ENDOCRINES IN THEORY AND PRACTICE

This article is one of a series on Endocrinology contributed by invitation

THE ADRENO-GENITAL SYNDROME AND TUMOURS OF THE SUPRARENALS

BY

A. W. SPENCE, M.D., M.R.C.P.

Tumours of the suprarenal glands of clinical importance may be conveniently classified as follows:

CORTEX

Innocent: Adenoma.

Malignant: Hypernephroma.

Both may be associated with the adreno-genital syndrome.

MEDULLA

Innocent: Pheochromocytoma (hyperchromaffinism)—associated with paroxysmal or continuous hypertension.

Malignant: Neuroblastoma, causing clinical features of (a) Pepper type; (b) Hutchison type.

The Adreno-genital Syndrome (Adrenal Virilism)

The adreno-genital syndrome is a reversion to masculinity, associated with carcinoma, adenoma, or simple hyperplasia of the suprarenal cortex, but these cortical changes are more often present without any somatic or sexual disturbances. On the other hand, in some cases of the syndrome the glands may be apparently normal. The clinical manifestations depend on the type of lesion and on the time of onset. Malignant tumours are associated with more rapid changes than benign tumours of slow growth or simple hyperplasia. The disease may arise at any age, even developing *in utero*, but when it supervenes during the period of rapid growth of the individual—for example, up to puberty—the changes will be more marked than when growth is not so rapid—for example, after maturity. For this reason it is convenient to describe the condition as it occurs in different age groups, but it must be realized that there is no definite demarcation between each group and that each picture merges gradually into the other. It is pre-eminently a disease of the female sex and afflicts males only during childhood. It may be divided into four main clinical types: those which arise—(1) during foetal life; (2) before puberty; (3) after puberty; and (4) after the menopause.

DURING FOETAL LIFE

When the disorder arises before sexual differentiation the changes are those of feminine pseudo-hermaphroditism. Externally the bodily configuration approaches the male type, with perineal hypospadias, a large clitoris peniformis, and a vulva-like cul-de-sac. Internally a uterus and ovaries are present. When it appears later in foetal life these changes are less pronounced: a large clitoris and hypospadias are present; there may be growth of hair on the face, axillae, and pubes; but the uterus and ovaries are atrophic.

BEFORE PUBERTY

Manifesting itself during this period the condition is one of precocious puberty.

In girls statural growth increases and the configuration of the body may approach the male type; the voice may deepen and there may be a growth of hair of male dis-

tribution—that is, on the face, in the axillae, on the legs and forearms, and on the pubes extending towards the umbilicus. They may become obese, but the obesity is not that of childhood, but of the plethoric type seen in middle age. As a rule the mentality is consistent with the true age of the patient, but occasionally there may be retardation of mental development or even severe mental disorder. The external, but not the internal, sex organs develop precociously, especially the clitoris, which is hypertrophied. Although the condition is termed “pubertas praecox” it is in effect a false precocity, as it is most uncommon for these patients to menstruate. Ossification and dentition are often hastened, but as the epiphyses join earlier than usual their height is eventually less than normal. Excessive muscular development, as in the male counterpart, is not generally found.

In boys there are also increase in growth, deepening of the voice, and excessive growth of hair. Ossification and dentition are hastened, with early union of the epiphyses. The external genitals are greatly enlarged, resembling those of an adult, but usually there are no sexual changes such as libido. In some cases, however, there may be increased sexual activity. In one group there is a generalized obesity of the plethoric type; in another excessive muscular development and strength, described by Parkes Weber as the infant Hercules type; in others obesity and muscular development may be combined. Finally the patient may become enfeebled through muscular wasting, develop a prematurely aged appearance, and die at an early age.

AFTER PUBERTY

In adults the adreno-genital syndrome is practically confined to women, occurring most often between the ages of 18 and 25. One of the most troublesome symptoms in these patients is the hirsuties, which may be slight in some but very marked in others. It is characteristically of the male type and may be widespread in its distribution. It appears most commonly on the face as a beard and moustache, and on the forearms, thighs, and legs; the hair in the pubic region spreads upwards in a triangular fashion to the umbilicus, and may even cover a large part of the abdomen. It may appear on the chest between the breasts, around the nipples, and on the back. In older women the hair of the scalp may fall out, particularly in the frontal region.

