is the excess of these vital hormones which produces atrophy of the opposite adrenal. As Crooke points out, this likewise would help to explain the occasional incidence of Addison's disease in some children of Group I virilism due to bilateral hyperplasia if it be assumed that large amounts of abnormal androgens are being produced at the expense of vital hormones.

The present case, so far as carbohydrate metabolism is concerned, comes more into line with certain cases of Addison's disease than with cases of virilism, in which the tendency is in the direction of lowered sugar tolerance. With one adrenal apparently normal, the destruction of the adrenal medulla by the tumour would hardly seem sufficient cause in itself for the marked hypoglycaemia.

In view of the exceptional rate of secretion of androgenic steroids it cannot be excluded that these may have suppressed the anti-insulin action of the right adrenal without causing an atrophy of the gland such as would be expected if the tumour was of the type producing vital hormones.

Some of the present perplexities in this field will most likely be resolved when more clues to the differences in the androgens in clinically distinctive groups are available. The introduction of the relatively simple qualitative dehydroisoandrosterone test is an important step in this direction. As a test of malignancy the potentialities would seem to be not less than those of such acknowledged diagnostic aids as the gonadotrophin assays for chorion epithelioma and the serum acid-phosphatase estimation applied to prostatic carcinoma.

Addendum.—The dehydroisoandrosterone test referred to above is applied to the type of urinary extract used for 17-ketosteroids. The dry extract is first treated with concentrated sulphuric acid at 25° C. for 20 minutes, the solution diluted with an equal volume of water while being kept cold, and then heated for one minute in a boiling-water bath. A blue or blue-violet colour developing in the final stage indicates the presence of excess dehydroisoandrosterone and its closely related steroids in the extract—a feature of tumour urine extracts but not of the corresponding urinary extracts for cases of adrenal hypertrophy.

In the case described the distinct reaction was readily obtained even when the amount of extract used was reduced to the equivalent of no more than 0.1 ml. of original urine.

Summary

A case is described in which a new test for carcinoma of the adrenal gland has been established.

This test differentiates carcinoma from hyperplasia.

Gross abnormalities of metabolism were present in the terminal stages of the condition.

REFERENCES

- Crooke, A. C. (1946). *Proc. R. Soc. Med.*, **39**, 516.
Patterson, J. (1947). *Lancet*, **2**, 580.

Unlike the doctors and dentists, pharmacists welcomed the new National Health Service Act, said Mrs. J. K. Irvine, president of the Pharmaceutical Society of Great Britain, speaking in Edinburgh on April 2. Subject to satisfactory terms of service and remuneration they were prepared to take their part in the new service. Under the Act pharmacy became a complete public service applying to the whole population. The new service was going to change pharmacy just as much as the medical benefit part of the Act of 1911 had revolutionized the pharmacy of that day. Pharmacy welcomed the Act because it put an end to the dispensing doctor. Practically all the dispensing would be done by pharmacists. It meant the complete separation of prescribing and dispensing. Pharmacy, so far, was taking the Act on trust, because as yet they had little idea of the terms of service or the remuneration. They hoped that trust would be justified, for the time was now short for any extended or controversial negotiations with the Minister of Health.

ADRENAL FEMINISM DUE TO CARCINOMA OF THE ADRENAL CORTEX

A CASE REPORT AND REVIEW OF THE LITERATURE

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Feminism can be defined as the development of female characteristics in a male. This is usually manifested as a feminine distribution of subcutaneous fat and gynecomastia, often with testicular atrophy and a feminine type of hair distribution. We do not consider that syndromes associated with the failure of development or regression of primary or secondary male characteristics alone as feminism.

Parkes Weber (1926) describes gynecomastia as a rare occurrence in hypogonad states, whether this hypogonadism be primary and possibly due to pituitary insufficiency, or secondary following disease or trauma of the testes. He quotes some remarkable cases, including unilateral gynecomastia following injury or disease of the testes which has itself sometimes been unilateral. Cases of gynecomastia after castration and prostatectomy have been described in the literature. Very rarely, gynecomastia occurs in chorion epithelioma of the testes. Gynecomastia has been reported amongst men engaged in the handling and packing of oestrogen preparations, and has been seen in cases of advanced liver disease, apparently due to the failure of the liver to carry out its role of detoxicating the normally occurring oestrogens.

