CARCINOMA OF THE ADRENAL CORTEX CAUSING FEMINISM IN AN ADULT MALE

BY

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Several well-known clinical syndromes are associated with carcinoma, adenoma or hyperplasia of the adrenal cortex, but that of feminizing changes in the adult male is very rare. The following is a report of such a case, in which also the giant size of the tumour is worthy of note.

CASE REPORT

History

Male, aged 47, an army officer, married. At examination for life insurance a large swelling had been discovered on the left side of the abdomen, of which the patient had been quite unaware. He was admitted to hospital in September, 1950, on a provisional diagnosis of an enlarged spleen.

He had always been fit and athletic, did not admit to any complaints, and had not suffered from any serious illnesses or accidents. It was, in fact, difficult to obtain a satisfactory history from him, and some of the details were only obtained later from his wife. There were two children, a daughter born in 1928, and a son born in 1945.

After returning from India in 1947, he put on weight and his wife noticed that his breasts were slowly enlarging, the left more than the right. His sexual appetite became gradually but completely lost, whereas formerly it had been quite normal. Early in 1950 he experienced a few attacks of severe abdominal pain and sickness, but he paid little attention to them and did not consult a doctor.

On Examination

External Appearance.—He was moderately stout, the adiposity having a distinctly feminine distribution and the "mons veneris" being especially prominent. The breasts were very large for a male and were pendulous. The
penis was fairly normal in size, but the testes were only about one-third of the normal size. He had always been fairly hirsute and the distribution of hair was of the normal masculine type; there had been no recent alteration.

**Abdominal Examination.**—There was no complaint of pain, tenderness or even discomfort on examination of the abdomen. On palpation, a very large firm mass was made out protruding from underneath the left costal margin and extending downwards in the flank and forwards towards the umbilicus. The inferior pole was round and smooth, there was no splenic notch, and posteriorly it filled up the left renal angle, being easily palpated bimanually. It was completely dull on percussion, the stomach and colon being displaced medially by it. The impression was that of a massive, solid tumour.

**Physical Examination** otherwise showed no points of interest. The blood-pressure was 140/90. Examination of the blood and urine showed no abnormality, and there was no evidence of any condition which might be associated with splenic enlargement.

**Biochemical Tests.**—Unfortunately, no estimation was obtained of urinary androgen and oestrogen excretion.

**Radiological Examinations**

**Intravenous Pyelogram.**—There was no concentration of the dye by the left kidney, but normal function on the right.

**Cystoscopy and Retrograde Pyelogram.**—Cystoscopy showed a normal bladder; both ureters were catheterized. There was a brisk flow of urine from the right kidney, but only a very small amount from the left. On the right side a normal pyelogram was obtained; on the left the kidney was low, the upper end of the ureter and pelvis were distorted as by pressure from above, and there was incomplete filling of the calyces.

**Barium Meal.**—The stomach was normal, though displaced medially and forwards.

**Chest.**—There was a moderate degree of elevation of the left half of the diaphragm, but no other abnormality.

**Diagnosis**

The full significance of the state of the breasts and testes had not then been appreciated and the probable diagnosis seemed to be a retroperitoneal tumour or a large tumour of the kidney.

**Operation**

A long curved transverse incision was made below the left costal margin, carried posteriorly into the loin as in a kidney exposure, and anteriorly almost to the edge of the rectus abdominis. On retroperitoneal dissection, a huge, smooth, lobulated mass was encountered, but, in order to improve the exposure, it was necessary also to incise the posterior parietal peritoneum lateral to the
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colon. The mass was intimately attached to the upper pole of the left kidney, but after dividing the renal pedicle it was discovered that the tumour was not growing from the kidney, being merely adherent to and distorting it; the kidney was thus removed separately.

