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*

BY

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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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hormones? From the histological point of view I can imagine the placenta of the early months being a distillery, but not in the late months, when the chorionic epithelium has so much the appearance of passivity. There are also phylogenetic objections to the view that the placenta is a gland of internal secretion, because it appears so late in the scheme of evolution compared with the recognized endocrine glands. On the other hand, Phillips² and Ehrhardt and Mayes³ found that during pregnancy the anterior pituitary lobe itself was poor in its secretions, an observation which certainly suggests that its work is temporarily taken over by another organ.

The positive Aschheim-Zondek reaction in cases of chorion-epithelioma, and its consequent diagnostic value in that condition, are so well established that no detailed reference need be made to them. Chorion-epithelioma of the testicle in the male also gives rise to a positive reaction, and this brings me to the question whether the test for pregnancy can be falsified by positive results in cases of cancer or other new growths. Zondek⁴ claims that neoplastic disease, especially cancer of the genital tract, causes a slight increase in the anterior pituitary hormones in the urine as compared with the non-pregnant condition. While there is reason, I understand, to doubt the accuracy of any quantitative estimations of anterior pituitary hormones in units, the proportions which he gives—five mouse units per litre in non-pregnant women, 100 to 150 units in tumour cases, either malignant or benign, and 5,000 units in normal pregnancy—are indicative of how slight is the practical risk of fallacy from this source. With the possible exception of chorion-epithelioma, therefore, tumour growth does not affect the practical value of the pregnancy test in any real sense, and the number of cases in which the diagnosis lies between chorion-epithelioma and incomplete abortion is fortunately small. Research is going on as to the effect of the anterior pituitary hormones on tumour growth, but so far the results are conflicting. The whole subject is replete with interest when we consider the similarity in some respects between cancer tissue and trophoblastic tissue; nor is this diminished by the chemical relationship between oestrin and carcinogenic substances recently demonstrated by Cook, Dodds, and Kennaway.⁵

Another diagnostic field of great importance is to be found in the application of our knowledge of the hormonal mechanism of menstruation to irregular uterine bleeding. So far the interpretation of these haemorrhages is not by any means complete, because there are still serious gaps in our knowledge of the menstrual mechanism. The bulk of the evidence suggests that menstrual bleeding is due to a withdrawal of hormones rather than to the interposition of a positive bleeding factor such as Hartman has postulated. I have repeatedly confirmed Fraenkel's observation that the excision of the human corpus luteum in the second half of the menstrual cycle induces menstrual bleeding within thirty-six hours, and this seems strongly suggestive of the removal of an inhibitory factor. Most authors now subscribe to the view that it is the withdrawal of oestrin which causes the menstrual flow; and, experimentally, menstruation can be produced in this way. But I would remind you of the work of Smith and Engle⁶; these observers took sexually mature monkeys and treated them with anterior pituitary hormones in doses calculated to increase oestrin formation, adding large doses of theelin in the last few days of the treatment. They then stopped the injections and removed both ovaries, thus eliminating, so far as we know, all sources of oestrin and providing a doubly pronounced stimulus to uterine bleeding on any theory of oestrin withdrawal. Notwithstanding this, they succeeded in preventing bleeding by injections of large doses of corpus luteum extract, which contained only a minimal quantity of theelin—far too small to

vitiating the experiment. This brings us back to the older view that the actual cause may be the withdrawal of progesterin by the retrogression of the corpus luteum, and that progesterin has an inhibitory action on menstrual bleeding as it has on follicular growth. At the least it suggests that the withdrawal of both ovarian hormones is necessary. Moreover, there is another point to which Wiesner has drawn my attention—namely, that the reactivity of the uterine muscle is a part of the menstrual phenomenon—and we now know that progesterin or some associated corpus luteum hormone seems to have an inhibitory action upon uterine contractions.

The recognition of the possibility of anovular "pseudo-menstruation" occurring with periodic regularity in women is an important contribution to our knowledge which both throws light on some cases of sterility and introduces an element of possible error into many of our so-called cures of amenorrhoea.