The most striking group, however, comprises those cases with an adrenal origin. Seven cases of feminism due to carcinoma of the adrenal cortex have been reported—the one described below is the eighth. Broster also describes feminism in cases of hyperplasia of the adrenal cortex, and has performed unilateral adrenalectomy, with improvement. Roholm and Teilum (1942) also discuss the possibility of such a hyperplasia causing feminism.

Review of Recorded Cases

It is with the clinical picture of feminism due to adrenal neoplasm that this paper is concerned. The first case was described by Bittorf in 1919, and since then Parkes Weber (1926) and zum Busch, Holl (1930; 2 cases), Lissner (1936), Simpson and Joll (1938), Roholm and Teilum (1942) have published cases. The ages of the eight patients were 15, 26, 27, 33, 34, 40, 44, and 44. The presenting symptom varied in the series: five out of the eight had gynecomastia and complained from the onset of swelling or pain in the breasts; the remainder of pain, discomfort, or a lump in the upper abdomen—i.e., of the causal neoplasm. In three cases there were also reduction in size of the external genitalia—penis, testicles, or both—and loss of libido or potency. Our patient complained of loss of weight and of sweating—and Holl's second patient of obesity. Haemoptysis due to secondary deposits occurred in one case.

Clinical examination revealed gynecomastia in all cases, varying in degree from "as in a girl" to "feminine" size and appearance. Holl's second case had great tenderness. The breasts are described as being nodular or "glandular" to palpation. Holl and Lissner recorded secretions from the nipples. Pigmentation of the areola and hypertrophy of Montgomery follicles are also mentioned. In four of the

cases the penis and testes were small, and testicular atrophy in some instances was extreme—the “size of a pea” (Bittorf). Two authors reported the genitalia as “normal,” two others made no mention of their state. A varicocele occurred in two cases on the same side as the adrenal tumour. Secondary sex characters seemed to show little changes, and most cases had a normal masculine hirsuties, although in two instances the beard area was described as becoming softer. In a 15-year-old boy there was no facial hair, and the pubic hair was described as transverse female type. In Bittorf's case the voice was high-pitched, but there had been no recent change. Holl, who recorded acne and dilatation of skin veins in one of his cases, was the only author to describe changes in the skin.

The general nutrition and body weight were normal in four of the cases, Holl's second case was grossly obese, and Simpson and Joll's (1938) case gained weight before becoming emaciated. Two cases had lost weight. Facies is described in only three of the cases—two as being “soft” (one patient changed so greatly that his acquaintances failed to recognize him), and the third (our case) as normal. There was a loss of libido and potency in three cases; the patients seem to have become sexually indifferent. The development of homosexuality is not recorded. A palpable abdominal mass or “fullness” was present in all cases, and in all but one was left-sided. Two cases showed increased pigmentation of the skin, in two it was absent, and in the remainder it was not commented upon. Blood pressure was normal where it was recorded.

Pyelography was carried out in four cases, and in each there was depression downwards of the kidney, and in some there was rotation. Two radiologists observed a mass above the kidney. The single glucose-tolerance curve in the series revealed an impaired tolerance to glucose. No basal metabolic rate estimations have been recorded. X-ray examination of the skull and sella turcica, when made, was normal.

Estimations of oestrogens and androgens were recorded in three cases: all showed moderate excess of androgens, and in the two cases investigated gross excesses of urinary oestrogens were found, as follows:

Simpson and Joll.—Androgens: comb-growth capon units, 25-100 per litre (normal, 8-25). Oestrogens: 100-6,400 M.U. per litre (normal, 20). Aschheim-Zondek test negative.

Roholm and Teilum.—Androgens: 54-164 C.C.U. (normal, 8-25). Oestrogens: 750-8,000 M.U. (normal, < 20). Gonadotrophin: 30-50 R.U. (normal, < 30).

