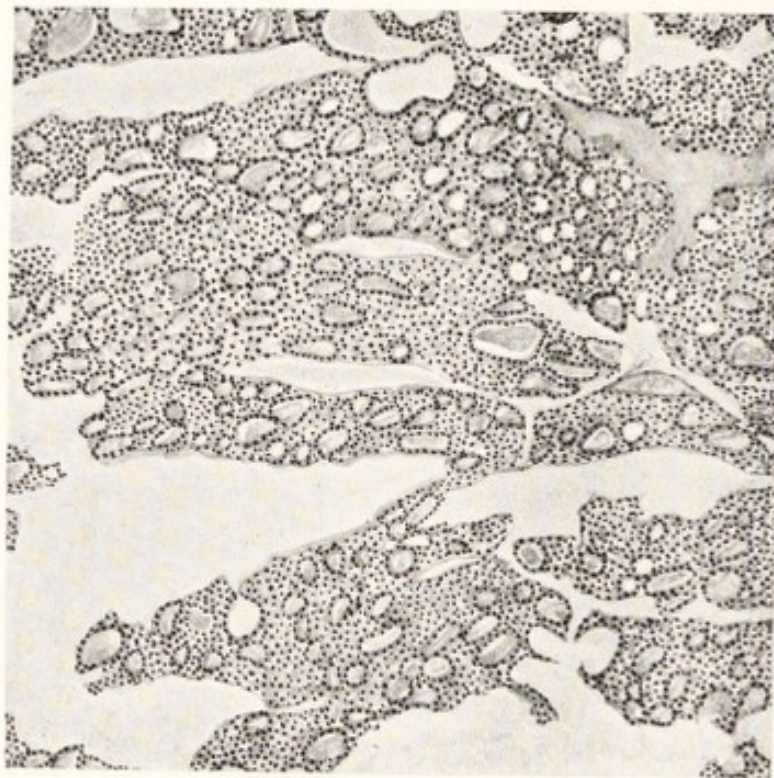Section of the thyroid of the normal rabbit, showing but little
colloid in the vesicles and much interstitial tissue.

$\times$ 60.

in other members of the endocritic system after removal of one of their number are in some cases compensatory, and, consequently, that disturbances in the metabolism may thus be made good or prevented.

EFFECTS OF OÖPHORECTOMY ON THE THYROID

If one were to select any other order of mammal than the rodent one would come to the conclusion that the alteration in the functional activity of the thyroid after oöphorectomy was of little or no importance in so far as histological evidence was concerned. For instance, in the cat I have been unable to detect any material difference after oöphorectomy in the thyroid itself or in the parathyroids. But when the thyroid of a normal female rabbit is compared with the thyroid of another animal of the same species after removal of the ovaries a very different picture may be seen.

The thyroid of the normal non-œstrous and non-pregnant female rabbit is not a very active organ so far as the production of colloid is concerned (fig. 12). But after the removal of the ovaries the vesicles are greatly distended with colloid (fig. 13). Further, one notices that the colloid is basophile in character, and therefore stains blue with hæmatoxylin instead of pink with eosin; whereas the normal thyroid colloid is, of course, acidophile and stains with eosin.

Before attempting any explanation of the changes in the thyroid after oöphorectomy, we must not forget that this organ in the pregnant rabbit shows a relatively great increase in the amount of colloid, but it is then eosinophile in character. This is not the place to discuss the significance of the normal colloid collections in the vesicles, as opposed to the absence of colloid seen

in conditions associated with excessive function. There can, however, be little doubt that the normal thyroid of the non-pregnant adult rabbit is not a very active structure, because removal causes little or no disturbance, an observation I have myself made on many occasions. On the other hand, in pregnancy, when, as is well known, increased thyroid activity occurs, we find that the colloid content is increased to a considerable extent in these animals, as already stated.

It may, then, safely be asserted that there is a considerable increase in the functional activity of the thyroid, so far as colloid production is concerned, in rodents after oöphorectomy. Why the colloid should be basophile instead of eosinophile we can only conjecture. The question of an artefact has been carefully considered, but this explanation must be rejected for many reasons, into which we need not enter here. We are, however, assisted in our attempt to arrive at a conclusion by observations made on the pituitary body, some of which will be referred to more fully later. The normal colloidal secretion of the anterior lobe and pars intermedia of the pituitary is basophile, but under conditions of increased activity it may be eosinophile. Further, as with the thyroid, in a condition of greater hypophysial activity no 'colloid' is formed, but the secretion is abstracted directly from the eosinophile cells. In the state of the greatest activity of all the secretion is directly abstracted by the blood or lymph from faintly staining basophile cells—the so-called 'chromophobe' cells. There is, in fact, a cycle of events to be demonstrated in the hypophysis according to the needs of the moment. It is probable, then, that the basophile colloid found in the rabbit's thyroid after oöphorectomy represents a storage secretion, which is formed to meet the altered conditions of
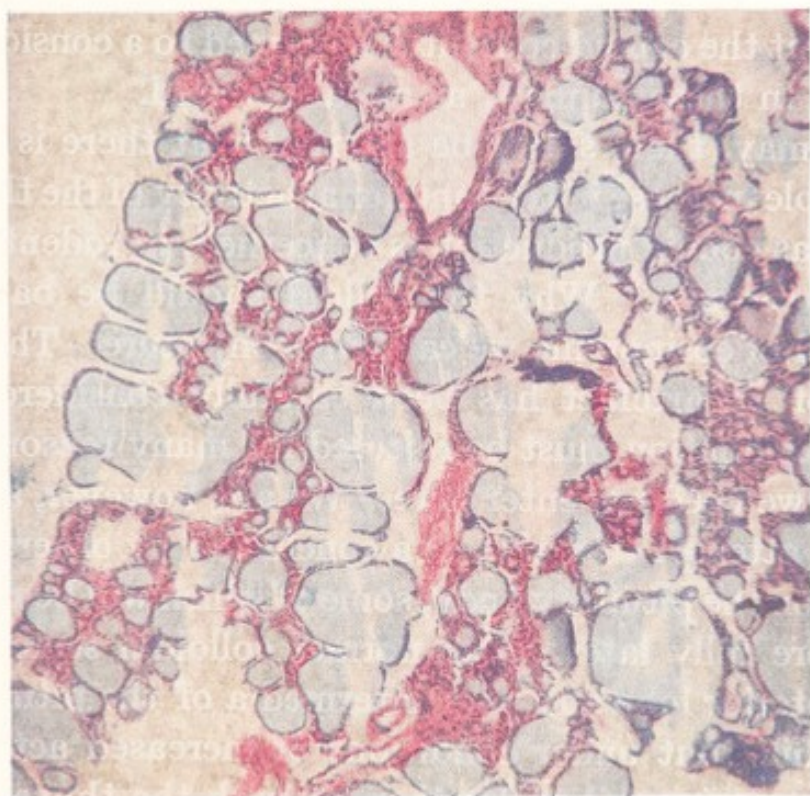
FIG. 13.

Section of the thyroid of the rabbit after oöphorectomy,
showing distension of the vesicles with basophile colloid.

(Direct colour photomicrograph.)

× 150

metabolism, but is not of a great degree of physiological activity in this order of mammals.

As we have previously suggested[1], the inactive thyroid which is found in rodents is probably related to the very remarkable development of the interstitial cells in the ovaries of these animals. In consequence of this a marked reaction is produced in the thyroid of rodents by oöphorectomy, and not to the same degree in other mammals such as the carnivora. Some have argued that the distance of the parathyroids from the thyroid in herbivora prevents their removal at the operation, and that the effects produced in carnivora are due to the removal of the parathyroids. This is not necessarily so, for we have been able to keep alive a cat with myxœdema for over a year.

McCarrison[2] and others, however, have pointed out that the thyroids of animals of the same species kept under similar conditions vary enormously, consequently great care is needed in drawing conclusions concerning changes in this organ.

EFFECTS OF OÖPHORECTOMY ON THE THYMUS

Calzolari[3] first showed that castration produces hypertrophy of the thymus. His experiments were carried out on rabbits. It has, also, been noted by Marrassini[4] and by Gellin[5] that castration after genital activity has been established gives rise to enlargement of the thymus. No work has been done in regard to

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[1] Bell, W. Blair, and Hick, P., *Brit. Med. Journ.*, 1909, vol. i, p. 655.

[2] McCarrison, R., *Lancet*, 1914, vol. i, p. 931.

[3] Calzolari, A., *Arch. Ital. de Biol.*, 1898, vol. xxx, p. 71.

[4] Marrassini, A., *Arch. Ital. de Biol.*, 1910, vol. liii, p. 419.

[5] Gellin, O., *Zeitsch. f. Exper. Pathol. u. Therap.*, 1910, vol. viii, p. 1.

women, but eunuchs have been found to possess thymus glands which have not undergone involution.

In experiments on cats I found the thymus much larger after oöphorectomy than in the normal adult animal ; and on section the gland appeared to resemble the normal organ in the active stage before puberty. The significance of this will be discussed later when the thymus gland is being considered in more detail.

EFFECTS OF OÖPHORECTOMY ON THE PINEAL GLAND

I have myself made no observations concerning the pineal gland after oöphorectomy—indeed, very little physiological work has been done in this connexion.

In 1912 Biach and Hulles[1] published a paper in which they gave the results of castration of male and female kittens a few weeks old. The animals were kept subsequently for periods of seven or eight months. These investigators arrived at the conclusion that atrophy of the pineal gland occurred in all cases. Other observers have been unable to find changes in this organ in these circumstances.

Later I shall consider the interesting effects on the genital functions of pathological changes in the pineal.

EFFECTS OF OÖPHORECTOMY ON THE SUPRARENALS

I have examined many suprarenals after oöphorectomy in rabbits and cats, and have found that there appears to be a definite increase in the reticulated portion of the cortex at the expense of the zona fasciculata. What the interpretation of this is I cannot say, unless

[1] Biach, P., and Hulles, E., *Wien. Klin. Woch.*, 1912, vol. xxv, p. 373.

it be that the removal of an antagonistic secretion allows hypertrophy to occur in the part concerned.

EFFECTS OF OÖPHORECTOMY ON THE PITUITARY BODY

The close relationship between the pituitary body and the genital system has long been recognized, and I have made a number of observations concerning the effect of the removal of the ovaries on this intracranial organ, and *vice versa*.

The interpretation of the first mentioned of these observations necessitates the formulation of definite ideas as to what the changes observed in the pituitary mean. We read of ' hyperplasia ', or of ' increased activity ' of the anterior lobe, which can convey little meaning to anyone until we have decided what are the appearances associated with increased activity and the reverse in the pituitary body. So far, tentative views only have been put forward, and no very decided statements have been made concerning this complex and interesting organ.

The pituitary consists of three parts—the pars anterior, the pars intermedia, and the pars nervosa. To each of these various portions, or perhaps more especially to the pars anterior, and to the pars posterior—which consists of the pars intermedia and pars nervosa—have been assigned different functions, concerning which authorities are still very much in disagreement.

Thus, we find that Harvey Cushing arrived at the definite conclusion, as the result of the experiments of himself and his co-workers[1], that the anterior portion was largely concerned in the well-being of the genital

[1] Crowe, S. J., Cushing, H., and Homans, J., *Bull. Johns Hopk. Hosp.*, 1910, vol. xxi, p. 127.

organs, and in the metabolism of the carbohydrates and of the bony skeleton. As the result of some clinical observations he completely changed his opinion, and now asserts[1] that it is the posterior lobe which is responsible for the integrity of the genitalia, and for the carbohydrate metabolism. Bernhard Fischer[2] had previously propounded this view.

After careful consideration and observation I have come to the conclusion that we must look upon the pituitary body as *one organ*, and not two. In this way only can we reconcile all the facts of morphology, experimentation and clinical observation. The secretion of the active chromophobe cells of the anterior lobe, such as are seen in pregnancy, is probably not greatly different from that of the pars intermedia before it is altered in the way about to be described. The secretion of the cells of the pars intermedia, which are developmentally the same as those of the pars anterior, may be regarded as pro-infundibulin, and it is only after passing into the pars nervosa that this pro-infundibulin becomes modified and acquires pressor qualities[3]. In connexion with this passage of secretion into the pars nervosa there are many other very important and interesting facts which are not actually concerned with our subject, so I refrain from discussing them here.

Next, we must come to some definite conclusion concerning the interpretation to be placed upon the remarkable differences in staining properties possessed by the cells of the anterior lobe. Although these

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[1] Cushing, Harvey, *The Pituitary Body and Its Disorders*, 1912.

[2] Fischer, Bernhard, *Hypophysis, Akromegalie und Fettsucht*, 1910.

[3] This statement was written and published (*Lancet*, 1913, vol. i, p. 814) before the recent work of P. T. Herring (*Quart. Journ. Exper. Physiol.*, 1914, vol. viii, p. 245).
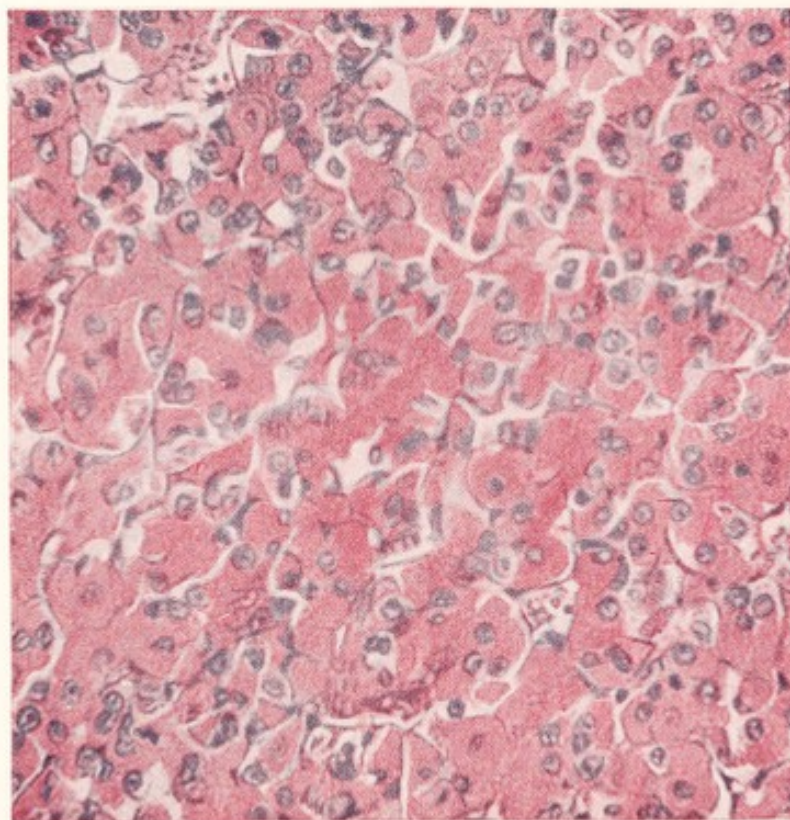
FIG 14.

Section of the pars anterior of the cat after oöphorectomy,
showing well-marked eosinophile cells only.

(Direct colour photomicrograph).

$\times$ 500.

variations in staining affinities are well known, I must recapitulate them here in order to explain my own views concerning their significance. The cells, then, of the anterior portion are chromophobe or chromophile; that is to say, they stain indifferently or well. The chromophile cells are either eosinophile (acidophile) or hæmatoxylinophile (basophile) : with eosin the cells stain pink, and with hæmatoxylin blue. The chromophobe cells stain lightly with hæmatoxylin.

There are two opinions held concerning this extraordinary grouping. The one, first put forward by Saint-Rèmy[1] and Benda[2], finds expression in the belief that these appearances represent different phases of secretory activity. While the alternative view, propounded by Gemelli[3] and others, represents the idea that each type of cell has a special secretion. My own view coincides with the first suggestion, and after careful investigation I have come to the following conclusions regarding the cycle of events :—

Firstly, the eosinophile cells represent the normal actively secreting cells, which ordinarily discharge their secretion into the blood-vessels or lymphatics. If there be no great demand for the secretion the cells may enlarge and become basophile ; they then gradually become darker and more swollen until finally they discharge basophile 'colloid' among the neighbouring cells, which may form a vesicle-like wall around the secretion. After the discharge of 'colloid' the basophile cells become small, shrunken and faintly staining (chromophobe cells) with large nuclei in which a network

[1] Saint-Rèmy, G., *Compt. Rend. de l'Acad. des Sci.*, 1892, vol. cxiv, p. 770.

[2] Benda, C., *Berl. Klin. Woch.*, 1900, vol. xxxvii, p. 1205.

[3] Gemelli, A., *Folia Neuro-biol.*, 1908, vol. ii, p. 167.

of chromatin fibres can be seen. I have elsewhere[1] illustrated these phases from direct colour photographs.

Secondly, in certain circumstances, as in pregnancy or after removal of the thyroid or suprarenals, there is immediate demand for secretion—in the first cases from the anterior lobe, and in the last from the posterior. In pregnancy, and after thyroidectomy, the small chromophobe cells in the anterior lobe regenerate into large chromophobe cells, and eosinophilia—a more leisurely process—does not occur to the usual extent. These chromophobe cells have been called ' pregnancy cells ' owing to their constant appearance in the pars anterior during pregnancy. After removal of the suprarenals there is an increased invasion of the pars nervosa by cells from the pars intermedia.

It is most important, too, in experimental work not to lose sight of the fact that the phases of secretory activity vary in different orders of animals and at different ages in the same animal, and that the large basophile cells and basophile 'colloid' are not seen, so far as my experience goes, either at all or with the same regularity in the various species of rodents, as in the higher mammals.

Further, it must be mentioned that the pars intermedia secretes a granular ' colloid ', normally basophile in reaction, but in some circumstances, to be mentioned directly, eosinophile.

The ' colloid ' which is formed both in the pars anterior and in the pars intermedia is probably a storage secretion, like the colloid seen in the thyroid. The most active method of secretion in both parts of the pituitary is intracellular. In the actively secreting pars intermedia the cells swell up and become fused, and the

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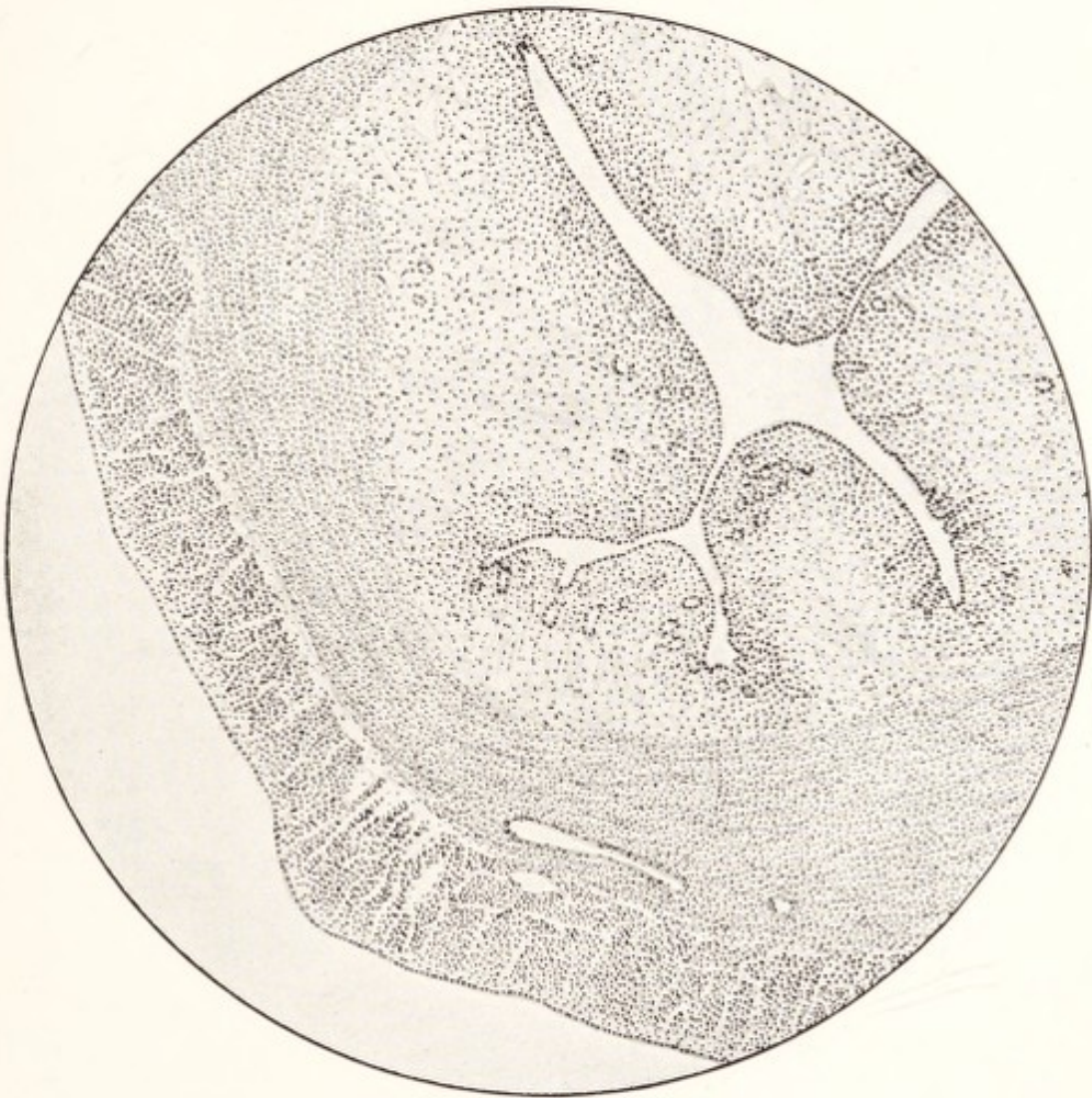[1] Bell, W. Blair, *The Pituitary*. (*In the press.*)

FIG. 15.

Section of the uterus of the rabbit, showing the normal muscle coats.

× 60.

FIG. 16.

Section of the rabbit's uterus, illustrated in figure 15, 80 days after transplantation of both ovaries from the normal sites to the muscles of the abdominal wall: the muscle coats are normal.

$\times$ 60.

secretion is, I believe, for the most part taken up immediately by the blood or lymph. Nevertheless, some of the masses of secretion which may be seen in the pars intermedia, and even the actual cells, pass directly into the pars nervosa, whence absorption occurs; and it is in the pars nervosa that, as already stated, the pressor qualities of infundibulin are acquired.

To return from this necessary digression. Removal of the ovaries appears to cause a certain increase in the secretory activity of the anterior lobe of the pituitary body on the lines indicated; but in my experience the change is moderate and not quite constant. Thus in one experiment—cat no. 5 of the ovarian removal series recorded above—after an interval of 208 days there was no divergence from the normal to be recognized histologically.

The effect appears to be more or less temporary, and in no way comparable with the genital lesions seen after partial extirpation of the pituitary. In most of my cats, however, definite changes were found as long as 245 days after oöphorectomy. In these circumstances, there was a large preponderance of brightly stained eosinophile cells in the anterior lobe (fig. 14)—a condition indicating increased activity, but not the great activity seen after the thyroidectomy.

In the pars intermedia the cells were fused and there were 'colloid' vesicles, and sometimes 'colloid' cysts. This 'colloid' stained with eosin, in contradistinction to the normal condition of basophilia.

It is interesting to note that the changes which we find in the pituitary after oöphorectomy—that is, with ovarian insufficiency—are not the same as those found in pregnancy; consequently the relation of the pituitary body to the genital glands differs, in this respect at least,

from the ovarian-thyroid relationship in similar circumstances. Fichera[1], however, believes that the " hyperplasia and hypertrophy " which follow oöphorectomy resemble the condition seen in the anterior lobe during pregnancy. Accordingly, this authority thinks that the change found in the anterior lobe during pregnancy is due to ovarian insufficiency. As already stated, I have seen nothing in my experimental results to lead me to adopt this view, however plausible it may appear at first sight.

OVARIAN TRANSPLANTATION

Probably Knauer[2] was the first systematically to test the effect of ovarian transplantation. I worked with rabbits and dogs, and found, as Knauer had done, that if the ovaries be excised and implanted in the muscle of the uterus or abdominal wall, atrophy of the genital ducts will not occur (figs. 15 and 16). Since these experiments by Knauer many observers have confirmed his findings regarding the integrity of the uterus after oöphorectomy followed by transplantation. Limon[3] noticed that the follicles in the graft tend to degenerate after a time, while the interstitial cells remain unaffected. I found, as Marshall and Jolly[4] had previously observed, that the follicles first become cystic (fig. 17) and then degenerate ; that is to say, they ripen, but, if completely buried cannot expel the contents, and therefore become cystic and retrogress.

[1] Fichera, G., *Il Policlinico*, 1905, vol. xii (Chir), pp. 250, 299, 319.

[2] Knauer, E., *Centralbl. f. Gynäk*, 1896, vol. xx, p. 524.

[3] Limon, M., *Journ. Physiol. et Pharmacop. Gen.*, 1905, vol. vi, p. 864.

[4] Marshall, F. H. A., and Jolly, W. A., *Quart. Journ. Exper. Physiol.*, 1908, vol. i, p. 115.

FIG. 17.

Section of the graft of the rabbit's ovary, which had been implanted in the muscles of the abdominal wall 93 days previously, showing cystic degeneration in a Graafian follicle.

$\times$ 36.

FIG. 18.

Section of a graft of the rabbit's ovary, which had been implanted in the muscles of the abdominal wall 24 days previously, showing (in serial sections) interstitial cells only. There was no atrophy of the uterus.

$\times$ 250.

I also noted a fact of considerable importance: namely, that in the rabbit if only the central portion of the ovary, which contains no follicles, be implanted (fig. 18), the interstitial cells of which the graft is composed can maintain the integrity of the uterus alone.

Halsted[1] has stated that grafts of the organs of internal secretion ' grow ' better when a condition of insufficiency exists in regard to the particular secretion. There was no evidence of this in my experiments with the ovaries of rabbits; for the grafts ' grew ' as well when one ovary was left *in situ* as when both were removed.

It is probable, then, that ovarian transplantations in general, and transplantations of the interstitial cells in particular, are capable of keeping normal the uterus, the mammæ, the other endocritic organs, and the general metabolism in the female animal. And, since the isolated interstitial cells are effective in this respect, it is probable that the follicular secretion has no function beyond nourishing the ovum and influencing the dehiscence of the follicle—at any rate in the rabbit.

In my experience ovarian transplantation in women is not so certainly successful as it is in the lower animals. Indeed, it is in rabbits, in which the interstitial cells are very well developed, that the best results have been obtained.

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[1] Halsted, W. S., *Journ. Exper. Med.*, 1909, vol. xi, p. 175.

THE RELATION OF THE THYROID TO THE GENITAL SYSTEM

The accessible position of the thyroid gland has enabled clinicians to pay some attention to the obvious connexion of this organ with the genital functions.

At puberty a temporary enlargement—especially during menstruation—may often be observed in women ; and in all mammals we invariably find the thyroid considerably increased in size during pregnancy.

This temporary enlargement indicates, of course, a change in the secretory activity of this organ to meet the metabolic requirements in these circumstances.

We shall, perhaps, be in a better position to appreciate the changes that occur in the rest of the genital system if we first consider the effects on the general metabolism of removal of this organ.

EFFECTS OF THYROIDECTOMY ON THE GENERAL METABOLISM

Different mammals vary very much in their power of withstanding the disastrous results which may follow complete removal. Grave effects never supervene on the removal of the thyroid in rabbits; and this exemption has been explained, as we have already seen, on the ground that the parathyroids are relatively large, and lie well away from the thyroid itself, and consequently cannot be removed without a careful search—in

other words, they escape removal during the operation of thyroidectomy.   Swale Vincent and Jolly[1] have shown that after thyroidectomy the parathyroids actually secrete colloid, and, in fact, after this operation perform the functions of the thyroid just as they resemble it in structure.   But I do not believe that this question of the remaining parathyroids is the whole truth. Herbivora have less need of the thyroid than other mammals, such as the carnivora.   It may be because the diet is different, but I feel sure it is also due in some measure to the variations in the structure and function (or degrees of function) seen in the other endocritic organs.   I have already alluded to the differences in structure between the ovaries of rodents and those of the higher mammals.   If, however, we take cats and remove their thyroids, many die in a few days, usually with convulsions.   In these cases it is probable that the immediate result is due to the removal of the whole thyroid apparatus (thyro-parathyroid).   Some cats, however, may survive the operation for a long period of time ; and in all these cases one can demonstrate the removal of the whole thyroid together with the internal parathyroids, one of which is embedded in each lobe of the thyroid.   In these animals, therefore, the true effects of thyroid insufficiency may be obtained.   Further, it has been stated by Stanley Kent[2] and confirmed by Hick and myself[3], that castration minimizes the effect of thyroidectomy.

The number of cats in my experiments in which the metabolism after thyroidectomy was investigated fully

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[1] Vincent, Swale, and Jolly, W. A., *Journ. Physiol.*, 1904–5, vol. xxxii, p. 65.

[2] Kent, Stanley, *Journ. Physiol.* (*Proc. Physiol. Soc.*), 1894, vol. xv, p. 18.

[3] Bell, W. Blair, and Hick, P., *Brit. Med. Journ.*, 1909, vol. i, p. 517.

was small, for, as already stated, many died too soon for the metabolism, as represented by the urinary excretion, to be estimated. The record of one non-pregnant cat (table III, cat no. 1) which was destroyed two and a half months after operation, has been selected as typical. Other experiments were complicated by the cats having had kittens shortly before operation, and in consequence the figures obtained from them did not appear to be suitable for averaging with those from the uncomplicated cases.

It will be seen that in this animal acetone was present three times in 20 estimations after operation.

The calcium excreted after operation was the same in quantity as before operation. There was a drop in the phosphorus excretion, in spite of the increase in the specific gravity after operation; and the total nitrogen and urea are increased out of proportion to this rise in the specific gravity. It will be noticed, also, that the ammonia coefficient is slightly increased.

I am well aware that the records of one animal cannot carry much weight; but this was the only uncomplicated and reliable result out of five non-pregnant animals on which I operated in this series.

Before considering the effect of thyroidectomy on the rest of the organs of internal secretion I will first recount a rather important series of experiments in which thyroidectomy was performed on three pregnant cats which survived the operation for some time. They were carried out in order to observe the influence of the thyroid on the metabolism during pregnancy, especially with reference to the possible production of the symptoms of eclampsia with marked alterations in the ammonia coefficient. Further, I had in my mind the possibility that the secretion of the fœtal thyroid might reach the

TABLE III.—*Removal of Thyroid. Averages of Metabolism Estimations of 24 hours' Specimen Urines.*
Cat No. 1 (Non-pregnant).

Date.	Number of specimens examined.	Specific gravity.	Diacetic acid.	Acetone.	Albumin.	Sugar.	Indican.	Ca %.	Cl %.	P_2O_5 %.	Total N %.	Urea %.	NH_3 %.	Ammonia coefficient.		
														Urea N %.	NH_3N %.	Undet. N %.
Commenced 6/6/12 .. .. Operation 12/6/12	3	1040	0	0	0	0	Twice	0·0010	0·147	0·631	3·38	7·62	0·310	88·01	2·21	9·77
Destroyed 30/8/12	20	1047	0	3 times	0	0	Once	0·0010	0·144	0·607	4·48	8·84	0·320	92·03	5·62	2·35

TABLE IV.—*Removal of Thyroid. Averages of Metabolism Estimations of 24 hours' Specimen Urines.*
Cat No. 1 (Pregnant).

Date.	Number of specimens examined.	Specific gravity.	Diacetic acid.	Acetone.	Albumin.	Sugar.	Indican.	Ca %.	Cl %.	P_2O_5 %.	Total N %.	Urea %.	NH_3 %.	Ammonia coefficient.		
														Urea N %.	NH_3N %.	Undet. N %.
Commenced 28/5/11 .. .. Operation 31/5/11	3	1031	0	0	0	0	0	—	0·035	0·261	2·98	6·04	0·151	94·56	4·16	1·28
Had kittens 9/6/11	8	1009	0	4 times	5 times	7 times	0	0·0060	—	—	1·61	1·45	0·174	52·96	4·30	42·74
Destroyed 10/8/11	13	1040	0	12 times	4 times	9 times	6	0·0160	0·172	1·190	4·62	8·39	0·225	84·69	4·00	11·31
Cat No. 2 (Pregnant).																
Commenced 19/10/11 .. .. Operation 21/10/11 Had kittens 23/10/11	1	1044	0	0	0	Once	Once	0·0050	0·105	0·141	6·47	11·72	0·280	84·50	4·09	11·41
Died 20/11/11	8	1027	0	0	0	Once	4 times	0·0110	0·165	0·318	2·63	5·24	0·130	92·89	4·04	3·07
Cat No. 3 (Pregnant).																
Commenced 16/6/12 .. .. Operation 19/6/12	3	—	0	0	0	0	Once	0·0010	0·210	0·357	2·55	4·59	0·416	78·92	12·57	8·51
Had kittens 29/6/12	3	1028	0	0	0	0	Twice	0·0010	0·211	0·254	3·13	6·35	0·592	92·38	1·81	5·81
Destroyed 24/10/12	11	1044	0	Once	0	0	0	0·0015	0·148	0·729	3·42	6·26	0·304	85·35	6·95	7·70

TABLE V.—*Averages of Metabolism Estimations of 24 hours' Specimen Urines from the Three Pregnant Cats Before and After Removal of Thyroid.*

| —	Number of specimens examined.	Specific gravity.	Diacetic acid.	Acetone.	Albumin.	Sugar.	Indican.	Ca %.	Cl %.	P_2O_5 %.	Total N %.	Urea %.	NH_3 %.	Ammonia coefficient.		
														Urea N %.	NH_3N %.	Undet. N %.
Before operation	2 approx.	1037	0	0	0	Once	Twice	0·0030	0·116	0·253	4·00	7·45	0·282	85·99	6·94	7·06
After operation and before having kittens	5 approx.	1018	0	4 times	5 times	7 times	Twice	0·0030	0·211	0·254	2·37	3·90	0·383	72·67	3·05	24·27
After having kittens	11 approx.	1037	0	13 times	4 times	10 times	10 times	0·0095	0·161	0·745	3·55	6·63	0·219	87·64	4·99	7·02
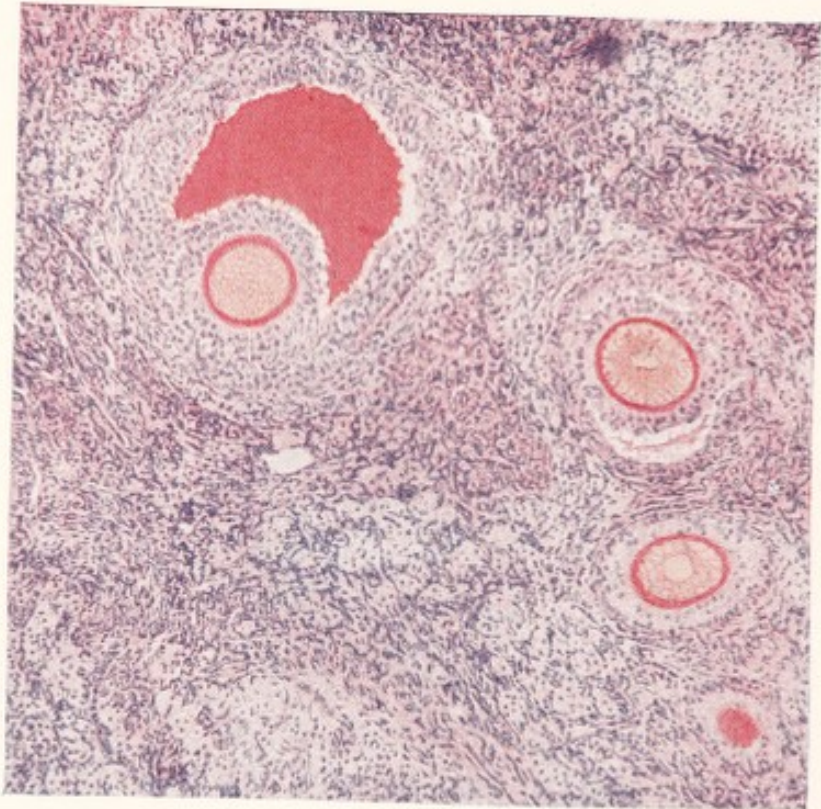
FIG. 19.

Section of the ovary of the cat after thyroidectomy, showing
eosinophilia of the Graafian follicles and
interstitial cells.

(*Direct colour photomicrograph*).

× 150

mother's circulation and mitigate the effects of the thyroidectomy performed on her.

The records of each case (table IV, cats no. 1, 2, 3) are drawn up to show the metabolism before operation, and in two cases after operation and before parturition. In one case the kittens were born alive at full term two days after the operation and before the estimations of the urinary metabolism had been resumed. It may be pointed out here that no estimations were carried out for a few days after any operation in order to avoid the effects produced by the anæsthetic.

It will be noticed that acetone, albumin and sugar were found a good many times after operation in cat no. 1, and more frequently after parturition than before, without any great disturbance of the ammonia coefficient. Cat no. 3 gave birth ten days prematurely to stillborn kittens.

Turning to the averages (table V) we see that so long as the cats remained pregnant the calcium excretion remained constant, but that after parturition it was increased to treble the quantity. The excretion of phosphates, also, after the birth of kittens showed a remarkable increase. There was no disturbance of the ammonia coefficient.

It does not appear probable, therefore, that the thyroid is in any way specifically connected with the production of eclampsia, as was originally suggested by Nicholson[1]. It is true that two of our cats (no. 4 and 5), which are not included in the series and were *in the first half of pregnancy*, died with convulsions in a few days, but the manner of death was similar in every respect to that seen in non-pregnant animals in the same circumstances.

The evidence of these experiments is in favour of the

[1] Nicholson, H. O., *Scot. Med. Surg. Journ.*, 1901, vol. viii, p. 503.

possibility that in the latter half of pregnancy the secretion of the fœtal thyroid may be conveyed to the mother.

EFFECTS OF THYROIDECTOMY ON THE OVARIES AND UTERUS

The normal ovary of the cat, with which animal we are concerned in these particular experiments, shows certain affinities for eosin in some of its elements. The zona pellucida, the liquor folliculi, the interstitial cells and the cells of the corpora lutea all stain faintly with eosin. After thyroidectomy all these elements show an increased avidity for eosin (fig. 19). This is especially true of the zona pellucida and the liquor folliculi, and it appears to be a matter of some importance.

It seems that removal of the thyroid calls for a response from the ovary, just as oöphorectomy did from the thyroid. The nature of this response, if these observations be correctly interpreted, is one of considerable interest, for it brings forward evidence that the granulosa cells of the Graafian follicle form an organ of internal secretion. But we have already seen (p. 47) that the follicular secretion is not necessarily connected with the integrity of the uterus, and the effect of thyroidectomy gives further confirmation of this fact, for after thyroidectomy the uterus atrophies to a remarkable extent. Figure 10 is a section of the uterus of a normal cat, while figure 20 that of a cat after thyroidectomy. It will be observed that the uterus of the thyroidectomized cat shows very considerable muscular atrophy, quite as much as occurs after oöphorectomy (fig. 11). In the case illustrated the cat was pregnant when the thyroid was removed, and
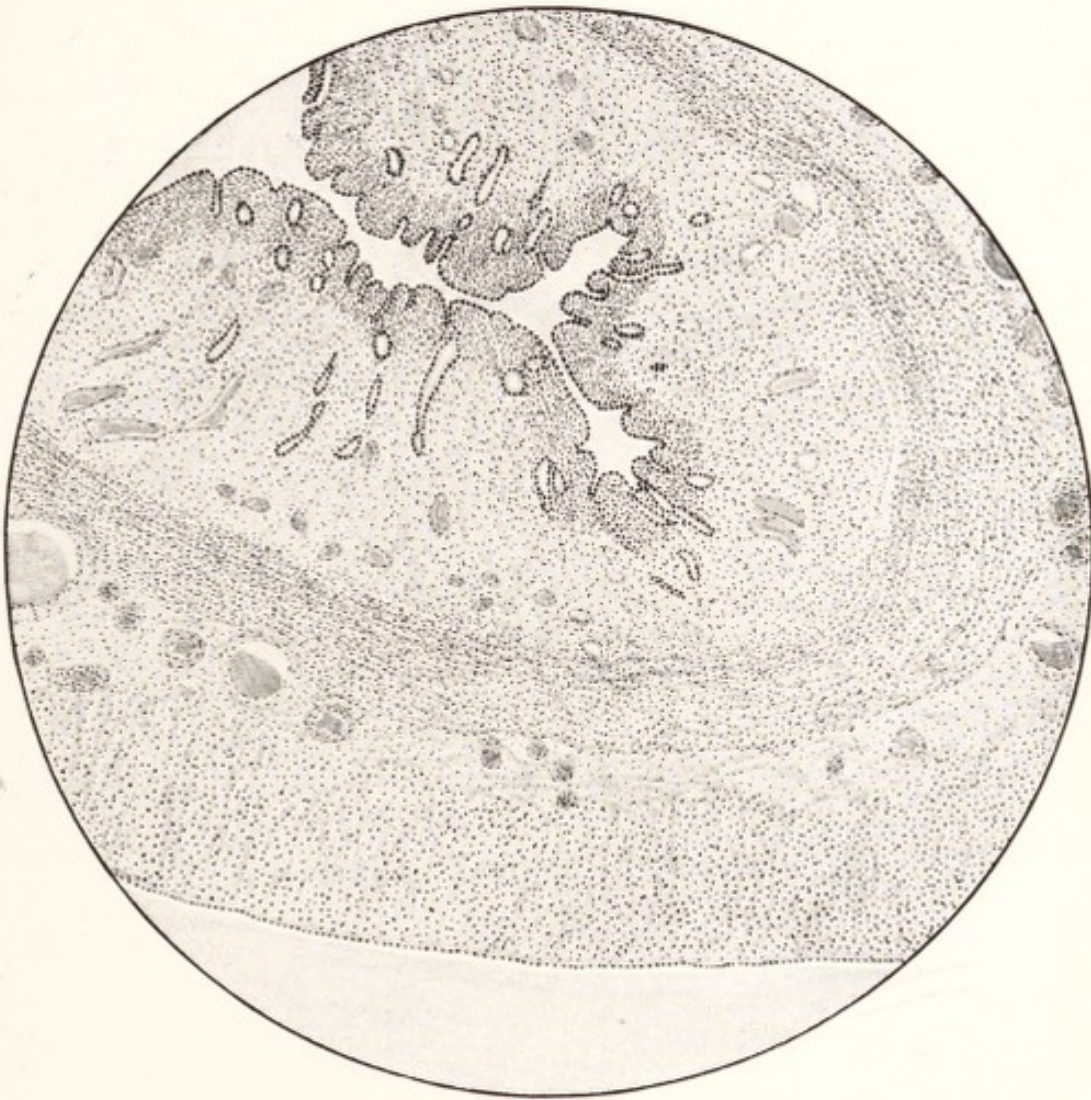
FIG. 20.