Neither space nor our present knowledge will permit an attempt to interpret irregularities of menstruation and functional uterine haemorrhages in detail, but some general bearings may be indicated. Regular normal menstruation is the outward and ultimate expression of a complicated hormonal mechanism involving at least three structures—the anterior pituitary lobe, the ovary, and the genital tract. There are thus three points of attack upon which a disturbing factor may act. It may act upon one or other of the glandular links in the mechanism and produce either over- or under-activity of internal secretion. It seems possible, also, that it may act on the genital tract and affect its reactivity to ovarian hormones, so that menstrual disorders may occur in spite of normal supplies of ovarian hormones. It is generally assumed that glandular over-activity or arrhythmic function is associated with excessive or irregular uterine bleeding, and under-activity with amenorrhoea or scanty menstruation. But no such generalization is really warranted, for the material from several hundred cases received at the Pregnancy Diagnosis Station, in which a rough hormone analysis has been made, shows that amenorrhoea in the non-pregnant woman can be found in association with either an excess or a deficiency of cornifying hormone; while irregular bleeding may occur in women whose urine, collected between periods of bleeding, is wholly or almost devoid of cornifying hormone. Furthermore, as the ovary and the pituitary are members of a larger group of endocrine glands whose interdependence on each other is axiomatic, the functions of the thyroid and the adrenals cannot be wholly neglected.

THERAPY

In approaching the subject of the therapeutic employment of the sex hormones, in which, it is probably safe to predict, the future of gynaecology lies, the first thing to be said is that, in the present state of our knowledge, very little can be expected. We are still far from having reached finality in regard to the physiology of menstruation or the pathology of uterine bleeding. Ten years hence our outlook on these matters will almost certainly be materially changed, and our therapeutic results should meantime be considered purely tentative. One cannot but feel dismayed at the present phase of indiscriminate use of these substances, which has been created almost exclusively by the deluge of often misleading and never disinterested brochures from manufacturing chemists. I would strongly support the protest in this respect which Lord Horder⁷ recently made in his admirable oration to the Medical Society of London on "New Treatments for Old."

Admitting this tentative basis, and admitting also that clinical experiments are on a very different plane as regards

exactitude both in performance and in interpretation from those of our laboratory colleagues, there are two methods of therapeutic approach. The one is the use of the ovarian hormones, oestrin and progestin (to use terms which seem to be becoming generic); the other is the use of anterior pituitary hormones (or in practice the nearly identical substances extracted from the urine of pregnant women) to stimulate the ovaries to produce their own hormones. In each case the important general principle must be kept in mind that the hormone of any endocrine gland is incapable of stimulating its parent gland. Hormone therapy is essentially substitutive. But the hormone of one gland may stimulate another, as in the case of the anterior pituitary lobe and the ovary.

The next point, and one which I think ought now to be stressed, is that the only rational basis for hormonal therapy, and the only fruitful way in which we clinicians can increase our knowledge, is the scientific investigation of the patient's hormonal state before treatment. It is irrational to inject any hormone unless one has evidence that the natural supply of it is deficient. I would urge that the patient's urine should be sent to a laboratory such as the Pregnancy Diagnosis Station in Edinburgh, where the presence or absence of anterior pituitary hormones and of oestrin can be demonstrated, even although wholly satisfactory quantitative tests for the former are still lacking. Obviously such a method of investigation requires to be supplemented by careful clinical study of the bodily evidence of pituitary, ovarian, or thyroid deficiency, but the laboratory provides the final and only accurate test of the actual hormone state of the patient's sexual organs, and the most reasoned basis for the administration of substitutive hormones.

My own observations in sex-hormone therapy have been largely in the use of the gonadotropic hormones prepared by Wiesner and Marshall from pregnancy urine—which are anterior pituitary hormones very similar to, if not identical with, Zondek's prolans—and in the use of some of the oestrin-containing preparations on the market. The two gonadotropic factors have not been separated, but there is good ground for the belief that small doses produce the follicle-stimulating action of rho I, while in larger doses rho II is dominant and stimulates the corpus luteum to progestin secretion. That is the tentative basis on which we have been working.

Primary amenorrhoea has so far proved a disappointment, possibly because we have usually been dealing with an intrinsic anterior pituitary deficiency. Secondary amenorrhoea is a more hopeful field because by stimulating the formation of oestrin by substitutive therapy (rho I, prolans A) and then stopping it, one can at least temporarily restore "menstruation" in many cases where the condition has been due to a minor disturbance of function. It is very probable, although I know of no direct evidence, that some of these cases may be due to the condition, recognized in the cow, of "corpus luteum persistens," in which event a restoration of the menstrual cycle produced by temporary substitution might be expected to continue. Treatment by oestrin may similarly be successful in such circumstances. If I may use a simple metaphor, a case of primary amenorrhoea due to anterior pituitary deficiency is like a clock which *cannot* go because it lacks the mainspring; some cases of secondary amenorrhoea are like a clock which *will* not go because of some trifling disturbance such as a piece of dust in its mechanism. No amount of shaking will ever make the first one go, but gentle shaking will often restart the second and make it go, at any rate for a time. But shaking the clock is empirical therapy, with all its potentialities of harm!

