tosis soon became apparent. In selected patients, therefore, and particularly in the slowly growing ACTH producing tumours, which have been previously described (O'Riordan *et al.*, 1966), metyrapone may be of value in reducing the distressing effects of hyperadrenocorticism. With a rapidly growing tumour metyrapone is probably ineffective and another approach with, for example, aminogluthetimide (Elipten, Ciba) would now be more appropriate.

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References

- AIKAWA, J.K., HASSELL, G.T. & EISENBERG, B. (1952) The exchangeable potassium content of normal women. *J. clin. Invest.* **31**, 367.
- ANDERSON, E.G. (1966) Non-metastatic syndromes associated with carcinoma of the bronchus. 1. The endocrine syndromes. *Hosp. Med.* **1**, 11.
- APPLEBY, J.I., GIBSON, G., NORBYMSKI, J.K. & STUBBS, R.D. (1955) Indirect analysis of corticosteroids. 1. The determination of 17-hydroxycorticosteroids. *Biochem. J.* **60**, 453.
- BAGSHAW, K.D. (1960) Hypokalaemia, carcinoma and Cushing's syndrome. *Lancet*, **ii**, 284.
- BORSTEIN, P., NOLAN, J.P. & BERNANKE, D. (1961) Adrenocortical hyperfunction in association with anaplastic carcinoma of the respiratory tract. *New Engl. J. Med.* **264**, 363.
- BOWER, B.F. & GORDAN, G.S. (1965) Hormonal effects of non-endocrine tumours. *Ann. Rev. Med.* **16**, 83.
- BROWN, W.H. (1928) A case of pluriglandular syndrome. Diabetes of bearded women. *Lancet*, **ii**, 1022.
- BUUS, O., BINDER, C. & PETERSEN, F. (1962) Metopirone dosage in pituitary function tests. *Lancet*, **i**, 1040.
- CHRISTY, N.P. (1961) Adrenocorticotrophic activity in the plasma of patients with Cushing's syndrome associated with pulmonary neoplasms. *Lancet*, **i**, 85.
- FRIEDMAN, M., MARSHALL-JONES, P. & ROSS, E.J. (1966) Cushing's syndrome: adrenocortical hyperactivity secondary to neoplasm. *Quart. J. Med.* **35**, 193.
- GREEN, H.N. & WHITELEY, H.J. (1952) Cortisone and tumour growth. *Brit. med. J.* **ii**, 538.
- HUGHES-JONES, P. (1964) A case of carcinoma of the lung with endocrine changes. *Brit. med. J.* **i**, 1492.
- MATTINGLY, D. (1962) A simple fluorimetric method for the estimation of free 11-hydroxycorticoids in human plasma. *J. clin. Path.* **15**, 374.
- MATTINGLY, D., KEANS, P.M., MCCARTHY, C.F. & READ, A.E. (1964) Adrenocortical hyperfunction and oat-cell carcinoma of the bronchus. *Bristol med. chir. J.* **79**, 6.
- MEADOR, C.K., LIDDLE, G.W., ISLAND, D.P., NICHOLSON, W.E., LUCAS, C.P., NUCKTON, J.C. & LUETSCHER, J.A. (1962) Cause of Cushing's syndrome in patients with tumours arising from 'non-edocrine' tissue. *J. clin. Endocr.* **22**, 693.
- NORBYMSKI, J.K., STUBBS, R.D. & WEST, H.F. (1953) Assessment of adrenocortical activity by assay of 17-ketogenic steroids in urine. *Lancet*, **i**, 1276.
- OBERHAUSEN, E. & ONSTEAD, C.O. (1965) *Radioactivity in Man*, p. 179. Thomas, Springfield.
- O'RIORDAN, J.L.H., BLANSHARD, G.F., MOXHAM, A. & NABARRO, J.D.N. (1966) Corticotrophin-secreting carcinomas. *Quart. J. Med.* **35**, 137.
- SHERLOCK, P. & HARTMANN, W.H. (1962) Adrenal steroids and the pattern of metastases of breast cancer. *J. Amer. med. Ass.* **181**, 313.
- VERNIKOS-DANELIS, J., ANDERSON, E. & TRIGG, L. (1966) Changes in adrenal corticosterone concentration in rats. Method of bioassay for ACTH. *Endocrinology*, **79**, 624.
- WOLF, J., SPEAR, P., YESNER, R. & PATNO, M.E. (1960) Nitrogen mustard and the steroid hormones in the treatment of inoperable bronchogenic carcinoma. *Amer. J. Med.* **29**, 1008.

Granulosa-cell tumour of the ovary causing sexual precocity in a girl aged 3½ years

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ACCORDING to Eberlein *et al.* (1960) isosexual precocity in girls may be arbitrarily defined as the appearance of feminine secondary sexual characteristics before the age of 7 years or menstrual bleeding before the age of 8. The majority of such cases are 'idiopathic' or 'constitutional'; there is a true precocious puberty,

gonadotrophins being present and ovulation occurring, and there is no reversal of the early pubertal development.

A rare cause of sexual precocity is the presence of functioning ovarian tumours which are usually granulosa-cell or theca-cell tumours. In these cases gonadotrophins are not usually

present nor does ovulation occur and removal of the tumour results in reversal of the development of the secondary sexual characteristics (Niswander, Courey & Woodward, 1965).

