Observations
ON
GYNAECOLOGICAL ASPECTS OF
ENDOCRINOLOGY*

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In the international exchange of ideas the medical profession is an exponent of the doctrine of free trade, for no scientific idea is dutiable, and no thought need be given to the laws of high or low tariff upon which the ordinary trade marts are so delicately balanced. Our ships are our medical journals, while more directly personal transmission of messages is possible through visitors from the profession of one country to that of another. Many of your distinguished gynaecologists and obstetricians have brought valued messages to our American medical organizations throughout the years, and a number of my American confreres have been honoured, as I now am, by the privilege of mingling with you and participating in the discussions at your annual meeting.

With the invitation to address you came also the suggestion as to a title, so that the usual first problem of the prospective speaker was very agreeably dissolved, especially as I could scarcely have selected a topic of greater general appeal. This widespread interest in endocrinology applies particularly to the field of gynaecology, which makes more numerous points of contact with endocrinology than does any other specialty in medicine. The reasons for this are obvious. Our daily work has to deal with aberrations not only in the structure but also in the function of the female reproductive organs. One of the most intensively worked problems in the field of physiology to-day is that of the female reproductive cycle, and pretty much all of the great deal we have learned about it in recent years has to do with its endocrinology. Much of this new knowledge is applicable in the clinical interpretation of our daily problems, particularly in the field of the so-called functional disorders. This has immensely broadened and deepened the scope of gynaecology, so that it is no longer to be looked upon, as was the tendency in past years, as merely a special branch of surgery. If I may quote from a very recent paper of my own, "If the proper study of mankind is man, so the proper study of gynaecology is woman, in all her varied biological aspects, rather than merely as a creature possessing pelvic organs of a certain size, shape, and position." The pursuit of gynaecology in this broader sense will often lure the clinician far beyond the pelvic brim, especially if his diagnostic nose is keen on the endocrine scent.

This is not the place—nor is it necessary—to bewail the rather maudlin endocrinology and organotherapy of an earlier day. This is past history, for the endocrinologist of to-day is trying manfully to hold his imagination under the leash of scientific control, though even now the leash may occasionally snap under the powerful tug put upon it. Nor would there be time, within the limits of a paper of considerable length, to review the development of our knowledge of the reproductive phenomena, though it might flatter our vanity to look back from our present complacent heights upon the centuries of superstition and speculation which have surrounded the discussion of these questions.

HORMONE FUNCTION OF THE OVARY

The hormone concept of menstruation belongs practically to our own generation, for it was not until 1899

that it was established that the essential role of the ovaries is dependent upon their internal secretion. Up to that time it had been believed that the influence of the ovaries is exerted through nervous channels, in accordance with the then rather generally accepted theory of Pflüger, enunciated in 1863. It is worth while digressing for a moment to point out that, even though the ovarian internal secretory function had not been demonstrated until 1899, ovarian preparations had been fed to patients for some years before this time, merely on an assumed analogy with the thyroid.

With the establishment of the hormone function of the ovary, there began the long discussion as to which element in the ovary is responsible for its internal secretion. The work of Fraenkel in 1903 called attention to the functional importance of the corpus luteum, both as a cyclical structure and as the source of a substance which, in rabbits at least, is essential to the maintenance of gestation in its early stages. The mistake was made, as it has been made so many times since then in endocrinological investigations, of applying to other animals the results of studies upon some one species. Although Fraenkel's work has been abundantly confirmed as applied to rabbits, it has been shown that in the human being the corpus luteum, while undoubtedly of importance in the first stages of pregnancy, is not quite so indispensable as it is in the rabbit.

Parenthetically it may again be noted that the over-eager clinician, on the basis of the work of Fraenkel and others who followed him, at once began to administer corpus luteum substance, in one form or another, to patients with supposed hypofunction of the ovaries. Following Fraenkel's work, and more especially after the demonstration by Hitschmann and Adler in 1908 of the menstrual histological cycle in the endometrium, there began an important series of correlative studies upon the ovarian and uterine cycles. As a result of these, and without much aid from the anatomist, physiologist, or biochemist, gynaecologists were able, largely on the basis of histological study, to construct an apparently satisfactory theory of menstruation. From a chronological standpoint the sequence of events thus postulated has been essentially confirmed by the more recent investigations along physiological lines.