The mass was next found to occupy the whole of the left cupola of the diaphragm and to stretch to the mid-line, but, after division of many vascular adhesions and by blunt dissection, it was eventually freed and delivered into the wound. A fairly narrow pedicle was ligated and divided deeply in the wound, and what appeared to be the entire tumour, a mass weighing 6 lb., was removed. On further inspection, a portion of the tumour, about the size of a normal kidney, was found to have been left behind near the mid-line, and it was hoped to be able to excise this also. On gently handling it on two occasions, however, the blood-pressure fell most alarmingly, but recovered at once on desisting. Any further attempt had to be abandoned and the operation was concluded.

Post-operative Condition.—Considering the severity of the operation, the patient was remarkably well at first. During and after the operation he received four pints of blood and thereafter intravenous saline was continued, together with Eucortone injections. Sudden deterioration took place fourteen hours after the operation, and death occurred four hours later.

Pathology

Post-mortem Examination.—As permission to perform a complete post-mortem had not been obtained, the operation wound was reopened some eight hours after death and the abdominal contents removed through it. The wound was healthy, clean and well-knit. The deeper layers were adequately and firmly stitched; there was no “dead-space” in the abdominal cavity, the plentiful supply of extrarenal fat making efficient packing-material. A piece of tumour which had extended over the mid-line to the right side, lying against the bodies of the vertebrae and about the size of a normal kidney, was removed. The right kidney was found to be healthy, but the right suprarenal was much reduced in size (3.1 g., as against the normal 5-6 g.) and largely autolysed.

The spleen was enlarged and distorted (284 g.). The liver was normal in size and showed at least two deposits, circular, and about half-an-inch in diameter. Numerous enlarged glands were scattered throughout the root of the mesentery, some of which resembled tumour tissue on naked-eye inspection of cut sections. The heavy build with feminine distribution of fat, especially marked in the breasts and supra-pubic pad of fat, was noted and the atrophic size of the testicles was also remarked.

Naked-eye Examination.—The tumour was shaped like a small rugby football, some 21 cm. in its longest diameter. It was largely encapsulated, but penetration into the surrounding tissues had occurred at some points. The cut surface was not unlike a hypernephroma in appearance, the general colour being orange-yellow. There were circumscribed masses of creamy colour varying in size from 7.5 cm. downwards. There were also darker areas of hæmorrhage, and the surface generally was friable (Fig. 1).
Histology.—The lobulated nature of the tumour illustrated in Fig. 1 is confirmed under the low power, the lobules being separated by fibrous septa. Under high power, the tumour cells present a most remarkably irregular and bizarre appearance (Fig. 2). In the most differentiated areas the cells are arranged in columns resembling closely those of the zona fasciculata. This is better illustrated in the sections stained by Vines' method (Fig. 3) in which cell outlines are more clearly defined. It can be seen in some of the sections that these areas surround arterioles. Other sections reveal lobulated sheets of cells of varied sizes separated by bands of fibrous tissue. These sheets of cells have no special arrangement and, in them, blood-vessels are conspicuous by their absence. Red blood cells are plentiful enough in clefts between cells; in fact in some of the lobules large hæmorrhages are evident, and these are associated with areas of necrosis. Blood-vessels, many compressed, are numerous in the inter-lobular fibrous septa. Sections of some parts of the tumour mass are so strikingly different from others that were this not evident on the same slide in some cases, one might be deceived into concluding they were in no way related. For example, the appearance in one portion of a particular section is that of a simple hypertrophy of a fairly normal-looking zona glomerulosa, i.e., the cells, which are of normal
polyhedral appearance, are broken up by rather wide spaces into rounded groups, some of which tend to an acinar arrangement. There are isolated collections of lymphocyte-like cells, and some more scattered ones amongst the normal-looking cortical cells. As one moves across the section the spaces separating the groups of cells become progressively wider, red blood cells appear, the cortical cells become more broken up and ragged in appearance and finally one comes to a pale eosinophilic necrotic area of ghostly structure. Separated from the relatively normal cortical field by a thin fibrous band is a denser collection of smaller and more deeply basophilic cells in which an arrangement resembling any normal cortical feature is difficult to define. These cells are comparatively uniform in size, about the size of a large lymphocyte, and have more numerous mitotic figures than in other parts of the tumour. Some of the nuclei are more bunched up and there is a suggestion here and there of circular acinar formation. In another section from a different part of the tumour, a lobule of fairly uniform cells arranged like a normal zona fasciculata is separated by a thick fibrous septum from a lobule of similarly arranged cells of strikingly varied sizes and shapes. Some of these cells are of dimensions approximately $60\mu \times 50\mu$ with nuclei of at least $20\mu \times 30\mu$. Many cells have an appearance suggestive of a high lipoid content. Many of the larger nuclei, particularly the more chromophilic ones, contain large oval vacuolated spaces.