Section of the uterus of the cat 30 days after thyroidectomy, showing
intense atrophy of the muscle coats.

× 60.
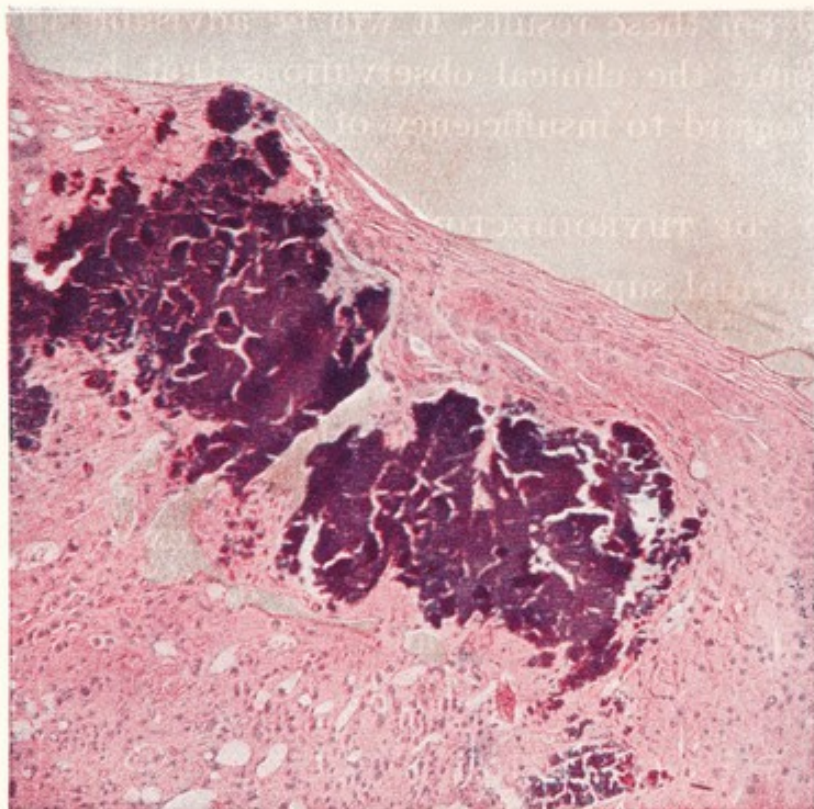
FIG. 21.

Section of the suprarenal of the cat after thyroidectomy, showing areas of calcification in the cortex.

(*Direct colour photomicrograph.*)

× 150

the kittens were born two days later. The animal died eventually at the end of a month. The condition might, therefore, be described as one of superinvolution. But the same effect on the uterus is to be observed in the non-pregnant animal after removal of the thyroid. The importance of this intense atrophy will be considered more fully later ; for, before drawing our final conclusions from these results, it will be advisable to take into account the clinical observations that have been made in regard to insufficiency of the thyroid.

EFFECTS OF THYROIDECTOMY ON THE SUPRARENALS

The normal suprarenal structure is well known, but I must refer to it briefly in order better to illustrate the changes that occur, physiologically and pathologically, in the cat. The suprarenal is divided into two parts, the cortex and the medulla. These have, apparently, different physiological functions when examined experimentally. The extract of the medulla produces the pressor effect of suprarenin, while that of the cortex is inactive. Abelous[1] and his co-workers suggested that the cortex produces pro-suprarenin ; this view is supported by Schäfer and Herring[2], and it appears highly probable. In addition, the cortex has direct genital functions to be referred to later.

Now the changes that seem to indicate increased activity of the suprarenals occur in the cortex ; they may be seen normally in pregnancy, and, so far as we know, in ordinary circumstances. The normal appearances differ, however, from those associated with the activity following thyroidectomy.

[1] Abelous, J. E., *Compt. Rend. Soc. Biol.*, 1905, vol. lvii, p. 301.
[2] Schäfer, E. A., and Herring, P. T., *Proc. Roy. Soc.*, 1908, vol. cxcix, Ser. B, p. 1.

In three of my animals actual calcareous deposits were found in the zona fasciculata subsequently to thyroidectomy (fig. 21). I have never seen this condition in a normal suprarenal gland. What probably occurs is the production of fatty substances in quantities greater than can be immediately dealt with ; then calcium soaps are formed, and finally the calcareous deposits are produced—just as may occur elsewhere in the body after a similar series of chemical reactions. Apparently, and somewhat paradoxically, thyroidectomy stimulates the suprarenal cortex to excessive secretion, and this no doubt tends to produce calcium retention and prevent its excretion.

EFFECTS OF THYROIDECTOMY ON THE PITUITARY

It has long been known that changes occur in the pituitary after thyroidectomy ; Rogowitsch[1] was the first to call attention to them. Herring[2] states that the only change to be noted is an increase in the number of what he calls ' hyaline bodies ' in the pars nervosa. These so-called ' hyaline bodies ' are supposed to represent the secretion of the pars intermedia ; but there can be no doubt that some, if not all, represent degenerated pars intermedia cells which have migrated into the pars nervosa. There the secretion, as already stated, becomes converted into a pressor substance (infundibulin).

While it is, of course, quite certain, as Herring first observed and Crowe, Cushing and Homans[3] also noted,

[1] Rogowitsch, N., *Ziegler's Beitr. z. Pathol. Anat. u. z. allg. Pathol.*, 1889, vol. iv, p. 453.

[2] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, vol. i, p. 281.

[3] Crowe, S. J., Cushing, H., and Homans, J., *Bull. Johns Hopk. Hosp.*, 1910, vol. xxi, p. 127.
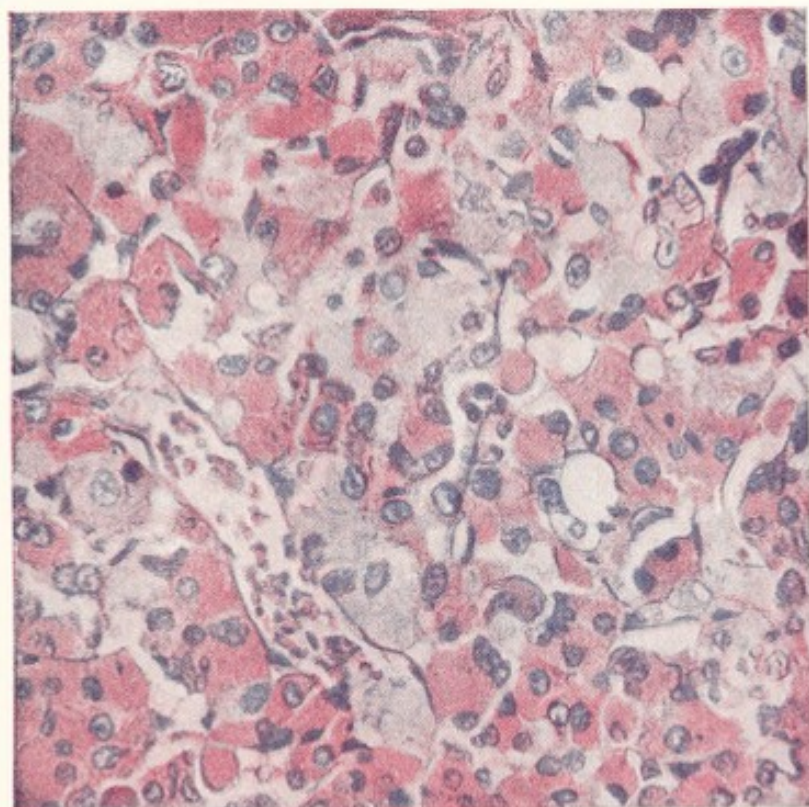
FIG. 22.

Section of the pars anterior of the non-pregnant cat after
thyroidectomy, showing large chromophobe cells,
masses of nentrophile secretion and eosinophile cells.

(Direct colour photomicrograph).

× 500
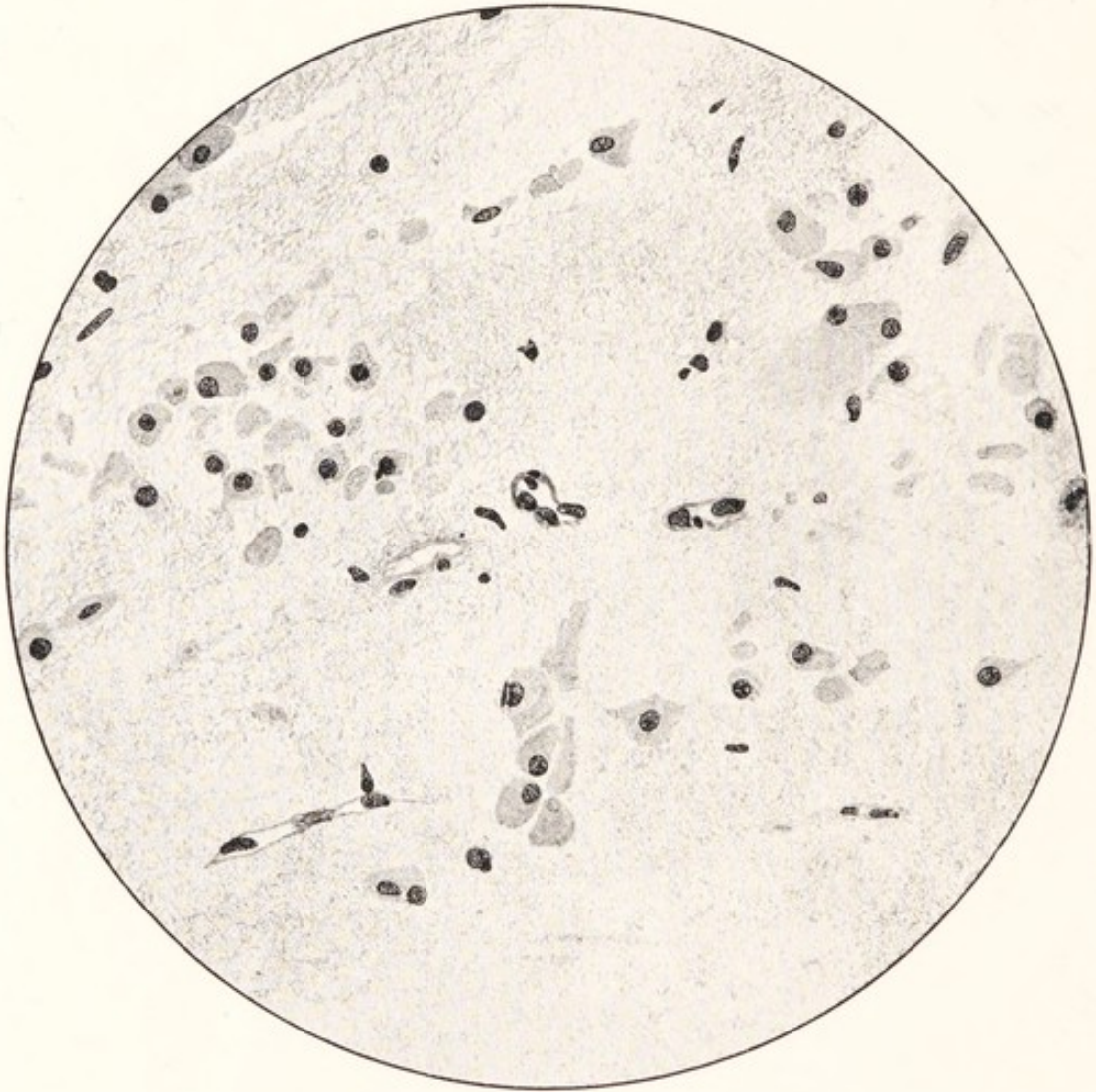
FIG. 23.

Section of the pars nervosa of the pituitary of the cat 2 days after thyroidectomy, showing invasion by the cells of the pars intermedia.

$\times$ 500.

that this process does occur, I have found that it is not always so marked as one was led to expect. Also, in contradistinction to the findings of Herring, I have observed definite changes in the anterior lobe. These were most marked in animals which were pregnant when thyroidectomy was performed.

The changes that occur in the anterior lobe include an increase in active eosinophile cells at the expense of the large basophiles ; and both in the pregnant and non-pregnant animal there is an increase, such as occurs normally in pregnancy, of large, active chromophobe cells. The latter are, however, most pronounced in an animal in which thyroidectomy has been performed during gestation. The condition was well seen in cat no. 3 of my thyroidectomy series. Ten days after operation two premature kittens were born. After a further interval of 117 days the animal was destroyed. In this length of time all the chromophobe ' pregnancy cells ' would have disappeared in the ordinary course of events ; yet, as the result of thyroidectomy, they not only persisted but showed an increase in secretory activity. The secretion appeared to form vacuoles among the cells. In this case the pars nervosa showed no abnormal invasion of pars intermedia cells. Again, in the pituitary of a non-pregnant cat (no. 1), killed 79 days after thyroidectomy, many active chromophobe cells were to be seen in the pars anterior, and an increase in active eosinophile cells at the expense of the baso-philes (fig. 22). In the pars nervosa there was a consider-able invasion of cells from the pars intermedia (fig. 23).

We learn, then, from these observations that thyroid-ectomy may cause an increase in the secretory activity of all parts of the pituitary body.

THE RELATION OF THE PARATHYROIDS TO
THE GENITAL SYSTEM

That the parathyroids, which are four in number in the human subject and in most mammals, are embryonal thyroid tissue was first propounded by Gley[1] in 1891, but ten years later he reviewed his work on the subject[2], and substituted for his original theory of an anatomical relationship between the thyroid and parathyroids the view that the relationship was a functional one. Subsequently, Vincent and Jolly[3] verified the fact that after removal of the thyroid the parathyroids may develop the structure of true thyroid with colloid formation, and they maintained that the thyro-parathyroid apparatus formed one organ, and not two distinct entities; but, on the other hand, there is a considerable body of evidence to show that the parathyroids have functions different from those of the thyroid, and in this connexion I have already mentioned the dissimilar effects produced by the removal of these organs. However, the *functional* unity of closely connected parts of apparently double endocritic organs—the pars anterior and posterior of the pituitary, the cortex and medulla of the suprarenals, and the thyroid and parathyroids—is not improbable, in spite

[1] Gley, E., *Compt. Rend. Soc. Biol.*, 1891, vol. iii, p. 843.
[2] Gley, E., *Arch. Ital. de Biol.*, 1901, vol. xxxvi, p. 57.
[3] Vincent, S., and Jolly, W. A., *Journ. Physiol.*, 1904–5, vol. xxxii, p. 65.

of morphological and other reasons which tempt us to hold a contrary opinion.

In pregnancy there is normally some hyperplasia in the parathyroids, and this is probably connected with the importance in this condition of the calcium metabolism, with which these organs are intimately associated.

EFFECTS OF REMOVAL OF THE PARATHYROIDS

Apparently the removal of some of the parathyroids does not produce any definite symptoms; and Swale Vincent asserts[1] that the complete removal of the parathyroids will not give rise to symptoms, unless the thyroid itself or the nerve supply to this organ be damaged. In short, this authority considers that, unless the integrity of the thyro-parathyroid apparatus be damaged, removal neither of the thyroid nor of the parathyroids causes symptoms. But such a statement seems a contradiction in terms, and, as a matter of fact, these views are not supported by the results obtained by others, nor by my own experiments; but I have not myself carried out experiments on the parathyroids as distinct from the thyroid.

From the other point of view probably the work of MacCallum and Voegtlin is the best known. MacCallum[2] showed that the removal of the parathyroids alone results in tetany and death. Subsequently he and Voegtlin[3] demonstrated that the tetany produced is connected with the calcium metabolism; that is to say,

[1] Vincent, Swale, *Internal Secretion and the Ductless Glands*, 1912, p. 302.

[2] MacCallum, W. G., *Med. News*, 1903, vol. xxxiii, p. 820.

[3] MacCallum, W. G., and Voegtlin, C., *Bull. Johns Hopk. Hosp.*, 1908, vol. xix, p. 91.

there is a depletion of lime salts from the nervous system and blood after parathyroidectomy. Continuing their investigations they found, also, that the injection of calcium salts into the blood stream prevents tetany supervening after parathyroidectomy.

As a result of these experiments attempts have been made to base the causation of many conditions associated with tetanoid spasms on lesions of the parathyroids. It must, however, not be forgotten that the parathyroids are only one of the many regulators of the calcium metabolism. It may be mentioned in respect of these observations that the work of Ringer and Buxton[1] proved conclusively many years ago that the calcium salts control the excitability of skeletal muscle, probably through the neuro-muscular junctions; consequently it followed that with insufficiency of lime salts in the blood and tissues excitability amounting to tetany would occur.

Now, the connexion of these findings with the genital functions, which are so largely concerned with the calcium metabolism, appears obvious from what has already been said; but extremely little direct investigation has been made to define the relation of the parathyroids to the genital functions. Silvestri[2] has stated that castration delays the onset of tetany after parathyroidectomy, but Massaglia[3] was unable to obtain the same result. It will be remembered that castration has been found to prevent tetany in cats from which the thyroid with most of the parathyroidal tissue had been removed. It may be that in these circumstances

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[1] Ringer, S., and Buxton, D. W., *Journ. Physiol.*, 1887, vol. viii, pp. 15 and 288.

[2] Silvestri, T., *Policlin. Sez. Prat. Roma*, 1910, vol. xvii, p. 1571.

[3] Massaglia, A., *Gaz. Delgi. Osped. e. delle Clin. Milano*, 1911, vol. xxxii, i, p. 422.

a considerable calcium retention is produced, for apparently the parathyroids and gonads—especially the ovaries—are antagonistic in their relation to the calcium metabolism.

However, until more work has been done on the histology and physiology of the parathyroids at different ages and in different circumstances, especially in the female, we cannot discuss further the relationship of these organs to the genital system with any advantage.

THE RELATION OF THE PINEAL TO THE GENITAL SYSTEM

The pineal gland has never been completely removed from mammals, although many experimenters have attempted to do so; partial removal, however, has been effected. Sarteschi[1] states that after *partial* extirpation of the pineal the rabbits on which he operated became very emaciated and remained under-developed. Exner and Boese[2] operating on a large number of rabbits were unable to find any changes in regard to the reproductive functions or somatic development.

Foà[3] found that it was possible to perform complete extirpation on the fowl. He removed the pineal from a large number of chickens a few weeks old. As a result there was a great degree of sexual precocity in the males, both in respect of the primary and secondary character-istics; but pullets after this operation showed no altera-tion in regard to the sex characteristics.

An interesting review of the literature of the pineal body has been written by L. J. Kidd[4]. This contains an analysis of the recent work on the subject.

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[1] Sarteschi, U., *Folia Neuro-biol.*, 1910, vol. iv, p. 675.

[2] Exner, A., and Boese, J., *Deutsch. Zeitsch. f. Chirurg.*, 1910, vol. cvii, p. 182.

[3] Foà, C., *Arch. Ital. de Biol.*, 1912, vol. lvii, p. 233.

[4] Kidd, L. J., *Med. Chronicle*, 1912, vol. xxiv, p. 154.

The effects of castration on the pineal have already been mentioned. The only other evidence in connexion with the genital functions of this interesting organ is that which has been obtained clinically, and with this I shall deal later.

THE RELATION OF THE PITUITARY TO THE GENITAL SYSTEM

Some of the normal physiological changes that occur in the pituitary are well known; but there is much need for a systematic investigation into the age changes in this organ, for up to the present time only a few isolated observations have been recorded.

There is reason to believe that the secretions of the pituitary determine many of the metabolic functions necessary for the establishment of puberty or sexual maturity.

We fully recognize the remarkable enlargement and the histological changes that occur in this gland as the result of pregnancy : the eosinophilia disappears, and a large proportion of all the cells in the pars anterior become chromophobe, constituting the so-called ' pregnancy cells'. No doubt this change is brought about by the needs of the maternal metabolism which the development of the fœtus entails.

Some years ago Hick and I showed that an extract of the posterior lobe produces powerful uterine contractions[1]. Previously Dale[2] had incidentally mentioned this effect in a paper on ergot. It is possible that uterine contractions may be produced normally in labour by the infundibular secretion.

[1] Bell, W. Blair, and Hick, P., *Brit. Med. Journ.*, 1909, vol. i, p. 777.
[2] Dale, H. H., *Journ. Physiol.*, 1906, vol. xxxiv, p. 163.

Ott and Scott[1] first showed that the same extract is a galactogogue. It is not definitely known how this result is produced. It would be interesting if it were a fact, of which we have no proof, that the pituitary hormone normally promotes the secretion of milk. It is, however, most probable that after the birth of the child the stream of metabolic products directed to its maintenance and growth in the womb are diverted to the mammary secretion, which is to supply the post-natal necessities of the young infant.

The experimental work which has been carried out in regard to extirpation of the pituitary, partial or complete, in so far as it is of importance to our subject must now be recapitulated. At the same time it is necessary to state that very little of the experimental work has fulfilled the highest ideals owing to the difficulty of removing completely and separately the different portions of the organ *in vivo ;* consequently the last word has probably not been said in regard to the results that may be obtained.

EFFECTS OF REMOVAL OF THE PITUITARY (PARTIAL OR COMPLETE)

Most of the early work on the extirpation of the pituitary was absolutely unreliable, and it was not until Paulesco[2] improved the technique, which Crowe, Harvey Cushing and Homans[3], Biedl[4] and I myself

[1] Ott, I., and Scott, J. C., *Proc. Soc. Exper. Biol. and Med.*, 1910–1911, vol. viii, p. 48. .

[2] Paulesco, N. C., *Journ. Physiol. Pathol. Gen.*, 1907, vol. ix, p. 441 ; *L'hypophyse du cerveau*, 1908.

[3] Crowe, S. J., Cushing, H., and Homans, J., *Bull. Johns Hopk. Hosp.*, 1910, vol. xxi, p. 127.

[4] Biedl, A., *Innere Sekretion*, 1913, 2nd ed.

subsequently adopted with slight modifications, that results worthy of any consideration were obtained.

The conclusions drawn by Cushing and his co-workers from their experiments may be summed up as follows :—

Complete extirpation causes death in a short time. The same effect is obtained by complete extirpation of the pars anterior. Partial removal of the anterior lobe leads to the condition known as *dystrophia adiposo-genitalis*—that is to say, there is great obesity with atrophy of the genital organs, and in young animals somatic infantilism. Separation of the stalk has the same effect as removal of the whole organ and immediate transplantation ; and removal of the posterior lobe produces no symptoms.

Biedl, without giving details, states that he has confirmed most of these findings, but he asserts that while the posterior lobe (pars intermedia and pars nervosa) may be removed without producing symptoms, yet severing the stalk results in death. Paulesco had previously obtained results similar to those of Biedl.

It may be thought difficult to believe in the results of experiments in which the anterior or posterior lobe are said to have been removed separately and completely. There can be no doubt, however, that partial removal of the anterior lobe is easily accomplished, and the results following this procedure should be reliable ; total re-moval of the anterior lobe leaving posterior lobe intact is almost impossible ; but total removal of the posterior lobe can be performed without very great difficulty, and separation of the stalk is easy.

I have myself operated on 27 bitches, and have performed partial removals of the component parts of the pituitary, and complete removals of the whole

pituitary and of the pars posterior; I have been able to clamp or separate the stalk, and to put artificial pressure on the pituitary by leaving a foreign body in the sella turcica[1].

It is the effect of *dystrophia adiposo-genitalis*, said to be caused by partial removal of the anterior lobe, which is particularly interesting to our present study. It is to be noted that Cushing[2] in his recent book on the Pituitary Body, if I understand him correctly, puts forward views diametrically opposed to the results obtained in the experiments which were previously published by him. In the later work he attributes the symptoms mentioned to insufficiency of the posterior lobe. Thus the confusion that has so long existed becomes " confusion worse confounded " and, as already stated, can in my opinion only be dispelled by considering the whole pituitary as one organ.

In my own experiments I was unable to produce the syndrome *dystropia adiposo-genitalis* by removal of large or small portions either of the anterior or posterior lobe. I found, however, that separating or clamping of the stalk produced in bitches this interesting syndrome in a greater or lesser degree: in one case the increase in weight amounted to 66 per cent. of the original body weight in 50 days; in another animal the increase was 20 per cent. in 73 days. In these animals there was a remarkable degree of genital and mammary atrophy with general infantilism.

It may, therefore, be presumed that interference with the blood supply to the pituitary can cause the condition of *dystrophia adiposo-genitalis*.

I, in agreement with Cushing and his co-workers,

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[1] These experiments have not yet been published in detail.

[2] Cushing, H., *The Pituitary Body and Its Disorders*, 1912.

and with Paulesco, found that removal of the whole gland was uniformly fatal. Sweet and Allen[1], however, assert that the pituitary gland is not essential to life.

Removal of large portions—it is practically impossible to remove all—of the anterior lobe is usually fatal; the uncertainty of the results depends no doubt on the quantity removed.

EFFECTS OF REMOVAL OF A PORTION OF THE PARS ANTERIOR ON THE OVARIES AND UTERUS

There is no doubt that the ovaries usually undergo hypoplastic changes after partial removal of the anterior lobe. No good description of the histological appearances has previously been given, but Cushing[2] states that the follicles disappear while the interstitial cells persist. Cushing also states that the uterus undergoes atrophy. I, also, found that removal of moderate or large portions of the anterior lobe generally produces well-marked atrophy of the uterus—both of the muscular coats and of the endometrium (fig. 24).

With regard to the ovaries, I found that the Graafian follicles—that is, the ova and the cells of the membrana granulosa—degenerate and disappear, and that the primordial ova lose their transparency and network appearance (chromatin fibres), becoming shrunken, opaque and structureless (fig. 25). Further, I found, as opposed to the observations of Cushing, that the interstitial cells disappear, and that the stroma becomes dense and fibrous.

Removal of small portions of the anterior lobe

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[1] Sweet, J. E., and Allen, A. R., *Ann. Surg.*, 1913, vol. lvii, p. 485.
[2] Cushing, H., *The Pituitary Body and Its Disorders*, 1912.
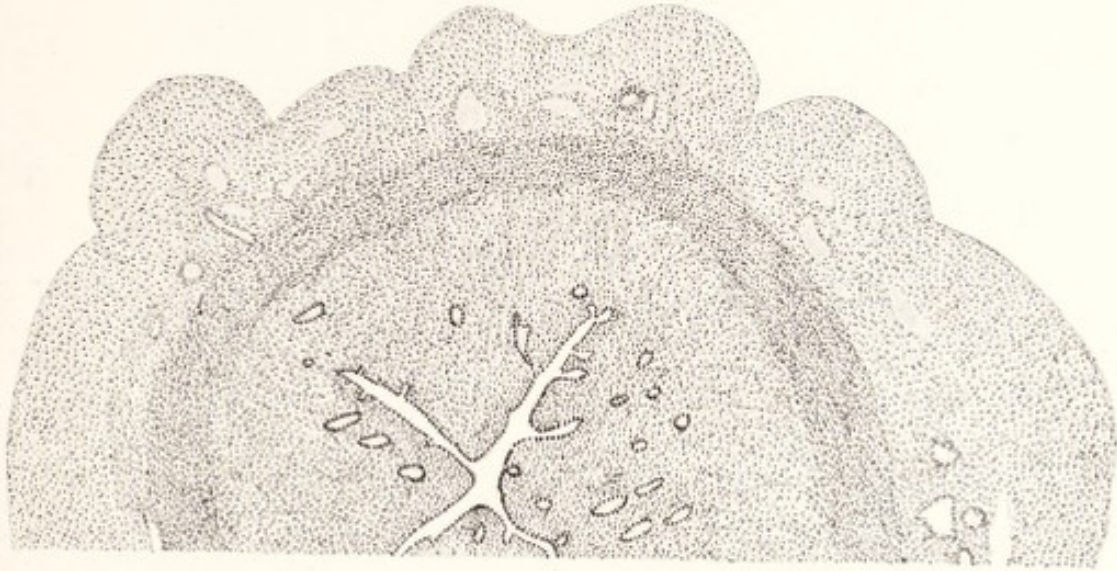
A

A. Section of the uterus of the bitch before partial removal of the pars anterior of the pituitary.
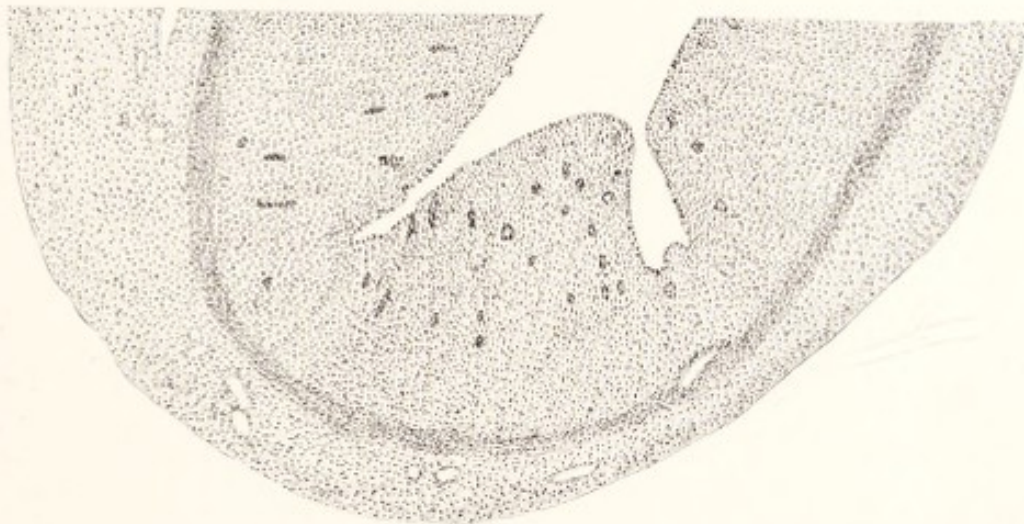
B

B. Section of the uterus of the same bitch after partial removal of the pars anterior of the pituitary, showing intense atrophy of the muscle coats.

FIG. 24. $\times$ 60.
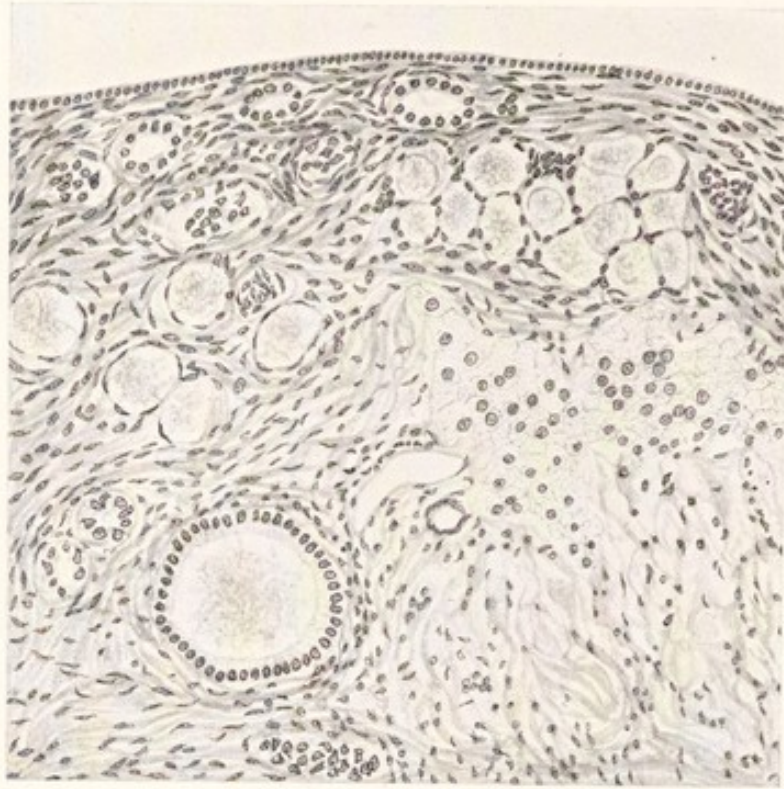
A

A. Section of the ovary of the bitch before partial
removal of the pars anterior of the pituitary.
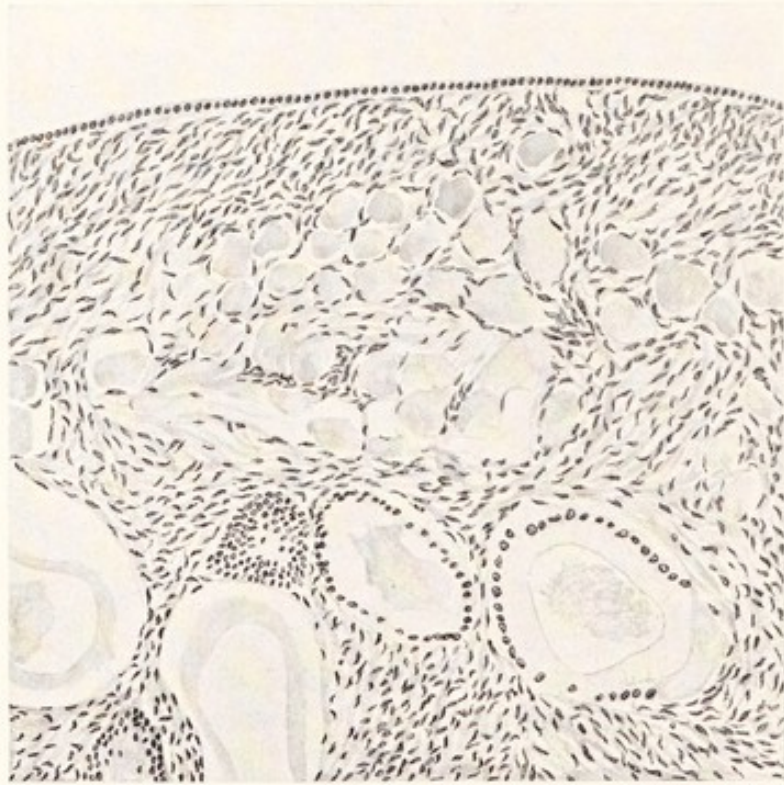
B

B. Section of the ovary of the same bitch after partial
removal of the pars anterior of the pituitary.

Fig. 25.   × 250.

causes no changes in the genitalia. The bitches came on heat, and one had coitus without being fertilized.

In all my experiments portions of the uterus and of one ovary were removed a few days before the operation on the pituitary, in order that I might have accurate controls in regard to subsequent changes in these organs.

EFFECTS OF REMOVAL OF A PORTION OF THE PARS ANTERIOR ON THE THYROID

It has been noted by Cushing and others that there is a remarkable degree of hyperplasia in the thyroid after partial removal of the anterior lobe. This condition is said to subside eventually, and to be superseded by a considerable colloid formation, apparently with the disappearance of epithelial activity. I was unable to recognize any definite or constant change in the thyroid after partial removal of the anterior lobe of the pituitary—even after so long a period as 210 days after operation. Changes no doubt do occur, but in an organ of so variable an appearance in normal circumstances it is very difficult indisputably to demonstrate small alterations in epithelial activity and colloid formation.

EFFECTS OF REMOVAL OF A PORTION OF THE PARS ANTERIOR ON THE THYMUS

This operation is said to lead to hypertrophy of the thymus, just as the condition of hypopituitarism is often associated with thymus enlargement. I found that many months after partial removal of the anterior lobe the thymus is as well developed as at a much earlier period of life, the epithelial aggregations, known as

Hassal's corpuscles, being particularly prominent and unchanged.

EFFECTS OF REMOVAL OF A PORTION OF THE PARS ANTERIOR ON THE SUPRARENALS

The operation, according to Cushing[1], is followed by hyperplasia and lipoid vacuolation of the cells of the zona fasciculata.   In my own experiments I was unable to detect any alteration from the normal in any part of the suprarenals in these circumstances.

EFFECTS OF REMOVAL OF THE PARS POSTERIOR ON THE OVARIES AND UTERUS

Neither complete nor partial removal of the posterior lobe in any way affects the genital organs.   The uterus and ovaries continue their development normally in accordance with the age and growth of the animal concerned (fig. 26).

EFFECTS OF REMOVAL OF THE PARS POSTERIOR ON THE OTHER ENDOCRITIC ORGANS

I was unable to discover any changes in the other endocritic organs after removal of the posterior lobe of the pituitary, unless it be that there was an increase of colloid in the thyroid ; but, as already mentioned, it is difficult accurately to estimate a slight alteration from the normal in this respect.

EFFECTS OF SEPARATING OR CLAMPING THE INFUNDIBULAR STALK ON THE OVARIES AND UTERUS

As might be expected, I found that this procedure causes intense atrophy of the uterus and ovaries—an

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[1] Cushing, H., *The Pituitary Body and Its Disorders*, 1912.

a   A   a′

b   B   b′
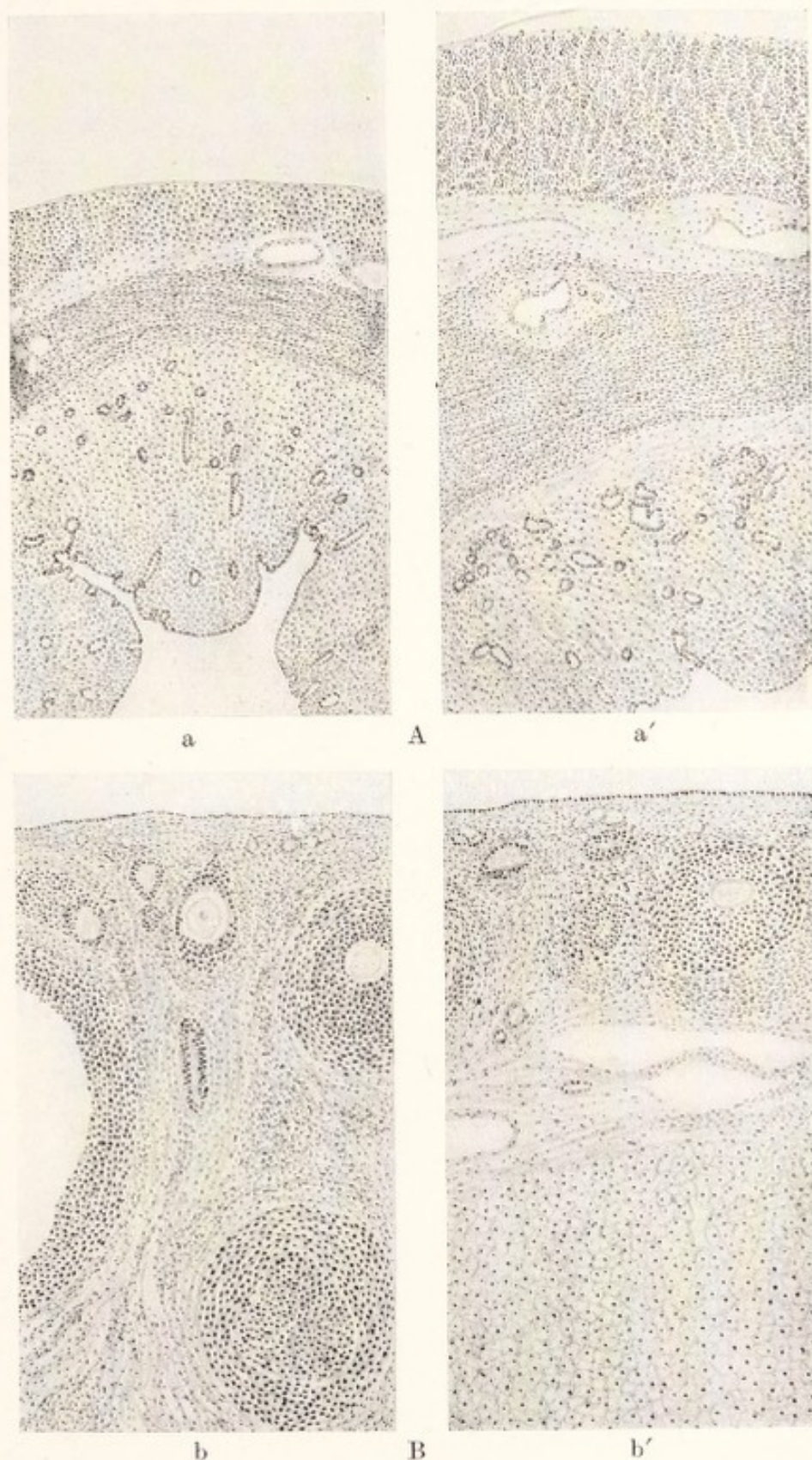
FIG. 26.