Up to 1917, as a matter of fact, anatomists and physiologists had shown very little interest in reproductive physiology, as a glance through any of the older textbooks will show. It was the discovery of the vaginal smear method of chronological study of the sex cycle in the laboratory animals which lighted up the interest of the experimental worker, and most of the advances in recent years have been made through laboratory investigations. The work of Frank, Allen and Doisy, and many others upon the ovarian follicle hormone, that of Corner and W. Allen upon the hormone of the corpus luteum, that of Smith and Engle in America and Zondek and Aschheim in Germany upon the anterior hypophyseal function—all these marked milestones in our knowledge of the subject. In all these investigations the British school of investigators has occupied an important front-line position.

To jump at once to a discussion of present-day viewpoints, it is now universally accepted that the ovary produces two distinct hormones. One of these is folliculin (oestrin, theelin, menformon), the characteristic hormone of the active Graafian follicle. With the cessation of a menstrual period and the removal of the corpus luteum inhibition a crop of follicles begins to mature. For some curious reason one of these outstrips its fellows, reaching full maturity and thus achieving the distinction of becoming the presiding follicle of the particular cycle and of giving off the ovum for that cycle. The less fortunate

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follicles die at various stages of maturation through the mechanism designated as atresia folliculi.

During the process of maturation of the follicles a steadily increasing amount of folliculin is secreted, and this produces in the uterus two chief effects—namely, hyperaemia and growth, in both the endometrium and the musculature. With the rupture of the follicle begins the corpus luteum phase of the cycle. During its period of activity the corpus luteum produces two hormones, folliculin and progesterin, the latter being its own characteristic hormone. That the yellow body, in the human at least, continues the secretion of folliculin was not established until quite recently, but the work of Allen, Frank, and others leaves no doubt concerning this fact. It clears up a point which hitherto has been difficult to explain, for the follicle reaches its maximum at the mid-interval period, while blood hormone studies show a large amount of folliculin in the blood shortly before menstruation. The significance of this observation as regards the cause of the menstrual bleeding will be emphasized later.

The folliculin effects of growth and hyperaemia are therefore carried beyond the ovulation phase, but, in addition, the endometrium is then subjected to the influence of progesterin. This is responsible especially for the secretory activity of the glandular epithelium, which is never observed before ovulation. It will thus be seen that the folliculin influence is continuous from the end of one menstrual bleeding to the beginning of the next, while progesterin is a factor in only the latter portion of the intermenstrual phase.

The underlying cause of the corpus luteum retrogression, the endometrial desquamation, and the onset of bleeding is still unknown, as I have discussed in a recent paper. The doctrine of "primacy of the ovum," so strongly championed by Robert Meyer, must be abandoned. According to this, it is the death of the ovum which determines the retrogressive phenomena above mentioned, and thereby the occurrence of bleeding. To mention only one of a number of obstacles to the acceptance of this belief, the cycle goes on quite undisturbed, even though the ovum be washed out of the genital canal shortly after ovulation.

OVULATION AND MENSTRUATION

Another important question which has been opened up in the past few years has been as to the relation, if any, which exists between ovulation and menstruation. To raise the question a few years ago would have seemed heretical, for there seemed to be general acceptance of Meyer's dictum that "Ohne Ovulation, keine Corpus luteum; ohne Corpus luteum, keine Menstruation." The studies of Corner, Hartman, and Allen upon monkeys have shown beyond the shadow of a doubt that in these animals perfectly typical periodic bleeding, certainly menstrual in a clinical sense, very frequently occurs in the absence of ovulation. Meyer contends that this bleeding is a "pseudo-menstruation" and not a genuine menstruation, inasmuch as it is not accompanied by the same endometrial changes as those characterizing the usual human cycle. With this the above-mentioned investigators would unquestionably agree, even though the bleeding is clinically identical with the human phenomenon as regards periodicity, rhythm, duration, and amount. After all, the discussion appears to be merely a play on words, the outstanding fact being that a type of periodic bleeding indistinguishable from menstruation can occur in the absence of ovulation.

