

ADRENAL HYPERNEPHROMA IN AN ADULT FEMALE ASSOCIATED WITH MALE SECONDARY SEX CHARACTERS.¹

By ERNEST GLYNN, M.A., M.D., F.R.C.P., *Professor of Pathology University of Liverpool, Bacteriologist and Pathologist to the Liverpool Royal Infirmary*; and J. T. HEWETSON, M.D., F.R.C.S., *Honorary Surgeon, Birmingham and Midland Hospital for Women, Assistant Professor of Midwifery and Gynaecology, Gynaecological Curator Pathological Museum, University of Birmingham.*

(PLATE IV.)

THE occurrence of sex abnormalities in children, especially females, such as precocious growth of hair, with neoplasms of the adrenal cortex, is well known since Bulloch and Sequeira's paper (1905¹).

One of us (E. G.²) collected in 1912 a group of six young adult females in whom cessation of menstruation, the development of hirsutes, or other abnormal sex characters were associated with similar neoplasms.

A most interesting example of this type of case came under the notice of one of us (J. H.), and we think it is worthy of record. M. M., female, æt. 44, single, was admitted to the Birmingham Hospital for Women, under the care of Dr. Hewetson, on June 8, 1909.

DESCRIPTION OF CASE.

FAMILY HISTORY.—Her father lived to be an old man, but her mother died from unknown cause when patient was 2 years old. There were four brothers and two sisters alive and well. One brother died at 40 from heart disease.

PAST HISTORY.—*Catamenia began at 14 and was of the 28-day type, lasting three to four days; it was regular until the patient was 28 years of age, when it ceased entirely. The patient had never been ill before. Soon after cessation patient grew stouter, and hair appeared upon her face, chest, abdomen. The growth of hair was especially noticeable during the last three or four years. At 30 her voice became deeper and harsher.*

¹ Received June 16, 1913.

PRESENT ILLNESS,—began two years ago in 1907 with gradual swelling of the abdomen. After Christmas 1908 patient was attacked with severe pain in the left hypochondrium, lasting twenty-four hours; the diagnosis made was a weak heart and pleurisy. Since that date she had had similar attacks accompanied by vomiting; they occurred once or twice a month, and always compelled her to go to bed for three or four days. She also became subject to periodic attacks of palpitation. Her weight had diminished from 14 stones to 10 stone 8 lbs. in six months. The bowels were regular. Micturition became more frequent, she had to get up two or three times during the night. About two weeks before admission there was a blood-stained discharge from the vagina which led her to consult Dr. Hewetson.

On Admission.—The patient was moderately stout and weighed 10 stone 8 lbs., her height was 5 feet 7. Her face was red from general acne rosacea. She was in the habit of taking alcohol. *The chin, neck, and upper lip were covered with strong hair, for which she had shaved regularly for four or five years. She was morbidly sensitive about her appearance, wore a thick black veil, and was very reluctant to enter the general ward of the hospital. The chest and abdomen were also covered with thick hair exactly like those of very hairy men. The breasts were flattened and of the masculine type.* The abdomen was markedly distended owing to a large rounded nodular soft solid tumour occupying its left side and middle. The tumour was about the size of a large football and measured 10 inches vertically and 7 inches transversely; it extended from the left costal margin to within $4\frac{1}{2}$ inches of the pubes. It was dull on percussion, not tender on pressure, and moved with respiration. A vaginal examination demonstrated that the uterus was retroverted and small, measuring 2 inches with the sound; the appendages appeared normal. The urine was clear, acid, sp. gr. 1030, and contained neither albumin nor sugar. The heart was normal. There was an occasional rhonchus in the lungs. The blood was normal, microscopically.

Dr. Hewetson diagnosed an abdominal tumour, probably arising from the left kidney, and almost certainly malignant. Removal was not advised; but the patient insisted, as the pain of the attacks was so severe that she wished to die rather than live.

Operation.—On 10th June 1909, laparotomy was performed by Dr. Hewetson. A large retroperitoneal tumour was found occupying the left side of the abdomen and depressing the left kidney into the iliac fossa. After considerable difficulty the tumour was removed; it was adherent to the kidney under surface of the diaphragm and liver. The largest vessels supplying the tumour arose from the aorta just above the renal vessels. The patient died gradually from shock eighteen hours after the operation.

POST-MORTEM EXAMINATION revealed no internal hæmorrhage. There was no injury to the viscera. The heart was flabby and dilated, but otherwise normal, the lungs were slightly congested. The liver and spleen were normal. *There were no secondary growths and no enlarged glands anywhere. The uterus was atrophied and the ovaries small and fibrotic.*

DESCRIPTION OF TUMOUR.