In some patients the voice deepens, the breasts atrophy, and the body tends to become masculine in appearance, but not to the same extent as in children, in whom feminine characteristics have not fully established themselves before the onset of the disorder. Other sufferers may become rapidly and excessively obese, with supra-clavicular pads of fat, large pendulous breasts consisting mainly of fatty tissue, and folds of fat on the abdomen and back. In these patients there may be purplish cutaneous striae situated over the lower abdomen. At first menstruation becomes scanty and irregular, and later there is amenorrhoea, which is often accompanied by pains in the pelvis, nausea, and vomiting. As in the other age groups the clitoris is often enlarged.

Psychological changes may be a marked feature, although these are unusual. Langdon-Brown and Girling Ball have reported a case of a woman whose earliest symptom was an obsessional neurosis that she was

changing into a man, which produced in her a state of terror. There may be a lack of modesty, a masculine outlook, an indifference to or a complete loss of sexual desire, and in a few deviation of the sexual instinct to homosexuality.

There may be acneiform eruptions, and, rarely, greyish spots of pigmentation on the forehead, axillae, and back. An abdominal mass may sometimes be palpable in those cases associated with a tumour. It is unusual to find metastases, but when they occur they are situated in the bones, lungs, and liver. Occasionally there is osteoporosis. There may be vascular hypertension, hyperglycaemia, and glycosuria. The basal metabolic rate, which varies considerably, is often slightly increased.

AFTER THE MENOPAUSE

The clinical picture in these cases is not so well marked, as hirsuties may be absent. Obesity is common in most patients, who occasionally suffer from menorrhagia.

Diagnosis

A palpable tumour in the renal region is good evidence that the disturbance is of adrenal origin; in many cases, however, no such sign is present. Recently a method of demonstrating the suprarenals by x rays has been devised. Air is introduced into the perirenal fascia and its position observed by means of an x-ray film. The mass of air is then forced by manual pressure into the tissues surrounding the suprarenals. The best results are obtained by an x-ray film taken eighteen to twenty-four hours later. By this means suprarenal enlargement may in some cases be detected. Another method is to determine the position of the kidneys by x-ray examination after intravenous uroselectan.

The diagnosis of precocious puberty as a manifestation of the adreno-genital syndrome may be difficult in the absence of a palpable adrenal tumour, and the condition must be differentiated from those cases associated with pineal tumour, lesions in the region of the hypothalamus and mid-brain, ovarian granulosa-cell tumour, and testicular tumour, all of which are extremely rare. In girls a reversion to the masculine form, hirsuties, and amenorrhoea are in favour of an adrenal origin. Pineal tumours are not as a rule associated with virilism and occur in boys, whereas adrenal virilism is commoner in girls. In addition to increased skeletal growth, precocious development of the external genitals, and obesity, pineal tumours may give rise to such disturbances as somnolence, psychological changes, deafness, blindness, ocular palsies, and symptoms and signs of increased intracranial pressure. Localizing signs may also be present in cases of tumour in the region of the hypothalamus and third ventricle. Granulosa-cell tumours, which arise from granulosa-cell rests in the ovary, have a feminizing influence. They are generally unilateral, vary considerably in size, and usually occur in elderly women, in whom they cause uterine bleeding. In the few cases which have been described in children they produce a precocity characterized by increase in skeletal growth, premature development of the feminine form, premature growth of the mammary glands, external genitals, and uterus, and periodic uterine bleeding. The precocious appearance of axillary and pubic hair has also been observed. It must be noted that in the false precocity of the adreno-genital syndrome premature development of the mammary glands and uterine bleeding are rare features.

When the obese type of the adreno-genital syndrome appears in adults the most important condition from which it has to be distinguished, if this be possible, is

Cushing's syndrome, a pluriglandular disturbance ascribed by Cushing to an increase of the basophil cells of the anterior pituitary with secondary adenomatous or hyperplastic changes in the suprarenal cortex. The group of cases of pluriglandular disease described by Achard and Thiers as "diabetes of bearded women," and characterized by hirsuties, obesity, amenorrhoea, hypertension, cutaneous striae, and glycosuria, have features similar to those of Cushing's syndrome. In the cases that came to necropsy pituitary or adrenal tumours were found. It is disputed whether such cases should be considered examples of Cushing's syndrome or are types of the adreno-genital syndrome. Cases of the adreno-genital syndrome have been described which were practically identical with Cushing's syndrome and in which at necropsy an adenoma of the adrenal cortex was found and no increase in the basophil cells of the anterior pituitary. Langdon-Brown, two years before Cushing described his syndrome, remarked on the similarity of the signs produced by lesions of the anterior pituitary and the adrenal cortex. Clinically, and even pathologically, it may be impossible to reach a definite conclusion.