The application of this new fact to the human problem opens up new possibilities. Certainly the usual menstrual cycle in woman is of the traditional type, with ovulation, corpus luteum formation, and the characteristic endometrial cycle above described. That an anovulatory

periodic bleeding can occur, however, is demonstrated in the frequent cases of functional menorrhagia, in which corpora lutea are characteristically absent. It is illustrated also in the occurrence of such menstrual, or pseudo-menstrual, bleeding in women far beyond the menopause in association with granulosa-cell tumours of the ovaries. With such tumours ovulation and corpora lutea, or for that matter even ova, are not found.

I have previously expressed the belief, though I cannot yet produce the evidence, that the anovulatory type of cycle is perhaps more frequent than we now believe, even in apparently normal women, just as it often occurs in normal monkeys. If this is true, it may well explain certain cases of sterility in which both partners are apparently perfectly normal in every way. If eggs are not thrown off from the ovary, pregnancy is obviously impossible, although we unfortunately have no means of determining by examination which women ovulate and which do not. In this respect we are less fortunate than those working with monkeys, for Hartman seems to have shown the possibility of establishing the occurrence of ovulation by the simple method of bimanual pelvic examination. In these animals the mature follicle is obviously a more prominent structure than it is in the human patient, in whom, furthermore, the frequent occurrence of large atretic follicles on the ovarian surface would make palpation findings very unreliable.

The third physiological problem to which I should like to allude is that dealing with the hormonal mechanism involved in the actual bleeding of menstruation. The phenomenon immediately preceding this is the retrogression of the corpus luteum, a structure which appears to mother and protect the endometrium. So long as the corpus luteum itself is thriving and functioning, the endometrial development advances, so that, in the case of the corpus luteum of pregnancy, the pregravid endometrium passes by an easy transition into actual decidua. Once retrogression of the corpus luteum occurs, or once it is excised, the endometrium degenerates, is cast off in considerable part, and bleeding begins; if the corpus is excised four or five days before the normal menstrual date, it may be confidently predicted that premature menstruation will appear in from twenty-four to forty-eight hours after the operation.

Against this must be placed certain observations made upon the effects of excision of the growing follicle. If this is done bleeding likewise occurs, although usually not for a number of days afterward, depending chiefly upon the stage of development of the follicle. Moreover, if folliculin be injected into a castrated animal for a series of days bleeding will occur, but not until a number of days later. Similarly at least some amenorrhoeic women will exhibit bleeding after sufficiently large and sufficiently prolonged folliculin treatment, although here likewise the bleeding occurs some days after the cessation of the injections.

Since the follicle contains only folliculin, it is apparently the withdrawal of this hormone which determines bleeding. The bleeding after corpus luteum excision or regression, formerly a disturbing factor in this regard, is readily explained by the now demonstrated fact that the corpus likewise is a producer of folliculin, as well as of its more characteristic progesterin. On the basis of such evidence as this there seems no escaping the view that the withdrawal of folliculin, or at least a drop in the folliculin level, is the immediate hormone cause of menstrual bleeding.

This concept carries with it many important implications, and may change our views of various types of uterine bleeding. For example, the rupture of the follicle is followed by a temporary drop in the folliculin level, as is apparently borne out by blood hormone studies. This

is a logical explanation of the intermenstrual staining, at times fairly free, which is observed in some women at about the time of ovulation. In monkeys, such intermenstrual bleeding, either macroscopic or microscopic, is a constant finding.