In regard to functional bleeding we have had one or two striking successes with luteinizing doses of anterior

pituitary hormones in the menorrhagia of puberty; and I can confirm, in a few isolated instances, Novak's results with similar treatment in bleeding of the "metropathia haemorrhagica" type, using rho factors where he used a proprietary preparation. But most of these cases occur in women between 40 and 50, and access to an ample supply of radium has led me to treat them by intrauterine radium after curettage as the speediest and most permanent method of cure.

In cases of habitual abortion in which all recognizable pathological causes had been excluded we have had more than a dozen successes with luteinizing doses of anterior pituitary hormones. Presumably they were women in whom there was an absence, or a low content, of these hormones in the urine, although I plead guilty that the earlier cases were not investigated in the way that I have been urging. Wiesner, Marshall, and I⁸ published a note of them in the *Lancet* last autumn which evoked the editorial censure. The writer of the leading article in the *Lancet* painted the dangers of indiscriminate and permanent luteinization of the ovaries in terms which suggested a new "yellow peril" and, incidentally, his own detachment from clinical experience, for he overlooked the fact that the quantities we had injected were vastly less than the quantities of the same hormones excreted in normal pregnancies. Recently Marshall has proved that the injection of rho factors into mice in doses incomparably greater in proportion than any we used in women, far from causing sterility, is actually followed by increased fertility. While, therefore, the fears of the editor were unwarrantably exaggerated, yet we must agree with him that the indiscriminate use of potent hormones is unwise. To adapt the phrase of Opie, recounted by Dr. John Brown,⁹ and to say that before administration sex hormones should, like the artist's paints, be "mixed with brains," is but to reiterate in other words my plea for a previous laboratory diagnosis of the hormone state of the patient.

Study of the time relationship of the two ovarian hormones involved in menstruation naturally suggested the hope that dysmenorrhoea might find therein its explanation. The work of Knaus,¹⁰ of Robson and Illingworth,¹¹ of Reynolds and Allen,¹² and of others now warrants the view that the corpus luteum secretes a hormone which, in presence of oestrin, desensitizes the uterine muscle against the action of posterior pituitary hormone, which is presumably its natural stimulant, and reduces its spontaneous activity. The question at once arises, whether the pain of dysmenorrhoea may be due to the lack of this desensitizing hormone, and whether the injection of corpus luteum extract or of luteinizing doses of anterior pituitary hormone would not prevent the pain. My colleagues (Young and Haultain of Edinburgh, and Hendry of Glasgow) and I have been studying this subject for the last two years, and our results will be published as soon as the number of cases seems to us to justify definite conclusions. Meanwhile, I can only say that treatment on these lines in suitably chosen cases has given a very encouraging degree of success. There must always be so many factors in dysmenorrhoea, psychical as well as physical, that it is impossible to imagine that any one line of treatment can ever prove a specific.

The last point I would mention is the menopause. It is hardly too much to say that our real knowledge of what takes place in the sphere of sex hormones at this epoch is in inverse proportion to its frequency. We have long *assumed* that the physiological changes at this time are due to the natural cessation of ovarian secretions, and the symptoms associated with it to the consequent imbalance of the whole endocrine group. It is only since some scientific clinicians have made a hormonal examination of such cases that we are beginning to have a rational

understanding of them. Kurzrok,¹³ for example, has shown that whereas in cases of artificial menopause by radio-destruction or removal of the ovaries the ovarian hormones are necessarily absent, in cases of spontaneous menopause these hormones may or may not be absent. Manifestly, it is only where they are absent that their therapeutic injection can be expected to do good. Many papers have been published in the last two or three years on the treatment of menopausal symptoms, by oestrin-containing substances in which there is no evidence of uniform success, just as in earlier years there was the same discrepancy of results in the use of the solid and largely inert ovarian extracts. The psychical factor in the menopause is probably as important as in dysmenorrhoea, and must always be taken into account in estimating the success of any treatment, especially treatment by hypodermic injections. But, when all is said and done, it is certain that if only patients whose urine showed an absence of oestrin were treated by oestrin therapy, the results would be more uniform, the treatment would be rationalized, and our understanding of the real physiology of the menopause would be increased.