Vines' stain shows that the cytoplasm is diffusely fuchsinophil, but well-defined fuchsinophil granules are lacking (Fig. 3). No granules of golden-yellow pigment, such as are associated by some authorities with feminizing tumours, were seen, and Perls' reaction reveals free iron in only an occasional cell. Lendrum's phloxine-tartrazine shows a few phloxine-positive bodies, some of which appear to be intranuclear.

The liver deposit resembled the more bizarre portions of the main tumour.

**DISCUSSION**

*Clinical Classification*

A useful classification of the clinical syndromes produced by adrenal cortical tumours has been given by Cahill, Melicow and Darby (1942), as follows:

1. No recognizable hormonal changes.
2. Changes due to excess of androgens:
   - (a) In female child towards adult masculinity.
   - (b) In female adult towards masculinity.
   - (c) In male child towards adult masculinity.
3. Changes due to excess of oestrogens:
   - In male adult towards feminism.
4. Changes due to excess of androgens and other steroids:
   - Cushing's syndrome with associated sexual changes, usually in females.
5. Changes due to excess of other steroids related to metabolism:
   - Cushing's syndrome without sexual changes, in males or females.
FIG. 2.

FIG. 3.—Vines' Stain.
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It may be noted that there has not been a recorded instance of Cushing's syndrome associated with feminism in the male adult. There has been one published case (Wilkins, 1948), of feminizing changes in a male child. To the above may be added the possible relationships to precocious puberty in a female child and also to various pluriglandular syndromes.

General Clinical Picture of Feminism in Adult Male

Although few cases have been recorded, the clinical picture is striking and remarkably constant. The onset is insidious, with tiredness an early complaint, and there is usually a history of slow but progressive changes over a period of from one to three years. The most outstanding features are loss of sexual desire and potency, both previously being normal, progressive atrophy of the testicles and gradual enlargement of the breasts. Clinical examination always reveals a large abdominal tumour protruding from below the costal margin. There are no significant changes in the blood-pressure.

Pyelography demonstrates a downward displacement of the kidney with distortion of the renal pelvis; there is little or no excretion of a dye, and the calyces fill very imperfectly on retrograde injection. The urine is normal except for a high excretion of oestrogens; there is no haematuria.

Operation may be carried out, but more often than not to no purpose, death occurring soon after excision of the tumour, or the tumour being removable. Some cases have survived excision only to die of metastases a year or two later; the only assumed cure was in the second case of Holl (1930), but the follow-up was only for twelve months. Metastases in the liver, retroperitoneal glands, lungs and other sites are almost universal and may already be present at the initial clinical examination, prohibiting operation. The rate of growth is variable, most often being rapid after an insidious onset. The prognosis is therefore very grave, as it is in other syndromes caused by carcinoma of the adrenal cortex.

Certain other features have been noted in individual cases, such as increasing obesity (Simpson and Joll, 1938), lactation (Parkes Weber, 1926; zum Busch, 1927; and Lisser, 1936), and decreased growth of the beard, with restoration to normal after operation (McFadzean, 1946). After operative removal of the tumour there was fairly rapid recovery of sexual desire (Holl—second case, Simpson and Joll, McFadzean), with increased size of the genitalia and decreased size of the breasts in the last instance.