Again, in the exceedingly common functional type of bleeding, seen so often in the menopausal years, during puberty or adolescence, or at various periods during reproductive life, it has been generally accepted that the cause is of endocrine nature, consisting of a relative excess and persistence of folliculin, and an absence or deficiency of progestin, for corpora lutea are characteristically absent in such cases and the endometrium never shows secretory changes. The mere hyperfolliculinism, however, is not an adequate explanation of the bleeding, for there must be some additional factor which brings about a drop in the folliculin blood content, and thus induces the bleeding. Since the latter is so often periodic, as in the common functional menorrhagias, we must assume that the high folliculin content is lowered at intervals by some other periodic factor. The nature of the latter cannot be stated with any precision, but it is almost surely dependent upon the intimate and apparently reciprocal relations existing between the ovaries and the anterior hypophysis.

The work of Hisaw, Moore, and others indicates that this relationship is automatic and self-regulatory, so that an excess of folliculin, for example, inhibits the pituitary function, with corresponding inhibition of the ovarian activity. If this thermostat-like mechanism is the one concerned, we have at least a broad explanation of the principles involved in these functional haemorrhages, though we must look to future investigations for the details. The same principles may be invoked to explain the periodic bleeding, not distinguishable from menstruation, seen in very young children or very old women suffering from granulosa-cell tumours, already alluded to.

PITUITARY SEX HORMONES

No consideration of ovarian function can be complete without some reference to the closely intertwined endocrine function of the anterior hypophyseal lobe. The dominating role of the latter over the ovary has been firmly established by the brilliant experimental studies of Smith and Engle, in our country, and Zondek and Aschheim, in Germany. While there is general acceptance of the main fact, several controversial questions have been thrown into the ring. One of these is as to the unity or duality of the pituitary sex hormones. Zondek especially has urged that two separate hormones are involved, one (prolan A) a follicle-ripening principle, responsible for the mobilization of folliculin, the other (prolan B) being concerned with luteinization and the production of progestin. An increasing number of investigators, however, believe that the two effects represent merely different phases in the activity of the same principle.

The second moot point concerns the identity or non-identity of the pituitary sex hormones and the so-called pituitary principles found in such large amount in the urine of women during even very early pregnancy. The German gynaecological journals have been full of this discussion between the "identicists," led by Zondek, and the "non-identicists," of whom Philipp has been the chief champion. In most respects there seems to be no doubt about the identity of the physiological effects of the substances in question, but differences have been pointed out, as for example recently by Evans and his collaborators, which must be explained before any final conclusion can be reached. Whether the "prolan" in the urine of pregnancy is actually of pituitary origin, or whether it is produced elsewhere, and whether or not it is to be looked upon as merely an activator of pituitary

function, as Evans and his co-workers suggest, the fact remains that it is increased in amount, almost explosively, in the early stages of pregnancy. The Aschheim-Zondek test, with its various modifications, has been one of the most important by-products of the present-day feverish interest in the problems of reproductive physiology. Its value and reliability in the diagnosis of early gestation are now universally accepted, as is its frequent usefulness in the diagnosis and management of cases of hydatidiform mole and chorion-epithelioma.

GYNAECOLOGICAL ORGANOOTHERAPY

I have said nothing as yet as to the matter of gynaecological organotherapy, nor does it seem necessary to discuss this except along very broad lines. It would be unfortunate if one's interest in endocrinology were predicated upon one's evaluation of the efficacy or inefficacy of organotherapy. This would be a very narrow and unsound point of view, for the results of gynaecological organotherapy have been disappointing, while the accomplishments of gynaecological endocrinology have been numerous and brilliant. Our interest in endocrinology should be based chiefly upon the fact that it has put into our hands a mass of knowledge directly applicable to the interpretation of many of our everyday clinical problems, as I emphasized at the outset of this paper.

To attempt anything but a cursory and general consideration of these various clinical problems in gynaecological endocrinology would be out of the question within the limits of a single paper. The approach to all of them should be along the pathways which have been cleared by scientific investigation. It is therefore scarcely necessary to go into the details of organotherapy with anyone who is at all familiar with what has been learned concerning the endocrinology of the reproductive processes. What is sound and what is unsound is obvious to anyone so equipped.