A. Sections of the uterus of the same bitch before (a) and after (a′) removal of the pars posterior of the pituitary.

B. Sections of the ovary of the same bitch before (b) and after (b′) removal of the pars posterior of the pituitary. Part of a corpus luteum is seen in the lower half of b′.

× 60.

atrophy which appeared to be even more marked than that produced by the removal of a portion of the anterior lobe. The histological changes were identical with those already mentioned as occurring after partial removal of the anterior lobe (figs. 24 and 25).

EFFECTS OF SEPARATING OR CLAMPING THE INFUNDIBULAR STALK ON THE OTHER ENDOCRITIC ORGANS

The only change which stood out prominently was in connexion with the thyroid. In all cases in which this operation was performed and the animal killed after many weeks, the colloid secretion in the thyroid was found on histological examination to be undoubtedly excessive. Macroscopically, too, the glands on removal were noted to be about twice the normal size.

EFFECTS PRODUCED ON THE UTERUS AND OVARIES BY ARTIFICIAL TUMOURS IN THE NEIGHBOURHOOD OF THE PITUITARY

In one case in which the animal became thin and ill, and had traces of sugar in the urine, the uterus showed a slight degree of atrophy. In this case the ovaries, also, appeared to have undergone slight retrogressive changes.

EFFECTS PRODUCED ON THE OTHER ENDOCRITIC ORGANS BY ARTIFICIAL TUMOURS IN THE NEIGHBOURHOOD OF THE PITUITARY

No changes of importance were noted except that the thyroid contained a large amount of colloid, and that the thymus appeared to be much atrophied.

THE RELATION OF THE THYMUS GLAND TO THE GENITAL SYSTEM

It is believed that the thymus is intimately connected with the development of the individual and of her reproductive functions. It is probable that once the genital functions are established the thymus rapidly undergoes atrophy, and plays no part in the metabolism of reproduction. We have already seen that the thymus undergoes hyperplasia after removal of the ovaries.

EFFECTS OF THYMECTOMY ON THE OVARIES AND ON THE CALCIUM METABOLISM

Paton[1] found that if the operation be performed before puberty there is a rapid development of the genital gland. It appears, therefore, that the thymus either inhibits the development of the ovaries (Biedl[2]), or that their development causes atrophy of the thymus.

It is highly probable that the thymus is intimately connected with the calcium metabolism; but it can hardly be, as Biedl suggests, that the effect of its secretion is to cause calcium retention in the bones—although several investigators (Basch[3], Cozzolino[4], Tarulli and

[1] Paton, N., *Journ. Physiol.*, 1904, vol. xxxii, p. 59.
[2] Biedl, A., *Innere Sekretion*, 1913, 2nd ed.
[3] Basch, K., *Wien. Klin. Woch.*, 1903, vol. xvi, p. 893.
[4] Cozzolino, O., *La Pediatria*, 1903, vol. i, pp. 144, 620.

Lo Monaco[1]) have found that rickets follows thymectomy in young animals, an effect not confirmed by Paton—for the skeletal structures become much more heavily laden with calcium phosphate after puberty when the gland atrophies.

The matter is one of considerable difficulty. But if thymectomy were to lead to increased calcium excretion and bone softening, the growth of the genital gland which promotes the excretion of calcium would not tend to improve matters, unless—and this is possible—the development of the genital gland causes an increased secretion from the suprarenals, which causes calcium retention.

EFFECTS OF THYMECTOMY ON THE OTHER ENDOCRITIC GLANDS

No reliable work appears to have been done on these lines. It is urgently needed, in order to clear up many of the difficulties concerning the relation of the thymus to the general metabolism.

[1] Tarulli, L., and Lo Monaco, D., *Bollettino d. R. Accademia Medica di Roma*, 1897–8, vol. xxiii, p. 311.

THE RELATION OF THE SUPRARENALS TO THE GENITAL SYSTEM

In pregnancy certain changes occur normally in the suprarenals. So far as my own observations go these appear to be confined to the cortex: the cells of the zona fasciculata appear swollen and cloudy. Some observers (Guieysse[1] and Gottschau[2]) have found that in pregnancy the zona fasciculata increases in thickness at the expense of the zona reticularis and medulla. My own observations are in accord with this. The zona reticularis does not increase at the expense of the zona fasciculata in pregnancy, as it does after oöphorectomy.

Conflicting views as to the effects of castration have been put forward by Schenk[3], Cecca[4], and others. A source of error in the estimation of the thickness of the various zones is liable to arise unless care be taken to cut mesial sections, or, better still, serial sections.

EFFECTS OF THE REMOVAL OF THE SUPRARENALS

In most mammals complete removal of the suprarenals causes death in from a few hours to a few days.

[1] Guieysse, M. A., *Compt. Rend. Soc. Biol.*, 1899, vol. l, p. 898.

[2] Gottschau, M., *Arch. f. Anat. u. Physiol., Anat. Abt.*, 1883, p. 412.

[3] Schenk, F., *Arch. f. Exper. Pathol. u. Pharmacol.*, 1910–11, vol. lxiv, p. 362.

[4] Cecca, R., *Presse Médicale*, 1904, vol. xii, p. 341.

The animal does not eat ; it sits very quietly and gradu-
ally becomes weaker ; tremors occur, and death super-
venes. This sequence of events follows so rapidly that
as a rule no estimation can be made of the metabolism,
and any changes observable in other endocritic glands
must be of an acute character, and therefore of less value
from a practical point of view than those which are
obtained by the production of chronic insufficiency—
a condition difficult to bring about experimentally in
the suprarenals. Acute effects may, however, be useful
as indicating the trend of physiological events.

Many rats, owing to the fact that a large percentage
of them have accessory interrenals consisting of cortical
substance, are said to be able to survive extirpation of
the main organs. I have had no experience of extirpa-
tion experiments on these animals.

My investigations were carried out with rabbits and
cats. Those animals from which both suprarenals were
removed, either at one or at two sittings, died within
48 hours of the complete extirpation. I tried, therefore,
the effect of the removal of one suprarenal in the hope of
being able to produce insufficiency, since it is known the
other suprarenal hypertrophies in these circumstances,
and shows a condition somewhat comparable with the
hyperplasia of pregnancy. Two cats gave negative
results in regard to the metabolism, but with two rabbits
definite results were obtained. One of the animals was
destroyed at the end of 30 days, as it was obviously
dying. It was much emaciated, its weight having
dropped from 2000 grammes to 1400 grammes. The
post-mortem notes run as follows : " No cause of death
found. The site of the previous operation unrecognisable
except for the absence of the gland." The other rabbit
died at the end of 127 days. It, also, was greatly

emaciated, the weight having decreased from 1710 grammes to 1020 grammes. At first the animal gained weight after the operation, and then steadily lost ground. No cause for death was found, other than the absence of one suprarenal.

These results are apparently of some value, for according to most recent authorities, unilateral extirpation in rabbits produces no symptoms.

EFFECTS OF REMOVAL OF ONE SUPRARENAL ON THE METABOLISM

With regard to the metabolism I obtained very interesting records from these cases of chronic insufficiency. In both cases a considerable increase in the excretion of calcium was observed (table VI) : in one the average quantity excreted after operation was seven times as much as that excreted before operation ; in the other case it was more than sixteen times as much. The average for the two cases was, of course, between these figures (table VII). The excretion of phosphorus, also, was much greater ; and the urea excretion was increased out of proportion to the differences between the specific gravities before and after operation.

Now, this increase of the calcium excretion is of very considerable interest, and I much regret not having a longer series of cases. As is well known, the view has been advanced that osteomalacia is due to insufficiency of suprarenal secretion, and Bossi[1] first called attention to the beneficial results to be obtained by the injection of suprarenin in these cases. I shall have more to say on this subject when dealing with pathological conditions. My experiments give very strong support to

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[1] Bossi, L. M., *Centralbl. f. Gynäk.*, 1907, vol. xxxi, p. 69.

TABLE VI.—*Removal of Left Suprarenal. Averages of Metabolism Estimations of 24 hours' Specimen Urines.*
Rabbit No. 1.

Date	Number of specimens examined	Specific gravity	Diacetic acid	Acetone	Albumin	Sugar	Indican	Ca %.	Cl %.	P_2O_5 %.	Total N %.	Urea %.	NH_3 %.	Ammonia coefficient.		
														Urea N %.	NH_3N %.	Undet. N %.
Commenced 23/8/12 Operation 28/8/12	4	1023	0	0	0	0	0	0·0030	0·170	0·206	1·16	2·25	0·070	87·78	3·69	8·53
Destroyed 27/9/12	13	1026	0	0	0	0	0	0·0210	0·192	0·623	1·58	3·09	0·036	91·26	1·86	6·88

Rabbit No. 2.

Commenced 30/8/12 Operation 4/9/12	2	1018	0	0	0	0	0	0·0017	0·152	0·200	0·64	1·12	0·227	80·69	3·27	16·04
Died 9/1/13 ..	33	1030	0	0	0	0	4 times	0·0280	0·268	0·531	1·59	2·93	0·045	85·84	2·32	11·84

TABLE VII.—*Averages of Metabolism Estimations of 24 hours' Specimen Urines from Two Rabbits Before and After Removal of Suprarenals.*

	Number of specimens examined	Specific gravity	Diacetic acid	Acetone	Albumin	Sugar	Indican	Ca %.	Cl %.	P_2O_5 %.	Total N %.	Urea %.	NH_3 %.	Ammonia coefficient.		
														Urea N %.	NH_3N %.	Undet. N %.
Before operation	3	1020	0	0	0	0	0	0·0023	0·161	0·203	0·90	1·68	0·148	84·23	3·48	12·28
After operation	23	1028	0	0	0	0	4 times	0·0240	0·230	0·577	1·58	3·01	0·040	88·55	2·09	9·36

this view of Bossi, not only in the metabolism results, but in a most striking way in regard to the bones of one of these animals, in which the forelegs were found to be markedly bent. Figure 27A is a skiagram of the normal bones of the forelegs in the rabbit, while figure 27B is one showing the condition found in one of the rabbits after operation. The bones of the hind legs, which are thicker, were only slightly curved. It is to be noted that it was in this animal that the larger quantities of calcium were excreted. This is, however, an isolated instance of the change in the bones, so produced, consequently undue importance should not be attached to it, unless confirmation be forthcoming from further experiments.

EFFECTS OF REMOVAL OF THE SUPRARENALS ON THE PITUITARY BODY

The changes that occur seem to be much the same whether the insufficiency be acute or chronic. Thus, in one cat in my series of suprarenal removals the glands from both sides were removed at the same operation. There was an interval of 36 hours between operation and death. The cells of the pars anterior show a marked degree of chromophobia with a moderate degree of faint eosinophilia. In many places the nuclei are very deeply stained with hæmatoxylin. In the pars intermedia the cells are discrete—that is to say, they are not fused— and show no special activity; the nuclei stand out prominently. The pars nervosa is freely invaded by the cells of the pars intermedia, but the nuclei, in which there is hyperchomatosis, only are prominent, as though they were left stranded after the disappearance of the cell cytoplasm (fig. 28).

Exactly similar changes were noted in the rabbit in
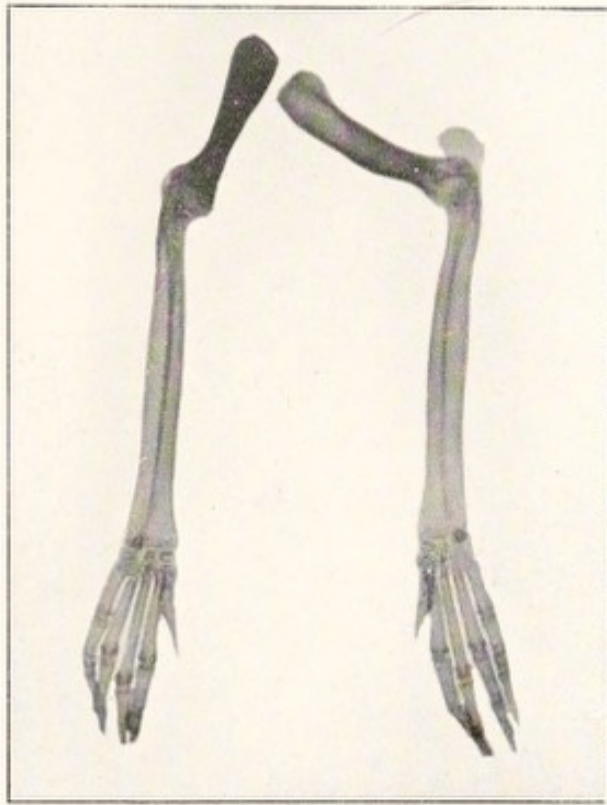
A

A. Skiagram of the forelegs of the normal rabbit.

B

B. Skiagram of the forelegs of the rabbit 30 days
after removal of one suprarenal.

FIG. 27. $\times \frac{1}{1}$
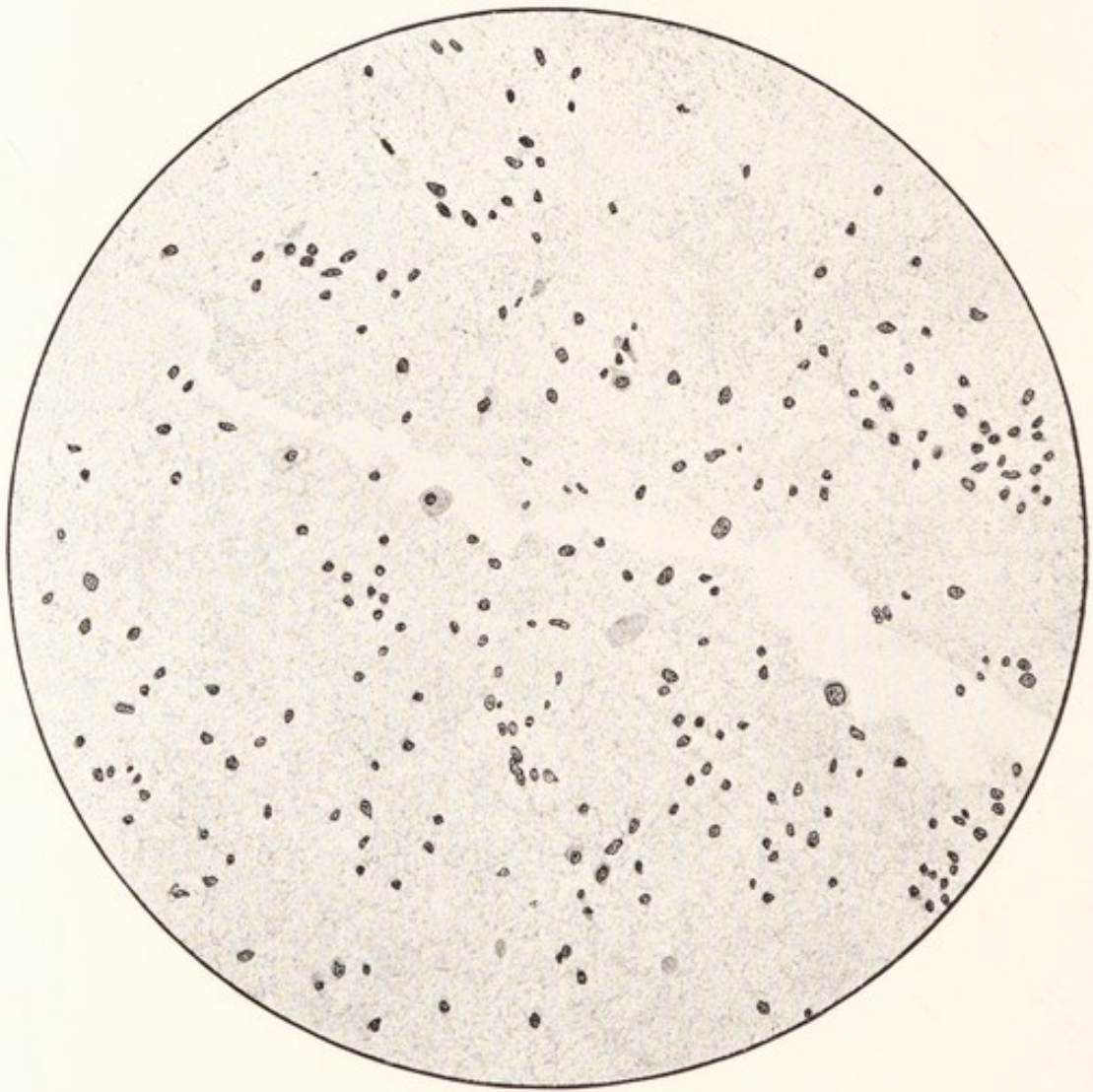
FIG. 28.

Section of the pars nervosa of the pituitary of the rabbit after removal of the suprarenals, showing invasion by cells from the pars intermedia, and the stranding of their nuclei.

× 250.

which there were such marked symptoms of chronic suprarenal insufficiency, as already recorded.

Taking all the facts into consideration we can hardly come to any other conclusion than that the anterior lobe shows greatly increased activity with suprarenal insufficiency. The pars intermedia is apparently in a 'used-up', and consequently not in an actively secreting, condition; but the extensive invasion of the pars nervosa by pars intermedia cells and the immediate disappearance of the cell cytoplasm appear to indicate that an attempt is being made to counterbalance the loss of suprarenin by the rapid production of infundibulin.

EFFECTS OF REMOVAL OF THE SUPRARENALS ON THE THYROID

I have been unable to trace any histological change in the thyroid either in acute or chronic suprarenal insufficiency.

EFFECTS OF REMOVAL OF THE SUPRARENALS ON THE OVARIES AND UTERUS

There appears to be no histological change of importance in the ovaries, but it is worthy of note that the normal eosinophilia of the zona pellucida is not decreased, rather is it slightly increased. After removal of one suprarenal, if insufficiency be produced, the uterus appears to undergo changes comparable with those that are seen after thyroidectomy, but the muscular atrophy is much less in extent; probably this is due to the state of incomplete insufficiency.

THE RELATION OF THE PANCREAS TO THE OTHER ORGANS OF INTERNAL SECRETION

It is probable that the endocritic cells of the pancreas have no direct relation to the genital functions, although no doubt the influence of the pancreas on the general metabolism and possibly on the other endocritic organs of the individual may exert an indirect control.

It has been shown by Lafon[1] that when the pancreas is removed from a pregnant bitch, no glycosuria is observed until the uterus is emptied, when the same train of symptoms as that seen in the non-pregnant animal—glycosuria, emaciation and death—rapidly supervenes. Lafon therefore came to a conclusion regarding the probable passage of the fœtal pancreatic hormones into the maternal circulation in these circumstances, similar to the one I formulated concerning the results of thyroidectomy in pregnant cats. This is a matter of extreme interest and importance, and one which requires further investigation.

Crowe, Cushing and Homans[2] have studied the effect on the pancreas of partial removal of the anterior lobe of the pituitary, but the results obtained have not been very conclusive of any definite changes. In my experiments I was unable to find any alterations from

[1] Lafon, G., *Compt. Rend. Soc. Biol.*, 1913, vol. lxxv, p. 266.
[2] Crowe, S. J., Cushing, H., and Homans, J., *Bull. Johns Hopk. Hosp.*, 1910, vol. xxi, p. 127.

the normal in the pancreas : in all cases it appeared to be active. Sweet and Allen[1] lay particular stress on the secretory activity of the pancreas after complete or partial removal of the pituitary.

Pemberton and Sweet[2], after a careful study of the relation of the internal secretions to pancreatic activity, have come to the following conclusions : " (1) The " inhibition of pancreatic activity by adrenalin and " pituitary extract (infundibulin) is independent of the " systemic blood pressure, as shown by its persistence " when the blood pressure is much below normal and " by other evidence. (2) The inhibition by extracts " of pituitary and suprarenal bodies also occurs when " the pancreas is stimulated by its normal excitant, " hydrochloric acid, in the duodenum."

It is possible, therefore, that alterations in the carbohydrate metabolism are not always directly attributable to primary pituitary, suprarenal or pancreatic disease, since the activities of these organs in this direction are closely related, but that the suprarenals and pituitary may indirectly affect the functions of the pancreas and *vice versa*.

[1] Sweet, J. E., and Allen, A. R., *Ann. Surg.*, 1913, vol. lvii, p. 485.
[2] Pemberton, R., and Sweet, J. E., *Arch. Inter. Med.*, 1910, vol. v, p. 466.

THE MAMMARY GLANDS

In spite of many assertions to the contrary, based on pure conjecture, I do not think there is any evidence that the mammary glands are organs of internal secretion in the accepted sense of the term. As already suggested, it is probable that every cell in the body should be considered to be an organ of internal secretion, but apart from such a generalization we cannot place the mammary glands in the same category as the ' regulators of metabolism ' previously mentioned.

The mammary glands have a definite function to perform : they abstract from the maternal economy nourishment for the infant after birth, and in this way carry on the function performed by the placenta before parturition. There is not, of course, an exact analogy between the two, but the general principle is the same in both cases, after due allowance has been made for the altered circumstances and environment after birth, which induce pulmonary respiration, digestion and other developments making for independence in the child.

It is obvious, therefore, that maternal lactation is of more importance to the child than to the mother. Hence, we may look upon mammary secretion as a side issue—even if it be an important one—so far as the maternal economy is concerned.

Well-developed breasts form one of the secondary characteristics of the female sex ; but only so as evidence

of her ability and readiness to perform the functions of reproduction.

In the human subject if the mother cannot nurse, both she and the child may suffer; but, on the other hand, the absence of mammary secretion subsequently to parturition does not necessarily affect either. We shall consider this matter more fully later.

The chief questions that we are called upon to consider here with respect to the mammary glands are: first, what the hormones are that affect the development, growth and function of the mammæ; second, what effect the function of lactation has on the maternal metabolism; and, last, what are the physiological effects of an extract of mammary gland.

THE HORMONES THAT INFLUENCE THE MAMMÆ

Much speculation has existed as to the causal factors in the development and functional activity of the mammæ. They have, of course, a very definite function to perform in the adult female subsequently to parturition; but given sufficient stimulus—generally mechanical—the mammæ of males or virgin females may also be induced to secrete ' milk '. It is probable that the secretion from the breasts of males and virgin women is rarely of the same composition as that secreted by the normal woman after parturition; but the facts that such abnormal secretion can occur and that it may be true milk are of considerable importance, as we shall see directly.

It is necessary, further, to call attention to a point— too well-known to require discussion—that has an important bearing on the ultimate understanding of the mammary function: namely, the secretion obtained from

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the mammæ before parturition is not milk ; that is to say, although during pregnancy the breasts enlarge and the contained glands become active, true milk is not in normal circumstances secreted until some short time after the birth of the child. In this connexion it is interesting also to note that milk is usually secreted after the premature birth of a live child, just as it is after full-term parturition.

It is, therefore, an obvious deduction that so long as the child remains *in utero* milk will not be secreted.

This, of course, confirms the view, already stated, that the stream of nutrient materials, which has reached the fœtus *in utero* by way of the blood stream, is now directed as quickly as possible to the breasts, in order that the child may continue to subsist on the most suitable food—that which is elaborated for the purpose from the maternal tissues.

It seems, then, that the actual secretion of milk is not due to any special hormone or the removal of some inhibitory substance of fœtal origin, as suggested by Hildebrandt[1], Lane-Claypon and Starling[2], and others, but rather to a definite redirection of certain elements in the maternal economy from the placenta to the breasts—a phenomenon almost comparable, indeed, with vicarious menstruation.

This point of view was clearly expressed by the ancients, whose observations were not obscured by the mass of conflicting experimental ' information ' at our command.

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[1] Hildebrandt, P., *Hofmeister's Beitr. z. Chem. Physiol. u. Pathol.*, 1904, vol. v, p. 1463.

[2] Lane-Claypon, Janet E., and Starling, E. H., *Proc. Roy. Soc.*, *Ser. B*, 1906, vol. lxxvii, p. 505.

Hippocrates[1] wrote : " If in a woman with child, much milk flow from the breasts, it indicates that the fœtus is weak ; but if the breasts be firm, it indicates that the fœtus is in a more healthy state."

Celsus[2] states that " The nourishment, which they (mammæ) draw to themselves passes from the womb (after parturition) to the breasts."

It follows, therefore, that those hormones which favour the nutrition of the fœtus *in utero*, will subsequently stimulate the secretion of milk. But before we come to this point we must consider what influences lead to the original development of the breasts, and give rise to their increased activity during pregnancy.

As just stated, the breasts form a secondary feminine characteristic, and in consequence should normally be well developed subsequently to puberty in every woman. That they are not always so agrees with what is found in regard to the other sex characteristics, for if there be variety in regard to the degree of total femininity present in different women it follows that the individual characteristics must vary. In this connexion we may say, without fear of contradiction, that the woman who can and does suckle her children is strongly feminine, and that the future of the race is safe so far as she is concerned.

The hormones, then, that lead to the development of the sexual functions and characteristics are responsible for the development of the mammæ ; and it must be remembered that all the endocritic organs, and not the gonads alone, are so concerned.

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[1] Hippocrates, Sydenham Soc. Transl. by Francis Adams, 1849, vol. ii, *Aphorisms*, § v, no. 5, p. 747.

[2] Celsus, A. C., quoted by R. Temesváry, *Journ. Obstet. and Gyn. Brit. Emp.*, 1903, vol. iii, p. 511.

Attention must be called to the fact that the casual observer may be misled into the inference that adiposity, which may occur in the region of the breasts as elsewhere, is indicative of true (glandular) mammary development; but, as a matter of fact, large breasts due to adiposity may be associated with atrophy of the glandular tissue.

The ovaries and the mammæ.—In the development of maturity in the female ovarian activity plays a large part. As is well known, removal of the ovaries before puberty leads in all animals (and would almost certainly, therefore, do so in woman) to infantilism in the mammary glands[1]. I have myself observed this on many occasions in young rabbits. Nevertheless, the castrated animal, as will be remembered, grows to a larger size and is fatter than normal.

In regard to the further development which may take place in the mammæ a distinction must be made between that which occurs during gestation and immediately preceding lactation, and that actually concerned in the secretion of milk.

It is certain that once the mammary glands have become fully developed the ovary exerts little direct influence over their further activity; indeed, some assert[2] that during the reproductive period the ovarian secretion inhibits mammary activity. I believe, however, that it is not so much a question of 'inhibition' as that the ovary causes the excretion of lime salts, a process in which the mammary glands are also concerned. Attention has already been drawn to the fact that normally the two processes—ovary-induced and mammary

[1] Marshall, F. H. A., *The Physiology of Reproduction*, 1910, p. 314.
[2] Battuaud, J., *Rev. de Mal. de la Nutrit.*, 1909, vol. vii, p. 260.

excretions—may not be compatible, since they are concerned with more or less identical processes ; and this fact is well demonstrated by the absence of menstruation during the first months of lactation in normal circumstances, although subsequently, when a metabolic readjustment has taken place, menstruation may be, and normally is, re-established during the later months of lactation—often to the detriment of the mother (p. 199).

Further, it has been shown quite definitely by veterinary surgeons[1] that in cows in which lactation has been present for many years oöphorectomy increases the quantity and richness of the milk. It is obvious, of course, that this effect of oöphorectomy can only be observed in those animals which have borne young.

It has been suggested by Bouin and Ancel[2], O'Donoghue[3] and others that the corpus luteum furnishes an internal secretion which stimulates mammary growth during pregnancy. The evidence, however, on this point appears to be against such an inference, for the corpus luteum is most prominent early in pregnancy before the mammæ undergo much change ; and oöphorectomy during pregnancy does not interfere with subsequent lactation[4].

Again, Ott and Scott[5] state that extract of corpus luteum increases the flow of milk ; but, on the other hand, Frank and Unger[6] have shown that no stimulation

[1] Hobday, F. T. G., *Castration and Ovariotomy*, 1914, 2nd ed.

[2] Bouin, P., and Ancel, P., *Compt. Rend. Soc. Biol.*, 1912, vol. lxxii, p. 129.

[3] O'Donoghue, C. H., *Quart. Journ. Micr. Soc.*, 1911, vol. lvii, p. 187.

[4] Marshall, F. H. A., and Jolly, W. A., *Proc. Roy. Soc.*, Ser. B, 1905, vol. cxcviii, p. 99.

[5] Ott, I., and Scott, J. C., *Proc. Soc. Exper. Biol. and Med.*, 1910–11, vol. viii, p. 48.

[6] Frank, R. T., and Unger, A., *Arch. Inter. Med.*, 1911, vol. vii, p. 812.

of the mammæ can be obtained by the injection of the extract, even when homogenous, in non-lactating animals.

Further, in women at a menstrual period the breasts may show signs of activity, and this has been held to prove that the internal secretion of the corpus luteum is responsible for the change. The investigations of Bouin and Ancel[1], and also those of O'Donoghue[2], apparently support this view, but it seems to me doubtful whether it represents the whole cause and effect. I shall discuss mastidynia later, but it may be mentioned here that menstrual swelling and tenderness in the breasts is probably due to an attempt on the part of regulators of metabolism to excrete lime salts by way of the mammary glands at this period; or, alternatively, that a high calcium content in the blood, such as is found before menstruation, leads to activity in the mammæ. This is entirely confirmed by the fact that with the onset of menstruation the pain and swelling in the breasts immediately disappear; for this would not happen if the corpus luteum were the cause of the disturbance. Further, the ripening of the corpus luteum does not necessarily coincide with menstruation. This last objection, however, is open to the argument that all women do not suffer with tenderness in the breasts during menstruation; nevertheless, the majority probably do.

It may be said, then, that the ovary influences the development of the breasts as an important sex characteristic, but that subsequently the functions of the ovarian secretion are not specially or directly related to mammary activity.

[1] Bouin, P., and Ancel, P., *Compt. Rend. Soc. Biol.*, 1912, vol. lxxii, p. 129.

[2] O'Donoghue, C. H., *Quart. Journ. Micr. Soc.*, 1911, vol. lvii, p. 187.

The pituitary and the mammæ.—Crowe, Cushing and Homans[1] showed that the infantilism produced by removal of a portion of the anterior lobe of the pituitary included an arrest in the development of the mammæ. In my own experiments on the pituitary the mammæ were found to be infantile in those cases in which the genitalia showed retrogressive changes after operation—that is to say, after removal of large portions of the anterior lobe, and after the stalk had been clamped or separated.

Whether this mammary infantilism is secondary to the ovarian hypoplasia which follows partial hypophysectomy, or is direct, we have no certain means of knowing. It is obvious, of course, that the ovarian hypoplasia, produced by pituitary lesions, would lead to infantilism of the mammæ, but it is quite impossible with our present knowledge to say whether the pituitary lesion itself directly affects the development of the mammæ. This point may some day be decided by investigations on the state of the mammary glands in animals in which the pituitary has been subjected to lesions during early pregnancy. It is well known that there is increased activity in the anterior lobe during pregnancy, and that the secretion so produced, like that of the posterior lobe (infundibulin), influences the retention of lime salts which are required for the fœtus and also for the secretion of milk.

There is, moreover, another fact of importance in this connexion. In 1910 Ott and Scott[2] observed that the extract of the posterior lobe of the pituitary has a

[1] Crowe, S. J., Cushing, H., and Homans, J., *Bull. Johns Hopk. Hosp.*, 1910, vol. xxi, p. 127.

[2] Ott, I., and Scott, J. C., *Proc. Soc. Exper. Biol.*, 1910–11, vol. viii, p. 48.

powerful augmentative influence on mammary secretion in the lactating animal. This has been confirmed by Schäfer and Mackenzie[1] and others. There has, however, been much discussion whether the extract produces this effect by its well-known action on all involuntary muscle —an expressor effect, in fact—or whether there is a selective action on the mammary epithelium ; possibly both factors are brought into play.

I have recently carried out experiments, in which injections of anterior lobe extract and infundibulin have been made into adult virgin and into non-pregnant parous guinea pigs, in order to test the effect of these extracts on the mammary glands in circumstances which would avoid the possibility and consequent confusion of an expressor action. In these experiments portions of the mammæ were first removed as controls, and subsequently the animals received many injections of the extracts mentioned. In no case was any histological difference found in the mammary gland before and after the injections.

The thyroid and the mammæ.—Very little experimental work has been recorded in this connexion. In my own experiments it was noted that in one cat from which the thyroid was removed during pregnancy suckling occurred after the birth of the kittens. This showed that, like the removal of ovaries, thyroidectomy does not interfere with the milk secretion provided the breasts be active—that is, under the influence of pregnancy—at the time. In animals from which the thyroid is removed at other times inactivity persists, as one would expect.

[1] Schäfer, E. A., and Mackenzie, K., *Proc. Roy. Soc., Ser. B*, 1911, vol. lxxxiv, p. 16.

According to Ott and Scott[1], iodothyrin inhibits the mammary secretion.   On the other hand Hertoghe[2] states that the administration of thyroid extract to lactating animals increases the flow.

The suprarenals and the mammæ.—So far as I know no observations have been recorded on this point except those made by Ott and Scott[1].   These observers found that suprarenin inhibits the secretion of milk.

The thymus and the mammæ.—Ott and Scott[1] state that injections of thymus extract excite the secretion of milk.

It will be obvious from the foregoing remarks how little is known of the influence of the internal secretions on mammary secretion.   It appears that the most feasible method of reaching a conclusion, apart from direct experimentation which would be extremely complicated, is the application to the question of the metabolism of milk-secretion of the principles of the maternal-fœtal metabolism, and its relation to the internal secretions.

The fœtal hormone.—Since the work of Lane-Claypon and Starling[3] attention has been riveted on the hormonic theory of mammary activity and milk

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[1] Ott, I., and Scott, J. C., *Therap. Gaz.*, 1912, vol. xxxvi, p. 761.

[2] Hertoghe, E., quoted by H. R. Harrower, *Practical Hormone Therapy*, 1914, p. 186.

[3] Lane-Claypon, Janet E., and Starling, E. H., *Proc. Roy. Soc.*, *Ser. B*, 1906, vol. lxxvii, p. 505.

secretion; and at the present time it is unnecessary to discuss the nervous theory, or the way in which it has been refuted by transplantations of mammary gland tissue[1], and by observations made on paraplegic patients who have become pregnant and have nursed their children subsequently[2]. It is now accepted that the whole cycle of breast activity is biochemical.

Lane-Claypon and Starling performed a number of experiments which proved, they thought, that the growth of the mammary glands during pregnancy is due to "the action of a specific chemical stimulus produced in the fertilized ovum"[3].

Further, they stated that "lactation is due to the removal of this substance, which must therefore be regarded as exerting an inhibitory influence on the gland cells, hindering their secretory activity and furthering their growth".

These authors, however, do not believe that the fœtus is the only factor concerned in activating or inhibiting the mammary development—a reservation that has often been overlooked by subsequent writers who have alluded to this work.

Lane-Claypon and Starling found, then, that the mammary glands of virgin animals were stimulated to growth by fœtal extract, and those of multiparous animals to secretory activity. These observations have been supported by further evidence; and Foà's[4] investigations seem to show that the hormone is not specific to the species.

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[1] Ribbert, A., *Arch. f. Entwick.-Mechanik.*, 1898, vol. vii, p. 4.

[2] Routh, A., *Trans. Obstet. Soc.*, 1897, vol. xxxix, p. 191.

[3] Lane-Claypon, Janet E., and Starling, E. H., *Proc. Roy. Soc., Ser. B*, 1906, vol. lxxvii, p. 505.

[4] Foà, C., *Arch. di Fis.*, 1908, vol. v, p. 520.

Before Lane-Claypon and Starling's researches Halban[1] had put forward the view that the stimulus to mammary development during pregnancy originates in the placenta.

On the other hand, the views put forward by Lane-Claypon and Starling have been criticized by competent authorities[2]. Nevertheless, it is evident that their claim concerning the fœtal hormone is accurate so far as it goes; but, as they themselves admit, this explanation does not contain the whole truth of the matter, for it seems that many organic extracts have the same effect as fœtal extract.

Hill, quoted by Marshall[3], and O'Donoghue[2] state that in certain marsupials the amount of mammary development at each period of ovulation is such that it is difficult to distinguish the condition of the mammæ in these circumstances from that associated with pregnancy; and consequently these authorities believe that the stimulus to the mammæ comes from the internal secretion of the corpus luteum. Further, as Heape[4] has described, virgin bitches have often been known to suckle puppies successfully; and, as I have myself observed, bitches subsequently to œstrus and without fertilization may have milk in the mammæ at the time when parturition would have occurred had they been fertilized. Males, too, have been known to perform the function of lactation.

[1] Halban, J., *Arch. f. Gynak.*, 1905, vol. lxxv, p. 353.

[2] O'Donoghue, C. H., *Quart. Journ. Micr. Sci.*, 1911, vol. lvii, p. 187.

[3] Marshall, F. H. A., *The Physiology of Reproduction*, 1910, p. 576

[4] Heape, W., *Journ. Physiol. (Proc. Physiol. Soc.)*, 1906, vol. xxxiv, p. 1.

All these facts go to show that however stimulating the fœtal hormone may be in regard to the mammary activity, which subsequently leads to the secretion of milk, it is neither specific nor essential; for various hormones, mechanical stimuli, and other exciting causes such as pelvic tumours, not infrequently arouse mammary activity, even in the absence of pregnancy and parturition.

It may be stated, therefore, that although the breasts have a special function connected with conception, which is probably the most powerful stimulus to the preparation of the breast—the sensitizing of the mammæ, as we might call it—the subsequent flow of milk is merely a diversion of excretion through the sensitized glands. There are, moreover, many sensitizing agents, and many secretory stimulants.

INFLUENCE OF LACTATION ON THE MATERNAL META-BOLISM AND FUNCTIONS

Lactation is of benefit to the normal woman, as I shall explain directly. If, however, a woman is unable to nurse, the stream of nutrient material utilized by the child during gestation is either consumed by the mother or excreted through channels other than the mammæ; and this may necessitate a considerable readjustment in her metabolism, and be associated with various disturbances. If a woman be delicate and have felt the strain of pregnancy, during which her tissues may have been depleted of lime salts, mammary inactivity may be a natural method of allowing the mother to recuperate.

With regard to the benefits which may accrue to the mother if she be able to suckle her child, it is commonly stated that in these circumstances involution of the

uterus occurs more quickly and completely than if she be unable to do so.

Temesváry[1] made observations on this point, and found a considerable difference in the rate of involution in those who suckled and in those who did not. Observations with the same results have been made by Mueller[2], Hansen[3], and others.

Pfister[4], also, studied the relation between lactation and uterine contractions, and found that this was very definite: contractions of the uterus occurred within three or four minutes of the baby being put to the breast, and returned every five minutes during suckling—a phenomenon which was noted up to the eighth day after delivery. It is probable that this effect is the result of a nervous reflex. In Routh's[5] case of paraplegia, in which the patient conceived and was able to suckle (showing there is no nervous reflex in regard to the secretion of milk), the involution of the uterus was normal.

The ' sucking reflex ', as we may call it, is probably a reverse of the reflex associated with erection of the nipple which has been noted to occur on coitus[1].

In spite, however, of the probability of a nervous reflex in the production of immediate uterine contractions, there is no doubt that the high calcium content in the blood during lactation, which I have found to exist, has a beneficial influence on both lactation and involution.

[1] Temesváry, R., *Journ. Obstet. and Gyn. Brit. Emp.*, 1903, vol. iii, p. 511.

[2] Mueller, P., *Schmidt's Jahr.*, 1888, vol. ccvii, p. 250.

[3] Hansen, T. B., *Zeitschr. f. Geb. u. Gyn.*, 1886, vol. xiii, p. 16.

[4] Pfister, M., *Beitr. z. Geb. u. Gyn.*, 1901, vol. v, p. 421.

[5] Routh, A., *Trans. Obstet. Soc.*, 1897, vol. xxxix, p. 191.

Superlactation which is sometimes seen in the poorer classes is dealt with in Part II.

PHYSIOLOGICAL EFFECTS OF MAMMARY EXTRACT

Many observations have been made recently concerning the action of extracts of the mammary gland, in the belief that this structure is itself an organ of internal secretion. I have already discussed this question, but it will be worth while briefly to examine the physiological evidence on which the therapeutic use of this extract is based.

A short review of the work done on these lines up to the year 1913 is to be found in a contribution by Cavagnis[1]. This author arrived at the following experimental conclusions :—At the beginning of pregnancy the injection of mammary extract augments to a remarkable degree the tonicity of the muscle fibres of the uterus. This action is less marked on the non-pregnant uterus, and on the uterus towards the end of gestation.

Further, it has been stated[2] that injection of mammary extract will produce abortion in pregnant animals.

