- ¹⁷ Burkitt, D. P., in *Burkitt's Lymphoma*, ed. Burkitt, D. P., and Wright, D. H. p. 213. Edinburgh, Livingstone, 1970.
- ¹⁸ Stern, H., *British Medical Journal*, 1968, 1, 665.
- ¹⁹ Scott, T. F., McN., *American Journal of Ophthalmology*, 1957, 43, Part 2, 134.
- ²⁰ Knox, J. D. E., *Journal of the Royal College of General Practitioners*, 1968, 16, 23.
- ²¹ Smith, I. W., Peutherer, J. F., MacCallum, F. O., *Journal of Hygiene*, 1967, 65, 395.
- ²² Avery, G. B., Monif, G. G. R., Sever, J. L., and Liekin, S. L., *American Journal of Diseases of Children*, 1965, 110, 444.
- ²³ Report of the Public Health Laboratory Service Working Party on Rubella, *British Medical Journal*, 1970, 2, 497.
- ²⁴ Sever, J. L., Huebner, R. J., Castellano, G. A., and Bell, J. A., *American Review of Respiratory Diseases*, 1963, 88, Suppl. 342.
- ²⁵ Hildbrandt, R. J., Sever, J. L., Margileth, A. M., and Callagan, D. A., *American Journal of Obstetrics and Gynecology*, 1967, 98, 1125.
- ²⁶ Stern, H., Elek, S. D., Booth, J. C., and Fleck, D. G., *Lancet*, 1969, 2, 443.
- ²⁷ Nahmias, A. J., Alford, C. A., and Korones, S. B., *Advances in Paediatrics*, 1970, 17, 185.
- ²⁸ Nahmias, A. J., Josey, W. E., Naib, Z. M., Luce, C. F., and Guest, B. A., *American Journal of Epidemiology*, 1970, 91, 547.

Clinical Endocrinology

Gynaecological Symptoms

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Gynaecological symptoms such as menstrual disorders are a common feature of endocrine diseases. They may not be the most striking clinical manifestation of the condition, however, and the patient may not be seen by a gynaecologist. In this article the emphasis is on those conditions whose main symptom might be described as "gynaecological." Several symptoms, mainly menstrual upsets, will be considered, their endocrine causes indicated, and brief reference made to other possible explanations where this seems desirable.

Amenorrhoea

The terms primary and secondary amenorrhoea are often used, the first to describe the situation when a patient has never menstruated and the latter the development of amenorrhoea after menstruation has previously occurred. The terms have a useful descriptive value, though the possible causes of both types overlap to a considerable degree.

It should not be forgotten that amenorrhoea is physiological before the menarche, after the menopause, and during pregnancy and lactation. The age at the onset of menstruation is very variable and in the presence of apparently normal physical and sexual development special investigation before the age of 18 is not indicated. Before this, reassurance is all that is necessary, provided cryptomenorrhoea has been excluded. This is false amenorrhoea due to an imperforate hymen. The girl may experience lower abdominal discomfort each month when the endometrium is shed. The menstrual blood collects in the vagina and may eventually distend the uterus making it palpable abdominally. On inspection of the introitus the hymen may be distended by the retained blood. Treatment is by surgical incision of the hymen. Similarly there is a wide variation of the time of occurrence of the menopause. Though most women stop menstruating between the ages of 45 and 50, in 25% this occurs before the age of 45.

The most important cause of amenorrhoea to consider is, of course, pregnancy, the commonest cause of amenorrhoea in any practice. Only by thinking of it first in any woman in the reproductive age group who complains of amenorrhoea will

embarrassing mistakes be avoided. Denials of the possibility of pregnancy because the patient is on the pill, has not missed a period, has been bleeding continuously, or for a variety of other reasons are to be treated with reserve until pregnancy has been positively excluded. The return of menstruation after childbirth or abortion is also variable, though the first period will usually be at about six weeks. If the patient is lactating, however, the interval will be greater, usually three to four months.

HYPOTHALAMIC AMENORRHOEA

It is well known that emotional disturbances of various kinds can lead to amenorrhoea, owing to the influence of the cerebral cortex on the hypothalamus. Common examples of this are worries about examinations, living away from home for the first time, marital upsets, and nervous tension. Such factors should be specifically investigated in a patient who develops secondary amenorrhoea. Recognition of the relevant background factors and reassurance or help with them are the only appropriate therapeutic measures.