With reference to endocrinopathic amenorrhoea, for example, one should remember that the breakdown in the endocrine mechanism may involve any one or more of a group of ductless glands, perhaps most often the thyroid, the pituitary, or the ovary. That the suprarenal may be the primary offender, however, is illustrated by the fact that amenorrhoea may be one of the manifestations of defeminization seen with cortical tumours of the adrenals. The differentiation of causes is often difficult and not infrequently impossible. Efforts along this line must include not only careful clinical study, but also the employment of such laboratory methods as blood and urine hormone studies, basal metabolism determination, x-ray studies, etc. In this way one can often arrive at a fairly rational determination of the endocrinological type presented by the particular case.

Can we say as much for the rationale of the treatment available in most cases? I believe not. In the clearly hypothyroid cases, the administration of thyroid extract is rational and often successful. Not so, as a rule, with those which, with greater or less show of reason, we classify as hypopituitary or hypogonadal. Here also we frequently resort to the inevitable "pinch of thyroid," combining it with some form of pituitary or ovarian therapy, most often without success, and for reasons which often suggest themselves. Can we hope to awaken a non-functioning or under-functioning ovary by the hypodermic use of theelin? Unless every scientific worker is wrong, we cannot. At best we can in this way substitute for the normal ovarian secretions an uncertain and probably very inadequate amount of one of these secretions. The other hormone, progestin, is not yet available for clinical use. Even if both were used, prohibitively enormous dosage is necessary to reproduce in the human

endometrium the histological changes characterizing the menstrual cycle, as indicated by the recent experiments of Clauberg and Kaufman upon castrated women.

But even though it were possible thus artificially to replace the ovarian hormones, is there any reason to believe that the function of the ovary would be restored and the normal menstrual function re-established? I know of none. Indeed, if the dosage of theelin is sufficiently large or prolonged, ovarian function is injured, as Hisaw and his collaborators have shown. It is true that with theelin alone bleeding may at times be produced, occurring usually some days after the last injection, and clearly due to folliculin withdrawal, as I have already discussed. But such bleeding is not menstrual, it cannot be expected to occur regularly, it is not associated with ovulation, and of course does not enhance the chances of fertilization for the sterile woman. If I may quote from a recent paper of my own, "It is as if we pushed the pendulum of the run-down menstrual clock for a single idle, incomplete beat, when what we need is a key to wind the clock."

From what we have said as to the governing role of the anterior hypophysis, we might well consider this as the winding mechanism of the clock. But what can we do when the pituitary itself appears to be in need of winding? Shall we use pituitary preparations in a substitutional way, hoping that these will start the ovarian mechanism? And, if so, which shall we employ? As with the ovary, the various extracts for oral use are almost without effect both experimentally and clinically. What of the newer prolan-containing preparations for hypodermic use? Potent as these are upon the ovaries of certain laboratory animals, the available evidence indicates that they have little or no effect upon the human ovary. Whether this is merely a species difference or whether it indicates that prolan obtained from the urine of pregnant women is not the same as the sex hormone or hormones produced by the pituitary cannot as yet be stated.

Many combination forms of treatment have been suggested and tried, such as the use of the anterior pituitary growth hormone in combination with the prolan-containing substances, but the results to date have been unimpressive and we are still floundering in the morass of incomplete knowledge. This is a pessimistic picture which I have painted, but I believe it is not exaggerated. To mollify those who are more enthusiastic than I concerning the treatment of amenorrhoea, I should add that I am just as optimistic about the future of organotherapy along this line as I am pessimistic of its accomplishments to date. It would indeed be almost incredible that, with so many earnest workers in the field, further scientific advances should not yield therapeutic measures far more effective than any we now possess.