THE SPECIMEN weighed 12 lbs. and measured $11\frac{1}{2}$ inches vertically, $9\frac{1}{2}$ transversely, $5\frac{1}{2}$ antero-posteriorly. It was encapsulated and numerous vessels coursed over its surface. On section it was soft, friable, and contained numerous areas of dark-brown colour resembling liver tissue, the other tissue being bright red; there were also areas in which there was definite blood extravasation.

MICROSCOPICAL EXAMINATION.—The tumour was fixed in 4 per

cent. formol, and afterwards in methylated spirit, but fixation was imperfect, especially towards the central part; paraffin sections were cut and stained with hæmatoxylin and eosin, also with Van Gieson's stain.

The growth consists of irregular polyhedral cells, which vary somewhat in size and shape, a few being oval. The average size is about $24\ \mu$, the smaller $10\ \mu$; giant cells are occasionally present, these measure up to $50\ \mu$. The cytoplasm is as a rule homogeneous, though sometimes faintly vacuolated or even slightly foamy, having some resemblance to the cells of the adrenal cortex. The nuclei are small, about $6\ \mu$, round, or oval, and rich in chromatin; nucleoli are occasionally visible (Plate IV. Fig. 2). Some of the larger cells are multinucleated. Hyperchromatosis and pyknosis is frequent, especially in the multinucleated giant cells. The tumour cells are separated into small alveoli by a delicate connective-tissue reticulum, which is most easily seen in those parts of the tumour where shrinkage has occurred, owing to deficient fixation (Plate IV. Fig. 5).

Blood vessels are fairly numerous, and consist mostly of small channels lined by endothelium; there is no tendency for the tumour cells to arrange themselves around the vessels after the manner of perithelioma. Gland-like tissue and lumina are absent.

THE ESSENTIAL SIMILARITY IN MICROSCOPICAL STRUCTURE OF ADRENAL HYPERNEPHROMA IN CHILDREN AND ADULT FEMALES.

One of us (E. G.) has had the opportunity of examining microscopical sections of four adrenal hypernephromata associated with sex abnormalities in young children, namely, the cases of Adams (1905³), Ritchie (1905¹), H. French (1912⁴), Dun and Glynn (1912²). The tumour just described is *undoubtedly of the same type* (*vide* photographs, Plate IV.). Microscopically, it most resembled Adams' case (Plate IV. Figs. 2, 4, and 5). It is less atypical than the growths described by Ritchie (Plate IV. Fig. 3), and Dun (Plate IV. Fig. 1), and the differences may be summarised as follows:—

1. There is greater uniformity in the shape and size of the tumour cells. Giant cells are fewer. Oval or short spindle cells are practically absent.
2. The nuclei are smaller and more regular, and multinucleated cells less frequent.
3. The fibrous tissue reticulum producing an alveolar arrangement of the tumour cells is better developed.

The fact that the cells in our case are much less atypical than in those of Dun and Ritchie indicates that the tumour was growing more slowly and was less "malignant." This is consistent with the clinical history, for the patient died at 44 years of age, sixteen years after the first symptoms developed, while Ritchie's case died at 4 years of age,

and Dun's died at 5 years of age, two years after the first symptoms developed.

CLASSIFICATION OF TUMOUR.

The structure of these adrenal tumours varies somewhat in different cases. They consist, mainly, of round, oval, or polyhedral—but never cylindrical-epithelial-like cells, usually varying considerably in shape and size. The cytoplasm may be finely vacuolated or foamy from the presence of fat or doubly refractive material, myelin; but it is never dropsical.

The nuclei are round or oval; sometimes multinucleated giant cells are present. Unless the anaplasia is great, the cells are separated into alveoli or columns by a varying amount of delicate connective-tissue stroma or of thin-walled blood vessels, upon whose walls they directly abut; they are sometimes arranged in a perivascular manner. The general arrangement of the cells, connective-tissue stroma, and vessels recalls to a certain extent the adrenal cortex, and the growths may then resemble a *carcinoma*. True gland formation with lumina is probably always absent. In other tumours, or even other portions of the *same* tumour, the cells are more spindle shaped, and the general appearance is that of a *sarcoma* of a mixed celled or large round celled type with many giant cells.

The variability in the microscopical appearance of these tumours may be explained as follows. The specific cells of the adrenal cortex are developed from mesothelium, which is in turn developed from mesoblast, and, as Adami (1908⁵) and Woolley (1903⁶) have pointed out, it is quite natural in a markedly anaplastic growth from such tissue, that the epithelial (*i.e.*, mesothelial) characters and arrangement of the cells should revert to a more primitive sarcomatous (*i.e.*, mesoblastic) type. This variability in structure has given rise to considerable confusion in nomenclature. The tumours are described as sarcoma; as malignant hypernephroma (Kaufmann, 1909⁷); alveolar sarcoma (Beneke, 1891⁸); perithelioma, *i.e.*, angeio-sarcoma (Rolleston, 1898⁹ and others); malignant adenoma, *i.e.*, carcinoma (Ribbert, 1904¹⁰) mesothelioma (Adami, 1908⁵); suprarenal epithelioma (Marchand¹¹); hypernephroid tumour (Lubarsch, 1894¹²).