Pseudocyesis

The not uncommon condition of pseudocyesis or false pregnancy, which usually results from a great desire for or a fear of pregnancy, is also a hypothalamic disorder. The patient may develop all the signs and symptoms of pregnancy including abdominal swelling; fetal parts cannot, of course, be felt and the abdominal wall is held tense. Examination under anaesthesia will lead to disappearance of the swelling when the muscles of the abdominal wall are relaxed, but x-ray or ultrasonic examination of the abdomen should make this unnecessary.

Froehlich's Syndrome

Froehlich's Syndrome (dystrophia adiposogenitalis) is a hypothalamic disturbance in which primary amenorrhoea is a main feature, together with genital hypoplasia and obesity. Vigorous attempts at weight reduction may result in menstruation occurring. The Chiari-Frommel Syndrome, in which galactorrhoea (continuous secretion of milk) and amenorrhoea persist after pregnancy, is also believed to be of hypothalamic origin. It may be treated by stimulation of ovulation by clomiphene citrate.

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PITUITARY AMENORRHOEA

Amenorrhoea arising from a primary disorder in the pituitary gland is not common and the best, though rare, example is Sheehan's syndrome (postpartum pituitary necrosis). This results from ischaemia of the anterior pituitary after severe postpartum haemorrhage or shock. The patient fails to lactate after delivery and subsequently amenorrhoea and symptoms of lack of trophic hormones develop—notably hypothyroidism and evidence of adrenal cortical insufficiency: loss of axillary and pubic hair, loss of libido, and decrease of skin pigmentation. Treatment of the condition is by replacement therapy with steroids and thyroxine.

Pituitary Tumours

Pituitary tumours, all of which are rare, may be accompanied by evidence of gonadal failure, due to destruction of the anterior pituitary with widespread evidence of pituitary hypofunction. Gonadotrophin loss with consequent amenorrhoea is often the first sign of the lesion, and an x-ray film of the pituitary fossa is a necessary step in the investigation of such patients. The lesion in Cushing's syndrome may be a corticotrophin-secreting tumour of the pituitary.

Pituitary Failure

In the absence of a tumour or necrosis pituitary failure is responsible for some cases of amenorrhoea. There is a deficiency of gonadotrophin secretion but other hormones may not be affected. If an x-ray film of the pituitary fossa is normal and other causes of amenorrhoea have been excluded no treatment is indicated unless the patient wishes to become pregnant. Vaginal bleeding can be induced in these patients by cyclical replacement therapy, but this is pointless other than to show that the endometrium is capable of being stimulated. Such therapy may, if carried on for a long time, be harmful by further suppressing the pituitary. Should pregnancy be desired ovulation can be induced with clomiphene citrate or gonadotrophins. Careful monitoring of the patient's response to such therapy is essential.

ADRENAL AMENORRHOEA

Cushing's Syndrome

Cushing's Syndrome is a manifestation of hyperfunction of the adrenal cortex in which there is excess secretion of androgenic hormones and glucocorticoids. The characteristic obesity of the trunk is accompanied by hirsutism, amenorrhoea, hypertension, and hyperglycaemia. The lesion may be an adenoma or adenocarcinoma in the adrenal or a pituitary adenoma. In some cases no such cause can be demonstrated but adrenal hyperplasia exists. Diagnosis is aided by measurement of urinary keto-steroids and hydroxycorticoids, both of which are raised. Treatment is usually by surgery followed by replacement therapy.

Adrenogenital Syndrome

The adrenogenital syndrome may be present at birth or develop in childhood or after puberty. The cause is a tumour (simple or malignant) of the adrenal cortex or, more commonly, hyperplasia of the adrenal cortex. Amenorrhoea is present, often as a first sign, and is followed later by signs of virilism such as hirsuties, deepening of the voice, and enlargement of the clitoris. Secretion of adreno-corticotrophic hormone (ACTH) is increased and high levels of 17-ketosteroids are found in the urine. Treatment of adrenal hyperplasia is by the administration of corticosteroids, which suppress the exces-

sive secretion of ACTH and allow adrenal activity to return to normal. Secretion of gonadotrophins by the pituitary will follow with subsequent return of menstruation. Treatment of adrenal tumours, when present, is by surgical removal.