Concerning the treatment of the functional haemorrhages, I shall limit myself to the mere mention of the plan of organotherapy which seems to me to have yielded far better results than any other. To my mind, it has represented the most successful application of organotherapy in the gynaecological field. I refer to the use of the so-called luteinizing hormones obtained from the urine of pregnant women. This plan, suggested by us in 1931, was based upon the fact that corpora lutea and progesterin are characteristically absent in these cases. If progesterin were available, it should be possible to convert the hyperplastic endometrium into a functional, pregravid one, thus completing the cycle. That this can actually be accomplished has since then been shown by Clauberg, in an experiment upon a castrated woman. Large and prolonged dosage with folliculin produced typical hyperplasia of the endometrium, but further treatment with injections of progesterin converted the latter into a typical secretory one, corresponding to the normal premenstrual phase.

There seems at present little prospect of obtaining progesterin for general use, because of the fact that it is obtainable from corpora lutea in such tiny amounts, and no other source is as yet known. Since the prolan B principle in the urine of pregnant women has a strong luteinizing effect upon the ovaries of such experimental animals as the mouse and rat, it was hoped that it might serve as a substitute for progesterin, in that it would, through the production of luteinization, provoke the dysfunctioning ovary to produce its own progesterin. That the abnormal bleeding can be controlled in a very large proportion of cases we have convinced ourselves by an experience in more than 200 cases, and similar good results have been reported by others. So prompt is the effect in some instances that we were soon convinced that it could not be due to an actual histological change in the ovaries, and direct studies of the ovaries have since then been made bearing out this idea. Just how the haemostatic effect is brought about we cannot be sure, although I am inclined to think that it is in some way dependent upon the interaction of the hypophyseal and ovarian secretions.

Time does not permit of a discussion of other possible fields for the rather tentative organotherapy of the day. Reynolds and I have suggested the use of the prolan-containing preparations as adjuvants in the treatment of primary dysmenorrhoea, on the basis of the former's experimental studies, which indicate that these substances are powerful inhibitors of the rhythmic contractility of the uterine musculature. For the details of this subject I must refer to the original paper by Reynolds and myself, and to a second more recent paper by myself.

I should have liked also to discuss more fully the field of organotherapy in the occasionally distressing vasomotor symptoms of the menopause, either natural or artificial. The inefficiency of the oral administration of ovarian extracts is now conceded by practically all gynaecologists. At present the most popular treatment, in our country at least, is the hypodermic administration of folliculin in one or other of its commercial forms. Since there is a deficiency of this hormone in at least some phases of the menopause, and since folliculin is a substance of undoubted physiological potency, there is a semblance of rationale for this form of therapy. Whether through psychic channels or otherwise, many patients are improved, so that the practitioner, hard put to it as he is to give these patients relief, will probably continue to use folliculin for this indication until some better plan of treatment is evolved. I need not stress that simple regulatory and sedative measures should never be overlooked in such patients, and, for that matter, they are all that is necessary in the milder cases.

CONCLUSION

In this paper I have chosen to touch briefly upon many aspects of endocrinology rather than to select some one problem for more exhaustive consideration. In this way it has, I hope, been possible to give you a more panoramic viewpoint as to the trends in our country. I dare say that the process of scientific diffusion and osmosis between the nations has made our viewpoints not unlike your own in most respects.

The practice of gynaecology without at least some knowledge of endocrinology is fast becoming an incongruity. It is just this asset, plus a knowledge of gynaecological pathology, which most often, to my mind, marks the difference between the real gynaecologist and the mere gynaecological operator.

The goldfields of endocrinology are now being feverishly worked by many men in many lands, but the surface has been little more than scratched as yet. Perhaps the first nugget was dug up as far back as 1855 by one of your

countrymen, Thomas Addison, but the real rush to the goldfields did not begin until something like a quarter of a century ago. The yield already has been amazing, and the story of endocrinology constitutes perhaps the most fascinating chapter in the history of medical science. No longer need the endocrinologist be spoken of with derision as a "ductless gland faddist," for some at least of his early dreams have materialized into facts, and not a few of these facts have been successfully applied in the relief of human suffering and disease.