The action of mammary extract is, generally speaking, hypertonic in regard to all involuntary muscle, and it is said that the mammary extract from a pregnant female has the same action as that from the non-pregnant. If this be so, it is a point of some importance ; but of greater importance is the question whether an extract of the lactating breast gives a more marked

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[1] Cavagnis, G., *Ann. di Obstet. e Gyn.*, 1913, vol. ii, p. 563.

[2] Schiffmann, J., and Vystavel, A., *Wien. Klin. Woch.*, 1913, vol. xxvi, p. 261.

action than the extract of virgin mammæ in regard to the properties mentioned. If so, the pressor effect obtained might be explained by the fact that such breasts must be extremely rich in calcium salts, which themselves have a well-marked pressor action.

THE CORRELATION OF THE INTERNAL SECRE-
TIONS IN REGARD TO THEIR GENITAL
FUNCTIONS

I have endeavoured to trace, for the most part from my own observations, the disjointed facts concerning the influences exerted by the different members of the endocritic gland system upon one another, on the genital organs and on the metabolism generally, in so far as the reproductive system may be concerned ; and in so doing I have in some cases been able to show clearly the nature of the associations between the different organs. It is, however, absolutely impossible at the present time fully to correlate all their functions ; but in view of what was said at the commencement as to the necessity for a lead in this intricate matter, I cannot refrain from enunciating what I believe to be the general principles. I shall not further analyze the details.

It appears, from the evidence at our disposal, that in spite of great variations in the structure of the endocritic glands in different mammals, the *total functional result* is the same so far as the genital processes are concerned. The variations in function that depend on the differences of structure are probably related to differences in the food and habits of life ; and in adapting our knowledge to the requirements of human physiology we must take into account both the essential functions to which we have already referred—the individual

metabolism of the mother, and the metabolism of her reproductive functions—for they are completely inter-dependent in normal circumstances.

We have seen as the result of our studies that the ovaries, on the one hand, have as their share of these dual functions the onus of ensuring the reproduction of the species by furnishing the ova, and by keeping active the rest of the genital structures and functions. And, further, the secretions of the ovary are probably con-cerned in keeping the other members of the endocritic system in touch with the necessities of the reproductive situation. This last function is of the deepest import-ance, and is one which explains much that would other-wise be obscure.

Strictly speaking, then, the ovary is concerned in the temporary function of reproducing the species, and, by its hormones or internal secretions, of bending the metabolism of the body to this purpose. Any influence the ovary may have over the general metabolism is, then, related to and dependent on its primary reproductive functions. I do not believe that this organ influences the metabolism except in so far as this special function is concerned. Of course, removal of the ovaries may produce a temporary general disturbance, but this does not invalidate the view just mentioned.

On the other hand, the rest of the endocritic system is related to the genital functions in various ways. First, some of the members—the thyroid, pituitary, and suprarenals—influence the development and subse-quently preserve the integrity and activity of the genitalia, as I have already demonstrated; while others—the thymus and possibly the pineal—appear to prevent sexual precocity. Second, all the endocritic organs, acting in harmony, control the metabolism in

response to the necessities of the genital functions; but, in addition, they adapt the whole organism to the possibility of the situation, and regulate the secondary characteristics, both physical and psychical, to suit the needs of the individual. Once, however, the reproductive organs are removed or undergo atrophy, the genital functions of the rest of the endocritic system cease, and the rearrangement of the metabolism that follows produces the symptoms of the menopause, as we shall see later. Contrariwise, insufficiency of the thyroid, pituitary or suprarenals may cause the cessation of the genital functions with atrophy of the uterus.

As to the more particular parts played in the metabolism by each member of the ductless gland system, these have already been specified.

In spite, therefore, of the reluctance to correlate our knowledge shown by most investigators the matter is not one of very great complexity if the views expressed be correct in a general way, although there remains much detail to be filled in.

As soon as possible we must come to a conclusion as to what are the facts; so much of the work that has been done is contradictory. There is in consequence so much more need for further efforts. And I would again insist that in order completely to solve the problems surrounding the genital functions, we must focus at one and the same time the two essential processes of life—the individual metabolism and the reproductive metabolism. They are absolutely interdependent; indeed, the individual metabolism is the reproductive metabolism. It is the neglect of this point of view that has brought about much of the confusion that still exists.

Weismann and Ray Lankester describe the relation between the reproductive cells and those of the soma in

still more striking terms. The latter[1] says : " Among
" the multicellular animals, certain cells are separated
" from the rest of the constituent units of the body, as
" egg cells and sperm-cells ; these conjugate and con-
" tinue to live, whilst the remaining cells, the mere
" carriers as it were of the immortal reproductive cells,
" die and disintegrate. The bodies of the higher animals
" which die may from this point of view be regarded
" as something temporary and non-essential destined
" merely to carry for a time, to nurse and to nourish
" the more important and deathless fission products of
" the unicellular egg."

Whatever views we may hold as to details I question
whether this philosophical statement is open to con-
tradiction. The function of reproduction in all its
preparations and performances commences in the early
stages of segmentation, and may be said to continue
in Man until the care of the offspring is completed ; but
in many lower forms of life, male and female, the act
of reproduction is also the cause of death.

[1] Lankester, Ray, quoted by P. Geddes and J. A. Thomson, *The
Evolution of Sex*, Revised edition, 1901.

PSYCHOLOGICAL CHARACTERISTICS

Although I have indicated incidentally the fact that the psychical functions are related to the physical, it will be necessary briefly to consider whether we have any grounds for believing in what may be called the 'psychology of sex'; and, if so, what the special attributes may be. I shall endeavour to present the case as it appears to me and, I believe, to most unbiassed scientists.

In their work *The Evolution of Sex* Professor Geddes and Professor Thomson introduce their discussion of the biological aspect of sex psychology with the following words : " We cannot attempt a full discussion " of the question, but our book would be left without " point, and its essential thesis useless, if we did not, " in conclusion, seek to call attention to the fundamental " facts of organic difference, say rather divergent lines " of differentiation, underlying the whole of the problem " of the sexes."

Completely to explain sex psychology we should in the first place be obliged to study the nature of psychical processes. This difficult task I shall not attempt ; it is one that belongs to the domain of the pure psychologist, and it is one which has for its primary basis either purely material or partly 'spiritual' conditions. By saying " partly spiritual "—for want of a better term—as opposed to " purely material ", I leave undecided the

general aspects of the stormy disputation concerning the connexion of 'spirit' with matter; yet any views I shall put forward will not be affected—they are equally applicable whatever may be the opinions held concerning this question. I cannot, however, hope to accommodate those who assert that the mental functions are entirely 'spiritual'.

Without indulging in profitless discussion, I shall take it for granted that all engaged in biological pursuits, to whom my statements are addressed, hold the view that the psychical functions are partly or solely dependent on physiological processes; and it is on this belief that my own views are based. I shall, moreover, not enter into any discussion of what I have described as "partly spiritual" factors, whether they exist in reality or not; I shall merely deal with the material factors which, it is certain, influence mental processes.

The mental characteristics of the normal woman come under the dominating influence of her special functions. Before puberty, when the metabolism of girls does not differ appreciably from that of boys[1], the maiden is often self-reliant and somewhat of a 'tom-boy'. Some, it is true, like to nurse dolls, but many, especially when brought up among boys, prefer more masculine methods of enjoyment. At puberty a vast psychical change occurs in normal girls : they become shy and reserved, and adopt a modest demeanour in the presence of men. At this time they realize the influence of their fascinations on the opposite sex. Marriage may bring out the best or worst that is in a woman : if she be happy and contented her mind becomes turned in the direction of motherhood with joyous anticipation ; if discontented

[1] Bucura, C. J., *Geschlechtsunterschiede beim Menschen*, Wien. u. Leipzig, 1913.

and unhappy she often seeks distraction outside the home. Gestation, too, normally produces in a woman mental equanimity, and a special faculty for patience and endurance for the sake of her child. Parturition, with its attendant fears and pains, develops in the mother a very tender feeling of possession after a fight well won. Nurses have told me that women delivered by Cæsarean section usually have not the same feelings of passionate possession that fill the hearts of women who have endured ungrudgingly the pangs of labour; and it is possible that the so-called 'twilight sleep' induced during parturition will likewise produce a similar deficiency in the maternal emotions. Lactation, also, incites or increases the mother-love—as poets for countless ages have told us—partly by demonstrating, as it does, the dependence of the infant, and partly by inspiring the mother with the joy of self-sacrifice.

After the menopause the mental attitude once more reverts to a neutral type.

I shall only deal with the mentality of Woman during the reproductive period—that is to say, between puberty and the menopause—since it is then that her characteristic psychology is most evident, for the reasons given above.

It has already been stated that every person is dimorphic; in other words, all normal men and women contain the elements of both sexes. The total quantitative proportion varies in different individuals and in different characteristics; but the dominant characteristics usually indicate the declared sex of each, while the recessive characteristics remain more or less latent. This being so in regard to structural disposition, logically we may expect the functional activities to correspond therewith; as, indeed, they do. It is to be regretted,

however, that at present we know so little of the finer anatomical differences of the regulators of sex metabolism, for, were we able to point to definite and constant distinctions at all ages between the structure of the organs of internal secretion other than the gonads in the two sexes, it would be easier to convince those who are now sceptical of the differences of function dependent thereon. I believe, by reason of much physiological and pathological evidence, that there are such differences, and that if these cannot always be expressed qualitatively, they certainly can quantitatively. And, after all, quantity is capable of producing effects and results as surely and with as great variations as quality. Furthermore, it must be obvious to all that normally different metabolic effects are due to different demonstrations of function; and that different demonstrations of function must be dependent on qualitative or quantitative structural conditions.

Since the differentiation of sex is a process of evolution destined to meet the complexities of reproduction which arise in the life histories of the higher animals, we must look upon all the functions of the body, the mental no less than the physical, as harnessed to this purpose, which has reached the highest development in Man. In the lower animals sexual selection and maternal instincts are dependent, no doubt, on sensory stimuli, probably without the interference of the intellectual faculties of altruism and choice, which form additional factors in the equipment of the human female.

From a biological standpoint, according to the statements of Ray Lankester and others, already referred to, the individual exists merely to harbour the reproductive cells. Less crudely we may say the *raison d'être* of all existence is the furtherance of the universal

scheme of evolution. Retrogressions there may be, it is certain, but the total trend is towards the evolution of higher forms of life, and therefore of higher and more intricate functions. It is only to be expected, then, that all the functions of every individual subserve, however obscurely, this one vital purpose. Indeed, it might be urged that in serving the individual the so-called ordinary functions are indirectly assuring the welfare of the reproductive functions. It is not for us, therefore, who make a study of the processes of reproduction, to allow the possibility of any divergence of the mental functions from the path indicated. Still less is it for others with no knowledge of biology to take the mind from the body and enshrine it as a thing entirely apart— a parasitic function living on, but independent of the body.

It would, of course, be absurd to deduce from these remarks, as some may be inclined to do, the belief that the mind is centred on the actual reproductive functions alone, or is entirely dependent thereon. Beneath the wide issue of evolution lie many incorporated but individual parts : each is as independent as is the modern worker of the organizing capitalist who employs those under him. At the same time, just as the worker— often acting unconsciously, no doubt—is essential to the furtherance of his employer's schemes, while living himself an independent life—which, be it noted, probably often accounts for his value to his master—so, too, are the functions of the mind and body, perfected by *apparently* individual life, necessary for the advancement of the whole scheme of evolution through the channels of reproduction.

I say " apparently ", for although individuation is accentuated in the secondary reproductive functions

of Man, yet it so obtains for the benefit of evolution rather than of the individual. It is, of course, possible that too great a degree of individuation might lead to a decrease in fertility, but at present there is little evidence of this in regard to the human race.

The antagonism of Individuation and Reproduction has been discussed by Herbert Spencer[1], who takes the view that extreme individuation leads to a decrease in reproductive activity. If this be true from a general standpoint without regard to sex, it is of great importance to our argument, for undoubtedly the largest strain in connexion with the processes of reproduction falls upon the woman. Individuation to the extent seen normally in a man may, therefore, not be strictly compatible with the reproductive functions of a woman.

The ultimate object of all mental processes is the same—evolutionary progress, of which reproduction is an essential, if indirect, factor. Mental aspirations are the aspirations of the controlling factors of evolution, even though they appear to be the selfish ambitions of the individual. Nature adroitly furthers her scheme of evolution by teaching Man, before whom, but unknown to him, she places inducements to improve himself; and thus there are wheels within wheels, although the effect of the hand of Time alone is visible: Reproduction; Reproduction with individuation; Individuation with reproduction; Individuation . . . Evolution.

The higher mental processes, then, in the human subject are turned into account in the physiology of reproduction in a manner apparently not exercised in the lower orders of creation.

As I have indicated, sexual selection in animals is apparently dependent entirely on internal stimuli—due

[1] Spencer, Herbert, *The Principles of Biology*, 1867, vol. ii, p. 470.

to metabolic factors to be discussed directly—and on stimuli of external origin, emanating from the senses of sight, smell, hearing and touch. With regard to the instincts associated with maternity in the lower animals, these, also, appear to be directly referable to internal stimuli evolved by the processes of natural selection in the competition for survival.

To illustrate how purely metabolic are the maternal instincts, and even the functions associated with maternity in animals, I may mention the case of a bitch which lived for nearly seventeen years. When young she had several litters of puppies. Later in life, some weeks after the cessation of each œstrum 'milk' appeared in the mammæ, and at the correct period she made a nest for the expected young, although she had never been allowed access to a dog during the period of heat. Moreover, Marshall[1] and others state that the migratory instinct of birds is due to activity in the gonads, after a period of quiescence.

The human female, to whom the intellect is a source of personal pleasure and pride, utilizes—often quite unconsciously—the high state of perfection to which her mental processes have been evolved not only to assist her in sexual selection[2], but also in the care and up-bringing of her offspring. And while the environment and condition of women have undergone very little, and certainly no radical change in regard to their special reproductive functions, those of men have altered considerably. It is, of course, true that the higher

[1] Marshall, F. H. A., *The Physiology of Reproduction*, 1910.

[2] Modern 'Eugenics' have been introduced by Man in an attempt to assist the unerring laws of Nature which are concerned with sexual selection. This study may have been thrust into the mind of Man by Nature, in order to counteract the disturbances of the law of the survival of the fittest, which are produced by the humanity of mankind.

mental faculties of women must keep pace with the mental development of mankind as a whole, in order that the evolution of the mind may not be impeded ; but, properly speaking, that is the sole biological object of mental advancement in women in normal circumstances.   Men, on the other hand, must develop their intelligence not only to assist them in sexual selection, but also in order that they may be able to sustain their mates and offspring in an environment compatible with advanced civilization. This means that, whereas a strong arm, a good bow and arrow, and courage were the sole requirements of the primitive man rising above the beasts, in advanced conditions of civilization the mental faculties must be capable of all the intricate processes which go to make it possible to live under modern conditions. The earning of a livelihood by scientific enterprise, for instance, requires a vastly different intellect from that necessary for the manufacture of a bow and arrows and the hunting of wild beasts. The selection of a mate and the provision of a suitable environment for her and her offspring may be termed the secondary reproductive functions of the human male.

In considering the psychical characteristics of the modern woman we must bear all these facts in mind. We must, too, remember that the individual is merely a tool of nature—a unit in a vast scheme. The man is not superior to the woman in any possible sense of the word: his functions lie in one direction, and the woman's in another ; and each is the reproductive complement of the other.

If a man's primary reproductive functions may be described as fugitive owing to the claims of the secondary, a woman's may be said to be stationary or enduring.

As far as a man is concerned the sexual act—his contribution to reproduction—is an incident, but a woman's contribution is of long duration, including conception, gestation, parturition and lactation ; and thus we are reminded forcibly of Byron's well-known lines contrasting the love of Man and Woman. But while the primary reproductive process is short where a man is concerned, his secondary processes are, in our days, long and arduous. The course of education and the striving after the success necessary before he can ensure the proper environment for a family require physical strength and mental acquisitiveness, if he is to achieve his purpose, and fulfil his destiny as a factor in the progress of Nature. On the other hand, a woman's primary reproductive functions are, as we have seen, enduring, and her secondary—individual education, and the care of the child and home—are merely a direct preparation for and sequel of the primary.

Geddes and Thomson[1] ingeniously describe the male metabolism as katabolic and the female as anabolic. It may also be suggested that the mental processes in the two sexes functionate on similar lines. Be that as it may, it must surely be recognized by all that the male mind and masculine form are suited to the business of life which so nearly concerns his share in reproduction ; while the female mind is specially adapted to her more protracted part in the perpetuation of the species.

I cannot conclude this discussion of the more abstract aspect of the subject without an acknowledgment of the fact that the rejection of maternal functions by modern women may be Nature's plan for securing the disappearance of Man to ensure further evolution. It is

[1] Geddes, P., and Thomson, J. A., *The Evolution of Sex*, Revised ed., 1901.

strange that modern advocates of reproductive sub-jection have not advanced this, the only scientific reason for their point of view. Possibly they think nothing could be more perfect than themselves.

Let us now discuss more exactly the psychology of women, and the factors by which the mental processes are regulated.

It has already been indicated that the central motive of a normal woman's existence is the propagation of the species; and since in her this process may occupy the best period of her life almost exclusively, it is obvious that her metabolic processes must be particularly adjustable to the reproductive economy. And, as the mental attitude is considerably dependent on the general metabolism, it follows that the mental processes of every normal woman are largely subservient to the varying physiological conditions of her body.

It seems almost superfluous now to point out how the mind is affected by the physical condition of the subject; how different the mental outlook is at puberty and at the menopause; how different usually in the normal, reproductive woman and in the barren spinster. I know quite well these truisms are often denied by women, and I do not intend to digress : it is no business of ours that social conditions force women out of their natural sphere, and it is not in the province of scientists to suggest remedies. The very fact that women are continually asking for remedies and seeking them is a tacit admission of abnormal circumstances.

The mental condition of a woman is dependent on her metabolism; and the metabolism itself is under the influence of the internal secretions. As I have said before, probably every cell in the body is an organ of internal secretion and is intimately connected with

the life of all the other cells of the body. But those aggregations of secretory cells known as the endocritic glands afford us definite information as to the processes of metabolism with which they are connected, consequently we can trace their relations to mental processes. It is well known that women with hypothyroidism and hypopituitarism are lethargic ; and we have ample proof that hyperthyroidism produces mental energy and excitability. So, too, we are certain that the removal of normal functionating ovaries generally produces mental depression ; while women with very active ovaries, which can be discerned from the menstrual flow, sexual inclination and so on, are usually energetic and lively.

Now, these mental effects are due to changes in the metabolism which result from the conditions affecting the endocritic glands mentioned ; and our knowledge is such that we can often say exactly what metabolic disturbance is responsible for the abnormal mental attitude concerned ; and sometimes, too, we can directly remedy it. For example, excessive ovarian and thyroid secretions lead to an unusual excretion of lime salts ; and it appears obvious from the investigations of Sidney Ringer and Dudley Buxton[1] and from my own work[2] that the compounds of calcium are largely responsible for vasomotor stability and the control of nervous and muscular irritability. These views have recently received further confirmation from the experimental work of Hoskins and Wheelon[3].

All this is extremely interesting and important : it

[1] Ringer, Sidney, and Buxton, D. W., *Journ. Physiol.*, 1885, vol. vi, p. 154 ; 1887, vol. viii, pp. 15 and 288.

[2] Bell, W. Blair, *The Principles of Gynæcology*, 1910 ; *Liverp. Med. Chirur. Journ.*, 1912, vol. xxxii, p. 398.

[3] Hoskins, R. G., and Wheelon, H., *Amer. Journ. Physiol.*, 1914, vol. xxv, p. 119.

indicates that the mental processes can be regulated therapeutically, and it shows clearly how the mind is dependent for its normal functions on the condition of the body. We have, at the present time, no need for the crude evidences of insanity, of brain lesions, or even of such diseases as cretinism to prove our contention ; we know that merely the excessive excretion of a mineral salt will lessen the mental equanimity of the subject. I would point out, too, that this is only one example of many equally intimate relations between the mental condition and the metabolism.

How then does all this specially concern the psychology of women as opposed to that of men ?

We have seen that in men the reproductive calls on the metabolism are, unless excessive sexual indulgence be practised, not great. Their metabolism during the reproductive period, after growth has been established, is mainly concerned with their individual needs : the ' nerves ' must be steady, the mind stable and the physical strength great. These attributes are so assigned that men may be able to succeed—a term which implies a contribution towards the progress of evolution, as well as the assurance of a suitable environment for the family. All the endocritic organs are adjusted with this object in view : the preservation of a steady and uniform metabolism, in which no sudden alterations normally occur. Obviously the more masculine a man is the more this state of affairs will obtain. There is, therefore, little reason for pathological lesions of hyperplasia and hypoplasia to supervene in his organs of internal secretion. And this is exactly what we find ; for, unless the changes at puberty overstep the normal limit, it is exceedingly rare in men for hyperplastic or hypoplastic lesions to occur in the

organs of internal secretion. On the other hand, in women during the reproductive period there are sudden and rapid alterations due to the demands of gestation and lactation. To a certain extent a woman by the catamenia is kept 'in practice', as we may say, and protected from too sudden and great demands on her metabolic adaptability; and the periodic fluctuations in her economy are provided for by the capabilities of her endocritic organs—the 'regulators of metabolism', as Paton[1] has aptly called them.

Now, although we know that the corresponding organs of internal secretion in the two sexes differ with regard to their weights relative to the total body-weight, at the present time we know of no absolutely definite qualitative differences, except those produced by pregnancy, which can be set down as providing a means of sex distinction. This disability will soon be removed by the work which is being done upon the subject. Not infrequently it has been disputed that differences exist, either in the organs of internal secretion or in the general metabolism. It appears to me, however, that to dispute quantitative differences is to risk a reputation for logical inference; while to deny the possibility of qualitative differences is merely an indication of ignorance of actual facts, for differences have already been demonstrated in regard to the structural appearances associated with pregnancy—an essentially feminine function. It is, of course, reasonable to suppose that the qualitative and quantitative differences will vary in degree according to the proportions of dominant or recessive femininity.

The instability of metabolism, actual or latent, which is seen in women, is obviously the causal factor in the frequency with which they suffer from disorders of the

[1] Paton, Noel, *The Regulators of Metabolism*, 1913.

endocritic organs most concerned—the thyroid and the ovaries. We may look upon the pituitary, suprarenal cortex and pineal body in women as more or less recessive in function, except during pregnancy when large quantities of calcium salts are required for the foetus. This special masculine function of calcium retention is demanded in the interests of the foetus rather than in those of the mother herself.

We have, then, in the endocritic organs structures in which quantitative and qualitative changes influence metabolism towards masculinity or femininity as the case may be. In this connexion it is interesting and instructive to note that changes similar to those mentioned as occurring in the pituitary and suprarenals in pregnancy, which produce calcium retention for the benefit of the foetus without producing masculinity in the mother, may in the non-pregnant woman produce masculinity in her; and, included in secondary characteristics of masculinity so produced is a metamorphosis towards masculinity in the mental processes, as we shall see later.

There can, therefore, be no doubt that there is a sex psychology, which is related to the dominant physical characteristics and functions of the individual; and it only remains for me to indicate the traits of mind which, on the evidence of the facts recorded, constitute the essential attributes of feminine mentality.

Many philosophers, and among the most recent that precocious thinker Otto Weininger[1], have placed the character of woman in a false light. They have taken it for granted that the natural and proper absorption of the female in her reproductive career is a vastly inferior obligation to the more diverse and intellectual

[1] Weininger, Otto, *Sex and Character*, Eng. Trans., 1906.

secondary reproductive functions, as I have called them, of the male.

It is probably this attitude towards the feminine rôle in nature that has led to attempts at the so-called 'emancipation' of women. But surely we must look upon the patient and absorbing work of the female as a far greater self-sacrifice, and consequently more altruistic —especially when carried out in the present day amid all the distractions of modern life, and amid the intellectual temptations offered at the expense of the normal physical processes—than was the more purely animal acquiescence in the functions of reproduction which existed in a more primitive era.

The ideal attitude of mind of the modern woman towards reproduction is that in which the intellect is carefully cultivated and trained both in the higher knowledge and in the most essential feminine pursuits ; the former has for its object the progress of evolution in general and the advancement of the offspring towards the same end ; while the latter makes for an increase in the capability of the individual mother for attending carefully to the environment of her child. A normal woman, therefore, would not exploit her intellect for her individual gain : it is for the benefit of her descendants.

It is reasonable to suppose, then, that the application of feminine talents to the competitive work in which men are engaged, which is strictly speaking an evolutionary form of the hunter's craft, is adventitious and distinctly injurious to the finer psychical functions connected with the biological life of women[1]. So long as there are two sexes it is unlikely that women will,

[1] Cf. Pearson, Karl, 'Woman and Labour,' *Fortnightly Review,* May, 1894.

without detriment to their own sex psychology and physical attractions, which are so essential to sexual selection, develop the masterful mind of the male that may attain to the lofty height of genius—a level to which the intellect of no woman has ever yet ascended. Weininger[1], indeed, goes so far as to say that " a female genius is a contradiction in terms ". I am inclined to agree with this statement, for the simple reason that were a normal woman to develop into a genius, the person would no longer be a woman in the true biological sense of the word. We shall see later that more latitude must be allowed for the definition of sex than merely that dependent on the character of the gonads.

The essential higher psychological characteristics of the normal woman we have indicated ; and to those mentioned we would add, as a logical sequence, dependence on the male—dependence on his ability to do his special share while she does hers—as a specifically feminine characteristic, which is associated with an ardent desire to be loved.

Brief reference must now be made to the less idealistic characteristics of feminine mentality. I refer, of course, to those reproductive instincts which women have in common with the lower animals—instincts which, as already indicated, depend for their existence on internal biochemical stimuli. There is no doubt that these so-called animal instincts have become modified in educated women by the evolution of the higher mental faculties. It is difficult in a few words to trace the manner in which the human race has brought the strongest of all instincts into comparative subjugation : religion, family life, education and social exigencies have effected a result which is common to all civilized

[1] Weininger, Otto, *Sex and Character*, Eng. Trans., 1906.

races. The economic value of reproductive indifference from a natural standpoint we are not called upon to consider ; and what the final outcome and its effect on evolution will be we can only guess. It is, however, incumbent on us to observe facts as they exist, and, when possible, to identify the causal agents and their effect on the life of the individual. Such details are too often shunned by the scientist, and become the common property of those who merely record revolting details unadorned by useful information.

I propose, therefore, to glance now at the natural aspect of the subject in order that I may briefly refer to the pathological later.

We have seen that until puberty the sexual and reproductive instincts are more or less latent. I say "more or less" because girls vary : some are more feminine than others, and much depends on environment.

In the lower classes, in which, perhaps, the people live nearer to Nature, the sexual instincts of women are more natural, or animal—as some would say : the higher mental faculties play little part in modifying the reproductive instincts. But in the upper classes, in which education and social custom exert powerful influences, we find a different state of affairs.

It is an interesting fact, which I have often observed, that if a girl in the upper classes be brought up alone or only with other girls she shows more marked femininity during childhood, so far as her mental characteristics are concerned, than do girls who are brought up before puberty in company with boys. But, on the other hand, the former class of girls does not show an excessive mental change at puberty in regard to its relations with men ; while the latter suddenly seems to realize that the freedom which existed before puberty is no longer

possible, and in consequence such girls usually exhibit great self-consciousness in the presence of members of the opposite sex who are strangers to them.

At puberty, then, the internal secretions of the ovaries, which now become active, may bring about a great alteration in the outlook of the individual; but it is probable that this mental change is not entirely dependent on the ovarian secretion, but also on the hormones from the correlated organs of internal secretion. There is no doubt that all normal girls seek the company of men, even though the presence of a man fills them with modest confusion. The thoughts and conversation of girls after puberty are commonly centred on the opposite sex. There is, of course, in girls of refinement no actual idea of sexual matters; but, whereas prior to puberty no man interested them, at and after that epoch many do. And in this all women resemble the lower animals, in which when growth ceases the genital hormones stimulate the sexual instinct; but with this difference: in girls of the upper classes education, religion, family life, and the pursuits and enjoyments of modern existence in ordinary circumstances quell what might otherwise become lustful desire. So the girl grows into womanhood. The long train of civilized ancestresses, whose desires have been kept in subjection or have been distracted by the inventions of civilization, hands on to her the tradition of restraint.

The ordinary civilized woman, whose association with the opposite sex is much restricted—much more so in the upper than in the lower classes—probably remains only partly conscious of the natural desires until she falls in love and marries. Yet I have met with normal unmarried women, in whom the sexual feelings have never been awakened, who live in the hope that one day

they may have children. It is possible, therefore, for civilization to bring women to such a state of sexual subjection that the desire for children is the one reproductive instinct left. In the uneducated classes, as in animals, the sexual instinct is probably the stronger instinct of the two, at any rate in the first instance.

There can hardly be any doubt that the sexual instinct was originally protective ; that is to say, it was a lure to ensure the propagation of the species. In women, in whom the reasoning faculty has been developed, there is, from a natural point of view, less need for the lure of sexual gratification to ensure the perpetuation of the race, so long as the maternal instinct does not die out.

It seems that this is the curious stage to which the evolution of woman has come or is coming. We see all types. The most natural, or—as many would say—the lowest, who enjoy sexual intercourse, and who are, perhaps, somewhat promiscuous in their desires ; yet their maternal instincts are strong. On the other hand, there are many women with strong maternal instincts who are cold in their sexual relations ; and others in whom sexual and maternal desire can only be aroused by the one man of their choice.

The first type represents the natural woman untouched by civilization, whose instincts are under no restraint. The second represents the type of woman of whom we have already spoken—her whose maternal instincts are sufficient without the lure of sexual gratification. The third type is the ideal woman in the present stage of our evolution ; she alone fulfils all the requirements and fits in with all the restrictions of advanced civilization.

The woman who delights in sexual pleasures, but has

no maternal instincts, is not strictly speaking normal, although she may be as much a product of civilization as is the female who abhors the idea of both sexual intercourse and maternity.

Let us look a little more closely at these types and endeavour to find out, if we can, why such differences exist. It is important to do so in order that we may understand the pathological conditions to be discussed later.

The whole character of the individual in regard to her sexual and reproductive instincts is dependent on two factors—the psychological, which we have already discussed, and the biochemical. Both these factors are correlated, and are largely dependent on the original distribution of the sex characteristics. The larger the proportion of femininity in a woman, and the less the proportion of masculinity, the greater will be her inherent sexual and maternal capacity. If a woman have a comparatively large proportion of masculinity in her composition, it will be reflected in every cell of her body : the characterization of the organs of internal secretion will be modified, and the activity of her ovaries reduced. It is, of course, well known that a woman may have her sexual capacity unimpaired after the removal of her ovaries. In these circumstances she is, in regard to her other organs of internal secretion, largely feminine. So it comes about that the normal woman who finds pleasure in sexual intercourse, and who desires children, is truly feminine in all her characteristics : she menstruates freely, her breasts are well formed and her mind is feminine in its outlook and aspirations ; in other words, the functions of the normal woman, whether psychological or physical, are perfectly coördinated and correlated.

van Helmont said :—

" *Propter solum uterum mulier est quod est.*"

Later Chéreau changed this to :—

" *Propter ovarium solum mulier est quod est.*"

Virchow in modern times reiterated this statement, and, according to Biedl, added :—

" All the peculiarities of her body and mind . . . " everything, in fact, which in the true woman we admire "and revere as womanly, is dependent on the ovary."

But in the light of our present knowledge I venture to think that the following aphorism most accurately represents the cause and effect :—

Propter secretiones internas totas mulier est quod est.

PART II

PATHOLOGICAL CONSIDERATIONS

In considering the relation of pathological conditions of the internal secretions to the genital organs and their functions I shall follow as far as possible the arrangement adopted in describing the physiological processes ; that is to say, derangements in the normal development of the genital organs and their functions will first be discussed, and subsequently the derangements associated with the maintenance of these functions will be described.

DERANGEMENTS IN THE DEVELOPMENT OF THE GENITAL ORGANS, AND OF THE GENITAL FUNCTIONS

DERANGEMENTS IN THE STRUCTURAL DEVELOPMENT OF THE GENITAL ORGANS

Primary maldevelopment of the genital organs may result in the following conditions :

(*a*) Incomplete development of the genital ducts and gonads, which may otherwise be perfectly formed.

(*b*) Incomplete and imperfect development of the

genital ducts, with complete or incomplete development of the gonads.

(c) Imperfect development of the genital ducts with complete development of the gonads.

(d) Irregular development of the genital ducts, with or without irregular development of the gonads.

In the primary development of the female genitalia we must recognize three stages : the *foetal* which takes place during intrauterine life ; the *infantile* which extends from birth to puberty, and the *complete* which occurs at puberty. It is, therefore, possible for the development to be imperfect only, or imperfect and irregular in the first stage ; while later it is only possible for the further development to be incomplete.

In the first stage, then, the following anomalies may be produced : a rudimentary uterus and ovaries, all of which are otherwise normally formed ; or normal ovaries with a rudimentary uterus ; or, again, rudimentary or normal ovaries with imperfect development of the genital ducts, such as bicornute uterus, septate vagina and so on ; and, lastly, irregular development of the genital gland and (or) genital ducts, constituting hermaphroditism.

In the early period of postnatal development (infantile stage) there is normally a gradual development and enlargement of the genital organs ; the ovary, too, becomes functional. In this stage, however, we may see insufficient development, leading to the condition known as infantilism of the genitalia ; and at the age when development should be complete—that is, at puberty—this abnormal state of affairs may persist, or the genitalia may not undergo the further development, chiefly functional, normal to this time of life.
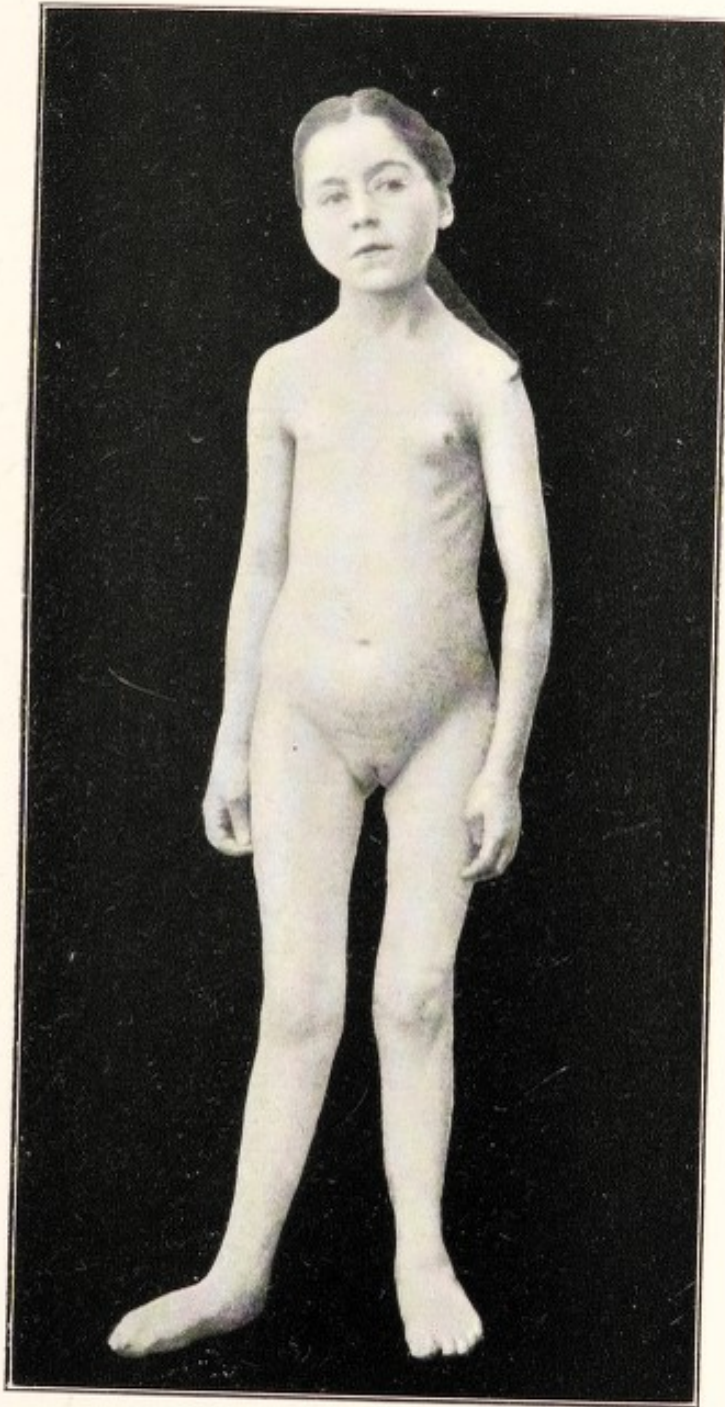
FIG. 29.

Photograph of a girl, æt. 19 years, showing general infantilism due to under-development of the pituitary. The patient measured 4 ft. 3 ins. in height, and weighed 4 stones 3 lbs.
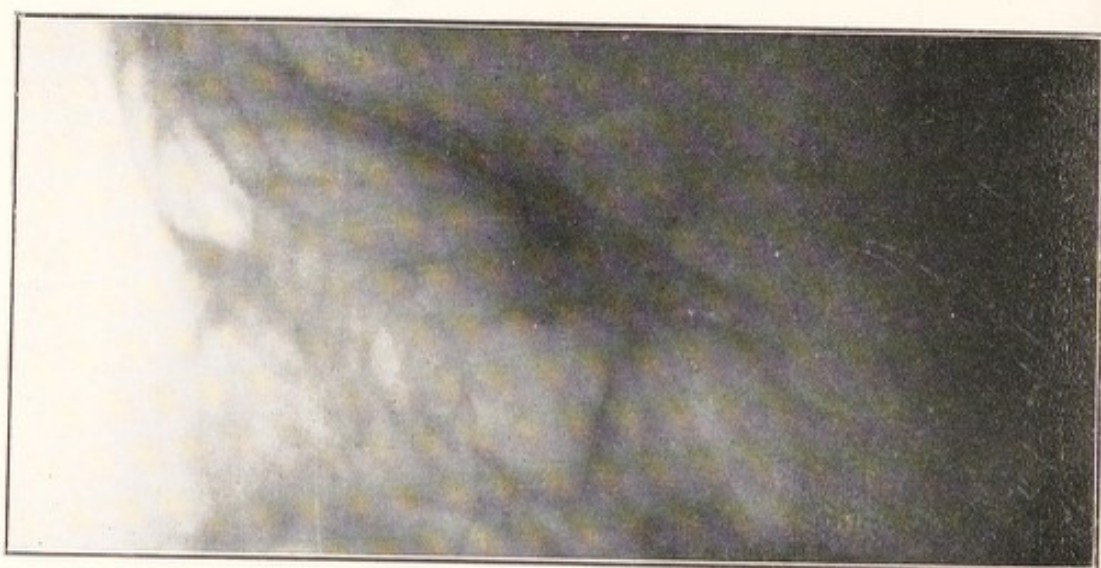
FIG. 30.

Skiagram of the sella turcica from the case of ateleiosis illustrated in figure 29. (*Direct photograph by C. Thurstan Holland.*)

$\times \frac{1}{1}$.

Incomplete development of the Genital Ducts and Ovaries, which otherwise may be perfectly formed

The pathological conditions under this heading are usually associated with what has been called ateleiosis, the cause of which is probably some general disorder of the endocritic system. In one case under my care lately (fig. 29) I found that the patient had a very small sella turcica, indicating a condition of under-development of the pituitary (fig. 30). Further, Byrom Bramwell[1] has recently shown that infantilism of the pancreas may be a cause of general (including sexual) infantilism. At the present time, although we have no very definite knowledge on this subject, it may be said that it is hardly possible that genital under-development with ateleiosis can be due to primary ovarian insufficiency alone, in view of our experimental and clinical evidence on this subject—indeed, in such circumstances girls are generally tall. Ateleiosis seems to be a condition of general infantilism, in which the genital organs may suffer together with the rest of the structures of the body.

Again, the foetal and infantile development of the genitalia is apparently uninfluenced by thyroid insufficiency, for I have found that in the cretin the genital organs may be perfectly developed although functionless ; that is to say, there is no interference with the primary development in foetal life, nor is the growth of the organs checked until puberty—then, however, the genitalia, although well-developed, remain functionless. I shall describe the condition of cretinism more fully presently (p. 152).

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[1] Bramwell, Byrom. *Edin. Med. Journ.*, 1915, New Ser., vol. xiv, p. 323.

Incomplete and imperfect development of the Genital Ducts, with complete development of the Ovaries

The anomalies included in this subdivision are seen not infrequently in clinical practice. Some of them, in which there is imperfect development of the genital ducts—such as absence of the vagina, bicornute or rudimentary uterus—arise during fœtal life. It is not known if in these circumstances the internal secretions alone are responsible for the malformation, or if local conditions contribute to or are entirely responsible for the abnormality present. It is probable that local conditions frequently contribute to the result[1]. Whether the local conditions are not themselves dependent on an asynchronous development of the frame, the result of some irregularity of sex determination, is an interesting question and one which it is not possible to settle satisfactorily on the evidence before us.