We prefer the name of "adrenal hypernephroma" for the following reasons:—

1. The term adrenal indicates the origin of the tumour, and distinguishes it from the so-called "renal hypernephroma," a tumour which has a totally different microscopical structure and which in the opinion of one of us (E.G.) is not derived from adrenal cortical rests at all.

2. The term hypernephroma does not postulate a "malignant" growth, for a certain proportion are not "malignant."

3. The term hypernephroma does not raise the difficulty of deciding whether the growth resembles a carcinoma or sarcoma, but it clearly distinguishes it from the only other *common* type of primary "malignant" growth, viz., the small round-celled sarcoma, or what Schilder (1909 ¹⁹) and others believe to be glio-sarcomata.

ADRENAL HYPERNEPHROMATA IN ADULT FEMALES, BEFORE THE MENOPAUSE, ASSOCIATED WITH CHANGES IN SEX CHARACTER.

We have tabulated below seven cases of abnormal sex characters in young adult females associated with adrenal hypernephroma which more or less closely resemble the one just described.

The evidence is very strong that the neoplasms of the adrenal cortex, directly or indirectly, cause the abnormalities in sex characters; this for several reasons; among others, the fact that in Goldschwend's case the tumour and hirsutes appeared simultaneously, while in Thornton's the hair on the face vanished with a surgical removal of the tumour.

An interesting feature of our own case is the long period, namely sixteen years, which elapsed between the cessation of menstruation with the development of hirsutes, and death. All the other patients lived only a few years, the maximum being six years in children (Adams 1905 ³) and three years in adult females (Goldschwend 1910 ¹⁷). We must assume that the tumour in our case, though growing slowly, produced for many years an abnormal internal secretion, which, directly or indirectly, caused the sex abnormalities. The patient became conscious of its presence only when it developed to a considerable size, producing abdominal swelling and displacement of the heart. The microscopical characters, and the absence of infiltration or metastases at the post-mortem are in accord with the non-"malignant" nature of the growth.

THE GENERAL RELATIONSHIP BETWEEN ADRENAL HYPERNEPHROMA AND ABNORMAL SEX CHARACTERS.

Abnormal sex characters do not always occur together with adrenal hypernephroma; the present position of our knowledge concerning their relationship to these tumours may be summarised as follows (Glynn ²):—

1. In children they are almost invariably present in the form of hirsutes and often other abnormalities (seventeen cases of hypernephroma collected; in sixteen, namely thirteen females and three males, sex abnormalities present).

2. In adult females before the menopause they are frequently present (twelve cases collected; sex abnormalities present in seven, while in two others menstrual disturbances occurred before death).

TABLE.—Occurrence of some Male Sex Characters in Adult Females, associated with Adrenal Hypernephroma.

Case.	Name of Recorder.	Age.	Hirsutes.	Menstruation.	Uterus.	Ovaries.	Breast.	Adrenal affected.	Microscopically.	Remarks.
1	Hewetson and Glynn	44	Face, chest, abdomen; shaved	Ceased at 28	Atrophied	Small, fibrotic	Male type	Left, enormous growth. No metastases	Adrenal Hypernephroma	Voice changed at 30. "Stout."
2	Thornton	36	Covered black and silky; shaved	(?)	(?)	Ovaries removed 6 years before	(?)	Right, malignant. Metastases	"Like adrenal"	Hair disappeared after removal of primary tumour.
3	Bulloch	32	Thick on extremities and face; shaved	Ceased	(?)	(?)	(?)	Right, malignant. Metastases not mentioned	"Soft cancer, vascular"	Very anæmic.
4	Bortz and Thummin	17	Chest, linea alba, moustache	Ceased at 15	Normal	Atrophied, no ovulation	Well developed	Left, small tumour; right, large tumour. No metastases	"Struma suprarenalis"	Voice changed, obesity.
5	Winkler (Case VII)	16	Profuse on upper lip	Probably absent	Very small 5 c.m.	(?)	Extraordinarily small	Right, malignant. Metastases	"Epithelioma suprarenalis"	...
6	Golschwend	39	Face and abdomen	Ceased at 36	Atrophied	Atrophied	(?)	Left, malignant. Metastases	Malignant adenoma	...
7	Ogston (Case III)	16	(?)	Always absent	Much atrophied	Exceedingly small; little cysts	Atrophied	Both half the size of kidneys. No metastases	(?)	An anomalous case.

3. In females after the menopause they are not recorded, though a growth of hair on the face or change in the voice, etc., might be thought worthy of note (eight cases collected).