Hormonal Excretion Studies

These have been carried out in few of the recorded cases, but, according to Armstrong and Simpson (1948), the essential features are a gross excess of oestrogens and a moderate or slight excess of androgens in the urine. In association with the recognized clinical picture, an excess of oestrogens in an adult male should make the diagnosis of carcinoma of the adrenal cortex quite certain, with the added implication of metastases being already present.

In the case of Roholm and Teilum (1942), the excretion of oestrogens in the urine attained a level of 5,000 mouse units, instead of the normal of about 20,
metastases being then noted. In the case of Simpson and Joll (1938), no estimations were made originally but, after removal of the tumour, the excretion of both oestrogens and androgens was less than normal for several months. Subsequently, with the final decline in the clinical condition, there occurred an excessive excretion of oestrogens, this being the first evidence of metastases. McFadzean (1946) recorded that the Friedmann pregnancy test was positive before the operation, but became negative twenty-one days after the removal of the tumour. No other reported case has demonstrated a positive pregnancy test.

In the unpublished case of Scott (quoted by Wilkins, 1948), the estimations were paradoxical, although the typical syndrome of feminism was present. In this instance the oestrogen excretion was only slightly above normal, but the androgen excretion was high before operation, falling to about normal after removal of the tumour. According to Frank (1942), excessive excretion of oestrogens may occur in cases of carcinoma of the adrenal cortex without feminizing changes. In his series only one patient was a male, but no clinical details were appended; the others were females either with Cushing's syndrome or without endocrine changes. An excellent review of oestrogen/androgen secretion studies in diseases of the adrenal glands has been made by Kepler and Keating (1941).

**Previous Cases of Feminism in the Male**

The following is a list of the authors of previously recorded cases, and, unless otherwise stated, the typical clinical and pathological features had been present.

5. Holl (1930). Age 44. Operation successful. Cure twelve months later, but not followed up longer.
12. Cahill et al. (1942). Age 53. No large abdominal tumour palpable, but enlarged right adrenal revealed on air insufflation. Case not followed up.
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In addition to the above cases, it seems desirable to consider three others in the same category.

(15) Cahill et al. (1942). Under the classification of "tumours with no recognizable hormonal changes," their third case was that of a man aged 36 in whom there was loss of sexual vigour, although previously virile. Operation was successful but metastases were present two years later.

(16) Wilkins (1948). A boy aged 4 years 8 months when first seen. Both breasts were of the adult female type, having enlarged progressively between the ages of six months and two years. The prostate was enlarged and a slight excess of oestrogens was excreted in the urine. Abdominal exploration revealed a slightly enlarged right adrenal, which was removed. An adenoma was demonstrated and there were no metastases. During the next four years growth and general health were normal and the breasts decreased in size, slowly and progressively; the prostate became smaller. This is the only recorded case of a feminizing tumour occurring in a male before puberty, but it differed from all the others in being due to an adenoma, not a carcinoma.

(17) Staffieri, Cames and Cid (1949). Age 25. Pluriglandular features were present, enlarged breasts, attacks of hypoglycaemia, a nodular goitre and enlarged liver and spleen. A malignant tumour of the adrenal cortex was removed and thereafter all the above features disappeared. The patient was in excellent health two years after the operation.

Large Adrenal Cortical Tumours in General

Very large adrenal cortical tumours may be associated with various endocrine features, or without them, or with Cushing's syndrome. Tumours associated with Cushing's syndrome have been much more frequently reported, but the clinical and pathological features and progress of all these tumours are remarkably alike. The lack of complaints by the patients, the large, solid abdominal tumour, the typical pyelogram, the operative risks and the almost invariable development of metastases are not specific for one particular syndrome.