When the postnatal development of the uterus is incomplete I have found that the pituitary frequently and sometimes the thyroid are at fault.

In one case, in which a girl of eighteen, otherwise well developed, was found to have an infantile type of uterus, the sella turcica was shown by a skiagram to be about one-half of the normal size (fig. 31). Evidence confirmatory of this diagnosis was found in the sugar tolerance of the patient, which amounted to over 350 grammes of dextrose.

Similarly, with insufficiency of thyroid secretion occurring during the infantile stage there may be

[1] Bell, W. Blair, *Proc. Roy. Soc. Med. (Obstet. and Gyn. Sect.)*, 1909, vol. ii, p. 311.

FIG. 31.

Skiagram of the human sella turcica in a case of under-development of the pituitary associated with a rudimentary uterus. (*Direct photograph by C. Thurstan Holland.*)

$\times \frac{1}{1}$.
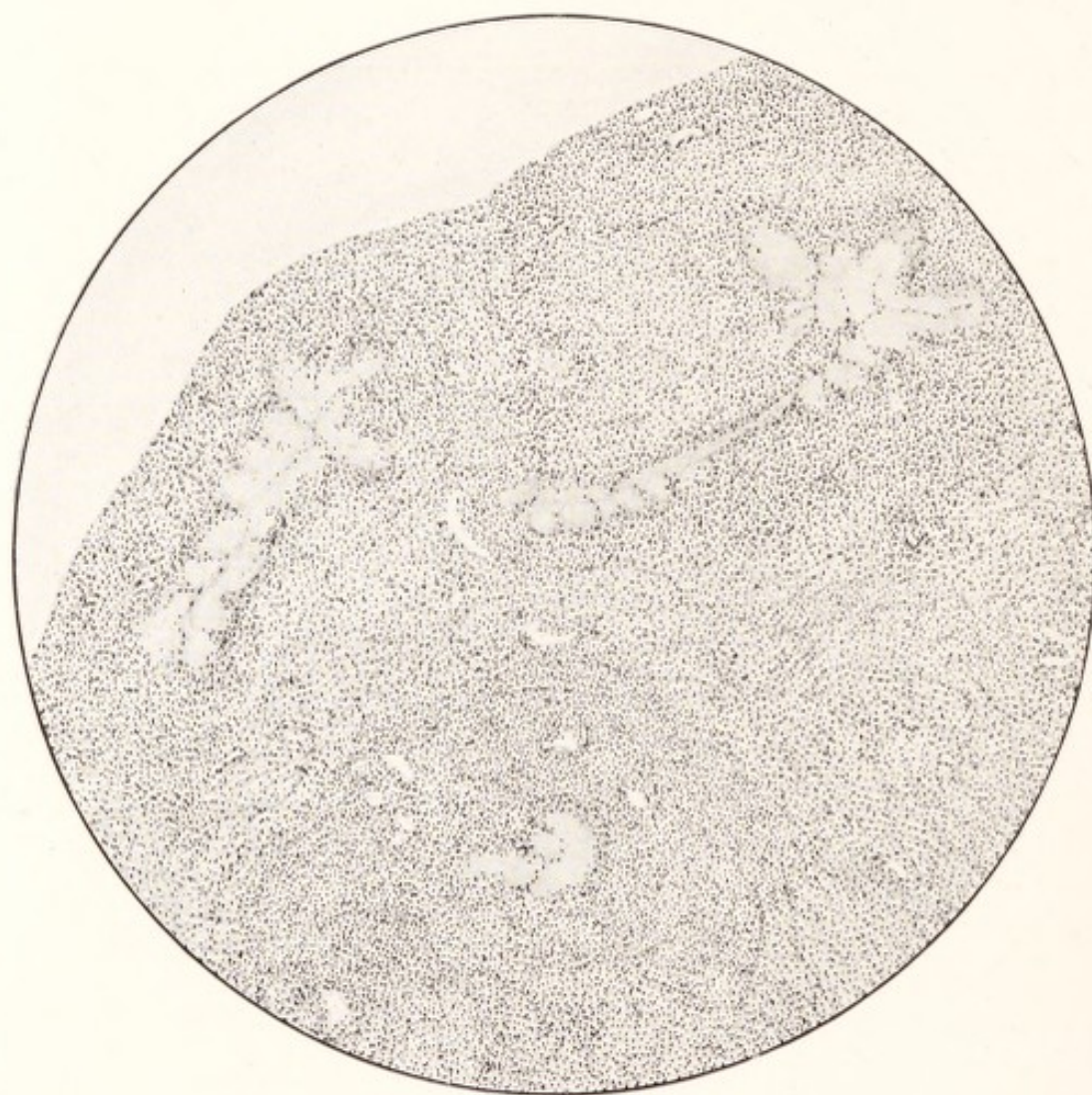
Fig. 32.

Section of an under-developed ovary from an inguinal hernia sac to which it was attached together with a unilateral uterine body, showing the remains of atretic follicles.

$\times$ 60.

incomplete development of the uterus, with retarded activity of the ovaries.

Moreover, it may be stated that under-development of the uterus continued after puberty leads before long to permanent inactivity in ovaries previously normal: this I have found to be so on several occasions on which I have had the opportunity of examining histologically ovaries from these cases. Ovarian in-activity is shown by the absence or scarcity of Graafian follicles, or by the presence of atretic follicles instead of corpora lutea (fig. 32).

Imperfect development of the Genital Ducts with complete development of the Ovaries

In these circumstances the genital ducts, although imperfectly developed from a morphological standpoint, may be functional.

What has been said already of the causes of imperfections in the development of the ducts probably does not apply to the malformations included in this category: these imperfections are believed to be reversions to a lower type[1]. This interesting view cannot be discussed here, as it has no special bearing on our subject so far as we know at present.

Irregular development of the Genital Ducts with or without irregular development of the Gonads (Hermaphroditism)

This subdivision comprises an extraordinarily interesting series of anomalies which arise during foetal

[1] Jones, F. W., *Lancet*, 1915, vol. i, p. 1113.

life. They are grouped under the general term 'hermaphroditism ', and I propose to consider them at some length for they throw considerable light on the sex functions of the internal secretions.

Hermaphroditism has been a subject of interest from the earliest times, but it is only within the last few years that the essential features of this condition have been scientifically investigated and considered. And in the study of hermaphroditism, in all its varieties, lies our hope of discovering the factors concerned in the determination of sex in the human subject subsequently to fertilization.

It must be remembered that hermaphroditism in man is probably an atavistic phenomenon, and one which is never complete. Berry Hart[1] has suggested dropping the word ' hermaphroditism ' and substituting the term ' atypical sexe-ensemble ' for all varieties of this condition. This, however, is not desirable for two reasons : first, since hermaphroditism exists normally in certain invertebrates, and is, therefore, probably only a reversion when seen in man, the term should be preserved ; and second, so-called 'true hermaphroditism ', better termed ' glandular partial hermaphroditism ', does occur in the human subject, although Berry Hart denies that it has ever been demonstrated. I shall myself describe an example of this anomaly presently.

The following is a classification of hermaphroditism drawn up to illustrate the forms in which the condition occurs normally and abnormally. A consideration of this scheme will also demonstrate the biological significance of the phenomenon.

With regard to ' total hermaphroditism ', which is only seen in the invertebrates, I shall have little to say,

[1] Hart, Berry, *Edin. Med. Journ.*, 1914, New Ser., vol. xiii, p. 295.

CLASSIFICATION OF HERMAPHRODITISM.

A. TOTAL HERMAPHRODITISM.

I. Structural and Functional (with power of self-fertilization).

Genital Glands	Functional ovary and testis
'Genital Ducts'	Functional male and female
'External Genitals' ..	Functional male and female

This condition is seen in various *Invertebrates*, such as some of the *Tunicata* (*e.g. Ciona intestinalis*), in some of the *Trematodes* (*e.g. Distomum*), and it has been observed in the *Cestoda* (*e.g. Tænia*). Unknown in *Vertebrates*.

II. Structural (with power of fertilizing others and of being fertilized).

Genital Glands	Functional ovary and testis
'Genital Ducts'	Functional male and female
'External Genitals' ..	Functional male and female

This condition is common in *Invertebrates* (*e.g. Nudibranchs* and many *Vermes*). Unknown in *Vertebrates*.

B. PARTIAL HERMAPHRODITISM.

I. Glandular.

Genital Glands	Ovo-testis on one or both sides
Genital Ducts	Male or Female or mixed
External Genitals ..	Male or Female or mixed

Not uncommon in some of the *Ungulates*. Three or four cases known in *Man*.

II. Tubular.

	External		Internal		Complete	
	Male	Female	Male	Female	Male	Female
Genital Glands ..	Testes	Ovaries	Testes	Ovaries	Testes	Ovaries
Genital Ducts ..	Male	Female	Female	Male	Female	Male
External Genitals ..	Female	Male	Male	Female	Female	Male

Common in *Man*.

for the subject is a most complicated and extensive one, and still awaits a complete description at the hands of a biologist.

It may, however, be of interest to point out that while ' structural hermaphroditism ' is a very common condition, structural and functional with the power of self-fertilization is very rare ; and probably for the following reason. In structural hermaphrodites the male and female gonads rarely become functional at the same time. The creature plays the part at one time of a male and at another time that of a female.

It is, of course, certain that total hermaphroditism could not exist in man. The so-called ' true hermaphroditism ' in man is represented by the variety better known as ' glandular partial hermaphroditism ', which I shall now consider.

Glandular partial hermaphroditism.—All the recorded cases of glandular partial hermaphroditism which may be accepted as authentic—and I can discover only two or three other cases of this extremely interesting and rare phenomenon in addition to one recently reported by myself[1], and to be described directly—have been found to possess mixed gonads, so-called ' ovo-testes ', with or without irregularities in the sex characterization of the genital ducts, external genitalia and secondary characteristics.

In 1873 Klebs[2], in his classical paper on the subject, claimed that ' true hermaphroditism ', as he called it, might occur in the following varieties in man.

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[1] Bell, W. Blair, *Proc. Roy. Soc. Med. (Obstet. and Gyn. Sect.)*, 1915, vol. viii, p. 77.

[2] Klebs, E., *Handbuch d. Pathol. Anat.*, 1873, vol. i, p. 725.

(1) *Bilateral hermaphroditism*, in which an ovary and testis are present on both sides.

(2) *Unilateral hermaphroditism*, in which there is an ovary or testis on one side, and an ovary and testis on the other.

(3) *Lateral hermaphroditism*, in which an ovary is present on one side and a testis on the other.

This classification has been adopted by many subsequent writers, and it is supported by Blacker and Lawrence[1], who in 1896 reported the first case of ovotestis, or combined ovary and testis. These writers investigated the literature up to that date, and came to the conclusion that of the enormous number of supposed cases of what was called ' true hermaphroditism ' there was only one—their own—recorded of the unilateral variety, after the classification of Klebs; and that there was possibly one—Heppner's[2], recorded in 1870—of the bilateral variety, and two—recorded by Schmorl[3] and Obolonsky[4] in 1888—of the lateral.

The evidence in regard to these, except possibly to Blacker's and Lawrence's, cannot, however, be considered satisfactory, and it has been demolished by Meixner[5] and others. Tuffier and Lapointe[6], also, in their paper published in 1911 apparently accept only the case of Blacker and Lawrence of those published prior to 1897 ; but they add to this case those of von Salen,[7]

[1] Blacker, G. F., and Lawrence, T. W. P., *Obstet. Trans.*, 1896, vol. xxxviii, p. 265.

[2] Heppner, C. L., *Reichert's Arch.*, 1870, p. 679.

[3] Schmorl, G., *Virchow's Archiv.*, 1888, vol. cxiii, p. 229.

[4] Obolonsky (No initial in original), *Zeit. f. Heilkunde*, 1888, vol. ix, p. 211.

[5] Meixner, K., *Zeit. f. Heilkunde*, 1905, vol. xxvi, p. 318.

[6] Tuffier, T., and Lapointe, A., *Rev. Gyn.*, 1911, vol. xvi, p. 209.

[7] Salen, E. von, *Verh. d. Deutsch. Path. Ges.*, 1899, vol. ii, p. 241.

Garré[1], Landau and Pick[2], and Schickele[3], all recorded subsequently to Blacker's and Lawrence's paper.

Pick[4], in an important paper published in 1914, discusses exhaustively the question of this so-called ' true hermaphroditism ', and comes to the same general conclusions as Tuffier and Lapointe—namely, that all the cases of this variety reported and accepted should be called ' glandular partial hermaphrodites '. This author records five cases of ovo-testes occurring in pigs, all of which he had himself examined. He states that the condition is only known in that species among all the orders of the lower mammals. Other authors, however, have published accounts of this phenomenon in moles and in other mammals.

Pick also states that there had been four genuine cases recorded in man up to the date of his paper. Of those already mentioned apparently he admits only the case of von Salen[5], but he adds those of Simon[6], Uffreduzzi[7], and Gudernatsch[8]. I have examined the reports of these cases, and believe that only that of Simon, in addition to von Salen's, could possibly be accepted, and that this case is somewhat doubtful.

I shall not discuss in detail the points for and against these and the other reported cases. Enough has been

[1] Garré (No initial in original), *Deutsch. Med. Woch.*, 1903, vol. xxxix, p. 77.

[2] Landau, L., and Pick, L., *Verh. d. Berl. Med. Gesellsch.*, 1914, vol. xliv, p. 186.

[3] Schickele, G., *Hegar's Beit. z. Geb. u. Gyn.*, 1907, vol. ii, p. 263.

[4] Pick, L., *Arch. f. Mikr. Anat.*, Bonn, 1914, vol. lxxxiv, p. 119.

[5] Salen, E. von, *Verh. d. Deutsch. Path. Ges.*, 1899, vol. ii, p. 241.

[6] Simon, W., *Virchow's Archiv.*, 1903, vol. clxxii, p. 1.

[7] Uffreduzzi, O., *Arch. de Antrop. Crim.*, Torino, 1910, vol. xxxi, p. 602.

[8] Gudernatsch, J. F., *Amer. Journ. Anat.*, 1911, vol. xi, p. 267.

said to indicate the rarity of glandular partial herma-phroditism ; but attention must be called to the fact, to which I shall again refer later, that in most of the cases an ovo-testis has been present. In Simon's case the ovarian and testicular portions were separate. Foster[1] has recently recorded a similar case, which, however, cannot be accepted, as no histological details are given.[2] It is interesting from a critical point of view to note that all the cases of ovo-testis have had mostly feminine secondary characteristics, while Simon's and Foster's cases have been masculine. As we shall see, this is enough to throw doubt on these two cases. Lastly, it may be mentioned that in some of the sup-posed cases, such as that of Landau and Pick, large tumours have been said to be ovo-testes. These growths can hardly be accepted as ovo-testes, for they must present many difficulties in the way of such a diagnosis.

I shall now describe my own case, which is probably the most complete example of glandular partial herma-phroditism on record, and may, therefore, be taken as a prototype of this class of case.

S.B., æt. 17 years, was first seen on 8th November 1912.

Past History.—Menstruation had commenced during the fourteenth year. The cycle had been $2\frac{3}{8}$ days. There had been no menstrual pain. The patient was said to have suffered with inflammation of the bowels when she was 7 years of age.

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[1] Foster, G. S., *New York Med. Journ.*, 1914, vol. c, p. 560.

[2] Owing to the kindness of Dr. Foster I have, since this work went to press, had an opportunity of examining sections from this case. In my opinion there is no real evidence that the so-called 'ovarian' portion contains the essential elements of the ovary. The most that can be said is that the arrangement of the connective tissue, of which it is entirely composed, is somewhat similar to that seen in the ovary.

Present History.—The patient has had amenorrhœa for 18 months, and there have been no menstrual molimina. The general health is good. There has been no trouble with the bowels or bladder. The voice has been getting deeper.

On examination nothing abnormal was felt in the abdomen, or *per rectum.* The thyroid was found to be slightly enlarged.

A diagnosis of hyperplasia of the suprarenal cortex was made, and the patient was treated with ovarian and thyroid extracts for some time.

On August 25th 1914 the patient, who had not been seen for eight months, again presented herself. It was then at once noticed that she had become more masculine in appearance : she had a slight moustache and a masculine distribution of hair on the body (fig. 33). There was still complete amenorrhœa.

The patient was examined under an anæsthetic a few days later. The clitoris was found to be much enlarged, measuring two inches in length, and there was a well-marked prepuce. *Per vaginam* the left genital gland could be felt somewhat enlarged. No tumour was discovered in the suprarenal region.

Subsequently the patient was admitted to hospital. She was then 19 years of age, and the amenorrhœa had lasted for over three years.

On September 3rd 1914 the abdomen was opened in the middle subumbilical line. The left genital gland was found to be of the same size as that of a plum. It had a very smooth surface, and resembled a testis ; the superficial blood vessels were injected, especially in the neighbourhood of the hilum. No adhesions were present. A wedge-shaped piece was removed length-wise from the convexity of the organ for histological examination. When cut into for the removal of this piece of tissue, the organ presented a yellow, fatty appearance. The raw surfaces were brought together with a cat-gut suture. The genital gland on the right side appeared to be a normal, but somewhat small,
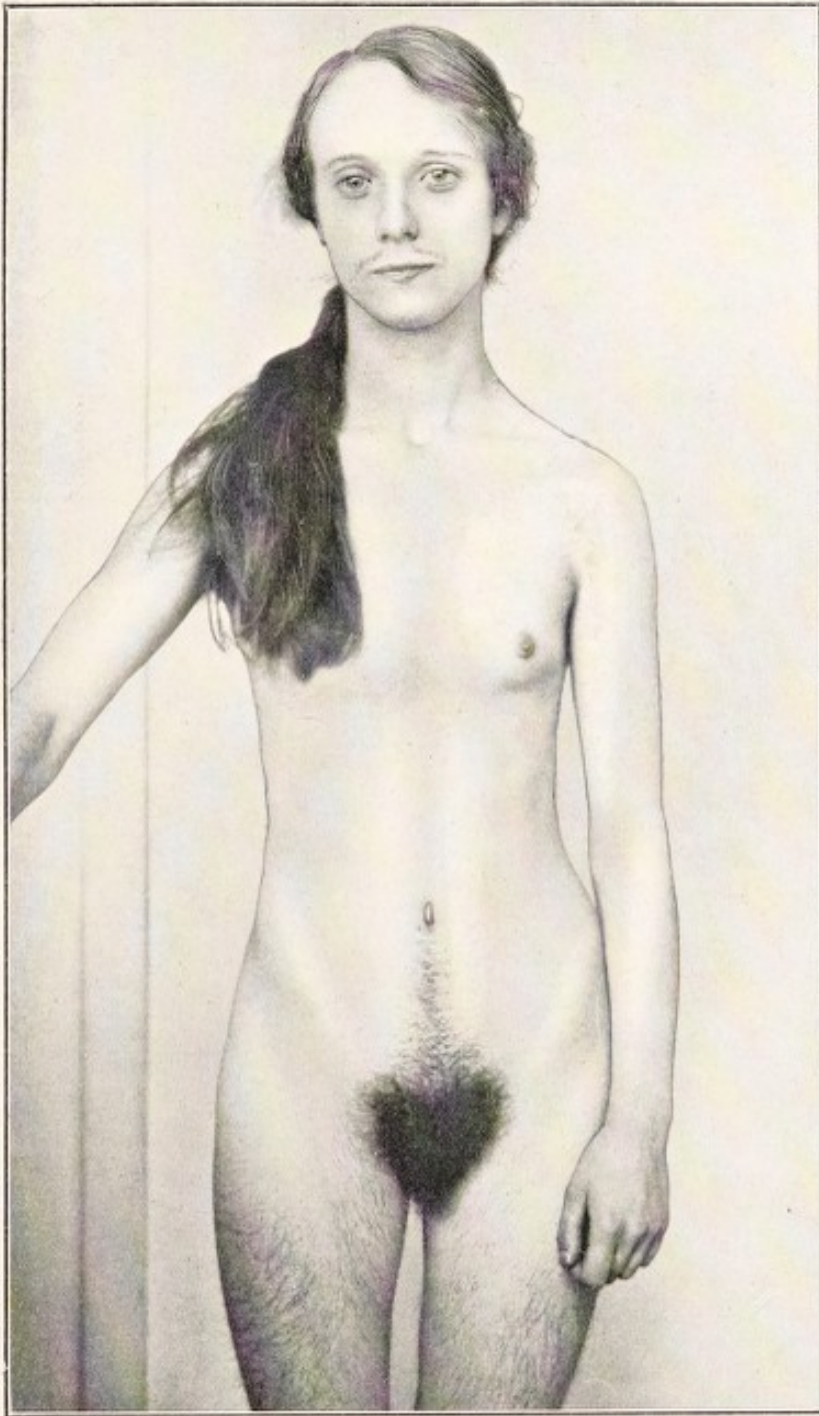
FIG. 33.

Photograph of a glandular partial—so-called 'true'—
hermaphrodite, showing the masculine contour of the
limbs and trunk, and distribution of hair.

ovary. A piece was removed for section in a manner similar to that adopted in the case of the left genital gland. Finally, a small graft from an ovary removed from a patient operated upon a few minutes before was implanted in the uterus.

The suprarenal regions were palpated with the hand in the peritoneal cavity, but beyond a slight rough feeling in the neighbourhood of the left, which might have been due to the tail of the pancreas, nothing abnormal was discovered.

Report from the Pathological Laboratory (Prof. E. E. Glynn) on the pieces excised.—" *Right ovary.* Section " shows an ovary, the stroma of which consists of very " dense connective tissue, but ovulation has taken place, " there being present a large corpus luteum and the " scars of the corpora lutea, and also an almost mature " Graafian follicle.

" *Left ovary.* Section shows what is undoubtedly " a columnar celled carcinoma with well-marked acini."

Placing an unwise faith in this report, I re-opened the abdomen on September 22nd 1914 and removed both ovaries, the tubes, and the fundus of the uterus.

When I came to examine the sections myself I came to the conclusion that the left genital gland was an ovo-testis, and not the seat of a malignant growth as reported[1].

After-history.—The patient made a good recovery from the operation, but subsequently suffered with slight menopausal symptoms. When she was examined eight months after operation I found that all the hair had disappeared from the legs and the upper lip. The voice was slightly higher in tone, and the figure and skin were greatly altered towards the feminine type. The breasts, however, showed very little development, but this was not to be expected in the absence of ovaries.

The specimen[2] consists of the fundus uteri, the

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[1] This opinion was afterwards confirmed by the report of the Pathological Reference Committee of the Liverpool Medical Institution, and by many independent authorities.

[2] Now in the Museum of the Royal College of Surgeons, London.

Fallopian tubes, and the gonads—the genital glands being in the position normal to the female and attached to the uterus by an ' ovarian ' ligament. Scars can be seen running lengthwise along the convexity of each gland, indicating the sites from which the pieces were excised for examination. The fimbriated extremity of the left Fallopian tube has become attached to the scar in the corresponding gonad. There is evidence also of a ' parovarium ' on this side. A portion of the ovarian graft, which on histological examination was found to be necrotic, can be seen in the anterior wall of the fundus uteri.

An X-ray examination of the patient by Mr. Thurstan Holland showed no ossification in the thyroid cartilage; but this would not be expected even in the male at such an early age.

A laryngeal examination was made by Mr. Guthrie who reported as follows :—

" I examined the larynx of your patient S.B. again " to-day. The larynx appears to me to present definitely " male characteristics ; the cavity is very roomy, and " the vocal cords are both broader and larger than those " of the ordinary female larynx. Using a graduated " laryngeal mirror I attempted to measure their length, " and, although it is difficult to do this with much " accuracy owing to the distance between the mirror " and the objects reflected in it, I was able to satisfy " myself that they measured not less than 24 mm. " which is scarcely below the average in the male. " The breadth appeared to be nearly $1\frac{1}{2}$ times what is " usual in the female. The epiglottis and arytenoids " are large for a female, but I think less strikingly so " than the true cords and the laryngeal cavity."

The histological findings in this case are probably typical of glandular partial hermaphroditism, in which there is an ovo-testis on one side only ; and therefore merit a short discussion.

The right genital gland is a normal ovary, although

FIG. 34.

Section of ovo-testis from the case illustrated in figure 33, showing central testicular portion—(the part that is enclosed in a ring is shown more highly magnified in figure 35)—and outer capsule of ovarian tissue containing a Graafian follicle in the lower part of the field.

× 40.
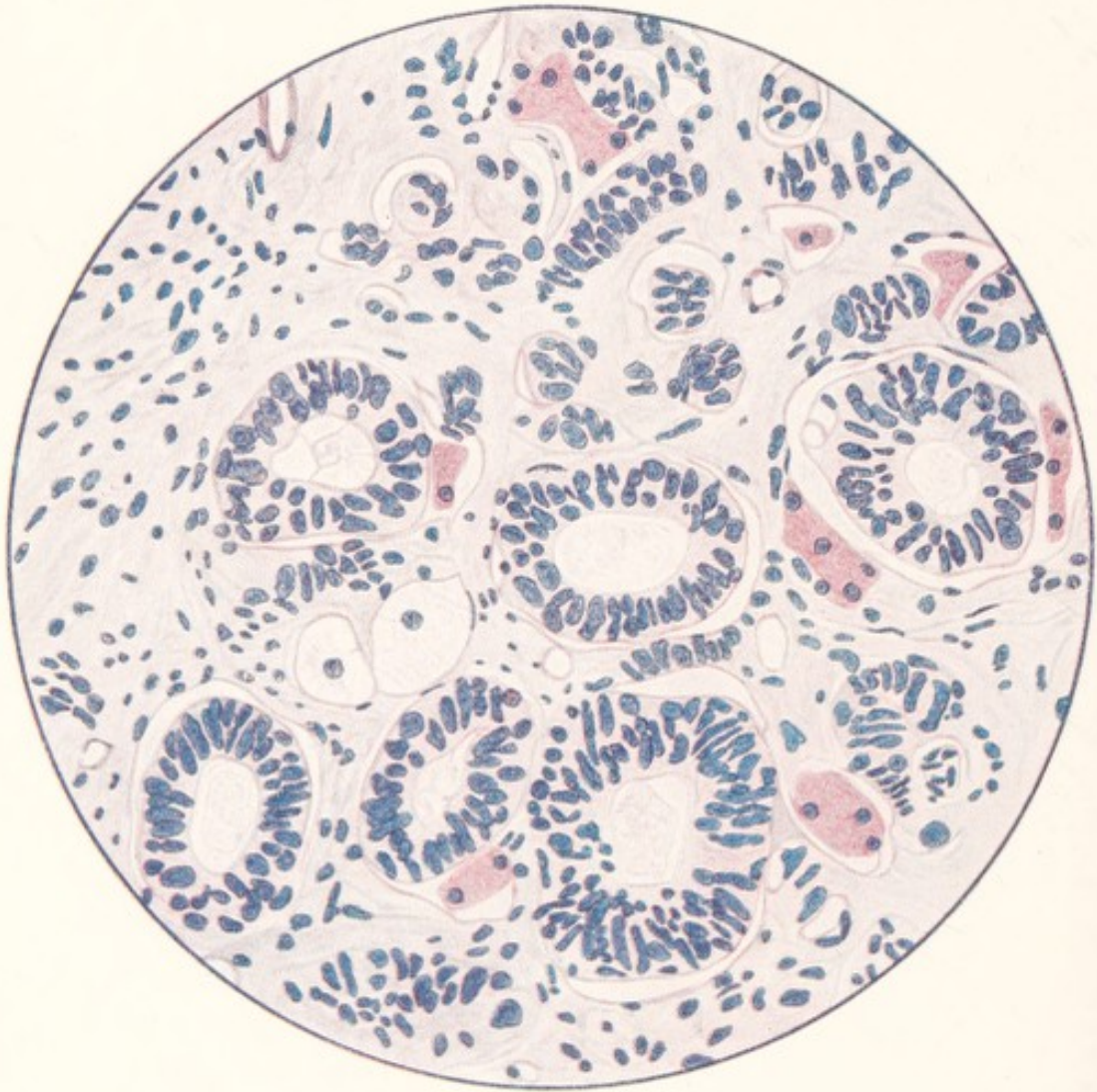
FIG. 35.

Section of ovo-testis stained with haematoxylin and eosin,
showing seminal tubules and large eosinophile
interstitial cells.

× 300.

small and not in a particularly active state. There are to be seen in section a mature Graafian follicle and small hyaline bands in the ovarian stroma—the remains of corpora albicantia. The histological appearances of the left organ present quite a different picture. A low power view shows that the central portion, which forms nearly the whole of the organ, is made up of what, in the first instance, was supposed by the pathologist to be a malignant neoplasm. A thin capsule of normal ovarian tissue—Graafian follicles, primordial ova, and stroma covered in places by capsular epithelium—surrounds this central portion (fig. 34).

The nature of the internal part of the organ is, of course, the interesting feature of the case. It consists of tubules lined for the most part with several layers of columnar cells, although in places the tubules are seen to be lined with one layer of epithelium and to be widely distended with secretion; also of irregular masses of columnar cells, and of a large number of interstitial cells which are eosinophile and resemble exactly the interstitial cells of the testicle (fig. 35). Among the epithelial cells lining some of the tubules are to be seen, here and there, large cells with big nuclei: these may possibly represent spermatogonia. There is, too, between the tubules, a large quantity of fat which stains well with Sudan III.

The masses and columns of cells, which do not form tubules, resemble what may be seen in the early stage in the development of the normal testis : they have none of the appearances of malignant cells, for their nuclei are regular and quiescent, and the cells themselves are nearly all of one size and appear stable in their mode of growth.

With regard to the interstitial cells it might be thought that they were ovarian and not testicular. As a rule, however, the interstitial cells of the ovary are

much smaller, and never have I seen them so well marked, either in normal or pathological circumstances, as here shown. Further, if these interstitial cells were really ovarian one would expect to find them in the ovarian portion of the ovo-testis—from which they are entirely absent—rather than in the testicular portion.

This is the general picture presented by an ovo-testis ; but in the histological diagnosis of the condition there must always be difficulty. In the first place there are masses of columnar cells which have no definite tubular arrangement. It was probably this irregularity of distribution which gave rise to the opinion, to which allusion has already been made, that in the case described the growth was malignant. In some parts, of course, there is a definitely tubular arrangement of the darkly staining columnar cells ; and in other places tubules may be found lined with a single layer of epithelium, and containing secretion. There is, however, never any definite spermatogenesis to be seen.

It is particularly interesting to note in regard to the case recorded above, that the patient commenced life and passed puberty as a normal girl, menstruating regularly for eighteen months ; that menstruation had then ceased and masculine characteristics had developed, and that in spite of this she suffered with slight meno-pausal symptoms after operation, and has now, eight months later, reverted almost entirely to the feminine type. This, surely, is dual sex characterization if ever there were such a thing : an interesting question which we shall discuss more fully after considering the other varieties of hermaphroditism.

With regard to the occurrence of the gonadal elements of the two sexes in one individual, one would naturally infer, from a developmental point of view, that the

different elements would be combined in one organ. A brief consideration of the development of the ovary and testis will make this point clear.

In the earliest stages of development—that is, until about the thirtieth day—the histological appearances of the gonads give us no indication as to the future sex differentiation about to take place. In this undifferentiated stage the gonad is divided into two portions—the *capsular epithelium*, and the central *epithelial nucleus* composed of ' indifferent ' cells. Subsequently, however, if a testis is to be evolved, very soon after this date the cells of the epithelial nucleus immediately underlying the capsular epithelium become condensed and form the tunica albuginea, while the rest of these indifferent cells, among which the genital cells lie, become arranged in the form of cell masses or cords. These cords, around which and in which the spermatogonia, as the genital cells are now called, are collected, become the seminal tubules and eventually join the genital (pronephritic) tubules outside the gonad. The interstitial cells of the testis are formed from connective tissue cells (mesoderm), which grow in from the direction of the hilum and fill the interstices between the seminal tubules. We shall see directly that the interstitial cells do not originate from primary or secondary genital cells.

If, on the other hand, an ovary is in process of formation the indifferent cells (epithelial nucleus) of the genital cell mass remain undifferentiated longer than in the case of testicular development, and they never become arranged in cell masses or cords. Instead, the epithelial nucleus becomes broken up by branching septa of ingrowing connective tissue, which divide the ovary into a mesh-work of compartments. The tunica albuginea is formed by the meeting of these septa beneath the capsular

epithelium. The indifferent cells enclosed in the connective tissue mesh-work are believed to form secondary oögonia ; but ultimately most of these degenerate, and the spaces they previously occupied in the mesh-work of connective tissue become filled by ingrowths from the septa. The interstitial cells of the ovary, like those of the membrana granulosa surrounding the surviving ova, are derived from the connective tissue stroma. In these circumstances, of course, the genital tubules outside the gonad atrophy, and their remains may be recognized, extending from the hilum of the ovary through the meso-ovarium into the mesosalpinx, as the epoöphoron.

It is not difficult to understand, then, that, if there be any hesitancy in the primary determination of sex, seminal tubules may commence to develop in the epithelial nucleus, even though they do not become functional in the ordinary sense of the word, and that the testicular interstitial cells may develop around them. But if in these circumstances masculine genital cells are absent and female are present the interstitial cells around the tubules cannot arise from genital cells, nor can there be spermatogenesis.

One great difficulty, so it appears to me, and one which requires further elucidation, is why an ovo-testis may be found on one side in these circumstances, and not on the other. In this connexion it is interesting to recall the fact that in ' true hermaphroditism ' (ovo-testis) in birds, unilateral distribution of the sex characteristics in regard to the plumage has been observed by Poll[1], Bond[2] and others. It must be remembered, also, that in hens the right ovary and ducts atrophy. Nevertheless, the plan of development

[1] Poll, H., *Sitzb. d. Ges. Naturf. Freunde*, Berlin, 1909, p. 331.
[2] Bond, C. J., *Journ. Genet.*, 1914, vol. iii, p. 205.

described above almost negatives the possibility of the development of a separate ovary and testis on the same side; for it is extremely difficult to understand how one part of the same genital cell mass could separate itself from the other and develop into a testis, while the remaining portion developed into an ovary.

It would seem, therefore, almost inevitable that, when there is dual characterization in the gonads, the only possible combination must be a testicular central portion surrounded by an ovarian, and that the predominating genital cells must be female rather than male. If this is found not to hold good in any well-investigated case, we shall have to revise our views concerning the normal development of the gonads and their sex differentiation. It is important to observe, in passing, that in some of those cases in which a testis or a testicular rudiment has been found on the same side but separated from the ovarian, as in Uffreduzzi's case, no interstitial cells have been present. This alone is enough to throw very grave doubt upon the true nature of the supposed male elements in the gonad concerned. In Simon's and Foster's cases the ovarian portion of the double gonad was not certainly ovarian. These are, so far as I know, the only cases which at all contravert the statements made, and this want of conformity renders them doubtful.

I would, therefore, lay down the following as essential conditions which must be established before any case can be considered one of glandular partial hermaphroditism :

1. The hermaphroditic gonad must be an ovo-testis, composed of ovarian tissue with definite Graafian follicles or primordial ova surrounding a central portion containing seminal tubules and testicular interstitial cells.

2. The subject must show in the primary or secondary characteristics, other than the sex glands, evidences of hermaphroditism.

If these conditions be considered critical very few cases, probably only three, including my own, would pass the test.

Tubular Partial Hermaphroditism. — Tubular partial hermaphroditism is the modern name for the variety of hermaphroditism which has been known, since Klebs' classification, as 'pseudo-hermaphroditism'. The subdivisions, according to the anomalies met with, adopted by this authority, hold good for tubular hermaphroditism. These subdivisions and the contained abnormalities are set forth in the table given above. It is, too, the custom in the present day to follow Klebs in regard to the criteria of sex; that is to say, a male tubular partial hermaphrodite is indicated by the testicular character of the gonads, and a female by the ovarian structures present. We shall see presently that this arbitrary ruling is open to very serious objections in many cases.

No useful purpose would be served by a discussion here of the details of the different varieties shown in the table (p. 129), for the relation of all these monstrosities to the principles of sex determination and sex characterization is the same, and what is said of one variety applies to the others, respectively for the different sexes.

The ' atypical sexe-ensemble ', as Berry Hart[1] terms it, of the genital ducts and (or) external genitalia is contrasted with the gonads; and it is interesting to observe that in these circumstances the secondary characteristics—the distribution of hair on the body,

[1] Hart, Berry, *Edin. Med. Journ.*, 1914, New Ser., vol. xiii, p. 295.
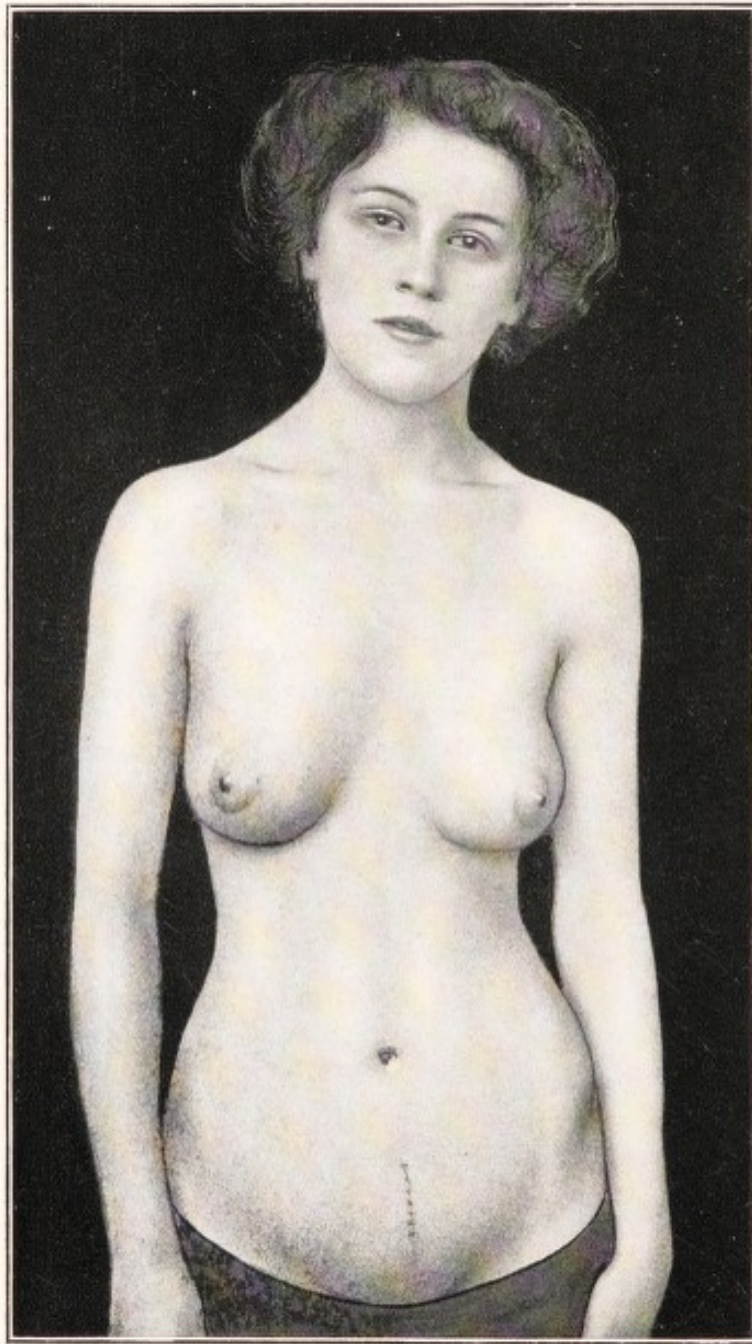
FIG. 36.

Photograph of a male partial tubular hermaphrodite, showing the complete development of feminine secondary characteristics.

contour of the limbs and trunk, breasts, psychical attributes, and the rest—are, almost invariably, of the sex character opposite to that of the gonads. This is a well-known fact and one which explains why these subjects are so frequently brought up as and pass for members of the sex different from that indicated by the gonads ; but it is a fact which has not been sufficiently emphasized, as we shall see presently.

Another most interesting point is that the gonads, in a very large proportion of all cases of tubular partial hermaphroditism, are testicular in structure : the subjects are what are known as male tubular partial hermaphrodites.

By way of illustrating the statements made concerning the peculiar conflict of sex characterization seen in most of these cases, I will first briefly mention a case, under the care of Dr. Russell Andrews, that I had an opportunity of seeing. I am indebted to this surgeon for permission to make use of the following particulars :—

The patient (fig. 36), supposed to be a young woman, was twenty-three years of age. ' She ' was very good-looking, and had typically feminine secondary character-istics. The external genitalia were of the normal feminine character, and there was a short vagina (urogenital sinus) ; the urethra opened in the position normal in women.

Laparotomy was performed, and the internal geni-talia were then found to consist of two testicles attached by the lower poles to thick bands (? gubernacula).

This patient was a woman in all particulars except in the character of the gonads, according to the nature of which it has been the custom to determine the sex. But in modern terms the individual was a male tubular partial hermaphrodite of the ' external ' variety.

Less difficult is the diagnosis of those cases in which the external genitalia conform to the sex type exhibited by the gonad: an *ensemble* which constitutes the 'internal' variety of tubular partial hermaphroditism. The 'complete' variety, in which the gonad differs in type from the rest of the internal and from the external genitalia, is probably the most obscure of all from a diagnostic point of view. In all these varieties the secondary characteristics differ in sex type from that of the gonads, as already stated.