Masculinization is also caused by the rare ovarian tumour termed "arrhenoblastoma," which arises from undifferentiated cells in the rete ovarii and has the structure of testicular tubules. In women with this tumour menstruation ceases and the breasts atrophy, there is a considerable growth of hair on the face, and sometimes on the chest, abdomen, and extremities, the clitoris enlarges, the voice may become deeper, and the configuration of the body approaches the masculine type.

Treatment

Laparotomy should be performed, and if a suprarenal tumour is found it should be removed. When a tumour is not found, Broster removes the larger suprarenal, with good results in post-pubertal virilism. Within a few days of the operation the excessive hair begins to be shed and can be pulled out with little or no pain. The mental outlook changes to the feminine type, the breasts develop, and normal menstruation returns. The results in pre-pubertal cases are disappointing, probably because the changes are more fundamental and long-standing. Some patients with precocious puberty, however, have improved after the operation—hair growth has become normal, the obesity has diminished, and the body has assumed more childlike form; but in a recent case of precocity in a boy of 5 the external genitals did not diminish in size.

Medullary Tumours

Phaeochromocytoma (Hyperchromaffinism).—This form of tumour, which is somewhat rare, is usually not malignant, and consists of highly differentiated chromaffin cells which secrete adrenaline or some allied compound. About half of the cases are associated with paroxysmal or continuous hypertension. A paroxysmal hypertensive attack is characterized by the sudden onset of dyspnoea, tachycardia, headache, pallor, and a feeling of constriction about the heart and epigastrium, often accompanied by nausea, vomiting, and apprehension. There may be glycosuria and hyperglycaemia. Pulmonary oedema may occur, and coma due to hypertensive encephalopathy. Sudden death has been reported in some instances. At the height of an attack there may be a sudden fall of blood pressure, which is accompanied by flushing of the face, contraction of the pupils, profuse sweating, and salivation. A tumour may be palpable in the renal region, or displacement of the kidney by a tumour mass may be

observed on x-ray examination. Paroxysmal hypertension may eventually become persistent, and hypertensive crises may supervene in continuous hypertension.

Neuroblastoma (Sympathoblastoma).—These tumours appear very early in life and arise from the sympathetic ganglion cells. They are highly malignant and were formerly regarded as sarcomata. They are divided into two main types, but the histology is essentially the same in each. The type described by Pepper occurs in the youngest infants, and is characterized by metastases in the liver, lungs, and abdominal glands. In these cases the primary growth is more often situated in the right suprarenal, which may be palpable. In the Hutchison type the primary tumour is more usually in the left suprarenal and metastases appear in the cranium and behind the orbit, causing proptosis and papilloedema, and simulating the clinical picture of chloroma and of intra-orbital haemorrhage in scurvy.

BIBLIOGRAPHY

Addison's Disease and Suprarenal Insufficiency

- Addison, T. (1868). *A Collection of the Published Writings of the late Thomas Addison*; London, New Sydenham Society.
Allott, E. N. (1936). *Lancet*, **1**, 1406.
Goldzieher, M. A., and Gordon, M. B. (1932). *Endocrinology*, **16**, 165.
Graham, G. (1936). *Proc. roy. Soc. Med.*, **29**, 1137.
Greene, C. H., Rowntree, L. G., Swingle, W. W., and Pfiffner, J. J. (1932). *Amer. J. med. Sci.*, **183**, 1.
Harrop, G. A., and Weinstein, A. (1932). *J. Amer. med. Assoc.*, **98**, 1525.
Hartman, F. A., Thorn, G. W., Lockie, L. M., Greene, C. W., and Bowen, B. D. (1932). *Ibid.*, **98**, 788.
Loeb, R. F., Atchley, D. W., Gutman, E. B., and Jillson, R. (1933). *Proc. Soc. exp. Biol.*, N.Y., **31**, 130.
— and Stahl, J. (1935). *J. Amer. med. Assoc.*, **104**, 2149.
Rowntree, L. G., Greene, C. H., Ball, R. G., Swingle, W. W., and Pfiffner, J. J. (1931). *Trans. Ass. Amer. Phys.*, **46**, 123.
Simpson, S. L. (1932a). *British Medical Journal*, **2**, 625.
— (1932b). *Quart. J. Med.*, **1**, 99.
— (1934). *Proc. roy. Soc. Med.*, **27**, 383.
— (1936). *Ibid.*, **29**, 1141.
Snell, A. M. (1934). *Proc. Mayo Clin.*, **9**, 57.
Susman, W. (1936). *Endocrinology*, **20**, 383.