Lumb (1950) gave an account of two cases without endocrine effects, and Cahill et al. (1942) recorded others. Stevens (1923), Gibson (1927), and Loeb (1941) have also reported such cases, and, without attempting a comprehensive account, tumours without endocrine effects are rare.

Virilizing changes are undoubtedly the most common, whether due to carcinoma, adenoma, or simple hyperplasia of the adrenal cortex.

The size and weight attained by some of these tumours is astonishing and there are few solid tumours, apart from uterine fibroids, which give rise to such massive abdominal swellings. The largest on record is 20 lb. in Thornton's case quoted by Richards (1905). Those reported by Lumb (1950) were 5,350 g. and 3,750 g. Roholm and Teilum (1942) recorded a weight of 2,650 g. and Broster
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(1950) noted a weight of 2,500 g. in a female case in whom hypertrichosis was the predominant feature. In the present case the combined weight of the tumour removed at operation and the remaining portion removed at autopsy was 2,640 g. The smallest size on record appears to be that of "a large walnut" reported by Guthrie and Emery (1907).

Post-operative Dangers

The development of acute adrenal insufficiency immediately or soon after the operation is a risk inherent in any operation on an adrenal cortical tumour. The severity of the shock may be dependent on the state of the opposite adrenal gland, which is liable to have become atrophic. This point is commented on by Kepler and Keating (1941) in their exhaustive review of diseases of the adrenal glands. It should be possible to anticipate the risks before operation, the most important steps being the administration of sodium chloride and sodium citrate, and of desoxycorticosterone, started before the operation and continued afterwards. This treatment should be maintained for several days after the operation until the remaining adrenal gland has had time to regain its functional capacity.

Cahill et al. (1942) consider that these dangers occur after operation only in Cushing's, and not in other, syndromes. Most authors, however, disagree with these views and believe that the dangers are considerable in any of the syndromes. Convincing support for this is suggested by the histological studies of Glynn (1921) and will be referred to in the subsequent discussion.

The present case certainly emphasized the risks both during and after the operation.

Discussion on Pathology

In his classical paper of 1912, Glynn distinguishes a group of malignant adrenal cortical tumours which he refers to as "adrenal hypernephromata." These in general have certain characteristics in common—viz., fairly large size (see above), lobulated and fairly well defined with a thin but strong fibrous capsule, and a much variegated appearance on section due to haemorrhages and necrotic areas, the predominating colour being yellow ochre. Microscopically the cells are arranged in columns resembling the structure of a zona fasciculata, but the greatest diversity of appearance may occur, from a fairly orderly picture of acinar arrangement (considered by Glynn to suggest hyperplasia rather than neoplasia), as in Bulloch and Sequeira's (1905) case, to an apparently disordered anaplastic mass of polygonal cells, multinucleate giant cells and large numbers of small cells with a single nucleus, as in Ritchie's case described in Bulloch and Sequeira's paper. The type of the latter was said to be a sarcoma, but the clinical effect was to accentuate female characteristics in an immature girl of 4, and from the histological description it appears to correspond with our case.

Although Glynn concludes from his Table I that the adrenal hypernephromata accentuate male characters in immature females, it appears that sometimes a precocious development of both characters occurs (e.g., Bulloch and Sequeira's case with hairy chin, big breasts and menstruation; Tilesius's case
(quoted by Linser, 1903) of hairy pubes and big breasts; Ritchie’s case (referred to above). Even in his first case (Dun and Glynn, in the 1912 paper), Glynn states that the child, aged 5, had the appearance of a girl “abnormally tall, about the age of puberty.” She had a moustache and never menstruated. The description of the microscopical appearance could be applied equally well to our case, as also, be it admitted, could the histological description of Guthrie and Emery’s (1907) case of an obese boy of under 5 who had had hairs on his face and pubes for three years and had a tumour the size of a walnut in contact with one kidney.