In the etiology of partial hermaphroditism lies much that has hitherto been obscure in regard to sex determination; and attention may be recalled to the fact that even though there be some sex dominance inherent in the early segmentation cells, there are probably other controlling factors, which come into action later and influence the sex differentiation of the gonads.

We have, indeed, some direct evidence as to the causative factors in partial hermaphroditism. Glynn[1], who analyzed the cases recorded in Neugebauer's comprehensive work on hermaphroditism[2], states that out of the 88 cases of female tubular partial hermaphroditism 15 per cent. had obvious suprarenal neoplasms; while, on the other hand, only 0·7 per cent. of the male tubular partial hermaphrodites had growths in the suprarenal cortex. Moreover, as will be mentioned directly, suprarenal tumours and disturbances in other organs of internal secretion may influence the secondary sex characteristics in women previously normal in this respect. I shall not, therefore, dwell on the etiology of partial hermaphroditism, beyond saying that all the evidence we have concerning the production and

[1] Glynn, E. E., *Quart. Journ. Med.*, 1912, vol. v, p. 157.
[2] Neugebauer, F. L. von, *Hermaphroditismus*, Leipzig, 1908.

FIG. 37.

Section of the testis from the male partial hermaphrodite illustrated in figure 36, showing a large number of interstitial cells and a scarcity of seminal tubules.

$\times$ 250.

maintenance of sex characteristics subsequently to fœtal life points to the paramount influence of all of the internal secretions. And, as this is so, it is not illogical to suppose that the same factors are responsible during fœtal life for the production of the normal primary characteristics : we have, in fact, as already stated, strong and direct evidence on this point in regard to the suprarenal cortex.

Before concluding these remarks on partial hermaphroditism, I wish to call attention to the method adopted in the specification of the sex of these individuals. As is well known, the character of the gonad is considered indicative of the sex of the person. I believe this to be as unjustifiable on scientific grounds as it is unfair from a social point of view, for the following reasons :—

In view of many pathological observations on the subject it appears probable that in female tubular partial hermaphrodites, with male characteristics in association with ovaries, certain of the other organs of internal secretion, such as the suprarenals and pituitary, are of a male type ; and that in male tubular partial hermaphrodites—the commonest variety—with testes in association with feminine secondary characteristics, the other organs of internal secretion are of a female type.

Again, it is extremely interesting to note how erroneous has been the view, generally held, that the interstitial cells of the ovary and testis are responsible for the secondary sex characteristics. For many years I have contended that the gonads play but a subservient part ; and this is emphatically demonstrated in the subject under discussion by the fact that in the testes of tubular partial hermaphrodites with feminine secondary characteristics, as in the case recorded above, the interstitial cells are always developed to a remarkable extent

(fig. 37)—to a degree which is rarely seen even in the undescended testis (fig. 38) and never in the normal testis (fig. 39). These cells cannot, therefore, be responsible for the secondary characteristics. Spermatogenesis, however, is not often present in the testes of partial tubular hermaphrodites, but it has occasionally been recorded.

The gonads, therefore, especially in the absence of active genital cells may be described as more or less indifferent organs in the matter of sex characterization. It is probable that the other organs of internal secretion must be admitted into the circle of primary characteristics, and that they usually act in conjunction with the *functional* gonad but often quite independently of it.

It is, also, an almost incontestable fact that the mental attitude and instincts of a partial hermaphrodite accord with the predominating secondary characteristics. This was very obviously so in Russell Andrew's case, already described, in Tuffier's and Lapointe's case, and in many other recorded cases. It is not possible to ascribe these psychological attributes to education alone.

Since, therefore, we can demonstrate the fact that the psychical and physical characters of sex are not necessarily dependent on the gonads, each case of partial hermaphroditism should be considered as a whole ; that is to say, the sex should be determined by the obvious predominance of characteristics, especially the secondary, and not by non-functional gonads alone. A few partial hermaphrodites have secondary characteristics of the same sex as the gonad ; but that common type of case in which the gonads alone, and then only on histological examination, proclaim the state of hermaphroditism should be considered on a separate basis, and the sex denomination should be adapted to the peculiar circumstances, and to our modern knowledge
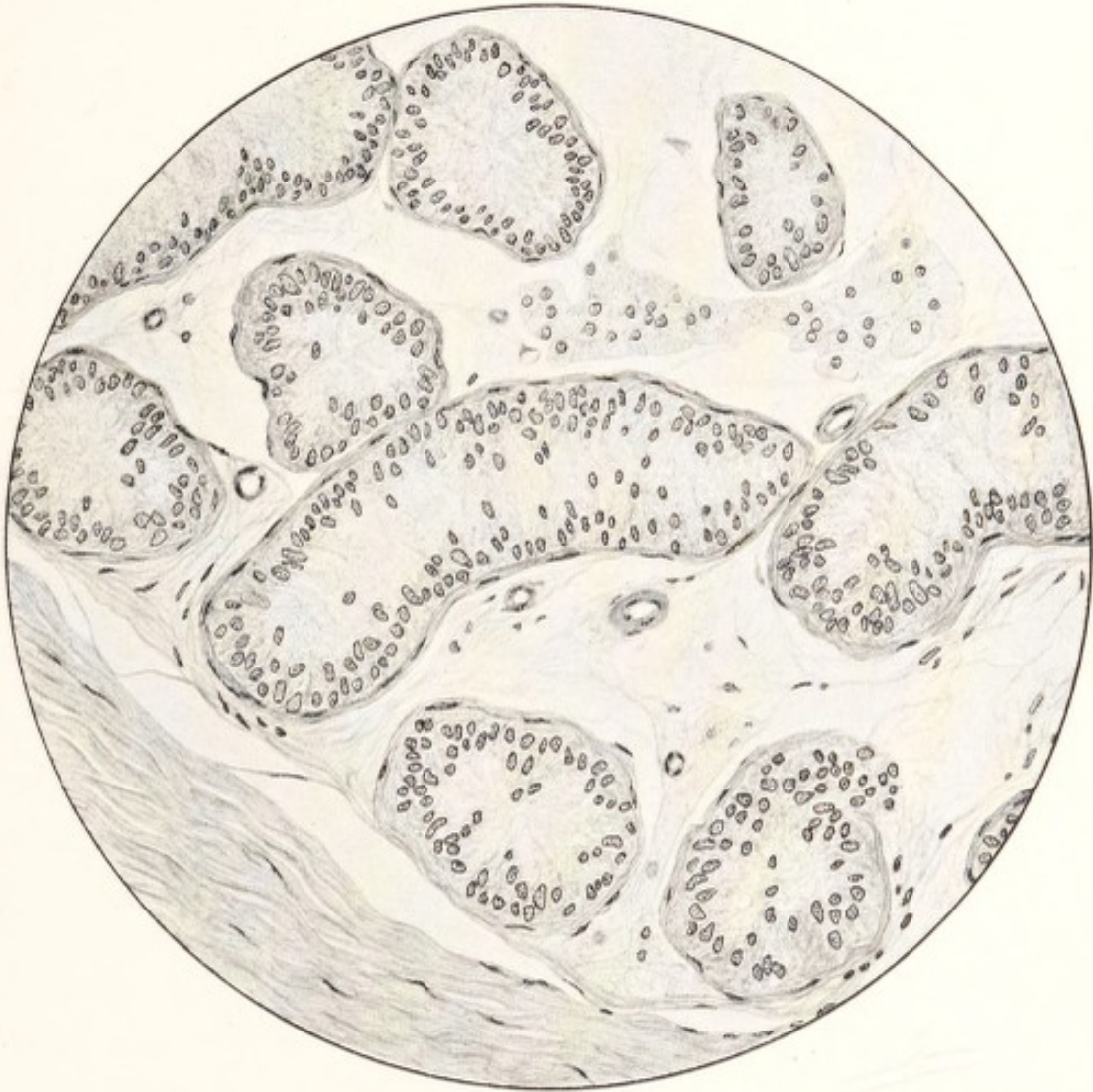
Fig. 38.

Section of an undescended testis, showing seminal tubules and a
few interstitial cells.

× 250.

Fig. 39.

Section of the normal testis, showing widely distended tubules, in which spermatogenesis is taking place, and a few interstitial cells.

$\times$ 250.

of the complexity of sex. It would be justifiable, too, to undertake surgical procedures in these special cases in order to establish more completely the dominant sex of the individual, and the one which is most in accordance with the social happiness of the person concerned.

DERANGEMENTS IN THE FUNCTIONAL DEVELOPMENT OF THE GENITAL ORGANS

The term ' functional development ' of the genital organs and secondary female characteristics refers to the changes which normally occur at puberty. The advent of functional activity in the genital organs and of the associated secondary sex characteristics, which become evident at this time, change the girl into a woman. Since the appearance of puberty is dependent on the general metabolism, which is influenced by the internal secretions, we can easily understand how disorders of the endocritic system may affect the phehomena associated with this period of life.

Precocious Puberty.—The usual age of puberty in this country is about the end of the fourteenth year, but the appearance of it between the tenth and sixteenth years cannot strictly be considered abnormal. Heredity, health, feeding and environment all play an important part in the result. When, however, a child under nine years of age shows definite signs of puberty—such as hair on the pubes, development of the breasts, and menstruation—we may look upon the condition as abnormal.

Now, a close investigation of the recorded cases has shown[1] that the production of precocious puberty

[1] Bell, W. Blair, *Proc. Roy. Soc. Med.* (*Obstet. and Gyn. Sect.*), 1913, vol. vii, p. 47.

in girls is not due to all those causes which may produce precocity in boys. This is a point of some importance, but future observations possibly may modify the following statements which are based upon our present somewhat limited knowledge of the subject.

On the one hand, there is no doubt that in boys sexual precocity may be produced by neoplasms and hyperplasia in the suprarenal cortex, in the testes and in the pineal[1, 2, 3, 4], and possibly also in the pituitary[4]. It is believed that in these circumstances there is an increase in the normal secretion of the endocritic organ concerned, except in the case of the pineal in which there is a decrease.

On the other hand, my investigations concerning the details of the recorded cases of sexual precocity in girls showed that true feminine sexual precocity appears to be produced by tumours and hyperplasia in the ovaries almost invariably; for changes in the suprarenal cortex, the pineal, and the pituitary, resembling those which in boys produce precocity, in girls tend to produce masculinity[4]. Now, masculinity cannot be considered female sexual precocity, although there is little doubt that in some of the recorded cases[5, 6] masculinity with, perhaps, adult manifestations, such as hair on the pubes, has been described as feminine precocity. The essential

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[1] Williams, Roger, *Brit. Gyn. Journ.*, 1902, vol. xviii, p. 85.

[2] Bulloch, W., and Sequeira, J. H., *Trans. Path. Soc.*, 1905, vol. lvi, p. 189.

[3] Glynn, E. E., *Quart. Journ. Med.*, 1912, vol. v, p. 156.

[4] Bell, W. Blair, *Proc. Roy. Soc. Med.* (*Obstet. and Gyn. Sect.*), 1913, vol. vii, p. 47.

[5] Orth, *Arbeiten aus den Path. Institut za Göttingen*, Berlin, 1893, quoted by W. Bulloch and J. H. Sequeira, *Trans. Path. Soc.*, 1905, vol. lvi, p. 189.

[6] Pitman, H. A., *Lancet*, 1865, vol. i, p. 175.

phenomena, however, associated with feminine sexual precocity are the early development of the adult feminine secondary characteristics, and the functional activity of those organs which are peculiar to the female sex.

It can quite easily be understood that the mere appearance of hair on the pubes and other signs of puberty may, as explained above, have no relation to *feminine* precocity, but, rather, to the change to adult (or precocious) masculinity, which may be produced in a true female or in a female partial hermaphrodite.

If this be so, we have almost always to consider precocious puberty in relation to ovarian neoplasms and hyperplasia. There is a number of such cases on record. One of the most interesting is that of a girl under the care of Clement Lucas[1]. This patient, who was seven years of age, had a large ovarian tumour which was associated with early menstruation and the usual signs of puberty. After the removal of the tumour menstruation and the other adolescent manifestations disappeared. I have lately seen a girl, seven years of age, belonging to the upper middle class, who had menstruated regularly, but very slightly, with definite molimina for two years. There was slight development of the breasts, but no axillary or pubic hair. No tumour could be felt in the abdomen, but a pelvic examination was not allowed.

Roger Williams[2] states that in eleven cases, which he had collected, of sexual precocity in female children associated with ovarian neoplasms, histological examinations of the tumours showed that eight were sarcomata, two cystomata, and one a fibroma. The same writer

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[1] Lucas, R. C., *Trans. Clin. Soc., Lond.*, 1888, vol. xxi, p. 224.
[2] Williams, Roger, *Brit. Gyn. Journ.*, 1902, vol. xviii, p. 85.

points out that in girls sexual precocity is not associated with excessive muscular or skeletal development as is the case in boys. This, of course, is what we would expect, for muscularity is not a feminine characteristic.

Gaudier[1] has recorded a case in which a tumour of the ovary, resembling a suprarenal cortical neoplasm, gave rise to sexual precocity. If the neoplasm were really a suprarenal growth, about which there is considerable doubt, the feminine precocity may have been due to hyperplasia of the ovary caused by the tumour.

Gautier (?), quoted by Williams[2], found that of twenty-three sarcomatous ovarian tumours in young children only four were associated with the signs of sexual precocity ; consequently it must not for a moment be assumed that all ovarian tumours in young girls cause precocious development. Indeed, as I have pointed out elsewhere[3], and have emphasized here, the whole endocritic system is concerned in the development of the genital organs and their functions, and the determination of sex characteristics ; so unless there are associated changes in the other organs of internal secretion as well as in the ovaries, sexual precocity will probably not occur. And in this connexion it may be suggested that insufficiency of the suprarenal medullary secretion, which normally is antagonistic to the ovarian, may lead to hyperplasia in the genital glands, and so to precocious puberty.

Apart, however, from those cases of precocious puberty which are produced by definite lesions in the

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[1] Gaudier, H., *Echo Med. du Nord*, 1908, No. 30, p. 357.

[2] Williams, Roger, *Brit. Gyn. Journ.*, 1902, vol. xviii, p. 85.

[3] Bell, W. Blair, *Proc. Roy. Soc. Med. (Obstet. and Gyn. Sect.)*, 1913, vol. vii, p. 47 ; Arris and Gale Lectures, R. C. S., Lond., *Lancet*, 1913, vol. i, pp. 809, 937.
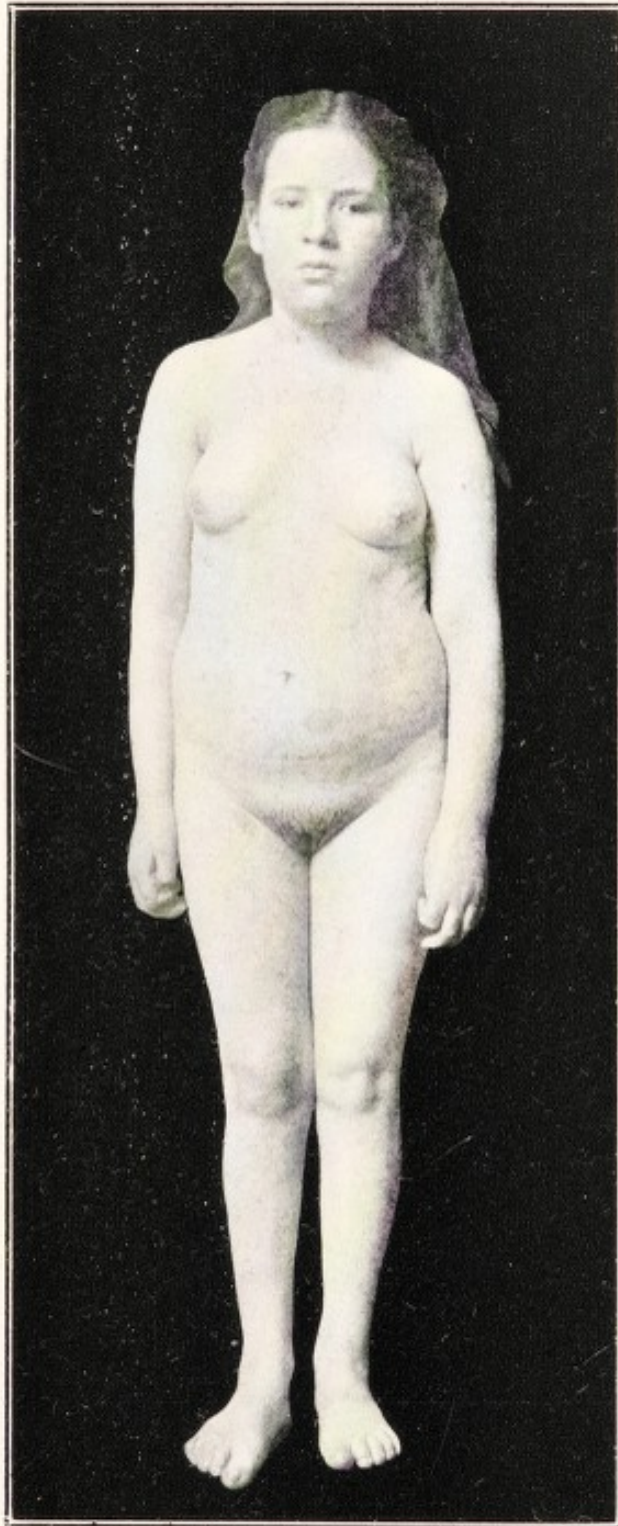
FIG. 40.

Photograph of a girl, æt. 8 years, showing
precocious development.

FIG. 41.

Skiagram of the wrist and part of the hand of the girl illustrated in figure 40, showing development equal to that seen in a girl of thirteen years of age. The pisiform and sesamoid bones are fully formed. (*Direct photograph by C. Thurstan Holland.*)

$\times \frac{1}{1}$.

ovaries, and which include almost all the examples of this condition, and apart from those cases which are not really instances of feminine precocity, but rather of precocious masculinity in the female with absence of menstruation and ill-development of breasts—quite apart from these abnormalities are certain anomalous cases of incomplete feminine precocity of doubtful origin. I have recently seen a case of this kind under the care of the late Dr. Percy Marsh, to whose courtesy in inviting me to investigate the case I was indebted, in which all the external secondary feminine characteristics were well developed in a child, eight years of age, whose mentality was much below that of a child of her own age, while her physical development resembled that of an adult (figs. 40 and 41). Menstruation, however, had never appeared. In this case no enlargement of the ovaries could be made out, and the uterus was found to be infantile on examination with the child under an anæsthetic. The pituitary fossa on skiagraphic examination was found to be of normal size, and the thyroid was well developed. The diagnosis of the lesion responsible for the precocious development in this case is extremely difficult in the absence of further evidence. It may be suggested that there is insufficiency of the suprarenal cortex. This condition would best account for the development of the adult secondary characteristics with inactivity of the internal genitalia. The absence of menstruation practically excludes ovarian hyperplasia.

Precocious puberty, however, in quite young girls is not usually complicated, and the treatment in the majority of cases is well defined : when there is an ovarian tumour it should be removed. These neoplasms are usually solid and often malignant ; and when the tumour is not benign the prognosis, so far as life is

concerned, is extremely grave.   If no lesion be found, or on bimanual examination the ovaries appear large (hyperplasia), the treatment will consist in the administration of some extract, such as that of suprarenal medulla, which is antagonistic to the ovarian secretion.

When puberty is slightly precocious—that is, occurs between the ninth and tenth years of age—ovarian hyperplasia or tumours are not often found.   Such cases may be due to inherited tendencies, or to early development of the ovarian function with associated changes in the other endocritic organs.   This in some obscure manner may be caused by the climate, feeding, and surroundings of the child ; or by masturbation, which will be considered later.

Absence of the Onset of Puberty.—In certain pathological conditions puberty may never supervene.   In such circumstances the patients are the victims of some severe general disorder, usually connected with the endocritic system.   Thus, with cretinism the patient remains in a condition of sexual inactivity, and the secondary sexual characteristics and functions are in abeyance.

In the case of a female cretin, who died at the unusually late age of thirty-three years, I had an opportunity of examining the genital organs, and the distant endocritic glands.   The ovaries were large and smooth, and the uterus was well formed.   On histological examination the ovaries were found to be devoid of Graafian follicles, but bands of hyaline substance, which represented the remains of atretic follicles, or possibly of corpora lutea, were seen (fig. 42).   The stroma of the ovary, which was very dense, was not composed of fibrous tissue for it was stained yellow by van Gieson's method.   The endometrium contained but few glands,
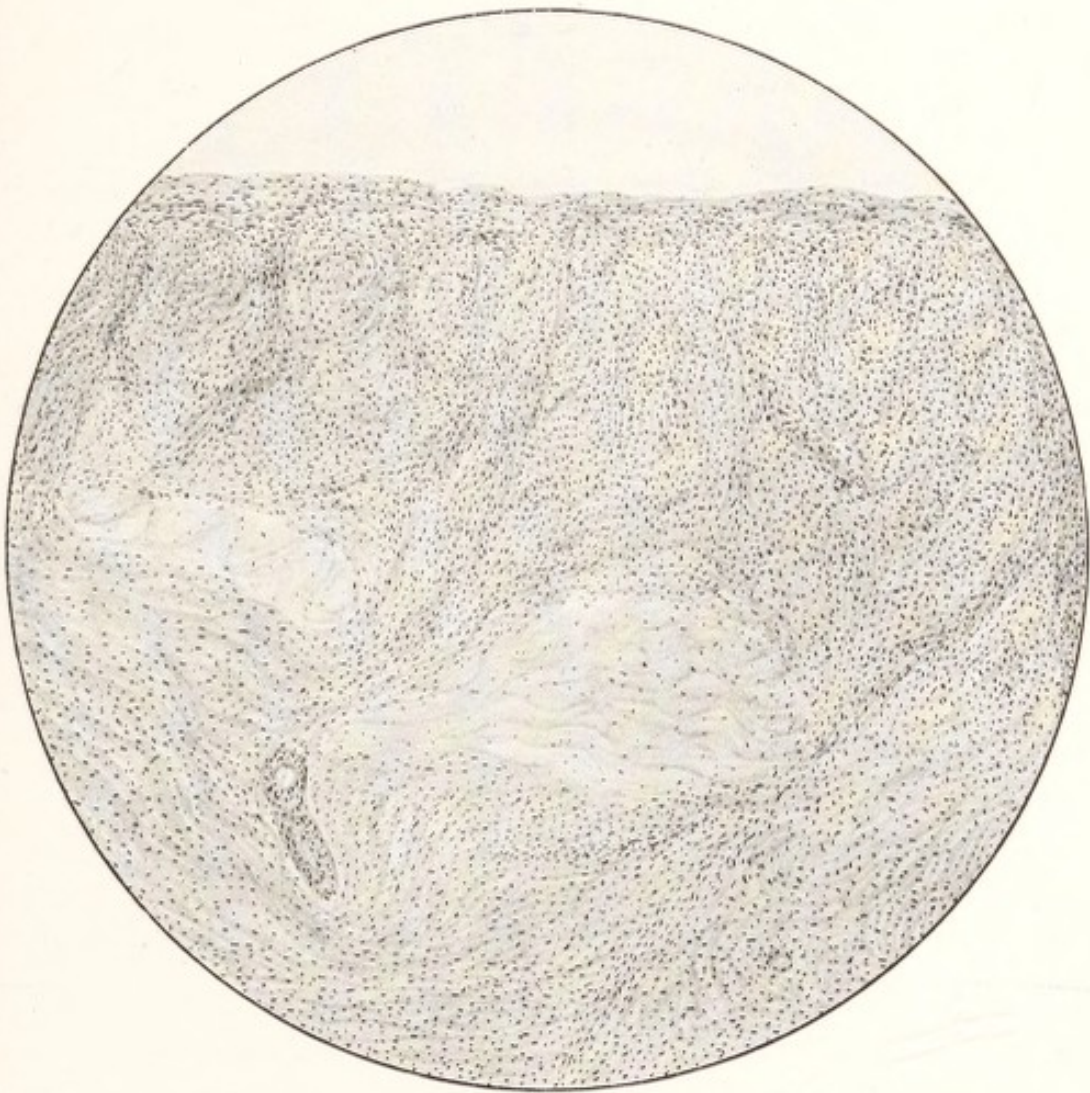
FIG. 42.

Section of the ovary of a cretin, æt. 33 years, showing a dense stroma and patches of hyaline material which may be the remains of corpora lutea or atretic follicles.

$\times$ 60.

Fig. 43.

Section of the uterus of a cretin, æt. 33 years, showing the under-developed
and inactive condition of the endometrium.

$\times$ 60.

and these were embedded in a very dense stroma (fig. 43). The thyroid was entirely absent, but the parathyroids were present and showed a tendency to form colloid (fig. 44). The pituitary was enlarged and altered in structure. The pars anterior was very rich in chromophobe and basophile cells, but there were very few eosinophile cells. This lobe was divided up by broad bands and masses of a structureless substance that might be secretion. There was a thick fibrous tissue capsule surrounding the whole pituitary body. The pars intermedia contained some 'colloid' and appeared normal. The pars nervosa also appeared almost normal. It was, however, more teased out in appearance than is usual.

This patient had taken thyroid extract for some years. It is possible that if she had been treated from an early age the genital functions might have been aroused, for there was no doubt that development of the reproductive organs had advanced far beyond the fœtal stage, and had, indeed, reached that seen at puberty.

Again, cortical neoplasms in the suprarenals which, as we have seen, lead to sexual precocity and muscular development in boys, cause atrophy of the genitalia in women, and when present before puberty would probably, if the child survived, prevent that period of development occurring.

In the type of infantilism described by Hastings Gilford[1] under the name of 'sexual ateleiosis', and in that defined by Byrom Bramwell[2] as 'pancreatic infantilism', the patient may remain under-developed in every respect, and the absence of sexual development

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[1] Gilford, Hastings, 'Infantilism', Hunterian Lect., *Lancet*, 1914, vol. i, p. 587.

[2] Bramwell, Byrom, *Edin. Med. Journ.*, 1915, New Ser., vol. xiv, p. 323.

is merely part of the general infantilism, as we have already seen. It is probable, then, that certain hormones arising from the endocritic system, which normally stimulate growth and development, are suppressed or are insufficient.

At the present time our knowledge is not definite enough to enable us to lay down specific lines of treatment in cases in which the patient remains infantile, except, perhaps, in those cases in which there is pancreatic infantilism. Yet even now a careful examination of any individual case may enable us to improve the condition of the patient, if we can trace it to the imperfect action of one of the organs of internal secretion.

Incomplete Puberty.—By 'incomplete puberty' is meant that the girl arrives at puberty with all her adult secondary characteristics fully developed, but that her genital functions are permanently in abeyance. This may occur as the result of:

(1) Incomplete or incomplete and imperfect development of the whole or part of the genital ducts, with normal ovaries.

(2) Incomplete development of the ovaries and genital ducts, with or without imperfect formation of the whole or part of the ducts.

(3) Constitutional disturbances.

With regard to the first condition, which is very common, we usually find that the parts forming the genital ducts—Fallopian tubes, uterus and vagina—are perfectly formed but that the uterus is infantile, and that in consequence menstruation does not appear. We are not concerned, however, with the malformations as such, but only in so far as they affect the genital functions.
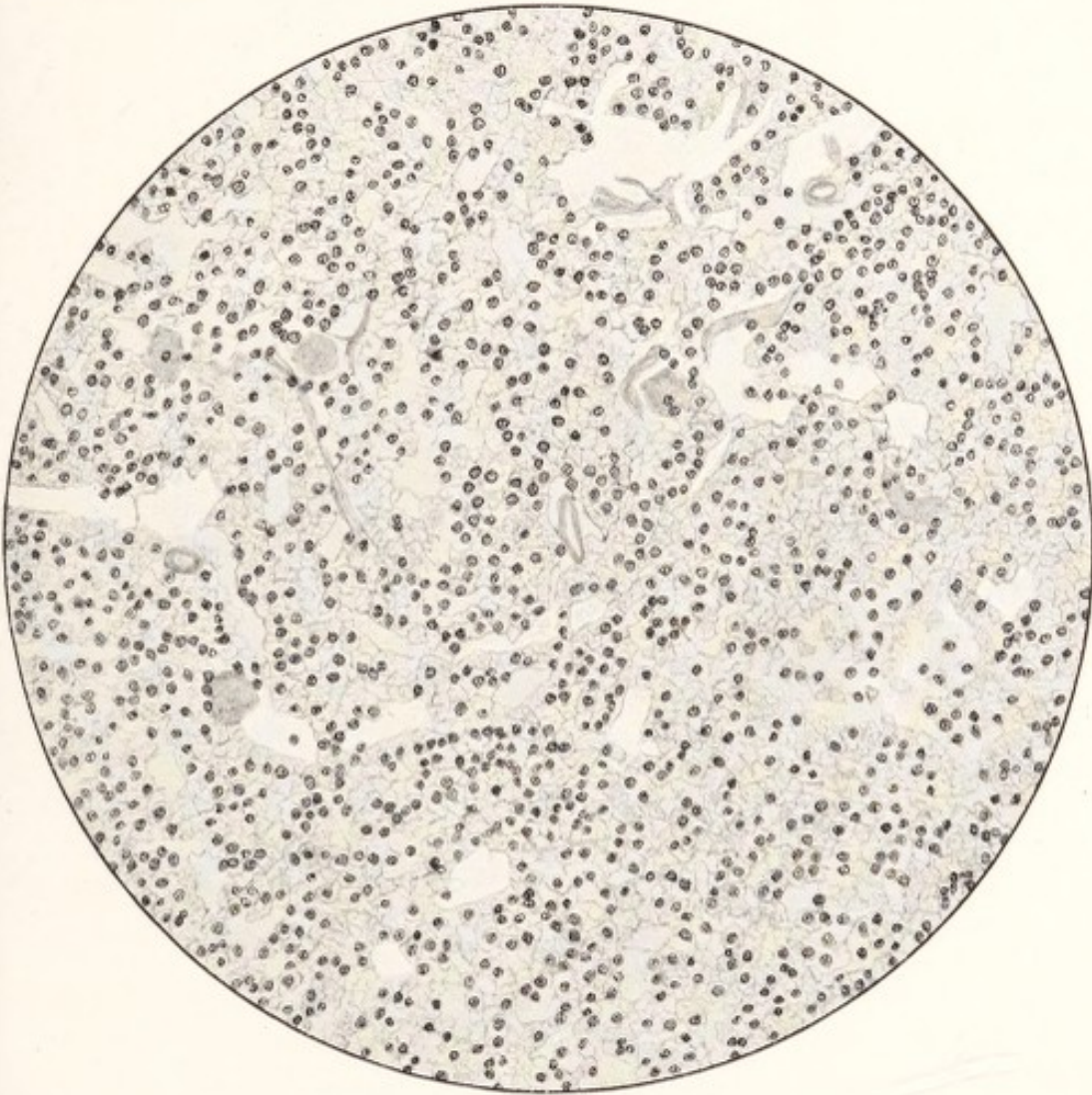
Fig. 44.

Section of the parathyroid of a cretin, showing attempts at colloid
formation.

× 250.

It is, of course, not always easy, without histological examination, to be certain that the ovaries of any given woman are active, since, as we have shown elsewhere[1], they are not necessarily concerned in the production of the secondary characteristics. If, however, the woman have strong sexual feelings and potency we may presume the presence of active sexual glands.

The causes of under-development of the uterus are now gradually being recognized. In the presence of normal ovaries we must seek for anomalies of the pituitary or the thyroid; in the latter especially there may be insufficiency not amounting to congenital cretinism. Occasionally both organs are at fault.

On several occasions I have seen under-development of the pituitary in cases of infantile or rudimentary uteri.

In the second class of case with incomplete puberty the ovaries are under-developed or inactive, and the uterus is usually rudimentary or infantile, and may be imperfectly developed. Such a condition is not very common, and of course nothing can be done to remedy the state of affairs. If the experiments of Paulesco[2] and of Crowe, Cushing and Homans[3] be correct, congenital under-development of the pituitary might be responsible for the pelvic anomalies. As already stated, my own experiments confirm the results obtained by the authorities mentioned.

In many cases, moreover, the condition of affairs just described must undoubtedly be due to local lesions,

[1] Bell, W. Blair, *Proc. Roy. Soc. Med.* (*Obstet. and Gyn. Sect,*), 1913, vol. vii, p. 47; Arris and Gale Lectures, R. C. S., *Lancet*, 1913, vol. i, pp. 809, 937.

[2] Paulesco, N. C., *Journ. Physiol. Path. Generale*, 1907, vol. ix, p. 441; *L'hypophyse du cerveau*, 1908.

[3] Crowe, S. J., Cushing, H., and Homans, J., *Bull. Johns Hopk. Hosp.*, 1910, vol. xxi, p. 127.

such as tuberculous or gonococcal infections, with pelvic peritonitis, and possibly in some cases to pelvic infection from appendicitis.

Delayed Puberty.—An undue delay in the appearance of puberty is a matter of considerable importance in many cases ; but first of all it will be necessary to define what we mean by ' delayed puberty '.

Strictly speaking ' delayed puberty ' should refer to the temporary non-appearance of all the phenomena of puberty in a girl who is past the period of life at which they appear normally (*complete delay*). But that is not what is always implied by the term : it is often employed to denote the temporary absence of menstruation in a girl who is otherwise fairly well developed, both in regard to the uterus and the secondary characteristics (*incomplete delay*); hence there is considerable confusion as to the pathological conditions which may be responsible for the delay. It will, therefore, make the discussion of the subject clearer if we consider the subject under the two headings indicated.

Completely delayed Puberty.—By ' completely delayed puberty ' is implied that not only menstruation is delayed, but also the development of the adult secondary characteristics. This condition may be distinguished from general persistent infantilism by the fact that there is merely delay in and not suppression of further development.

To understand best this retardation in reaching puberty we have only to look at the girls who come under our notice every day, and observe how differently they develop under different conditions. The influences at work may be divided into two classes—psychical and physical.

With regard to psychical conditions, there is no doubt that the mental character of the individual is altered at puberty by the physical changes which occur in the body at that time : the secretions from the endocritic glands play the chief part in effecting this result. On the other hand, it is certain that the mind itself can hasten or unconsciously delay the onset of sexual activity[1]. In this connexion it must be clearly understood that the mind can certainly influence function, and *vice versa*, however impossible it may be for the mind to alter structure. So in the first case we find that, with the onset of the physical phenomena associated with puberty, modesty and shyness develop in a girl hitherto untroubled with self-consciousness. Even then she may have but a vague instinctive knowledge of sexual matters. In the second case, in which the mind influences the onset of the physical phenomena of puberty, investigation has shown[2] that the effect of enlightenment concerning sexual matters, with perhaps the stimulation of the sexual appetite by various means, hastens the onset of puberty. Conversely seclusion and innocence tend to delay it.

Further, hard mental work, such as studying for examinations at school, may lead to a delay in the development of the girl. Such cases are seen by most gynæcologists, but we know of no statistics giving the age incidence in a large number of girls who have studied closely between the ages of twelve and twenty years, although Catherine Chisholm[3] denies that study affects either menstruation or the general health of these

[1] Engelmann, G. J., *Amer. Journ. Obstet.*, 1900, vol. xlii, p. 753.
[2] Ellis, Havelock, *Studies in the Psychology of Sex*, 1913.
[3] Chisholm, Catherine, *Journ. Obstet. and Gyn. Brit. Emp.*, 1913, vol. xxiii, p. 288.

girls. Further investigations properly carried out would have considerable interest at the present time, especially as her results not only lack support, but are diametrically opposed to the observations of others[1].

With regard to many of the physical causes of delayed puberty there is much conflicting evidence. It is, however, well established that general ill-health, bad feeding, unhygienic surroundings and hard work in factories tend to delay the development of the girl and the onset of puberty.

The disorders met with may be produced by the causal factors enumerated above in different ways : the food may be deficient in calcium salts, which are required for building up the skeleton before any can be spared for the reproductive functions ; there may be constipation and chlorosis ; or, again, hard muscular exercise or a sedentary life may each prevent the development of the sexual functions—the former by using up the reserve metabolic forces, and the latter by failing to stimulate metabolic energy. With regard to muscular exercise, evidence has been produced to show that in gymnasts puberty may be delayed or incomplete ; but, on the other hand, Angenette Parry[2], in an enquiry among members of this class of woman, found that they were nearly all normal with respect to their genital functions. The truth probably lies halfway between these extreme statements, as was pointed out in the discussion following the paper just referred to : moderate exercise is beneficial, and excessive harmful.

In races in which the women always perform muscular work, agricultural and domestic, heredity appears to

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[1] Cardew, G. A., Discussion, Brit. Med. Assoc., *Brit. Med. Journ.*, 1900, vol. ii, p. 792.

[2] Parry, Angenette, *Amer. Journ. Obstet.*, 1912, vol. lxvi, p. 341.

play an important part ; and by a process of selection women are produced whose functions remain undisturbed. The same argument may apply to healthy gymnasts, many of whom have a long line of gymnastic ancestresses. But if we were to take a girl of ten years of age from the upper classes and put her to work continuously in a factory or even in the fresh air in fields or bring her up as a professional gymnast, it is probable that the onset of puberty in her case would be delayed, if not prevented.

In the lower classes the effect of hard work, a sedentary life, or bad feeding on the onset of puberty is in part mitigated by heredity, by the close association with the opposite sex, and by the free discussion of sexual matters common among girls in this station of life ; but, in spite of all, the fact remains that girls of the upper classes who are well tended commence menstruating at an earlier age than their poorer sisters[1].

Incompletely delayed Puberty.—By this term I wish to imply a *temporary* state of incomplete puberty. In these circumstances the absence of menstruation is the only abnormal phenomenon.

Incompletely delayed puberty may be caused by all the conditions just described as responsible for completely delayed puberty, and also by minor degrees of insufficiency in the internal secretions, which may not be sufficient to delay the appearance of the secondary characteristics ; for instance, we usually find that, when there is deficiency of the internal secretion of the thyroid, the uterus is well developed, if a little small, but that menstruation does not occur. These cases are well known, and they readily respond to treatment with thyroid extract.

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[1] Engelmann, G. J., *Amer. Journ. Obstet.*, 1900, vol. xliii, p. 753.

DERANGEMENTS OF THE FULLY ESTABLISHED FEMALE CHARACTERISTICS AND FUNCTIONS

DERANGEMENTS OF THE SEX CHARACTERISTICS

The secretions of the endocritic organs, which have produced the normal adult female, continue subsequently to act in the same way—passively, no doubt—and it is only some extensive alteration in the structure of certain units of the internal secretory system which can bring about an alteration in the female sex characteristics, once they have been determined and developed to maturity. So far as we know, the withdrawal of any one secretion—such as the ovarian—will not produce any definite change. There must be some gross change in those parts of the endocritic system, especially apart from the genital glands, which normally produce masculinity—a potentiality that appears to be concentrated in the suprarenals, the pituitary, and probably in the pineal.

Apert[1] has asserted that masculine characteristics may be produced in women by simple ovarian tumours. I do not believe that this is so. As we have already seen (p. 147) such tumours may produce feminine precocity, but they never produce masculinity. It is possible that Apert overlooked an ovo-testis and considered it a new growth, as was done by an expert pathologist in the case already recorded (p. 135). With an ovo-testis, such as that described, masculinity may be produced

[1] Apert, M. E., *Bull. Med.*, Paris, 1910, vol. xxiv, p. 1161.

by the testicular elements in the gonad in part, but it is probable that in these circumstances other organs, such as the suprarenals and pituitary, are also more masculine than feminine in type.

It will not be waste of time to reiterate for a moment the essential differences that occur in the metabolism in response to stimulation from the masculinity-producing secretions. Probably the most important and obvious changes are associated with the metabolism of the lime salts. The male skeleton is far heavier and stronger than that of the female, so in men one of the most essential metabolic conditions is a considerable calcium retention during growth ; besides, there is normally in men a stable and invariable metabolism of calcium during the reproductive period. In women there is less calcium retention during growth, and throughout her reproductive life rapid alterations in the metabolism of lime salts occur during menstruation, pregnancy and lactation. It is not surprising, therefore, to find that those parts of the endocritic system which are largely concerned in the storage of calcium and the building up of the skeleton will also, when abnormally active in the female, produce or lead to the production of other masculine characteristics, such as growth of hair on the face and alterations in the formation of the larynx and breasts.

We have already seen, that hyperplasia and neoplasia of the suprarenal cortices in girls before puberty lead to the production of male characteristics. These growths have generally been found to be malignant, so no further relevant history has been obtained in regard to the cases recorded[1,2].

[1] Bulloch, W., and Sequeira, J. H., *Trans. Path. Soc.*, 1905, vol. lvi, p. 189.

[2] Glynn, E. E., *Quart. Journ. Med.*, 1912, vol. v, p. 157.

Many instances of suprarenal cortical tumours and hyperplasia in adult women associated with alterations in the sex characteristics have been described[1].

It is important to note that there is no case on record of a suprarenal lesion in a woman after the menopause associated with changes in the secondary characteristics. Yet we know that often after this period of life the characteristics may normally incline towards the masculine type, the skin becoming coarse and hair developing on the face. I have, however, seen a suprarenal tumour in a duck of considerable age, which had partially acquired the plumage of the drake.