Armstrong and Simpson.—Ketosteroids: May, 1942, 34 mg.; November, 1942, 108 mg. (normal 6-23 mg. in 24 hours).

Treatment.—In two of the four cases operated upon nothing could be done (Armstrong and Simpson; Holl, Case 1). In Simpson and Joll's case the tumour was removed, but the patient died from secondary deposits. Holl's second patient was operated on successfully by Hertle, and 12 months later was still alive and well, showing no evidence of secondary deposits.

Course.—In five cases the condition ran its course in a few months, the patients dying of cachexia and secondary deposits. In Simpson and Joll's case the duration was three years and in Roholm and Teilum's case five years. Holl's case remains unique as a possible cure. The younger patients have all died quickly; the older group survived longer.

Post-operative Results.—Holl's patient regained his masculine appearance; his penis and testes became larger; libido and potency returned. The breasts, which had become very tender and congested, rapidly became painless and soft, pigmentation disappeared, and when last seen they were still getting smaller. Simpson and Joll's patient gained weight, the breasts became smaller, the genitalia larger, and there was a partial return of libido and potency.

This was only temporary, and he redeveloped all his symptoms owing to secondary deposits.

Pathology.—All cases have been due to malignant adrenal tumour arising in the adrenal itself, except in Lisser's case, which arose from an adrenal rest. All metastasized except Holl's second case. Metastases have occurred in lungs, bones, liver, lymph nodes, and the opposite adrenal.

Case Report

The patient, a policeman aged 40, was admitted to hospital in February, 1942, complaining of pain below the left costal margin, night sweats, and loss of weight. Examination revealed a tender mass closely resembling a spleen protruding two finger-breadths below the left costal margin. The patient was of good physique and showed no signs of loss of weight. Whilst in hospital he ran a low-grade intermittent pyrexia. Splenomegaly was suspected, but full investigation revealed no clear cause for the pyrexia or the “splenomegaly.” He was discharged home and told to report to the out-patient department in two months. When seen again in May, 1942, he complained of a pain in the right breast, and was found to have developed bilateral gynaecomastia. On his readmission to hospital it was observed that the pain in the left side of the abdomen had worsened and now radiated to the left hip. He was then investigated as a possible case of adrenal neoplasm.

On examination the patient was of normal bodily contour, with no obesity or feminine distribution of fat. The facies and hair distribution were normal for an adult and had shown no recent change. To external examination the genitalia also appeared normal. There was no abnormal pigmentation. A well-marked bilateral mammary swelling could be felt, due to the presence of nodular glandular tissue. Clinical examination of the cardiovascular and respiratory systems revealed nothing of note; the blood pressure was 128/88. The central nervous system was normal, and urinalysis showed nothing abnormal. Haematological investigation revealed a slight hypochromic anaemia. The leucocyte count varied between 7,500 and 12,300 per c.mm., and there was a slight absolute lymphocytosis. The Wassermann reaction was negative.

Routine chest radiography showed a “possible calcified primary complex, but no evidence of recent disease.” The report on the intravenous pyelogram read: “Right pyelogram normal; left kidney seems to be displaced downwards and laterally, ? due to mass”; and the retrograde pyelogram: “No abnormality of pelvis or calices of left kidney, but the kidney is displaced downwards and laterally. Right side, nil.”

17-ketosteroid investigations gave the following 24-hour results: May 22, 34 mg.; Sept. 30, 108 mg.

At laparotomy on June 17 Mr. T. A. Hindmarsh found a large adherent and necrotic tumour above the left kidney. Because of the vascularity of the tumour mass, its size, and extensive adhesions, no attempt was made to remove it. Subsequently the patient deteriorated rapidly; he became emaciated and jaundiced, he developed ascites, and his liver became enlarged and nodular. Death occurred during November, 1942, some eleven months from the onset of his symptoms. There was a terminal haematuria.