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GYNAECOLOGICAL ASPECTS OF ENDOCRINOLOGY*

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Gynaecological interest in endocrinology is at present focused almost exclusively on the hormones of the ovary and the pituitary (particularly the anterior lobe), and on the substances identical with or at least closely similar to them which are found in the placenta and in the urine of pregnant women. Even within these relatively narrow bounds we have a subject of such complexity, with a recent literature so voluminous, that it would be impossible to review the whole subject within the limits of your tolerance. I shall therefore only touch upon certain matters which are of more particularly practical interest from the diagnostic and therapeutic points of view.

DIAGNOSIS

The Aschheim-Zondek test for pregnancy, although not the foundation of our knowledge, has perhaps done more than any other single discovery to stimulate interest and research on this subject. Following up the results obtained by the implantation of anterior pituitary substance into immature female mice, these observers found that the urine of pregnant women contained, from an early period of gestation, quantities of anterior pituitary hormones (or substances closely resembling them) sufficient, when injected into female mice, to bring about the same changes—namely, a rapid and intensive development

of the ovaries characterized by the presence of haemorrhagic follicles and corpora lutea. I shall not discuss the technique of the test, but rather its practicability.

Four years ago Crew and Wiesner of Edinburgh University, having in the Genetics Department a sufficiency of suitable animals, established a Pregnancy Diagnosis Station,* open to all practitioners at a nominal fee, for the purpose of trying out the practical value of the test. The station is not a commercial undertaking, but is carried on in the interests of the profession and of science. During these four years tests have been made in some 6,600 cases, and the actual error, as checked by subsequent clinical observation of the patients, has been approximately 2 per cent. In the last year it was reduced to 0.89 per cent. A degree of accuracy equal to 98 per cent., still more to 99.11 per cent., demonstrates the practical value of the Aschheim-Zondek test beyond all reasonable criticism. The Edinburgh Pregnancy Diagnosis Station, which has provided the only large-scale trial of the reaction in Britain, has also demonstrated the value of such a station as a practical diagnostic aid. Positive errors (that is, reaction positive but no pregnancy) are few. Negative errors (test negative but pregnancy existing) are more common in the early weeks, as might be expected. A negative result in the very early weeks should be accepted with caution if it runs contrary to clinical observations, and another test should be made later if necessary.

The explanation of these negative errors is that there is a smaller quantity of anterior pituitary hormones in the patient's urine than is normal in pregnancy; and in 1929, during the first year's working of the station, Crew¹ and Wiesner noticed that not infrequently these results occurred in cases in which abortion subsequently took place. This observation has been so often confirmed by them that a weak positive reaction may now be accepted as implying a definite risk of abortion. Moreover, it was found that in these cases the changes in the vagina and uterus in the experimental animals were frequently normal in degree, indicating that the oestrin content of the urine was approximately normal. There would thus appear to be a deficiency of the anterior pituitary hormones in these cases, and as the oestrin secretion is usually adequate, we have argued that the need is mainly for rho II (prolan B) to stimulate the corpus luteum to increased production of progesterin. On this basis we have successfully treated a number of cases of habitual abortion with luteinizing doses of "rho factors." Such treatment is, of course, unlikely to succeed in the presence of any organic conditions calculated to produce abortion, and it has never proved successful in our hands in actual threatened abortion. I would enter a plea here for the more general adoption of the Aschheim-Zondek test in early pregnancy, even where there is no particular reason to question the diagnosis, for the simple reason that valuable information on this point of a patient's liability to abortion may be forthcoming.

In hydatidiform mole the anterior pituitary hormones are present in the urine in great excess as compared with normal pregnancy, and it is natural to try to link this observation with, on the one hand, the abnormal growth of chorionic epithelium characteristic of that condition, and, on the other, the usual concomitant of lutein cysts of the ovary. Interesting speculations present themselves as to the nature of this link. Does the chorionic epithelium stimulate excessive luteinization directly or through the medium of the anterior pituitary lobe, or does the chorionic epithelium itself form the hormones in the urine? In other words, is the placenta, so to speak, a distillery or merely a "bonded store" for anterior pituitary

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