In Addison's disease or chronic adrenal insufficiency, amenorrhoea may be present but menstrual and gonadal function are often well maintained.

OVARIAN AMENORRHOEA

The most obvious example in this group is Turner's Syndrome or ovarian agenesis, in which the ovaries are represented merely by a streak, though the other pelvic organs are present, often underdeveloped. This condition is the result of the absence of a second X chromosome, there being 45 instead of 46 chromosomes. No Y chromosome is present, and consequently the patient always appears female. There may be characteristic physical abnormalities such as short stature, broad build, webbing of the neck, poorly developed breasts, sparse pubic hair, and cardiac abnormalities. These patients usually present with primary amenorrhoea and their appearance aids diagnosis. Oestrogen excretion is low but there may be high levels of gonadotrophins secreted from the pituitary. The diagnosis can be made by buccal smear and chromosome analysis. Laparoscopy will readily confirm the presence of streak gonads if this is thought necessary. Ovulation cannot be induced in these patients.

A second ovarian cause of amenorrhoea is the Stein-Leventhal Syndrome. In this condition normal oestrogen development in the ovaries is arrested at an androgenic stage. The underlying fault in the condition may lie in the hypothalamus or the pituitary rather than in the ovary. It presents clinically with either primary or secondary amenorrhoea or oligomenorrhoea with some virilism such as hirsutism or acne. The ovaries are enlarged, cystic, and have a thickened capsule. The urinary output of oestrogens and 17-ketosteroids is normal but the level of follicle stimulating hormone (FSH) may be raised. Laparoscopy and ovarian biopsy are valuable aids to diagnosis. Treatment is by surgical resection of the ovaries or by the administration of clomiphene citrate.

OTHER ENDOCRINE CAUSES

Hyperthyroidism in the adult may cause amenorrhoea or scanty menstruation, which responds to treatment of the thyroid disorder. Cretinism or less dramatic degrees of hypothyroidism in the young will cause impairment of physical and sexual development, and consequent amenorrhoea.

Diabetes mellitus in this age group may also cause amenorrhoea.

MISCELLANEOUS

Two other important causes of amenorrhoea which cannot, perhaps, be strictly described as endocrine disorders deserve mention here.

Obesity.—Considerable weight gain, especially over a short period, is not uncommonly associated with amenorrhoea. The reason for this is uncertain but the condition responds to strict dieting.

The Contraceptive Pill.—Occasionally after stopping oral contraceptives menstruation does not return. The cause of this phenomenon is not known but it is associated with endometrial atrophy. Usually menstruation reappears within a few months. There are no grounds for suggesting that patients should discontinue the pill for a few months intermittently to try and avoid this, for pregnancy is the commonest result. If, however, oligomenorrhoea develops while a patient is on the pill she should change to another form of contraception.

Oligomenorrhoea

This term means infrequent menstruation. It must be remembered that a cycle of 35 to 42 days is within normal limits and perfectly compatible with normal fertility. The endocrine causes of oligomenorrhoea are essentially the same as those of amenorrhoea but, of the conditions already mentioned, obesity and the Stein-Leventhal Syndrome are particularly likely to present in this way. With most of the others it is simply a matter of degree whether amenorrhoea or oligomenorrhoea is the manifesting symptom. An occasional but important organic cause of this symptom, tuberculosis of the endometrium, should always be excluded in such cases.

Menorrhagia and Metrorrhagia

Menorrhagia means that menstruation is unusually heavy or prolonged or both, but retains its cyclical character. Bleeding which is heavy and irregular or continuous is called metrorrhagia. There are many non-endocrine, organic explanations of these complaints which must be kept in mind, such as pregnancy disorders, fibroids, internal endometriosis (adenomyosis), and malignant disease of the pelvis. But several possible endocrine causes exist, as follows:

HORMONAL THERAPY

It is not unusual nowadays to see patients complaining of heavy or irregular bleeding who are receiving exogenous hormonal therapy—usually one of the standard oral contraceptives, or oestrogen therapy alone for menopausal symptoms, pruritus vulvae, or atrophic vaginitis. Specific inquiry should be made about such therapy. In the case of the pill the problem is often the occurrence of "break-through bleeding," which the patient interprets as a normal period. The pill is discontinued before completing the course and this leads to further bleeding and confusion. Careful instruction of the patient about taking the tablets and adjustment of the dose of progestogen in the pill should solve this difficulty.