The Adreno-genital Syndrome

- Broster, L. R., and Vines, H. W. C. (1933). *The Adrenal Cortex: A Surgical and Pathological Study*; London, H. K. Lewis and Co.
Brown, W. L., and Ball, W. G. (1930). *St. Bart's Hosp. Rep.*, **63**, 53.
Bullock, W., and Sequeira, J. H. (1905). *Trans. path. Soc.*, **56**, 189.
Collett, A. (1924). *Amer. J. Dis. Child.*, **27**, 204.
Glynn, E. E. (1911–12). *Quart. J. Med.*, **5**, 157.
Holmes, G. (1924–5). *Ibid.*, **18**, 143.

Medullary Tumours

- Belt, A. E., and Powell, T. O. (1934). *Surg. Gynec. Obstet.*, **59**, 9.
Hick, F. K. (1933). *Arch. Pathol.*, **15**, 665.
Hutchison, R. (1907–8). *Quart. J. Med.*, **1**, 33.
Pepper, W. (1901). *Amer. J. med. Sci.*, **121**, 287.
Rabin, C. B. (1929). *Arch. Pathol.*, **7**, 228.

General

- Kepler, E. J. (1935). *Arch. intern. Med.*, **56**, 105.
Rolleston, H. D. (1936). *The Endocrine Organs in Health and Disease*, Oxford University Press.
Rowntree, L. G., and Ball, R. G. (1933). *Endocrinology*, **17**, 263.

A David Anderson-Berry gold medal, together with a sum of money amounting to about £100, will be awarded in July, 1938, by the Royal Society of Edinburgh to the person who, in the opinion of the council, has recently produced the best work on the nature of x rays in their therapeutical effect on human diseases. A similar award will be made every three years. Applications for this prize are invited. They may be based on both published and unpublished work, should be accompanied by copies of relevant papers, and must reach the general secretary, Royal Society of Edinburgh, 22, George Street, Edinburgh, 2, by June 1, 1938.

WOMEN'S WELFARE AND BIRTH CONTROL

DEPUTATION TO MINISTER OF HEALTH

Sir Kingsley Wood, the Minister of Health, received on February 2 a deputation organized by the National Birth Control Association, representing twelve societies interested in the subject of women's welfare and birth control. The deputation was introduced by Lord Horder, and the other principal speakers were the Countess of Limerick, Dr. Jocelyn Moore, Mr. Cedric Lane-Roberts, Lady Denman, and Mrs. Freeth.

The deputation urged that the present provision of gynaecological clinics to deal with the medical care of married women, at which advice on contraception would be available to those women for whom further pregnancy would be detrimental to health, was inadequate and that but little exercise had been made by local authorities of the powers which they possessed in the matter. Increased provision was very necessary, and it would lead to a reduction not only in maternal morbidity and mortality, but in criminal abortion, which was due to the need felt by women to escape pregnancy on medical and other grounds.

The Case for More Clinics

The deputation urged the Minister to issue a circular to local authorities encouraging them to establish gynaecological clinics in which birth control should take its proper place as part of the general medical care of women, and indicating the lines on which the clinics should be run. The deputation attached great importance to the work being carried out as an integral part of the maternity and child welfare schemes of local authorities.

The Minister's Reply

Sir Kingsley Wood said he recognized the force of many of the arguments that had been advanced by the deputation, but that both Minister and local authorities were bound to observe the limitations imposed by Parliament on their activities. The local authorities, for instance, had at present no legal power to provide birth control clinics as such, and there was no statutory duty upon them to provide advice or medical assistance in relation to birth control. There were still differences of opinion, and in a matter of this kind particularly it was necessary and right that the legislative position should be fully maintained, and if any alteration in policy was made it should receive Parliamentary approval.

The Maternity and Child Welfare Act empowered local authorities to make arrangements for attending to the health of expectant mothers and nursing children under school age. A clinic provided under the Act could not, therefore, lawfully be used for any woman who was not an expectant or nursing mother. Such clinics were not primarily intended for sick women. In fact the object of the Act was preventive, and expectant and nursing mothers were encouraged to attend these clinics in order that sickness should, if possible, be avoided.

Existing Clinics

There were also the clinics provided under the Public Health Acts, and their functions were different from those of the maternity and child welfare clinic. They extended only to the provision of hospitals or clinics for the reception of sick persons, but any sick woman might attend such hospital or clinic for advice and treatment. Apart from the clinics for ante-natal or post-natal supervision of expectant or nursing mothers and clinics for the treatment of women who were sick, there was no statutory authority for the establishment of clinics providing for the facilities suggested by the deputation.

Sir Kingsley Wood emphasized that the maternity and child welfare centres were not ordinarily designed or