4. In adult males they are probably invariably absent. In this connexion it is of great interest that adrenal cortical rests or bilateral hyperplasia of the adrenal cortex was noted in 15 per cent. of female pseudohermaphrodites, but in only 0.70 per cent. of male pseudohermaphrodites.

5. There is no evidence that hypernephroma *in* the kidney, which has a totally different histological structure from that in the adrenal, is ever associated with abnormal sex characters.

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DESCRIPTION OF PLATE IV.

FIG. 1.—Adrenal hypernephroma, girl æt. 5 (Dun and Glynn). (× 195.)

FIG. 2.—Adrenal hypernephroma, woman æt. 44 (Hewetson and Glynn). (× 195.)

- FIG. 3.—Adrenal hypernephroma, girl æt. 4 (Ritchie). *Note.*—The tumour cells are more atypical in Dun's and Ritchie's cases than in Hewetson's. Dun's case lived two years after the onset of symptoms, and Ritchie's died aged 4, but Hewetson's lived sixteen years after the onset of first symptoms. ($\times 195$.)
- FIG. 4.—Adrenal hypernephroma, boy æt. 16 (Adams'), tissue badly fixed, shows stroma. ($\times 300$.)
- FIG. 5.—Adrenal hypernephroma, woman, æt. 44 (Hewetson and Glynn), portion of tissue badly fixed, shows stroma. ($\times 300$.)

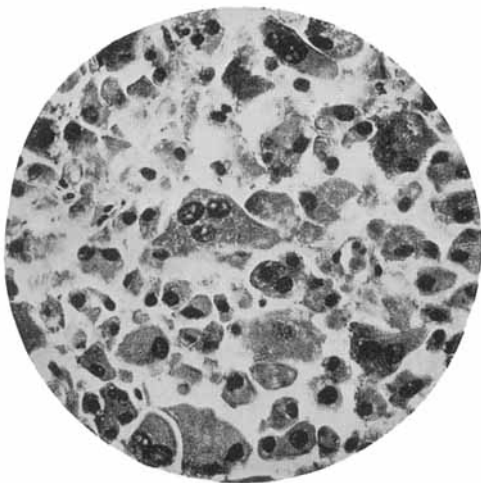


Fig.1.

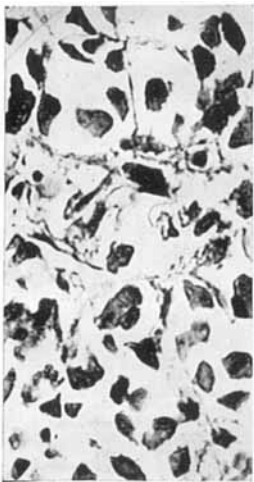


Fig. 4.

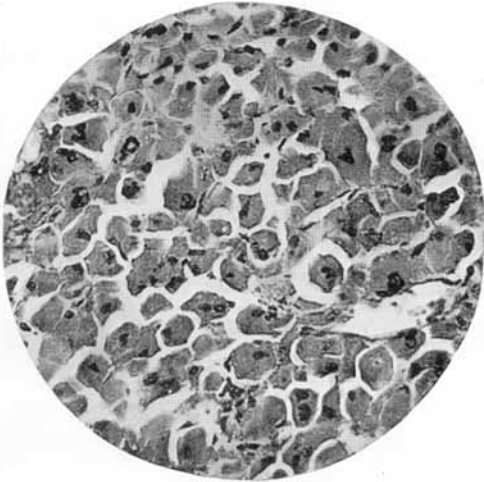


Fig.2.

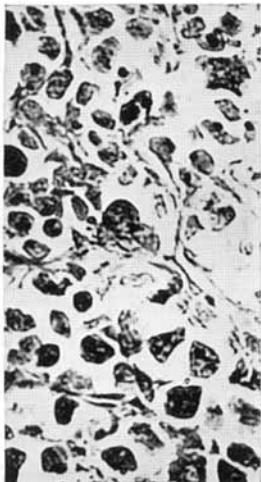


Fig.5.

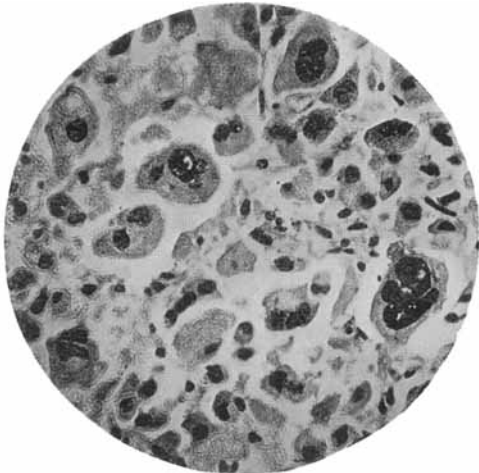


Fig.3.