Systemic oestrogen therapy for menopausal symptoms should be avoided as far as possible because of the possibility of causing abnormal bleeding: reassurance and sympathetic explanation should be used instead. Local therapy such as an oestrogen-containing cream or pessary is to be preferred to systemic oestrogens for the treatment of atrophic vaginitis.

HYPOTHALAMIC AND PITUITARY DISORDERS

Lesions of the hypothalamus and pituitary can cause excessive bleeding by over-stimulation of the ovaries. An eosinophil adenoma producing acromegaly is an example of this. The hypothalamus may also be responsible for the menorrhagia which can occur in emotional upsets related to anxiety states and worries about marital or social problems.

THYROID AND OVARIAN DISORDERS

Hypothyroidism may be associated with excessive and prolonged menstruation, usually without ovulation.

There are some ovarian lesions which scarcely qualify as endocrine disorders in the usual sense of the term but produce menstrual upsets by secreting oestrogens. The granulosa cell tumour can cause excessive bleeding, though, as it usually occurs in older patients, it more commonly produces postmenopausal bleeding. Simple follicular cysts of the ovary can similarly disturb menstrual function.

DYSFUNCTIONAL UTERINE BLEEDING

This is the name given to abnormal uterine haemorrhage for which no organic basis is demonstrable. It is, therefore, a diagnosis made by exclusion. The normal hormonal basis of menstruation is disrupted and a variety of clinical patterns follow. The cycle may be shortened or become irregular and ovulation may or may not occur. Metropathia haemorrhagica is one manifestation of dysfunctional uterine haemorrhage which has earned its special name owing to its characteristic clinical and histological features.

Dysfunctional bleeding may occur at any age but is most common at the extremes of menstrual life. In young girls dysfunctional bleeding is the commonest cause of menorrhagia and, provided that the haemoglobin levels remain satisfactory and clinical examination is normal, reassurance is usually all that is required. The condition at this age has a tendency to spontaneous cure. In the intermediate age group an organic explanation of menorrhagia is more likely, especially one associated with pregnancy, and in those patients approaching the end of their menstrual life malignant disease must be excluded by curettage. If organic disease is excluded and treatment is considered necessary because, for example, of anaemia, hormonal therapy can be employed to control the bleeding. One of the standard oral contraceptives is often satisfactory or a combined progesterone-oestrogen preparation with a higher dose of progestogen. In patients approaching the menopause, hormonal therapy is less successful and hysterectomy will often be the treatment of choice.

Other Gynaecological Symptoms

POSTMENOPAUSAL BLEEDING

Malignant disease is always uppermost in one's mind in dealing with this problem but possible endocrine causes, as above, are an oestrogen-secreting tumour of the ovary and exogenous administration of oestrogens. In both cases the endometrium is built up and then shed with resultant bleeding.

VULVAL AND VAGINAL MONILIASIS

Three groups of patients are particularly susceptible to monilial infections: patients with glycosuria, pregnant women, and women taking oral contraceptives.

Hitherto unsuspected diabetes may be diagnosed by the gynaecologist who sees a middle-aged or elderly obese patient who complains of pruritus vulvae and is found to have monilial vulvovaginitis. A glucose tolerance test is indicated in such a patient.

FRIGIDITY

Frigidity or loss of libido is not usually due to endocrine disease but may occur in patients who have loss of adrenal cortical function as, for example, in pituitary failure. Some women experience loss of libido with the onset of the menopause and the diminution of ovarian function. Nevertheless, this is by no means always the case.

In conclusion it should be emphasized again that the symptoms that have been considered as manifestations of endocrine disorders are common in gynaecology and may have a physiological or pathological basis other than in a disorder of the endocrine system. Most of the endocrine conditions described are rare when compared with the amenorrhoea produced by pregnancy, on the one hand, and excess bleeding from fibroids or malignant disease, on the other.