Abstract of Dr. J. G. Thomson's Necropsy Report

The body is of a well-developed but poorly nourished subject; there is deep jaundice. The breasts are larger than normal in a male and measure 7.5 by 8 cm., with a maximum thickness at nipple level of 1 cm. The nipples are prominent, free from hairs, and measure 0.7 cm. in diameter. Hair on the trunk shows the normal masculine distribution.

Internal Examination:—Lying above the left kidney, which is compressed and distorted but nowhere invaded, is a large lobulated tumour measuring 17 by 13 by 19 cm. It appears to be well encapsulated, and section reveals that the tumour mass is divided into lobules 3.5 cm. in diameter by fibrous septa. Approximately three-quarters of the growth is haemorrhagic or yellow and necrotic; the remainder is pink in colour and soft in consistency. No left adrenal is recognizable.

Secondary deposits are present in both lungs; they are mainly small, and measure up to 2.5 cm. in diameter (the left lung

has six secondary deposits, the right has eight). The liver is enormously enlarged to 8,010 g. by secondary deposits up to 7 cm. in diameter, most of which show extensive yellow foci of necrosis. An isolated secondary deposit is present in the twelfth thoracic body, and the first and second lumbar bodies are diffusely infiltrated by tumour. The breasts are readily separated from the surrounding tissues, and the left, without nipple, weighs 28 g.; section shows it to consist of firm fibrous tissue. The prostate is normal in size and appearance. The testes are not significantly reduced in size; they measure 4 by 2.5 by 2 cm. (with epididymis) and together weigh 28 g. The cut surfaces are brownish and atrophic.

The following organs show no obvious abnormalities: thyroid, pituitary, right adrenal, spleen (240 g.), brain (1,310 g.), heart (208 g.), and right kidney.

Histology.—This confirms the adrenal origin and carcinomatous nature of the tumour. Differentiation varies a great deal and nuclear irregularities are frequent, but even in the secondary deposits resemblances to adrenal cortical cells in nucleus and the lipid content of the cytoplasm are retained to a varying degree. Necrosis is everywhere a prominent feature, and in the sections studied half the tumour is necrotic. Whilst a fair degree of resemblance to adrenal cortical cells is present the picture nowhere approximates to that of the adrenal cortex or of a well-differentiated cortical adenoma, and in particular the normal relationship of cortical cells to sinusoids is nowhere evident. *Testes* show early atrophic changes with marked fibrous thickening of the walls of the tubules, diminution of the cellular content, and an increase of wear-and-tear pigment in the interstitial cells. *Breasts* show dilated ducts containing protein material and cells, and abundant glandular tissue, producing a picture not unlike that of a female breast.

Comment

Acquired feminism due to carcinoma of the adrenal cortex causes a well-defined syndrome of gynaecomastia, abdominal tumour, atrophy of the external genitalia, and loss of libido and potency. The condition is rapidly fatal, especially in the younger patients. Biochemically there are a moderate excess of urinary androgens and a gross excess of oestrogens. A most striking feature is the invariable presence of a palpable abdominal tumour.

The possibility that feminism might be due to hyperplasia of the adrenal cortex has been suggested by Broster and Vines (1933), who have clearly shown that virilism can be due to hyperplasia of the adrenal cortex as well as to carcinoma or adenoma. They consider that, similarly, feminism may be due to hyperplasia of the adrenal cortex. Roholm and Teilum (1942) also discuss this possibility.

In our clinic we are investigating cases of hypogonadism, with or without gynaecomastia, and are considering hyperplasia of the adrenals as a possible aetiological agent.

Summary

The condition of feminism is defined and discussed.

The eight reported cases due to carcinoma of the adrenal cortex are analysed in detail.

A clinical report and necropsy findings of a case of feminism due to carcinoma of the left adrenal are described.

Our thanks are due to Dr. J. G. Thomson, of the Department of Pathology, for the report on the necropsy and the histological findings, to Dr. Freda K. Herbert for the 17-ketosteroid investigations, and to Dr. S. Whately Davidson for the radiological reports.