The paradoxical circumstance that in women after the climacteric suprarenal lesions cause no considerable development of the masculine characteristics, which, however, may develop normally after that period of life, may be explained by the fact that Sex, as such, has ceased to exist; and that although the withdrawal of certain feminine functions and characteristics may lead to the latent masculinity developing to a slight extent, yet no further sex demonstration can be aroused, even though the masculinity-producing organs be disturbed.

During the reproductive period of life the changes in the sex characters of women, which may be brought about by suprarenal lesions, are remarkable. In one case of Krafft-Ebing quoted by Halban[2] the voice which was previously soprano became " like that of a lieutenant ", and the woman, previously gentle and amenable, became rough and aggressive. Amenorrhœa is a constant phenomenon in these circumstances, and the breasts atrophy. In fact, all the essentially feminine

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[1] Glynn, E. E., and Hewetson, J. T., *Journ. Pathol. and Bacteriol.*, 1913, vol. xviii, p. 81.

[2] Halban, J., *Arch. f. Gynäk.*, 1903, vol. lxx, p. 205.

FIG. 45.

Section of the suprarenal of a young woman who had developed masculine characteristics, showing encapsuled hyperplasia in the lower part of the picture. (*From a section kindly lent by Dr. J. Anderson.*)

× 60.

attributes of mind and body retrogress or disappear, while the male characteristics become pronounced. I have just explained why this can occur during the reproductive period and not after the menopause.

It has been mentioned that the pituitary is largely concerned in promoting the growth of bone and the retention of calcium salts. It is interesting, therefore, to note that when there is hyperplasia of this organ in women, such as is seen in acromegaly, the sex characteristics are disturbed. Every woman with acromegaly exhibits masculine characteristics : the heavy features, the coarse skin, the deep voice at once attract our notice. Yet this alteration of sex characterization does not appear to have been recorded as such until recently[1]. But the alteration may go further than the phenomena mentioned above, which are constant : amenorrhœa is nearly always seen ; and this is not primarily due to hypoplasia of genitalia but to the general change towards masculinity, in association with which menstruation would be anomalous.

Cushing[2] has stated that in men the onset of acromegaly is not infrequently associated with increased sexuality, which may indicate increased masculinity.

There is no doubt that in women hypoplasia of the pituitary (*dystrophia adiposo-genitalis*) leads to decreased function in the ovaries, consequently the apparent paradox of amenorrhœa with increased secretion in the anterior lobe of the pituitary can only be explained on the ground of the production of masculinity in these circumstances. If further evidence than that

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[1] Bell, W. Blair, Arris and Gale Lectures, *Lancet*, 1913, vol. i, p. 937 ; and *Proc. Roy. Soc. Med. (Obstet. and Gyn. Sect.)*, 1913, vol. vii, p. 47.

[2] Cushing, H., *The Pituitary Body and Its Disorders*, 1912.

mentioned of the production of masculinity in women with acromegaly were required it would be found in one case which came under my notice : in this patient the clitoris was enlarged to the size of a small penis.

We must, of course, always bear in mind the fact that in diseases of the endocritic system there may be—indeed, there usually is—what is called a pluriglandular syndrome ; that is to say, more than one organ of internal secretion is affected. So it might be suggested that in acromegaly there may also be hyperplasia in the suprarenal cortices, and that it is this latter condition which is responsible for the masculinity in this disease. According to Cushing[1], hyperpituitarism (acromegaly) is often associated with a low blood pressure, asthenia and pigmentation—symptoms which indicate insufficiency of the suprarenal medulla. Indeed, I have myself seen a case of acromegaly which also presented all the symptoms of Addison's disease. But it must not be forgotten that hyperplasia of the suprarenal cortex might be associated with insufficiency of the medulla (Addison's syndrome), even if we accept the view that the two portions are interdependent. An interesting case is recorded by Anderson[2] in which hyperplasia in the left suprarenal (fig. 45) was found in association with an adenomatous chromophobe tumour (fig. 46) in the pars anterior of the pituitary of a woman aged 28 years, in whom certain male characteristics had developed. A complete post-mortem examination was made. The author states that the anterior lobe was in a state of increased activity, and this is certainly borne out by the appearance of the chromophobia present in the cells of the pars anterior, apart from the tumour.

[1] Cushing, H., *The Pituitary Body and Its Disorders*, 1912.
[2] Anderson, J., *Glasgow Med. Journ.*, 1915, vol. lxxxiii, p. 178.
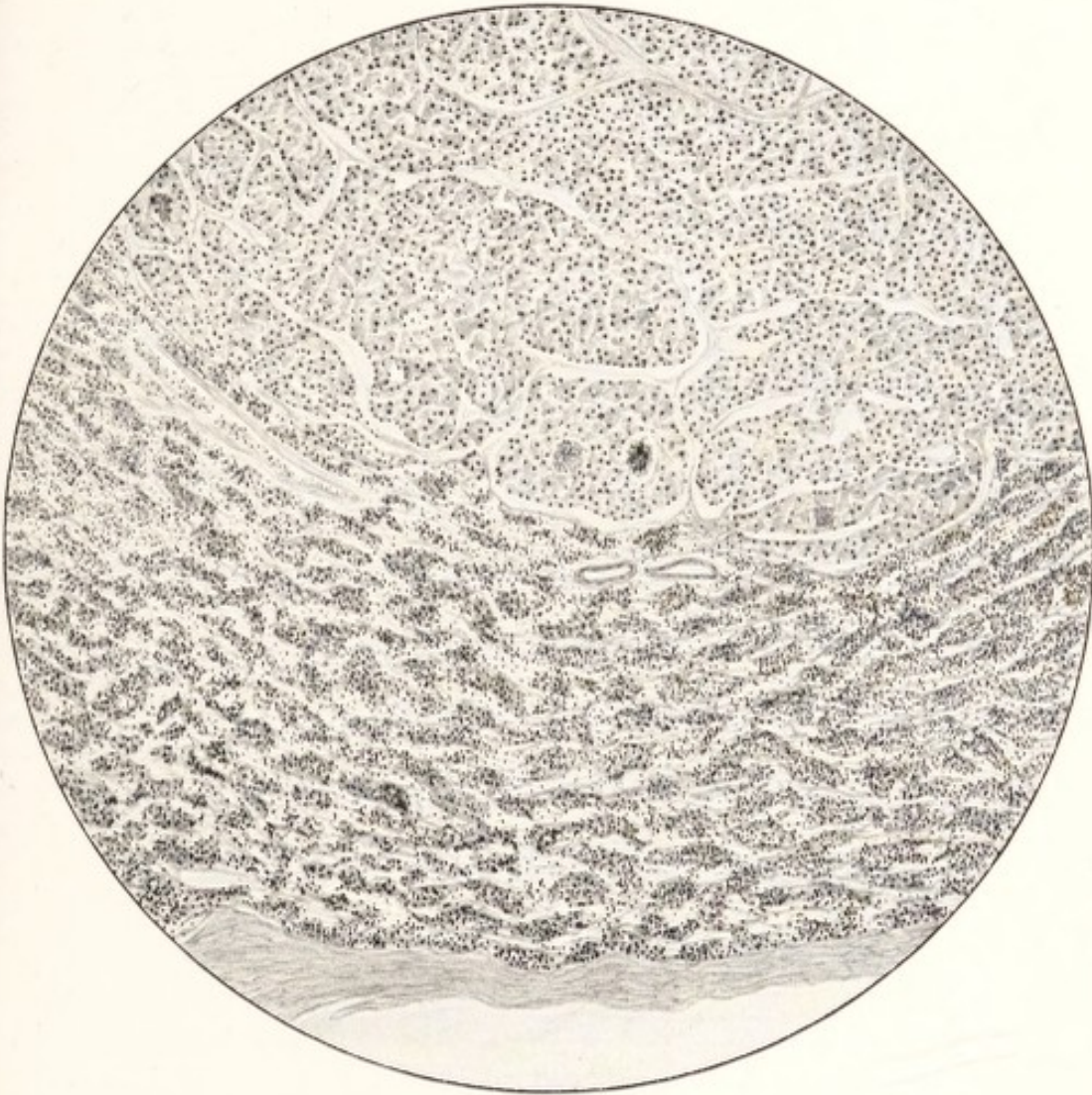
FIG. 46.

Section of the pars anterior of the pituitary of a young woman who had developed masculine characteristics, showing a chromophobe adenomatous tumour in the upper portion. (*From a section kindly lent by Dr. J. Anderson.*)

× 60.

FIG. 47.

Section of the uterus of a young woman who had developed masculine characteristics, showing atrophy of the endometrium. (*From a section kindly lent by Dr. J. Anderson.*)

× 60.

The uterus was atrophied (fig. 47), and so were the ovaries (fig. 48). Somewhat similar cases have been recorded by Cushing[1] and others. In these circumstances we would expect male characteristics to be produced by both lesions, with atrophy of the female genitalia, as was found in the case described. Nevertheless it appears to me certain that acromegaly alone may give rise to a change in the secondary characteristics of female towards the masculine type.

So far as I am aware, no cases are on record in which pineal tumours led to the development of masculine characteristics in adult women, although on the evidence at our disposal such an occurrence might be expected.

DERANGEMENTS OF THE FULLY ESTABLISHED GENITAL FUNCTIONS

In considering derangements of the fully established functions I shall take in order each of the chief organs of internal secretion, and endeavour to show how they are individually related to various gynæcological and obstetrical disorders. In some cases we have to take into account certain correlations; especially is this so when the ovary is concerned.

It will make this complicated subject clearer if it is treated in this manner, instead of being subdivided into the pathological anomalies themselves, although the latter is undoubtedly the more scientific method. Some day, when many more clinical observations have been recorded, and conditions such as those we are discussing here become matters of daily consideration, it will

[1] Cushing, H., *The Pituitary Body and Its Disorders*, 1912.

be possible to describe intelligibly the pathological phenomena related to the internal secretions as definite disorders.

It will be remembered that consideration has already been given to disturbances of genital development—anatomical and physiological—and of the sex characteristics; consequently the further discussion of the individual relationships of the endocritic organs to derangements of the fully developed functions will be largely complementary, and in many particulars necessarily fragmentary.

Primary derangements of the endocritic organs may be considered as giving rise to insufficiency or excess of the normal secretions; and I shall deal with them from these points of view.

Disturbances of the Ovarian Secretion

Absence and insufficiency of ovarian secretion.—These conditions are rare as primary disorders during the reproductive period, except when produced by operative interference. As we have already seen, when the ovaries are removed experimentally definite changes occur in the general metabolism, in the uterus and in the structure of the other organs of internal secretion; and these changes appear to be more marked in the higher than in the lower mammals.

From observations made on the human subject there is no doubt that a train of events similar to that seen in animals follows complete oöphorectomy. In women, however, there are, in addition to the phenomena already described, frequently to be noted psychical disturbances which are no doubt dependent on the general disturbance of the metabolism. It must not be
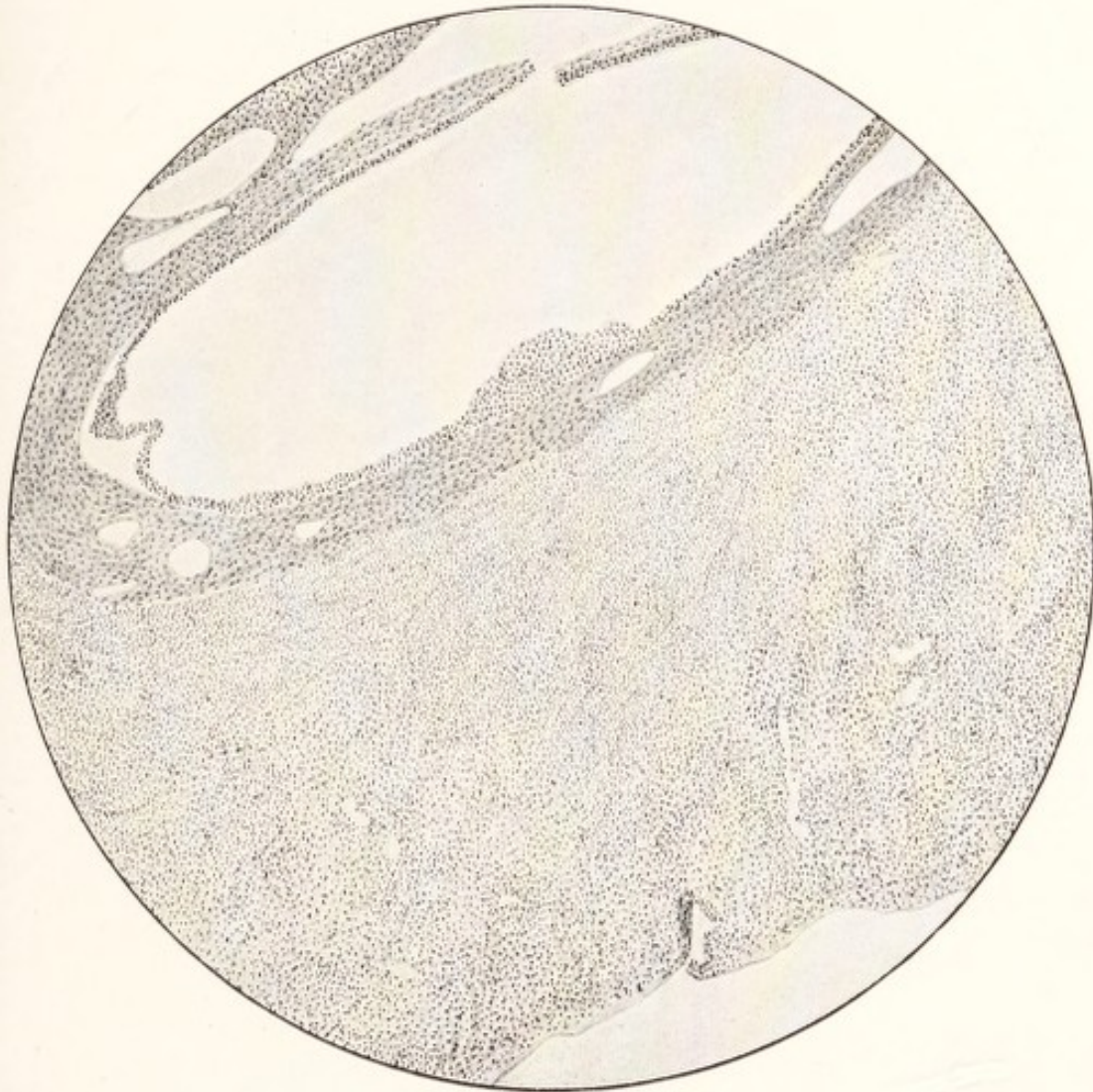
Fig. 48.

Section of the ovary of a young woman who had developed masculine characteristics, showing a dense stroma and an atretic follicle. (*From a section kindly lent by Dr. J. Anderson.*)

$\times$ 60.

forgotten, also, that marked individual variations exist in regard to the symptoms produced, just as normally there are considerable variations in the degrees of femininity in different women.

Many surgeons have stated that complete oöphorectomy produces no detrimental symptoms, or, at any rate, no disturbances worthy of consideration. Such surgeons remove both ovaries without the slightest hesitation. Nevertheless, those who have asserted that oöphorectomy is of small moment to the patient have failed to make good their scientific position in the matter by any reliable evidence. Of course, as already mentioned, women differ considerably in their reactions to oöphorectomy. Knowing this, by the exercise of a discretion that appears obvious in view of what has been said regarding individual variability, we might be able to avoid seriously injuring the patient. If one were to gauge the degrees of femininity and ovarian activity in women before operation—and in many cases it would not be difficult—it might be possible to assert that in those cases in which these were obviously in abeyance or below the average standard little disturbance of the metabolism would result from oöphorectomy ; and, consequently, it might be justifiable in such cases completely to remove the ovaries with a fibromyomatous uterus or with infected tubes. But unless such a scientific distinction, which undoubtedly exists and accounts for the individual variations to be observed after oöphorectomy, be made, it does not seem right blindly and systematically to remove the genital glands as some do in the circumstances mentioned.

The obvious explanation I have given of individual variability with respect to the disturbances following oöphorectomy has not been presented in this way

before ; that is to say, that the symptoms produced by oöphorectomy in any given case are directly proportionate to the degree of femininity.

Since the natural menopause bears a close resemblance to the artificial, I shall briefly discuss together the disturbances which may be associated with either.

It is more or less generally supposed that the natural menopause occurs in women as the result of the gradual withdrawal of the ovarian secretion ; and it is, of course, obvious that the artificial menopause is produced by the absence of it. At the natural or physiological menopause there is undoubtedly ovarian insufficiency sooner or later ; but, as with the artificial menopause, it has always seemed to me that the symptoms produced depend for their severity upon the correlations that exist between all the internal secretions, on the uterine changes which prevent the monthly excretions, and, lastly, on individual variability in regard to reproductive activity and to the stability of, and capacity for, readjustment in the endocritic system. That the phenomena associated with the physiological menopause depend partly on ovarian insufficiency is demonstrated by the onset of similar manifestations in most women after oöphorectomy ; and that they are related to the coincidental uterine atrophy is proved by the fact that women may suffer with the same symptoms after the removal of the uterus alone. Further, I have seen monthly molimina, which reminded one of some of the symptoms of the menopause, in women in whom there was congenital absence of the uterus, or malformations sufficient to prevent menstruation, but the presence of functional ovaries.

The chief types of menopausal phenomena to be observed clinically may be classified as follows :—

(1) Psychical.
(2) Vasomotor.
(3) General metabolic.
(4) Gross changes in the endocritic and mammary glands.

The psychical disturbances I shall deal with later.

Vasomotor disturbances.—The regulation of the vasomotor system is very definitely under the control of the internal secretions, although as yet we do not know exactly the different parts played by all the endocritic organs.

It has, of course, long been known that the chromaffin system, of which the suprarenal medulla is probably the most important element, exerts a controlling influence over the tone of the vessels. We have not only physiological evidence of this in the pressor action of the prepared extract, but also morphological, since the secretory cells of the suprarenal medulla are derived from the same *anlage* as the sympathetic nervous system.

Again, Weed, Cushing and Jacobson[1] have demonstrated that stimulation of the superior cervical sympathetic leads to an increased output of infundibulin, followed by glycosuria. It is true that this is merely a secretory nervous phenomenon ; but we know that the connexion does not stop there, and that the infundibulin has a powerful action on the blood pressure : not, of course, through the sympathetic nervous system, but owing to its direct, peripheral effect on the blood vessels.

With regard to the thyroid we know that the extract of this gland, when injected intravenously, lowers the blood pressure. The *modus operandi* is somewhat doubtful ; many authorities believe that the action is

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[1] Weed, L. H., Cushing, H., and Jacobson, C., *Bull. Johns Hopk. Hosp.*, 1913, vol. xxiv, p. 40.

not specific, but common to many animal extracts; others look upon the effect produced as specific for reasons which need not be discussed here.

Behind these direct effects of the internal secretions in regard to the vasomotor system are the indirect results brought about through the general metabolism. For instance, the calcium metabolism is directly influenced by most of the internal secretions. Some, such as infundibulin and suprarenin, induce the retention of calcium salts in the blood and tissues—that is to say, they are anabolic in respect to these salts; while others, such as the thyroid and ovarian secretions, are katabolic. Consequently, as lime salts themselves have a pressor action, an indirect effect of this nature is produced on the vasomotor system by those secretions which lead to the retention of calcium compounds in the blood, quite apart from their own specific pressor actions. And the converse is equally true of those secretions which promote the excretion of the lime salts.

When insufficiency of the ovarian secretion is brought about either naturally or artificially all the other endocritic organs of the body are also affected, and as a result vasomotor symptoms are commonly seen. The vascular disturbances met with are either visceral or cutaneous. The former are most frequent in connexion with the heart, the digestive tract and the brain; while to the latter are due the flushing and sweating of which the patient so often complains. These symptoms can usually be effectually treated by replacing secretions that are deficient, or by antagonizing those which are excessive; or, more empirically, by maintaining the blood pressure at a slightly higher level than is normal by means of calcium salts, alone or in conjunction with pituitary extract.

General Metabolic Disturbances.—These are frequently seen, but the various biochemical derangements have not been properly worked out. For example, although attention is always drawn to the adiposity which occurs in at least 50 per cent. of all women at the menopause, very few investigations have been carried out to define the causes underlying this physical change. My own observations make it obvious that there is an increased carbohydrate tolerance in these circumstances, associated with deficient oxidation. By this I mean : firstly, the endocritic organs, such as the pituitary, which are concerned with the carbohydrate metabolism, are disturbed and fail properly to carry out their functions in this respect ; and secondly, there is a diminution in oxidation, partly due to the insufficiency of ovarian secretion as demonstrated by Loewy and Richter[1], and partly to the sedentary life that the woman often leads.

As already stated, the metabolism, once the menopause is fully established and the disturbing symptoms have disappeared, usually settles down, and becomes uniform and less elastic than previously. Calcium, for instance, no longer needed for reproduction and lactation becomes deposited in the tissues ; and this is primarily brought about by the absence of ovarian secretion which in the reproductive period, when the woman is not pregnant, leads to the elimination of lime salts in the fæces and urine, and also in the menstrual discharge.

These metabolic derangements play an important part in the psychical disturbances and alterations which so frequently occur at the menopause.

Gross changes in the endocritic organs.—As already

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[1] Loewy, A., and Richter, P. F., *Centralbl. f. Physiol.*, 1902, vol. xvi, p. 449.

demonstrated by experimental evidence, alterations occur in the endocritic organs on the withdrawal of the ovarian secretion. As a rule, these changes are not extensive, and are only temporary. Sometimes, however, very marked disturbances are seen. It is not uncommon, on the one hand, to see enlargement of the thyroid, and even exophthalmic goitre, supervene after removal of the ovaries during the reproductive period. On the other hand, somewhat paradoxically perhaps, myxœdema is a disease which most frequently occurs in women after the menopause. The other organs of internal secretion are, apparently, less directly sensitive to the withdrawal of ovarian secretion than the thyroid ; and this organ I look upon as being the most closely correlated with and supplementary to the ovary.

Changes in the Mammary Glands.—Although the mammary glands cannot be considered organs of internal secretion, they are so closely related to the reproductive system that changes in regard to ovarian activity naturally affect them.

The alteration which takes place in the mammæ of women at the natural menopause is similar to that produced at the artificial (with a certain qualification to be mentioned directly)—namely, involution of the glandular elements. With this atrophy of the secretory structures the breasts become shrunken and in the glandular area fibrous tissue develops. These changes are, of course, most marked in women in whom lactation has occurred, except in the circumstances to be described. Indeed, in young and obese patients the breasts may remain bulky, and no change occur that is visible to the naked eye. However, on histological examination of the mammary gland atrophy will be found.

The qualification mentioned above in connexion with

this description is important. We have seen that in cows the quality of the milk may be improved by oöphorectomy[1]. This, of course, does not resemble what occurs in the human female unless she be pregnant at the time oöphorectomy is performed ; in these circumstances she may have a plentiful supply of milk after parturition. Cases are on record which demonstrate this fact.

Another point of interest which may be observed is the disappearance of adenomatous cysts in the breasts after oöphorectomy. I recently saw such a case, in which bilateral ovarian cysts coexisted with bilateral cystic adenomata of the mammæ in a woman who was forty-eight years of age. After both ovaries and the uterus, to which one ovary was adherent, had been removed, the cysts in the breasts, for which an operation had been planned, rapidly disappeared.

Apart from the natural and artificial menopause, insufficiency of ovarian secretion, with or without climacteric symptoms, may occur in various pathological conditions. When the insufficiency is temporary there are usually no untoward symptoms, but when it is permanent menopausal symptoms, usually mild, generally supervene.

As we have already seen, there may be congenital ovarian insufficiency which leads to primary amenorrhœa and reproductive incapacity; this is rare. After puberty insufficiency may arise as the result of disturbances of the other organs of internal secretion, such as pituitary disease. In the condition known as *distrophia adiposogenitalis* the effect is direct : insufficiency in the anterior lobe of the pituitary produces ovarian hypoplasia. In

[1] Hobday, F. T. G., *Castration and Ovariotomy*, 2nd ed., 1914.

acromegaly, on the other hand, the effect is indirect, and is due to the production of masculinity.

It has been asserted by some authorities (Freund[1], Verstraeten[2] and others[3]) that ovarian insufficiency is the primary cause of pituitary disease, but we have no real evidence that this is so. My experimental results point to an opposite conclusion, namely that ovarian insufficiency follows pituitary disease.

In the living subject it is always a difficult matter to know whether genital inactivity—such as is indicated by sterility and amenorrhœa—is due to primary ovarian or to uterine atrophy ; so when there is no evidence to enable us to come to a conclusion from clinical observations, we must be guided by the results of experimental investigation. In this way we are able to assert that the amenorrhœa which occurs with thyroid insufficiency, such as occurs in the disease known as myxœdema, is probably due to uterine rather than ovarian atrophy.

Besides these inter-endocritic disturbances there are other general diseases in which ovarian insufficiency may be seen, and these all come in the same etiological category, although the primary causal factors differ widely.

It must, however, clearly be recognized that in those diseases in which there is a general toxæmia, the result produced depends on the severity of the disease. Thus, with mild forms of tuberculosis, amenorrhœa and sterility are unusual; while with advanced stages of

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[1] Freund, H. W., *Volkman's Klin. Vortr.*, 1889, Nos. 329 and 330, quoted by Biedl, *Innere Sekretion*, 2nd ed., 1913.

[2] Verstraeten, C., *Rev. de Med.*, 1889, vol. ix, pp. 377 and 493.

[3] Tandler, J., and Grosz, S., *Wien. Klin. Woch.*, 1907, vol. xx, p. 1596.

the disease the genital functions may be entirely in abeyance. Probably this state of affairs is produced by the lowering of the metabolic—the vital—processes of the body. It is not difficult to understand that in disease the exhausting, but not vital, reproductive processes are first subject to suppression in order that the individual may recuperate. This is in accordance with natural laws.

The lime salts are among the most important physiological agents in resisting infections and in repairing the local ravages of disease; so it is no wonder that in the circumstances under discussion calcium cannot be spared for excretion or reproduction.

Sometimes, when the factor arresting the ovarian function has been very powerful—such as may be produced by a toxin—the effect may be permanent. This may occur after mumps, after typhoid fever and as a result of local infections. In these circumstances the effect is more than inhibition: there is probably destruction of the ovarian secretory cells by local and general infections; and lesions in the other organs of internal secretion may result from general infections. This is confirmed by our own experimental investigations[1].

It may be asked how we can recognize that it is the ovarian function which is in abeyance, and not merely the process of menstruation. There are several indications which assist us to come to a conclusion. On the one hand, when menstruation is in abeyance owing to general or constitutional disturbances sterility co-exists, proving that the ovary is at least quiescent in respect to its normal functions. Whereas, on the other hand,

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[1] Brown, T., Glynn, E. E., and Bell, W. Blair. (*In the press.*)

in the absence of menstruation during lactation conception may and does occur.

The ovary, as has been demonstrated, is concerned in causing the excretion of the excess of substances required by the mother in the absence of pregnancy, and a physiological readjustment occurs when the individual demands of the mother are such that she requires the very substances that are normally excreted in the menstrual discharge and other excretions; in which circumstances the functions of the ovary are inhibited. It would indeed be interesting if we could trace the processes that lead to this inhibition.

Hormones may be either stimulative or inhibitory; and they may be simple chemical substances, such as the respiratory hormone CO_2, or complicated organic products of unknown composition, such as secretin—facts which throw light on the metabolism of the body and simplify such considerations as those we have in hand.

Since, then, the whole body—every cell in it—works in organic harmony, it is easy to realize that the controlling link in the reproductive processes—the ovary—is disconnected by inhibitory or diverting hormones when the metabolism of the body requires all its energies to combat disease.

There are a few other pathological conditions by which the ovarian secretion is decreased. Superinvolution of the uterus following abortion or full-term parturition is difficult to explain. There is hardly any doubt that this lesion is the result of some disturbance in the endocritic system, but the nature of the derangement is unknown.

X-rays will destroy entirely the ovarian function; so also will destructive lesions of the ovaries, such as

new growths and infections. And, lastly, removal of the uterus may lead to ovarian atrophy, as was originally pointed out by Zweifel and Abel[1].

A few words are now necessary concerning the value of methods of treating ovarian insufficiency, based on the principles of what is known as organo-therapy.

This is a most difficult subject to dicuss in a few words, for every case must be treated on its own merits after careful investigations. Supplementary or antagonistic hormone-therapy, as the case may be, may be most useful, but it is necessary that full metabolic and other investigations, which cannot be detailed here, should be worked out if satisfactory results are to be obtained and disappointments avoided.

Ovarian transplantation which, as we have seen, can be satisfactorily accomplished in animals, is often useful in surgical practice. In my experience it is impossible to obtain permanent results, but much good may be done in the way of mitigating the violence of an artificial menopause, and of delaying it. Of recent years this procedure has been practised, but somewhat spasmodically; and apart from the reports of Professor Tuffier of Paris[2] no large number of cases has been recorded. This method of treatment is only applicable, of course, to patients on whom oöphorectomy has been performed before the menopause.

In the first place it is well to emphasize the fact that transplantation can only be required in extremely few cases: in all but those of malignant disease careful operative technique usually enables us to preserve some

[1] Zweifel, P., and Abel, K., quoted by Alban Doran, *Trans. Obstet. Soc.*, 1905, vol. lvii, p. 363.

[2] Tuffier, T., *Surg. Gyn. and Obstet.*, 1915, vol. xx, p. 30.

portion of one or other ovary; while in malignant disease it is quite clear it would be wrong to transplant any portion of an organ which may contain cancer cells, and, moreover, with malignant disease the woman is usually about or past the physiological menopause. It will be quite evident, then, how restricted is the field in which transplantation can or should be employed, especially when we add to the above statements the information that the ovarian grafts must be autogenous, for in the human subject heterogeneous grafts almost always perish (fig. 49).

When a transplantation is carried out I have found it best to use a wedge-shaped piece, not more than a quarter of an inch in thickness, from the centre of the ovary. Tuffier, however, buries in the abdominal wall a complete ovary after its removal. The disadvantages attending Tuffier's procedure are: first, such a large mass of ovarian tissue without raw surfaces cannot be properly vascularized; second, if it were to be partly vascularized pain and swelling might be caused by the ripening Graafian follicles, which would be unable to rupture owing to the encapsulation of the ovary; and third, the unruptured follicles would form cysts (see p. 46). These disadvantages are said to be frequently seen if the whole ovary be implanted.

If, however, a thin portion of ovary without the cortex be employed the uterus will often continue its normal activity in spite of the absence of Graafian follicles. As already described, I have found experimentally that an autogenous graft of interstitial cells alone from a rabbit's ovary (fig. 18, p. 47), which are easily isolated, is capable of maintaining the activity of the uterus.

Transplantation may be made anywhere, but the

FIG. 49.

Section of heterogeneous graft in the human uterus, showing
necrotic changes.

$\times$ 60.

more vascular the site the better. The best plan is partly to bury the wedge-shaped piece of ovary in the fundus of the uterus ; and if the surface of the graft be uncovered it is unnecessary to remove the cortex containing the Graafian follicles.

Excess of Ovarian Secretion.—The clinical effects produced by excessive ovarian secretion may be discussed under two headings :—

(1) Effects on the sexual functions, characteristics and psychology.

(2) Effects on the general metabolism.

It must not be forgotten, however, that the effects mentioned in the first group are primarily dependent on alterations in the general metabolism.

(1) An excessive ovarian secretion leads to an increase in sexual activity both locally and generally. The local effects may be seen in more profuse and protracted menstruation.

This condition occurs chiefly in girls about and just after puberty, in whom the correlations of the internal secretions in regard to the altered conditions have not been finally adjusted.

It may also be seen in girls who indulge in masturbation or are sexually insane, in unmarried women over 30 years of age, and in women whose married life is a failure from a sexual point of view. These patients are usually extremely feminine in appearance and character. I have alluded to this subject elsewhere[1], so I shall not further discuss it beyond calling attention to the fact that a corresponding condition may be seen in the lower animals ; for example, if a doe be

[1] Bell, W. Blair, *The Principles of Gynæcology*, 1910 ; *Practitioner's Encyclopædia*, 1912, p. 1005.

kept away from the buck during the breeding season she comes on heat every few days—a phenomenon seen in similar circumstances in most female animals.

Fortunately cases of ovarian excess are comparatively rare, but we meet with them from time to time, and may find considerable difficulty in dealing with them effectually.

The treatment of these cases consists of injections of antagonistic secretions, such as suprarenal and pituitary extracts. In this way the excess of ovarian secretion can usually be reduced, or at least the effects and symptoms associated therewith minimized. Should this simple method of treatment not be successful, and if the menorrhagia be serious and the psychical condition of the patient excessively irritable, then, if we can make a certain diagnosis—and this, of course, can only be done in some cases by knowing the circumstances of the patient—it is as justifiable to reduce the bulk of excessively secreting ovaries as it is to remove portions of the thyroid gland for the relief of hyperthyroidism. As a rule, the removal of one ovary is not enough, for the other may subsequently hypertrophy; at least one ovary and a wedge-shaped portion from the centre of the other should be removed.

(2) An excessive ovarian secretion affects the metabolism in a way opposite to that brought about by oöphorectomy; and one of the most important metabolic disturbances is the abnormally large excretion of lime salts.

In the non-pregnant woman this excessive excretion of calcium is a matter of no importance so far as her bony tissues are concerned, but probably it accounts for the nervous and muscular irritability, which are constant features of these cases. In pregnancy and lactation,
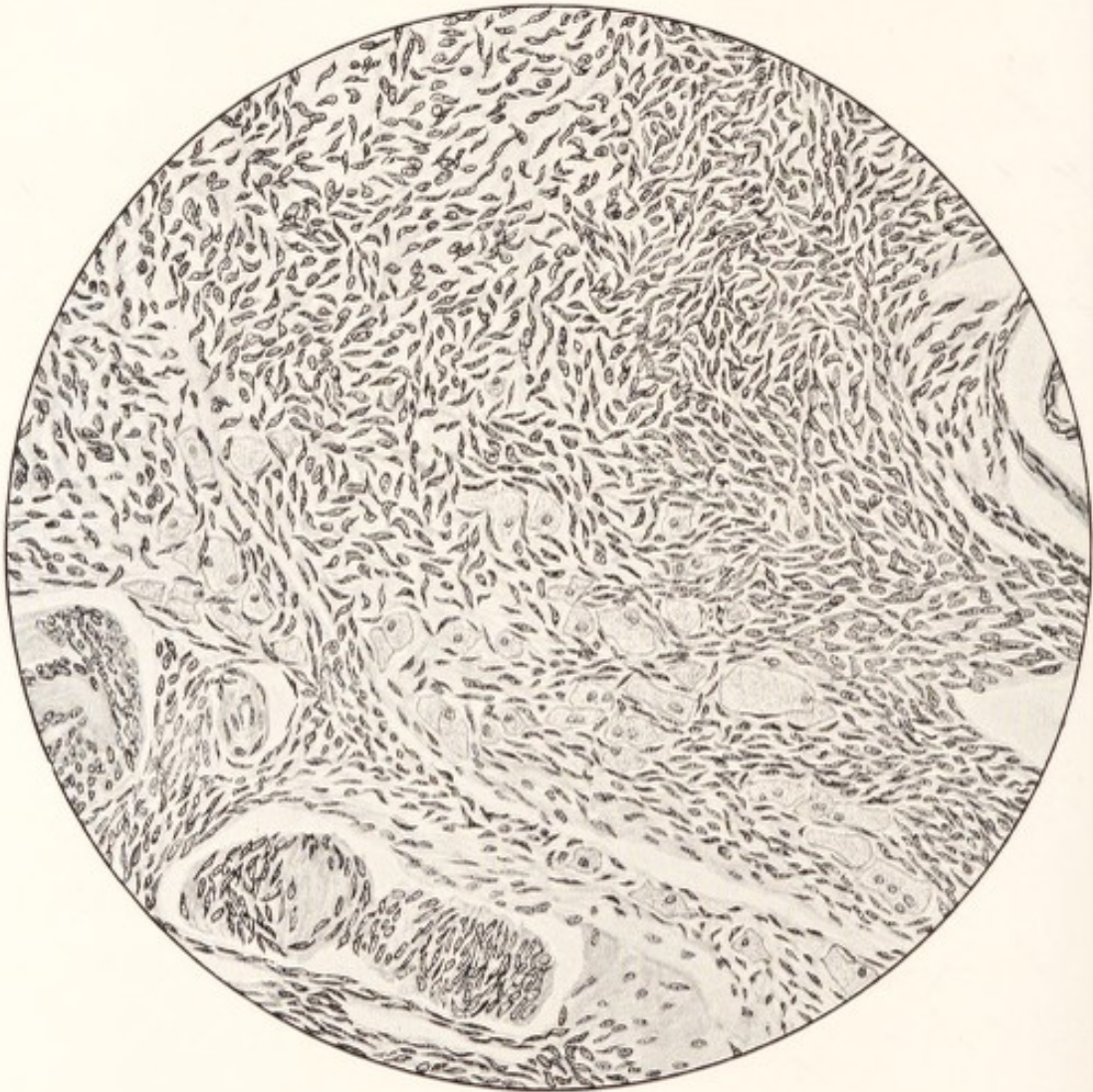
FIG. 50.

Section of the ovary from a case of osteomalacia, showing
hyperplasia of the interstitial cells.

$\times$ 250.

however, there is a large demand for calcium over and above the amount necessary for the normal maternal metabolism, and, as a result, softening of the bones may occur. This condition is known as osteomalacia.

Osteomalacia is not common in England, but is more frequently met with in other countries such as Italy, Austria and India. The disease used to be treated by removal of the ovaries, and many patients were cured. Figure 50 is of a section of an ovary, which was greatly enlarged, from a case of osteomalacia. It will be seen that the interstitial cells are very prominent, much more so than in normal ovaries during pregnancy.

Some years ago Bossi[1] of Genoa suggested the injection of suprarenal extract as an alternative to oöphorectomy; and apparently many cures have been effected by this treatment. I have also suggested treatment with injections of infundibular extract, and Miss Kate Knowles, of Srinagar, Kashmir, working in conjunction with me, has found that infundibulin is most beneficial in a number of cases of this disease. We hope to publish particulars at some future date.

It may, therefore, be argued that there is insufficiency in the suprarenals and pituitary as well as an excess of ovarian secretion; and this, indeed, is quite possible.

Further, Erdheim[2] has stated that with osteomalacia hyperplasia of the parathyroids is also found. If this be so, it would appear that the hyperplasia of the parathyroids represents an attempt on the part of these organs to counteract the effects of an excessive ovarian secretion, and thus lead to calcium retention.

Be this as it may, substitution of other extracts is a

[1] Bossi, L. M., *Centralbl. f. Gynäk.*, 1907, vol. xxxi, p. 69.
[2] Erdheim, J., *Sitz. der Akad. d. Wiss. Math. naturw. Klasse*, Wien, 1907.

great advance on removal of the ovaries in the treatment of osteomalacia ; and the success thus obtained indicates the line of attack that will probably be followed in the future in regard to all those diseases of the endocritic glands in which there is an excessive secretion ; that is to say, metabolically antagonistic extracts will take the place of removal of portions of the diseased organs.

Disturbances of the Thyroid Secretion

Absence or Insufficiency of Secretion.—Absence of thyroid secretion is, of course, extremely rare, and can only be seen in the congenital cretins. In these circumstances there is an absence of the onset of puberty, should the patient live to that period of life. A case of this character has already been described (p. 152). Although the genital organs were well developed it appears that they were unable to functionate in the absence of thyroid secretion.

With thyroid insufficiency there is always a decrease in or the complete cessation of the function of menstruation, according to the degree of insufficiency. We have already seen that complete atrophy is found to occur in the uteri of animals from which the thyroid has been removed, but that the ovaries do not undergo hypoplasia.

Apparently in the human subject atrophy of the uterus is never complete with pathological insufficiency of the thyroid—not even with myxœdema, for patients who have suffered with this disease for some years have been known not only to menstruate, but also to conceive after treatment with thyroid extract.

It is, however, chiefly the disturbances arising from minor degrees of thyroid insufficiency which come under

the notice of gynæcologists. Delayed puberty and menstruation have already been discussed. Secondary amenorrhœa and scanty menstruation, the latter also associated with dysmenorrhœa, are very frequently seen with thyroid insufficiency; and the patients are usually obese, lack energy, and have deficient sexuality. As a rule, the administration of thyroid extract entirely cures all these disabilities.

There is another menstrual disturbance of interest in this connexion, namely mastidynia, which sometimes occurs regularly each month before the onset of menstruation. Usually the menstrual cycle is protracted beyond 30 days in these cases. If, however, a ' period ' occur earlier than usual, the patient does not suffer with the pain in her breasts. The administration of thyroid extract relieves the patient by producing a shorter menstrual cycle. It appears not unlikely, therefore, that the protraction of the menstrual cycle with the accompanying mastidynia is due to a slight degree of insufficiency in the thyroid.

The thyroid secretion is associated with the integrity of the function of conception, just as it is with that of menstruation. It is well known that the thyroid gland enlarges in the early stages of pregnancy; and the enlargement is found to be due to the storage of colloid in the vesicles. This change is probably associated with the alterations in metabolism which occur in these circumstances.