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ISOLATION OF ENTERIC BACILLI FROM SEWAGE AND WATER AND ITS BEARING ON EPIDEMIOLOGY *

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In these islands the control of major outbreaks of typhoid fever had been secured before the specific bacillus had been isolated. Budd (1856) recognized that the living poison of the disease was present in the stools of the patient and of the convalescent, and that the disease was mainly acquired through the consumption of water, milk, and vegetables contaminated with such excreta. The measures which would reduce the occurrence of the disease were those which would secure pure water and clean soil; hence steps were taken to obtain water supplies from clean catchment areas or from pure wells, and to provide drains and sewers to remove filth rapidly from the premises. Abolition of privy middens and cesspools followed. The purification of sewage was studied, and it was found possible to purify it to the extent that secondary decomposition was prevented in the streams into which it was discharged. The control of typhoid was brought about by the water engineer and town surveyor, following the advice of the clinician. The bacteriologist had no part, since many decades elapsed before the typhoid bacillus was cultivated by Gaffky in 1884.

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The measures taken—good housing, good drainage, pure water supplies—were expensive but lasting, and were useful for the eradication of many other diseases. It was probably an advantage that bacteriology developed later than sanitary engineering, as it is possible that active immunization might have been advocated as being cheaper than the great public health schemes which were undertaken. Bacteriology has contributed much to our knowledge of the aetiology and diagnosis of enteric fevers, assisting in their diagnosis and calling attention to the part played by the "carrier" in their dissemination. The findings of many bacteriologists, however, if they had been taken seriously, would have indicated that much of the expense incurred to secure pure water was unnecessary; in fact, from laboratory investigations it was shown that the typhoid bacillus rapidly died out in the water, that 99 per cent. of the bacilli were dead after twenty-four hours, and that probably after three or five days all of them had lost their vitality. According to these results, a water-borne epidemic of typhoid fever was a practical impossibility, but epidemiological inquiries, on the other hand, showed that such outbreaks were by no means infrequent.

During the last five years the introduction of improved methods of isolation of the bacillus has thrown fresh light on the question, and has shown that to keep the disease in check the efforts of the sanitary and water engineer must not be relaxed, but must become more strenuous. Murchison, like Budd, believed that typhoid fever might be transmitted by water or milk infected with the excreta of a patient, but he also believed that the disease might arise *de novo*. He believed that the faeces from healthy persons, and other forms of filth, undergo fermentation outside the body, and that the virus of the disease is produced in this process of putrefaction. This "pythogenic" theory, if translated into terms of modern medicine to mean that the *B. coli* may undergo a ripening process and be converted into the *B. typhosus*, has no experimental evidence in its favour; but if it is taken to mean that the stools of normal individuals frequently contain the typhoid bacillus, and that in consequence the sewage of a moderately large institution or small town is liable to contain them, and that this sewage, if it gains access to a water supply, is liable to cause the disease, then it has, as recent work has shown, much to support it.

DISCOVERY OF TYPHOID BACILLI IN SEWAGE

In this paper I shall refer to the discovery of typhoid and paratyphoid bacilli in sewage and in water, and this when no clinical cases of the disease were recognized in the district. Whether the typhoid bacillus in sewage becomes more virulent it is impossible to say in the present state of our knowledge. Up to 1928 typhoid bacilli had never been found in sewage, but in that year, by means of a new bismuth sulphite medium, I was able to isolate typhoid bacilli from Belfast sewage and cockles, and Adams (1928) isolated them from the droppings of seagulls. In 1929 Gray, and in 1930 Begbie and Gibson, isolated *B. paratyphosus* B from the sewage of Edinburgh. Houston, by means of the bismuth sulphite medium, on two occasions in 1928 and on two occasions in 1929, succeeded in isolating the *B. typhosus* from the River Thames. In 1931 Wilson and Blair reported the almost constant presence of *B. typhosus* during two years in Belfast sewage, and also the isolation of *B. typhosus* and *B. paratyphosus* B from the River Lagan, the water being taken below the point of entrance of the effluent of Lisburn sewage works.

In 1930 Houston, on four occasions out of thirty-four experiments, isolated the typhoid bacillus, but no para-