BIBLIOGRAPHY

- Bittorf, A. (1919). *Berl. klin. Wschr.*, **56**, 776.
 Broster, L. R., and Vines, H. W. C. (1933). *The Adrenal Cortex*. Lewis, London.
 Cahill, G. F., et al. (1936). *Surg. Gynec. Obstet.*, **62**, 287.
 Glass, S. J., and Bergman, H. C. (1938). *Endocrinology*, **23**, 625.
 Holl, G. (1930). *Dtsch. Z. Chir.*, **226**, 277.
 Kenyon, A. T., et al. (1937). *J. clin. Invest.*, **16**, 705.
 Lissner, H. (1936). *Endocrinology*, **20**, 567.
 Mathias, E. (1922). *Virchows Arch.*, **236**, 446.
 Patterson, J., et al. (1942). *British Medical Journal*, **1**, 35.
 Roholm, K., and Teilum, G. (1942). *Acta med. scand.*, **111**, 190.
 Simpson, S. L., and Joll, C. A. (1938). *Endocrinology*, **22**, 595.
 Weber, F. Parkes (1926). *Lancet*, **1**, 1034.

IDIOSYNCRASY TO *d*-TUBOCURARINE CHLORIDE

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Since first introducing pure *d*-tubocurarine chloride as an aid to anaesthesia it has been clear to us that patients show a marked variability in their reactions to average clinical doses of this substance. The following factors are known to influence the individual response.

Age.—As with most drugs, the administration of *d*-tubocurarine chloride must be made with caution in the extremes of age. Children up to the age of puberty tolerate the drug well provided that a dose-for-weight ratio (2 mg. per stone (6.35 kg.) body weight) is used. The aged, on the other hand, show a varying susceptibility, and some patients past the allotted span have required as much *d*-tubocurarine chloride as their lusty brethren in the prime of life.

Body Weight.—In so far as it bears a relation to muscle mass—e.g., in children—this is a useful guide to dosage, but in adults a maximum initial dose of 15 mg. should not be exceeded. It is, however, a general rule for the muscular well-developed patient to tolerate *d*-tubocurarine chloride well.

Physical Condition.—The dosage must be modified considerably in cachectic and feeble patients.

Drug Tolerance.—There is clinical evidence to show that patients who show a natural or acquired tolerance to the opiates and barbiturates tend to require a larger dose of *d*-tubocurarine chloride than normal.

Some authorities would modify the dose in the presence of certain anaesthetic agents, ether in particular. In our opinion it is preferable to reduce the amount of the toxic anaesthetic agent.

These, then, are the salient factors upon which the initial dosage of this drug is computed, but they do not account for all the variations. Minor variations in reaction on either side of normal are often seen, and the following two cases demonstrate very clearly that this variability may be of serious degree and consequence.

Case 1

The patient, a man aged 40, was admitted to hospital with an obstructive lesion of his main bronchus. He was losing weight and had a cough with repeated haemoptysis. Five days before the present examination a bronchoscope had been passed under local analgesia, but it was decided to repeat the examination and carry out a biopsy. The following sequence of events took place.

1 p.m.—Anaesthesia was induced with *d*-tubocurarine chloride, 15 mg., and thiopentone, 0.5 g., and respiratory arrest ensued. The lungs were inflated with oxygen, and bronchoscopy was performed. On bronchoscopy the picture was that of an inoperable carcinoma of the bronchus. Owing to the non-return of respiration the surgeon was asked not to take a biopsy. The examination was speedy and at no time was the patient deeply cyanosed, oxygen being insufflated through the side tube of the bronchoscope and artificial respiration performed whenever he went a little "off colour." At the close of the examination there was no sign of any respiration and the patient appeared to be more than usually relaxed and flaccid. An airway was introduced, a facepiece applied, and artificial respiration maintained by manual compression of the rebreathing bag of a closed-circuit anaesthetic machine.

After 30 Minutes.—"Prostigmin," 5 mg., and atropine, 1/50 gr. (1.3 mg.), were given intravenously. No effect of this was observed. The patient continued in apnoea.