A marked degree of insufficiency, such as is seen in myxœdema, almost invariably leads to sterility unless it be treated. Cases, however, have been recorded in which pregnancy has occurred in minor or variable states of this disease; and in such circumstances an improvement has usually been produced in the general condition

of the patient as the result of an increase in the thyroid activity.

There is one more point in regard to thyroid insufficiency—namely, its relation to the toxæmias of pregnancy, which requires some notice.

Some years ago Nicholson[1] promulgated the view, which has been taken up extensively by clinicians, that eclampsia is due to thyroid insufficiency in the later months of pregnancy. It will be remembered that in my experiments no evidence, either metabolic or symptomatic, was obtained in support of this view; indeed, as indicated, it appeared that the animals from which the thyroid was removed in the later stages of pregnancy were considerably less affected than those which were not pregnant. An explanation of this has already been suggested (p. 51).

Excess of Thyroid Secretion.—It is a common experience to meet with an excess of thyroid secretion in connexion with pelvic lesions, and we must be careful to distinguish between those cases which are the result of genital affections and those which are the cause of them.

In a recent analysis of 93 cases of exophthalmic goitre it was found that 92·5 per cent. of the cases occurred in women, and that in 9 per cent. of these the origin of the disease could definitely be traced to disturbances in the genital organs[2].

It is certain that after the menopause the thyroid normally undergoes some retrogression, after, perhaps, a period of minor hyperthyroidism; and it is probable that removal of the ovaries leads, eventually at all events,

[1] Nicholson, H. O., *Scot. Med. Surg. Journ., Edin.*, 1901, vol. viii, p. 503.

[2] Gurney, Helen M., *Brit. Med. Journ.*, 1915, vol. i, p. 924.

to the same condition in the majority of cases. But, as previously mentioned, in some cases acute exophthalmic goitre may intervene.

Experimentally, we have seen that a considerable increase in the colloid formation follows oöphorectomy, but it is certain that this is a condition entirely different from Graves' disease. At the same time, we know far too little about exophthalmic goitre—especially in its relation to simple goitre, and to myxœdema with which it not infrequently alternates—to speak definitely on this question.

Excessive thyroid secretion may affect the genital functions in two ways : first, it may stimulate them to unusual activity ; or, second, the general metabolism may be so upset that the genital functions cease. There is no doubt that there is a condition of hyperthyroidism which produces excessive menstruation, and which is totally unassociated with any of the symptoms of exophthalmic goitre. This condition is usually seen in girls about puberty, usually just before and during menstruation. It may be that the excessive activity is due to the incomplete functional development of the ovaries ; but, whatever the cause, there is not infrequently menorrhagia. I have, however, seen this same enlargement of the thyroid with amenorrhœa. This paradoxical phenomenon is to be explained on the supposition of ovarian insufficiency in these circumstances, and of an inability of the thyroid in some cases, in spite of its enlargement, to meet the deficiency[1]. When there is menorrhagia I have found that it can always be controlled with calcium lactate.

[1] See also article by the Author on 'The Disorders of Function' in *The New System of Gynæcology*, edited by T. W. Eden and C. Lockyer.

It is usually stated that with true exophthalmic goitre amenorrhœa coexists. I have not been able to satisfy myself that this is so until the metabolism has been seriously disordered, and the increased quantity of calcium which is being excreted by way of the urine and fæces—a constant phenomenon in Graves' disease—is so large that there is no excess for the ovaries to excrete in the menstrual fluid. Usually in the early stages of the disease there is menorrhagia. Should a large body of evidence eventually disprove this view it will be a positive argument of great value that in Graves' disease the secretion is perverted even if there be also an excess of the normal. But in this matter, also, we must remain in comparative ignorance until our knowledge of the pathology of exophthalmic goitre is more definite.

Helen Gurney[1] found amenorrhœa in 15 per cent. of the cases analysed, but she makes no statement as to the stage of the disease in her cases. Further, she says that " in some cases it (amenorrhœa) appeared before the disease and improved when the goitre developed ". The same writer adds, " The effect of menstruation on exophthalmic goitre is not constant ; sometimes the goitre diminishes in size, and sometimes it is increased during the period ".

The relation of excessive thyroid secretion to pregnancy is very interesting, but very little has been written on this aspect of the subject. In 1911 Clifford White[2] briefly reviewed the literature, and found it as contradictory as the literature usually is on subjects connected with the internal secretions. I think there can be no doubt that excess of thyroid secretion, except that

[1] Gurney, Helen M., *Brit. Med. Journ.*, 1915, vol. i, p. 924.
[2] White, Clifford, *Journ. Obstet. and Gyn. Brit. Emp.*, 1911, vol. xx, p. 126.

seen in connexion with an advanced stage of Graves' disease, does not interfere with fertility. It would be strange if it did, for we know that there is an increase in thyroid activity during the early months of pregnancy, and possibly throughout ; but it is no less a fact that women with marked exophthalmic goitre rarely become pregnant, and if they do the disease is aggravated. In the case of one patient who had suffered with exophthalmic goitre for some years and had given birth to several children, there had always been hæmorrhage after delivery—an occurrence which has not infrequently been noted in these cases. One of my colleagues removed one half of the thyroid gland, with the result that there was marked amelioration in her symptoms. Shortly afterwards, however, she became pregnant again, and this caused her symptoms to become considerably worse than they had been since her operation, so I suggested that she should take large doses of calcium lactate, and should rest as much as possible. Subsequently she went comfortably to full term, and there was no post-partum hæmorrhage. The patient was advised not to nurse the child, which was normal, owing to the drain on her lime salts lactation would entail. There was very considerable improvement after parturition and the patient is now in good health.

It is most important that these women should be given large doses of calcium salts if they become pregnant, for there is an excessive excretion of lime salts in this disease, and consequently much danger of hæmorrhage *post partum*, and even *ante partum*. If no improvement follow this treatment infundibulin should be administered.

It may be mentioned here that some time ago I suggested injections of pituitary extract in the treatment of

hyperthyroidism. Suprarenal and pituitary extracts counterbalance the action of the ovaries and thyroid and lead to calcium retention ; this, as we have already seen, is a normal function of the suprarenals and pituitary. It is probable that both portions of each of these organs are concerned in the result. Infundibulin should, therefore, be given immediately after labour to all patients with exophthalmic goitre, in order that by its direct action on the musculature of the uterus bleeding may be prevented.

Whether pregnancy can cause exophthalmic goitre has recently been debated. Equally eminent clinical obstetricians have made diametrically opposed statements. Personally, I do not feel competent to express an opinion as to whether pregnancy can cause exophthalmic goitre, but I have certainly seen this disease *arise during pregnancy* on several occasions. In one case, contrary to expectation, the condition did not improve after parturition. Marked improvement, however, was effected by treatment with pituitary extract ; and when the patient was last seen she had no evidence of the disease beyond a somewhat rapid pulse and excitable temperament. In another woman the exophthalmic goitre commenced immediately subsequently to parturition and lactation, the latter being only possible for a few weeks. I saw her eleven months after her confinement, when there was amenorrhœa with superinvolution of the uterus. This patient, who was treated with pituitary extract, has completely recovered, and is now menstruating regularly from a uterus measuring $2\frac{1}{4}$ inches. After the disappearance of all symptoms the pituitary extract was discontinued ; but a fortnight later the patient returned and asked to be put back on it, as the palpitation of the heart was causing her much

discomfort. She immediately responded to treatment, and is now practically well again, except for a somewhat rapid pulse. Rapidity of the pulse should always be taken as a guide to the condition of the patient when one is considering the advisability of discontinuing treatment in these cases.

Disturbances of the Pituitary Secretion

In any attempt to understand the influence pituitary lesions exercise over the normal genital functions we are forced to recognize the unity of the pituitary body. By this statement I do not mean to create a paradox, for it has already been demonstrated that extracts of the two main portions of the pituitary do not produce the same physiological effects, and that removal of the two lobes separately in different individuals in the same species of mammal may lead to different results. At the same time these results in themselves are somewhat paradoxical, for the extract of the posterior lobe is active—and extremely so—while that of the anterior lobe is, so far as we know, inactive from an experimental point of view; whereas removal of the anterior lobe or a large portion of it may be fatal, but removal of the posterior lobe produces no symptoms (p. 62).

This unexpected diversity in regard to experimental results has led to much confusion when attempts have been made to correlate experimental data with clinical observations. Indeed, so conflicting apparently were these two methods of investigation in the results they gave, that Cushing[1] felt it necessary to discard experimental findings in favour of clinical evidence. But surely this is neither scientific nor helpful, especially

[1] Cushing, H., *The Pituitary Body and Its Disorders*, 1912.

when there is one simple and obvious way out of all these difficulties : namely, the acceptance of the view I have put forward[1] concerning the unity of the whole organ. There is certainly as much, if not more, evidence in favour of this opinion in connexion with the pituitary as there is concerning the same views in regard to the thyroid and parathyroids, and the medulla and cortex of the suprarenals. I shall not enter into a long discussion of this question here, as I have considered it more fully elsewhere[2].

Pituitary Insufficiency.—With this condition there is always scanty menstruation or amenorrhœa.

Since the development and normal functions of the genitalia are dependent on the full development of the pituitary body, it is only consistent that pathological lesions causing insufficiency and withdrawal of its secretion should lead to hypoplasia in the reproductive organs with the cessation of their functions.

Now the only specific lesions in the pituitary of which we have any clinical knowledge occur in connexion with the anterior lobe ; and insufficiency may result from : (1) Destructive lesions, such as cysts; (2) Hypoplasia, primary, or secondary to hyperplasia ; (3) Pressure from tumours in the neighbourhood, or distension of the third ventricle.

All these conditions may affect the posterior lobe indirectly—that is to say, by causing pressure on it. If the pressure be not too great, and merely irritative, glycosuria is produced, but it is doubtful if other symptoms can be caused by lesions of the posterior lobe :

[1] Bell, W. Blair, Arris and Gale Lectures, *Lancet*, 1913, vol. i, pp. 809 and 937.

[2] Bell, W. Blair, *The Pituitary Body.* (*In the press.*)

genital disturbances result from lesions in the anterior lobe. This conforms with Cushing's and my own experimental results, but not with Cushing's clinical observations. I think, however, that the confusion in the views of this authority has arisen—if I understand him correctly—from the fact that amenorrhœa is seen with hyperplasia as well as with hypoplasia in the anterior lobe. The explanation of this apparent paradox has already been given : hyperplasia in women causes masculinity, and therefore indirectly genital hypoplasia with amenorrhœa, while hypoplasia in the anterior lobe directly causes hypoplasia of the genitalia. With both of these pathological conditions sterility co-exists.

Sometimes there may be difficulty in distinguishing at first sight between thyroid insufficiency and pituitary insufficiency. In both cases there is obesity ; but the site of the lesion may usually be discovered by noting the state of the skin : with thyroid insufficiency it is rough and coarse, and with pituitary insufficiency it is smooth and fine.

I have found that in minor degrees of pituitary insufficiency an extract of the anterior lobe or of the whole gland occasionally produces good results. In the case of a man, who suffered from an extreme degree of *dystrophia adiposo-genitalis* with impotency, and of whose history I have an intimate knowledge, not only did sexual potency return, but his wife subsequently gave birth to a child. I have not come across any case either in the literature or in my own experience in which a woman suffering from a major degree of pituitary insufficiency has become pregnant.

We have already seen that infundibular extract appears to act as well as suprarenal medullary extract in

the treatment of osteomalacia ; it is possible, therefore, that there is a minor degree of insufficiency of this part of the pituitary in this disease, but it is more likely that a good result is obtained because this extract is antagonistic to the ovarian secretion in regard to the calcium metabolism.

Excess of pituitary secretion.—As a rule hyperplasia of the pituitary commences at puberty ; but there is no reliable evidence that hypoplasia in the gonads induces the condition. Nevertheless, it has been stated by Kalledey[1] and others that intravenous injections of ovarian extract will cure acromegaly. It must be remembered, however, that this disease shows remarkable remissions, even with the return of menstruation for many months. In Kalledey's case the patient became pregnant, but parturition had not taken place at the time his paper was written.

In connexion with acromegaly it is interesting to note that there is considerable calcium retention in the bones and tissues of the patient—a masculinity-producing phenomenon which would be incompatible with menstruation and pregnancy, as already explained.

For the same reason an increase in sexual excitability is never seen in women at the onset of acromegaly—a phenomenon described by Cushing[2] and others as sometimes occurring in men in these circumstances.

It is, of course, well known that an increase in the activity of the pituitary—particularly in the pars anterior—is to be found normally in pregnancy. Sometimes acromegalic symptoms, such as enlargement of the lips, tongue, lower jaw, hands and feet, have been

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[1] Kalledey, L., *Zentralbl. f. Gynäk.*, 1913, vol. xxxvii, p. 1030.
[2] Cushing, H., *The Pituitary Body and Its Disorders*, 1912.

observed ; indeed, the swelling of the fingers and face commonly seen during gestation has been attributed to the increased activity in the pituitary. After parturition these enlargements usually disappear. Marek[1] has recorded a case in which there was marked glycosuria with the typical symptoms of acromegaly, all of which disappeared during the puerperium. It is probable, then, that the pituitary may play some part in the disorders of pregnancy, but no facts have been discovered which can be considered definitely pathognomonic.

Another interesting question is whether the absence of milk secretion after parturition may be attributed to hypoplasia or insufficiency of the pituitary, for probably in normal circumstances the hyperplasia seen in pregnancy is maintained during lactation to influence the calcium metabolism, if not to stimulate directly the secretory cells of the mammary glands.

Disturbances of the Suprarenal Secretion

Suprarenal insufficiency.—This condition has received recognition in Addison's syndrome, in which there is an extensive derangement in the metabolism with general asthenia. Amenorrhœa with sterility is always found in this disease if it be at all advanced. From experimental evidence it is probable that the uterus undergoes some degree of atrophy.

It has been suggested by Silvestri[2] that excessive vomiting of pregnancy may be due to suprarenal insufficiency, and this writer claims to have treated hyperemesis successfully by the administration of

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[1] Marek, R., *Zentralbl. f. Gynäk.*, 1911, vol. xxxv, p. 1612.
[2] Silvestri, T., *Sem. Med.*, 1909, vol. xxix, p. 535.

suprarenin. If this be so, the therapeutical effect is probably somewhat complicated : the suprarenals, being damaged by the toxæmia of pregnancy, allow an excessive excretion of lime salts, and the loss of calcium may induce a condition of acid intoxication with associated vomiting.

Again, it will be remembered that Bossi[1] has shown that osteomalacia may be relieved by injections of suprarenin, and that this authority concluded that in this disease there is suprarenal insufficiency. Whether this be so is very doubtful, for both injections of infundibulin and the operation of oöphorectomy will also produce good results. Suprarenin, like infundibulin, causes the retention of lime salts in the tissues, and thus prevents the depletion of calcium salts from the bones ; and in this way it may be said that suprarenin and infundibulin are indirectly antagonistic to the excessive ovarian secretion which is believed to exist in osteomalacia.

Excess of suprarenal secretion.—I have already discussed the effect of suprarenal cortical hyperplasia in connexion with alterations of sex characteristics (p. 160). In well-marked cases there is always amenorrhœa with hypoplasia of the genital and mammary glands.

Disturbances of the Thymus Secretion

Insufficiency of Thymus Secretion.—This, so far as we know, is natural after puberty, when the genitalia are fully developed.

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[1] Bossi, L. M., *Zentralbl. f. Gynäk.*, 1907, vol. xxxi, p. 69.

Nothing is definitely known concerning premature involution of the thymus; but if it be that there is a close relationship between the onset of puberty—that is, ovarian activity—and involution of the thymus, there may be some connexion between retrogression in this organ and premature and precocious puberty. It is believed that the thymus secretion is concerned in promoting calcium retention in the tissues, and so in building up the growing skeleton : early involution would, therefore, be associated with stunting in regard to the growth of the girl, and this, in fact, is usually seen with precocious, or even early, puberty.

Excess of Thymus Secretion.—Enlargement of the thymus, presumably with excess of secretion, is found in the condition known as ' *status lymphaticus* ', in which the thymus does not undergo the normal involution but remains large and active. Persons with this disease are usually tall, and often are somewhat undeveloped mentally. It has usually been supposed that in these circumstances the gonads remain infantile, but this view, although probably true in many cases, is not universally so. I have had an opportunity of examining the ovaries of a woman who had died suddenly as the result of the *status lymphaticus*. This patient had borne children, and her genital organs were normal. This disease, therefore, needs further pathological investigation before definite statements can be made concerning the associated condition of the genitalia.

When more evidence has been collected in regard to the *status lymphaticus* we shall be in a position better to understand the relationship between the thymus and gonads.

Disturbances of the Parathyroid Secretion

As we have seen, the rôle of the parathyroids is probably directly connected with the calcium metabolism (p. 56), and possibly with the functions of the thyroid[1]. We have also some evidence of a relationship with the anterior lobe of the pituitary, but at present nothing definite is known of the connexion of these cervical organs with the rest of the endocritic system.

It is hardly necessary to repeat that all that concerns the calcium metabolism closely concerns the reproductive functions, as I first pointed out ten years ago ; consequently the parathyroids may be involved in many disorders of menstruation, pregnancy and lactation, although as yet we have little direct evidence that this is so.

Erdheim[2] has stated that in osteomalacia he has found hyperplasia of the parathyroids. If this exceed that seen normally in pregnancy, it is probable that this change indicates an attempt on the part of these organs to prevent the excessive excretion of the lime salts which occurs in osteomalacia, for it has been shown[3] that after removal of the parathyroids there is a deficiency of calcium salts in the tissues. And this action represents one phase of what we call ' antagonism ' between internal secretions : it is probable that although such antagonism may be direct or inhibitory, more often it is related to the results produced by the opposing

[1] Vincent, S., and Jolly, W. A., *Journ. Physiol.*, 1904–5, vol. xxxii, p. 65.

[2] Erdheim, J., *Sitz. der Akad. d. Wiss. Math. naturw. Klasse*, Wien, 1907.

[3] MacCallum, W. G., and Voetglin, C., *Bull. Johns Hopk. Hosp.* 1908, vol. xix, p. 91.

secretions in the general metabolism, as here shown; that is to say, an excessive ovarian secretion, such as may occur in osteomalacia, causes too great an excretion of lime salts, and if the parathyroids undergo hyperplasia in this disease it may be in order to bring about the opposite state of affairs in regard to the calcium metabolism.

Vassale[1] believes that insufficiency in the parathyroids is to be found in eclampsia—a toxæmia which he thinks may be successfully treated by an extract of these organs. It seems likely that this method of treatment acts indirectly—that is, calcium retention is promoted and excessive acidosis, so constant in this disease, is prevented[2].

It is possible, also, that the parathyroids influence the metabolism of the lime salts during lactation.

Disturbances of the Pineal Secretion

Beyond what has already been said of the influence of the pineal on sexual precocity and on the sex characteristics, very little is known of the relationship, if there be any, of the pineal to the genital functions.

Ott and Scott[3] state that injections of pineal extract have a galactogogue effect; but this was not confirmed by Schäfer and Mackenzie[4]. It is probable that since partial involution occurs at puberty the pineal exerts

[1] Vassale, G., *Arch. Ital. de Biol.*, 1905, vol. xliii, p. 177.

[2] For a discussion of the rôle of the alkaline bases in this connexion the reader is referred to an excellent review of 'Acidosis' by E. I. Spriggs, *Quart. Journ. Med.*, 1908–9, vol. ii, p. 325.

[3] Ott, I., and Scott, J. C., *Proc. Soc. Exper. Biol. and Med.*, 1910–11, vol. viii, p. 48.

[4] Schäfer, E. A., and Mackenzie, K., *Proc. Roy. Soc.*, B., 1911, vol. lxxxiv, p. 22.

but little influence in normal circumstances on the genital functions.

Kidd[1], in a comprehensive review of the literature concerning the pineal body, gives no case in which a lesion of this organ has been recorded in an adult woman ; indeed, practically all the known cases have occurred in male children.

The Mammæ and the Genital Functions

But little remains to be said in regard to the mammæ. Their influence on the genital functions is purely indirect ; but in this sense amenorrhœa and sterility may be temporarily produced during lactation.

Parke[2] has recorded a case in which a patient from whom both breasts had been removed subsequently became pregnant and 'carried' to full term. During parturition there was an entire absence of labour ' pains '. In the discussion that followed this paper it was stated by other gynæcologists that they had attended patients from whom both breasts had been removed, but they had not observed any alteration from the normal course of events.

Absence of breasts and absence of secretory activity.—Removal of the breasts has been practised for eclampsia[3], and the results were thought to be good. No explanation of this effect has been given, but it is possible that in these circumstances the calcium which would have been taken up by the secretory cells is retained in the maternal tissues. Amputation of both

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[1] Kidd, L. J., *Rev. Neurol. and Psychiat.*, 1913, vol. xi, p. 1.

[2] Parke, W. E., *Amer. Journ. Obstet.*, 1914, vol. lxx, p. 606.

[3] Cavagnis, G., *Ann. di Obstet. and Gyn.*, 1913, vol. ii, p. 563.

breasts, however, seems an unusually drastic method of securing this result.

Absence of secretory activity after parturition has been mentioned already (p. 92). In saying " absence of secretory activity " I refer to the effect of some unknown derangement in the maternal metabolism responsible for this abnormal state of affairs.

It is probable that the high calcium content which is found in the blood during normal lactation favours involution of the uterus, and that the absence of milk secretion not only interferes with normal involution, but is also associated with disturbances in the maternal metabolism.

Superlactation.—When the mother nurses, menstruation is absent normally, at any rate for many months. In these circumstances she is able to stand well the strain of lactation ; but if she nurse beyond the normal time—say, nine months—then her health is liable to give way : she may suffer with headaches, lassitude, and with menorrhagia and epimenorrhœa, or epimenorrhagia[1].

Now, these symptoms are all produced by the withdrawal of calcium salts from the tissues for the purpose of milk formation ; and the patient can be quickly cured if the child be weaned, and she herself take large doses of calcium lactate.

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[1] 'Epimenorrhœa', 'epimenorrhagia' : terms coined by the author to indicate too frequent, and too profuse menstruation. (See ' The Disorders of Function ', in *The New System of Gynæcology*, edited by T. W. Eden and C. Lockyer.)

SEXUAL AND REPRODUCTIVE PSYCHOSES AND NEUROSES

PSYCHOSES

I have emphasized repeatedly in the foregoing pages and elsewhere[1], that the mind is influenced by the metabolism, and therefore by the condition of the organs of internal secretion ; and I have already described what I believe to be the normal attitude of mind in Woman. These views—no doubt old enough so far as the general principle is concerned—are now being endorsed by alienists who are becoming alive to the fact that insanity may actually depend on the state of the internal secretions—a fact that has always been staring them in the face, but which hitherto they have failed securely to grasp.

Mott[2] has recently expressed his belief in the important part played by the internal secretions in insanity ; but the arguments set forth by him do not break any new ground. This writer states that " It must have struck everybody that has to do with insanity that there are two periods of life when its onset specially

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[1] Bell, W. Blair, Arris and Gale Lectures, *Lancet*, vol. i, pp. 809, 937; *Proc. Roy. Soc. Med. (Obstet. and Gyn. Sect.)*, 1913, vol. vii, p. 47.

[2] Mott, F. W., *Proc. Roy. Soc. Med. (Sect. Psychiat.)*, 1915, vol. viii, p. 1.

occurs—namely, early adolescence and the involutional period ". This has long been recognized, and a somewhat similar statement was made many years ago by Wynn Westcott[1]. This authority—a well-known coroner—said that out of over 200 inquests on female suicides " the majority of these women had killed themselves about the change of life, and of the younger women the majority appeared to have been menstruating at the time of suicide ".

We must now consider the nature of the stimuli concerned, and the abnormal effects they may produce.

In normal circumstances puberty supervenes in about the fourteenth year, but, as already described, with certain disturbances of the endocritic system puberty may be precocious. Now, in precocious puberty we have a phenomenon which gives us a clear indication of the effects of abnormal sex development, and of the causes which later in life may produce excessive sexuality; for in girls precocity is induced by ovarian hyperplasia or neoplasia. This is important, for it proves conclusively that when excessive sexuality, amounting perhaps to sexual insanity, exists in women we must look for an excessive ovarian secretion as the primary cause of the condition; and contrariwise we find that a deficient ovarian secretion may lead to melancholia, probably indirectly.

A brief description of the sexual and reproductive psychoses dependent on derangements of the internal secretions, which may be met with in women, must now be given; I shall not attempt, however, to classify these alienations on a psychological basis, but, rather, from a physical point of view.

In describing the *psychoses sexuales*, as they may be

[1] Westcott, Wynn W., *Brit. Med. Journ.*, 1900, vol. ii, p. 792.

called, we might classify our subject according to the period of reproductive life during which such disturbances may arise ; but such a classification would lead to much repetition. It will be better, therefore, briefly to consider the mental disturbances with regard to the actual cause to which they are due—that is to say, to excessive ovarian secretion, to deficient ovarian secretion, and to the metabolic disturbances associated with menstruation, gestation and lactation respectively.

I shall make no attempt to describe in detail the performances and mentalizations associated with the psychical disorders under discussion ; I shall merely give an indication of the mental tendency. Meanwhile it must not be forgotten that specific mental diseases may themselves affect the genital functions—an aspect of the subject, about which we know practically nothing, except in a general way.

In the consideration of all questions concerning psychical derangements it must be remembered that a neuropathic history is an important factor both in regard to the onset of the derangement, to the gravity of the mental disturbance, and to the prognosis.

Excessive Ovarian Secretion.—When this occurs early in life puberty may supervene precociously ; and in these circumstances with the development of the adult physical phenomena a mental change occurs which often produces a sexuality greatly in excess of the normal.

This mental disturbance is abnormal for two reasons : first, the stimulus from the ovaries to the brain is far stronger than that normally occurring at puberty ; and second, the mind of the child is taken by surprise, as it were, and before it has been educated slowly to self-restraint and decent conduct.

Such children may be sexually insane, and indulge in masturbation and any other form of gratification which presents itself to them.

Apart from precocious puberty there may be an excessive ovarian secretion not only at normal puberty, but also throughout the sexual life of the individual. We know how much more coquettish some girls are than others ; we know, also, how much more lax in their morals many women are than others, and how some women cannot obtain sufficient satisfaction from one man. It may be said that excessive sexuality always commences at puberty, whether the condition amounts to actual insanity or merely to excessive stimulation of the sexual instincts, which are normally kept within decent bounds. Indeed, we may say that the border line between sexual insanity and excessive sexual desire is merely a question of whether there be *shamelessness* in sexual conduct or not. Let me illustrate this statement by two examples which have come under my own notice.

In the first, a young lady at puberty developed habits of masturbation ; shortly afterwards she began to entice men to gratify her desires ; she kept a diary in which her thoughts and feelings were described ; and the climax came when she took to dropping notes in the road asking men to meet her—evidently in order that she might induce them to satisfy her cravings. She had no self-respect, no sense of decency or shame—the world was blotted out of her consciousness when the overwhelming stimulus of her ovarian secretion flooded her mind ; and she had no remorse, but, rather, took a pride and pleasure in the methods adopted to consummate her desires.

In the other case, a married lady, a little over thirty

years of age, who had several beautiful children, told me that she was never able to resist the advances of men she liked, and that she had indulged in immoral relations with three different men in one year. This patient recognized the error of her ways, and was full of remorse after each adventure; nevertheless, the sexual stimuli were so great that until they were exhausted her sense of right and wrong was completely obliterated.

It is certain that in the first case the patient, judged by any standard, was insane; while in the second the woman was merely intemperate from a social and moral standpoint. In both cases the stimuli consisted of the internal secretions of the ovaries; but in the former there was constant mental instability as well, while in the latter there was temporary mental aberration in the face of a stimulus temporarily stronger than those directing her will.

Excessive ovarian secretion in women may lead to masturbation or to habits associated with inversion. It is probable that if with the onset of puberty marriage took place in European countries, as it does in some Eastern countries, such indulgences would not be practised by educated women. Once, however, these habits have become established, even matrimony may fail to provide a satisfactory substitute, although, fortunately perhaps, it may sometimes do so.

Deficient ovarian secretion.—This, as we have seen, is most commonly secondary to disturbances in the distant endocritic organs, except when produced by the natural or artificial menopause; and, unless in the last-named circumstances, no positive mental disturbances are associated with a deficient ovarian secretion. Negative mental anomalies, such as aversion from sexual

intercourse and child-bearing are, however, not un-commonly seen—the stimulus from the ovaries, which normally induces reproductive instincts, is absent.

At the menopause, however, the mind may be affected not only by the diminishing or absent ovarian secretion, but also by the changes which then occur in the other organs of internal secretion, notably in the thyroid. Mott[1], indeed, emphasizes the importance of hypo-thyroidism in relation to insanity. This same author lays stress on the fact that the ovaries are often found to be atrophic in cases of insanity, but, while this is undoubtedly true in some cases, it is unfortunate that this author selects for his example the case of a woman, who at the advanced age of 67 years was found *post mortem* to have an " infantile uterus " and atrophic ovaries. One would expect to find the ovaries atrophic and the uterus *senile* (not infantile) at this time of life, apart from gonorrhœal infections or hypothyroidism, which, also, were said to have existed. The sexual and reproductive history of this case, although of considerable importance, was not given. As a set-off to these observa-tions, Mott points out that in cases of chronic ill-health with normal mentality atrophy of the ovaries has been found in young adults. No illustrations are given, so we can form no opinion concerning the ovarian atrophy which is said to occur.

Apart from the actual menopause—artificial or natural—the evidence that atrophy of the ovaries causes insanity is not very satisfactory. I have seen many cases in which there has been no mental dis-turbance at all in these circumstances ; and, as a matter of fact, in the cases referred to by Mott it is possible

[1] Mott, F. W., *Proc. Roy. Soc. Med. (Sect. Psychiat.)*, 1915, vol. viii, p. 1.

that ovarian insufficiency had always existed ; at least, we are given no evidence to the contrary. I think that when ovarian insufficiency gives rise to mental disturbances there has previously been normal activity in these organs.

At the menopause there is a more or less severe disturbance of the metabolism dependent chiefly on the degree of activity that previously existed in the ovaries. Many sexually apathetic women—that is, women with not very active ovaries—pass through the menopausal period with very little disturbance ; while women who have been sexually active often have the ' change of life ' late, and suffer from violent derangements of the metabolism. These sexually active women may at this period of life be subject to increased and almost insatiable sexual desire—probably due to the irregular output of the ovarian stimuli.

With an artificial or sudden natural menopause the patient, if she were previously sexually active, may suffer with melancholia : the rapid removal of the ovarian secretion, which previously moulded her temperament, and directed her pursuits and pleasures, involves the loss of the guiding force of her existence; consequently depression, if not melancholia, may supervene.

I have for many years treated these cases with thyroid extract alone or in combination with ovarian extract, and have found it most beneficial ; ovarian extract alone is useless. This indicates, apparently, that when the ovarian secretions are withdrawn the thyroid also atrophies, and the loss of thyroiodin leads to mental lethargy and physical adiposity.

There is one other aspect of diminished ovarian secretion in relation to the mentality of the individual

which requires brief mention here in order to complete the picture—I refer to the ovarian insufficiency seen in association with masculinity or reduced femininity in women.

When any of the masculinity-producing internal secretions become abnormally active in women the ovarian secretions are antagonized or inhibited, partially or completely, and the metabolism is directed towards the necessities of masculinity. In such circumstances, with the development of the physical changes towards masculinity, the mind becomes less feminine in its outlook. Cases of so-called 'true hermaphroditism' are, as we have seen, rare ; but there is little doubt that women with a larger share of masculinity than is normal are extremely common. These unnatural individuals are easily detected by the coarseness of their skins, by the size of their extremities, by the ill-development of the breasts and by the assertiveness and aggressiveness of their conversation and schemes. No doubt many of them have hyperplasia of the suprarenal cortices or of the pituitary ; and atrophy of the ovaries when it exists, is secondary to the primary changes in the other organs of internal secretion which are responsible for the development of masculinity.

Metabolic disturbances associated with menstruation.—During menstruation the metabolic disturbances may be so extensive that they affect the mind of the patient. Exactly what the anomaly is we do not always know, but it is probable that mental disturbances of an active or hysterical nature are due in part to an excessive excretion of calcium salts. And there may sometimes be a recognizable disturbance of the internal secretory system, especially in connexion with thyroid. In these

circumstances there may be mental depression or even melancholia, which are almost invariably relieved by the administration of thyroid extract—an indication that there is temporary thyroid insufficiency.

Moreover, different grades of psychical aberration are seen : there may be, on the one hand, only a slight alteration in temperament, or, on the other, a serious mental irresponsibility which may lead to self-destruction[1] or kleptomania[2].

Metabolic disturbances associated with gestation, the puerperium and lactation.—During pregnancy the mental attitude rarely undergoes profound alterations, but in nearly all cases it is normally affected to some slight extent. How far this is due to fœtal hormones, and how far to changes in the metabolism it is somewhat difficult to estimate. Apparently, the normal mental change is towards quietness and resignation, and if this be exceeded melancholia may supervene. Extract of the thyroid gland is most beneficial in these circumstances, hence it may be presumed that normally this organ is taxed to the fullest extent, and that sometimes it may partly fail in the supply of its internal secretion. In those very rare cases in which the patient is hysterical and excitable it appears probable that the cause emanates from the fœtus, and is of the nature of a toxæmia.

During the puerperium insanity may supervene, and the patient then usually suffers with delusions. It is probable that in most of these cases—as, indeed,

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[1] Westcott, Wynn W., *Brit. Med. Journ.*, 1900, vol. ii, p. 792.

[2] Bell, W. Blair, ' Disorders of Function ', C. Allbutt's and W. Playfair's *System of Gynæcology*, 3rd ed., edited by T. W. Eden and C. Lockyer.

in all forms of insanity—there is a bad neuropathic family history ; and, further, that the insanity is produced by exhaustion or sepsis (toxæmia) subsequently to labour, which probably involves the organs of internal secretion.

The insanity seen at a later period during lactation is no doubt excited by the drain on the maternal resources brought about indirectly by lactation, rather than by the direct influence of the endocritic organs.

The influence of psychoses on the genital functions.—Psychoses may arise quite independently of the genital functions, and, nevertheless, be associated with anomalies of those functions. Thus it is quite common to see amenorrhœa in association with insanities —indeed, some alienists describe an ' amenorrhœal insanity '[1], but most authorities look upon the amenorrhœa as a concomitant phenomenon and not as the cause of the mental derangement. Mott's view[2] that atrophy of the ovary is common in these cases is somewhat disproved by the fact that recovery frequently takes place in regard both to the mental and menstrual disorders.

Religious manias may lead to ideas which fill the patient with abhorrence of sexual intercourse, and in this way directly interfere with the genital functions. There is, indeed, no doubt whatsoever that the mind influences function just as function influences the mind ; for example, it has been shown that fright leads to an immediate increase in the output of suprarenin[3], and

[1] Ewart, C. T., and others, *Proc. Roy. Soc. Med.* (*Obstet. and Gyn. Sect.*), 1911, vol. v, p. 81.

[2] Mott, F. W., *Proc. Roy. Soc. Med.* (*Sect. Psychiat.*), 1915, vol. viii, p. 1.

[3] Cannon, W. B., and de la Paz, D., *Amer. Journ. Physiol.*, 1911, vol. xxviii, p. 64 ; *Journ. Amer. Med. Assoc.*, 1911, vol. lvi, p. 742.

we know well from constant clinical observations that hypothyroidism leads to mental depression.

The whole question of the influence of the mind on the reproductive functions is in its details intricate and difficult, and it would be out of place in this small work to invade the realms of psychiatry.

NEUROSES

It is, also, unnecessary here to discuss the question of neuroses in connexion with the genital functions. They are not uncommon, and I have discussed them at some length elsewhere[1].

Physicians have until now traced very little direct connexion between the endocritic system and neuroses, although most admit that such manifestations are largely related to the genital functions in the female.

At some future time when it has been decided how far disorders of the internal secretions are related to special diseases, it will be possible to link up many of the disorders of the reproductive system with those of the body generally, for what affects the internal secretions affects the whole metabolism.

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[1] Bell, W. Blair, 'The Disorders of Function' in *The New System of Gynæcology*, edited by T. W. Eden and C. Lockyer.

APPENDIX

In the foregoing pages only occasional reference has been made to the physiological effects which have been experimentally produced with extracts made from the endocritic organs, chiefly because we have very little certain information about the genital actions (with which alone we are here concerned) of many of these extracts, except in the specific cases and circumstances already discussed. But, in order that this work may be more complete in regard to all the possible evidence at our disposal concerning the genital functions of the internal secretory organs, the following brief notes are added. This addition is, perhaps, also necessary from the fact that the work published by the late Dr. Hick and myself early in the year 1909 appears to have escaped the attention of subsequent investigators.

The Physiological Effects of Ovarian Extracts.

It was found by Hick and myself[1] that the physiological effects on the uterus of intravenous injections of whole-ovary extract are as follows :

(a) No effect is produced on the inactive uterus.

(b) On the œstrous uterus a well-marked increase in the force of the contractions is obtained, and this effect is augmented by repeated doses. In some cases a considerable increase in the tone may also be produced.

(c) The pregnant uterus is somewhat remarkably affected by ovarian extract, which causes temporary *inhibition* of the contractions.

We observed no alteration in the blood pressure.

More exact information has recently been obtained by Itagaki working in Schäfer's laboratory.[2] This investigator found that extracts made from different parts of the ovary produce different effects on the uterus and blood pressure. He noticed that an extract made from the hilum, and believed to contain the active principle of the interstitial cells, alone produced inhibition of the uterine contractions ; and that an extract of the corpus luteum increased the tone and force of the uterine contractions, without affecting the blood pressure, while the follicular secretion increased the tone and the force of the rhythmic movements of the uterus and of all other involuntary muscle suspended in the liquor itself, or in an extract made from the follicles.

These observations are not incompatible with our earlier experience with whole-ovary extract, but the subject requires further investigation.

The effects of ovarian extracts on the secretion of milk have already been discussed (p. 84).

The Physiological Effects of Thyroid Extract.

It has long been known that intravenous injections of thyroid extract lower the blood pressure. Further, Hick and I[1] found that, in spite of this effect on the blood pressure, the force and tone of uterine contractions is considerably increased, and that this is more marked

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[1] Bell, W. Blair, and Hick, P., *Brit. Med. Journ.*, 1909, vol. i, p. 777.

[2] Schäfer, E. A., *The Endocrine Organs*, 1916.

with repeated doses, until eventually general convulsions with violent contractions of the uterus may occur.

The effect of thyroid extract on milk secretion has been considered (p. 88).

The Physiological Effects of Suprarenal Extracts.

An extract made from the cortex of the suprarenals has no known physiological action, but that made from the medulla has marked pressor effects ; consequently in nearly all animals uterine contractions are obtained. It is interesting, however, in view of the opposite effect obtained by us with ovarian extract, to note that in the *non-pregnant* cat and rat inhibition is said by some authorities to be the usual effect. It is possible that such an action may depend on seasonal inactivity of the uterus, and not of necessity on the absence of gestation.

Mention has been made of the action of the extract of the medulla on the secretion of milk (p. 88).

The Physiological Effects of Pituitary Extracts.

No definite physiological effect has been obtained with extracts made from the pars anterior, but as we have already seen (p. 62), an extract made from the pars posterior has a very powerful action on the uterus, causing a great increase in the tone and force of uterine contractions. Likewise infundibulin increases the flow of milk in lactating mammæ (p. 87).

The Internal Secretion of the Uterus.

In 1906 I suggested[1] that the uterus probably forms an internal secretion which influences the onset of menstruation and the integrity of the ovaries. Although very little experimental evidence has been obtained in support of this view, clinical observations have shown that this hypothesis is not entirely without foundation. Nevertheless, I am now inclined to think that I may have assigned to a chemical compound in the course of excretion the rôle of a specific hormone—a not entirely anomalous state of affairs if CO_2 may be considered a hormone—and that the calcium salts excreted by the uterus may be the active bodies in question, the uterus merely playing a part in their metabolism.

It has been shown by Hick and myself[2] that fresh uterine secretion—collected by tying the uterine cornua—has a remarkable agumentative action on the contracting uterus of another animal, together with a pressor action on the blood pressure. This secretion was found to be very fatal in its effects unless used in small quantities and well-diluted, intravascular coagulation readily occurring.

Further, we showed that calcium salts also cause a considerable increase in the force of uterine contractions.

Subsequently, Fellner[3] obtained with extracts made from the uterus results somewhat similar to those obtained by Hick and myself. Biedl[4], however, was unable to confirm Fellner's observations. This authority had apparently not seen the account of our experiments which preceded those of Fellner by nearly a year.

[1] Bell, W. Blair, *Liverp. Med. Chirur. Journ.*, 1906, vol. xxvi, p. 234.
[2] Bell, W. Blair, and Hick, P., *Brit. Med. Journ.*, 1909, vol. i, p. 777.
[3] Fellner, O. O., *Centralbl. f. Physiol.*, 1909, vol. xxiii, p. 347.
[4] Biedl, A., *Innere Sekretion*, 1913, 2nd ed.

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