The same cannot be said of the cases in Table II of Glynn’s (1912) paper. These are cases displaying some male characters in adult females associated with adrenal hypernephromata of which the histological appearances are but scantily described. The cases described in Table III, however, in which male sex characters occur in adult females with hypertrophy of the adrenals, are of considerable interest. It would appear that mere enlargement of the adrenals leads to an accentuation of male characters, at least in the majority of cases so far recorded.

It is not surprising that such varieties of histological appearance and of sexual manifestations as may occur in structural alterations and aberrations of the suprarenal cortex should have given rise to much confusion in the past. The arguments for the assessment of the nature of these tumours are ably considered by Glynn, who comes to the conclusion that there is no essential difference between the various patterns of “adrenal hypernephromata.” The fact that these may revert to a primitive mesoblastic ancestry has to be borne in mind in order not to confuse them with sarcomata which do not lead to sexual changes. The fact that such apparently primitive and even anaplastic growths appear to produce a functioning secretion suggests that the production of sexual hormones is phylogenetically an ancient function, a not surprising characteristic.

It is of course possible that hormones so produced may be abnormal ones, as described by Kepler (1935). Nevertheless, the fact that true adrenal hypernephromata can occur with little or no sexual changes is stressed by Glynn, and the two cases described by Lumb (1950) provide further evidence of this. The malignant nature of the two latter cases appears to be somewhat in doubt, and histologically certainly differs markedly from our case. Glynn (1921) points out how little the histological appearances of the (adrenal) hypernephromata are an index of their malignancy, or indeed that any real histological differences exist at all, whether they occur in young or old, in males or in females, with or without sexual changes. More recently Broster and Vines (1933) introduced a staining technique to demonstrate over-activity of the adrenal cortex. Professor Vines has kindly looked at our sections stained by his technique and showed one of us (R. S. V.) his cortical sections from a case of adrenal virilism for comparison. The difference was quite striking in that the stained material in his sections was a brighter red and much more concentrated, whereas in ours it was much paler and more diffuse. These findings appear to agree with those of Dr. Joan Ross, quoted in Simpson and Joll’s (1938) paper in comparing their case of feminisation in a man of 34 with Dr. Dorothy Hare’s case of masculinization in a woman of 34.
There would appear to be undoubted evidence that the functional differences of structurally similar tumours can be detected by purely histological techniques on extirpated tumours, and an attempt has been made to illustrate this by Goormaghtigh (1940). An advance in the clinical diagnosis of adrenal cortical tumours and hyperplasia has been made by Patterson (1947) in devising a urinary colour test, and an application of this test is described by Broster and Patterson (1948).

SUMMARY

A case of feminizing malignant adrenal cortical tumour with metastases in a man of 47 is described. This is believed to be the fifteenth recorded case. Its true nature was unfortunately not recognized until after removal. The clinical history is typical of that described for previous cases.

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REFERENCES

ARMY BARRACKS IN THE UNITED KINGDOM: A BRIEF REVIEW OF THEIR GROWTH AND DEVELOPMENT

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INTRODUCTION

British Army Barracks erected within the last twenty years may well be regarded as the unmarried soldiers’ “Ideal Home.” Their siting, design and construction have all been based on sound scientific principles in accordance with the current theory and practice of the hygiene of buildings. Intended primarily as a home, they conform to the modern trend in public health which considers suitable housing as one of the main factors in the maintenance and promotion of physical and mental health, and accordingly they incorporate all those amenities which contribute so much to the soldier’s welfare and morale. Airy, well-lit barrack rooms, sitting rooms and canteens, drying rooms and cleaning rooms, barber's shops, gymasia, swimming pools and playing fields—not to mention such essential requirements as artificial heating, modern sanitation, provision of hot water, up-to-date cooking facilities, etc.—all have become accepted by official authority as integral components of the soldier’s present-day permanent accommodation.

But it was not always so.