Case report

S.R., aged 3½ years, was the first child of a 27-year-old mother. Her birth weight was 6 lb 12 oz (3.06 kg) after a normal pregnancy lasting 41 weeks. The family history was investigated for evidence of reproductive system disorders. This revealed that the mother's sister had bilateral dermoid cysts of the ovary removed at the age of 36 years. The child's growth and development from birth were entirely normal and milestones were reached at the expected ages. However, she started talking early and from the age of 2 years was considered very intelligent for her age and very tall. She had no illnesses but had fractured her left clavicle 9 months previously. She had received all her prophylactic immunizations.

After 10 days of vague 'malaise' and lethargy without pyrexia but with very slight abdominal soreness, the child had a night of more severe central abdominal pain and vomited once. This prompted the mother to seek the advice of her family doctor. She stated at this time that for the previous 2 years the child had been a poor eater and had a tendency to constipation but that she had been otherwise healthy. One month before this consultation she had first noticed the presence of a few pubic hairs and also that her abdomen had been rather swollen. She was admitted to hospital the following day under the care of Mr William Gall, F.R.C.S.

On examination the child appeared pale but was apyrexial and the tongue was clean and moist. Her height, 43 in (109.2 cm), was above the 97th percentile and her weight, 39 lb (17.7 kg), was between the 75th and 90th percentiles. Coarse pubic hair was present, the mons pubis, clitoris and labia were well developed and there was a little white discharge at the vulva. There was no marked enlargement of the breasts but the nipples were well formed and there was recognizable glandular tissue deep to the areolae. Examination of the heart and chest were normal. The abdomen was definitely larger than normal and palpation revealed a large, hard, smooth, well circumscribed, slightly tender lower abdominal mass. It was movable within small limits and was about 4½ in (12 cm) in diameter. The liver, spleen and kidneys were not palpable and there was no evidence of ascites. Digital examination of the rectum revealed a normal rectum and it was just possible to palpate the

lower border of the mass high up through the bowel wall.

Investigations: Hb 80%, WBC 12,500/mm³ (69% polymorphs, 26.5% lymphocytes, 4.5% monocytes), ESR 42 mm/hr (Westergren), PCV 39.5%, MCHC 28.5%, blood urea 18 mg/100 ml, 24-hr urine specimen—total volume 440 ml, 17-ketosteroids 0.8 mg/24 hr (Normal 0–2 mg/24 hr). Chest X-ray—normal. IVP—large soft tissue swelling arising from pelvis. Good concentration of dye in both kidneys revealed duplex left kidney and left double ureter, but no other abnormality. Skull X-rays—normal. X-rays of knees and hands—the bony appearances suggested an age of 6 years. The epiphyses appeared normal and there was no evidence of early fusion.

The opinions of the paediatrician and the radiotherapist were requested and it was felt that there was a distinct possibility that this was a malignant tumour. It was decided, therefore, to administer actinomycin D preoperatively and she was given 270 µg intravenously per day in 1 litre of normal saline for 2 days. Laparotomy was then performed through a right paramedian incision. A large tumour was found arising from the right ovary with omentum lightly adherent to it, and at this area of adherence there was discoloration of the tumour suggesting recent haemorrhage. There was no evidence of lymphatic, haematogenous or transcoelomic spread. The left ovary was seen and appeared to be normal. A right salpingo-oophorectomy was performed.

Her post-operative course was uneventful and her blood count was not affected by the antimetabolic drug which had been administered preoperatively.

Eighteen months after operation she was very well. Her weight was 49½ lb (22.6 kg) and her height 45½ in (115.4 cm) both of which lie close to the 97th percentile. There was no evidence whatsoever of precocious sexual development. Her scar was sound and there was no evidence of recurrence within the abdomen.

Pathologist's report: The tumour measured 11 × 10 × 6 cm and weighed 480 g. At one pole of the tumour the cystic spaces and interstitial tissue contained blood. Histologically the structure was that of a granulosa-cell tumour of diffuse type in which the cells appeared to be luteinizing.

Discussion

Granulosa-cell tumours of the ovary may occur at any age and only 5% occur before puberty.

When confronted with a child exhibiting sexual

precocity it is important to distinguish between the more common idiopathic cause from the rarer functioning ovarian tumour because in the latter case treatment can halt or reverse the progress of the precocious sexual development. The most important diagnostic criterion is the presence of a palpable abdominal tumour. This is almost invariably present, although at least two authors, Eberlein *et al.*, 1960; Niswander *et al.*, 1965) have reported cases in which the finding of an abdominal tumour was delayed for some time, in one case (Eberlein *et al.*, 1960) for over a year. For this reason Niswander *et al.* (1965) emphasize that 'persistence in seeking an ovarian tumour, with frequent examinations, even with anaesthesia if required, is mandatory when precocious puberty is evident'. Usually, however, these tumours are fairly large before signs of sexual precocity develop and because of the small capacity of the pelvis in a child they rise up out of the pelvis and become palpable by the time other symptoms appear.

In our case the symptom of pain led the child's mother to seek medical advice. Ovarian tumours may be the cause of acute abdominal pain if torsion occurs. The incidence of torsion of ovarian tumours is 29% and it is probably the rapid rise out of the small pelvis as the tumour increases in size with elongation of the pedicle or ovarian ligaments that predisposes to this (Groeber, 1963). Abdominal pain may also result from rupture of a cystic tumour and such a case is reported in a 3½-year-old-girl by Litton, Litton & Fox (1965).

Concurrent with the development of secondary sexual characteristics there is a corresponding increase in general physical development, and in our case the child's height 43 in (109 cm) was above the 97th percentile and she was well developed physically and mentally. The fact that the X-rays of her hands and knees suggested a bone age of 6 years at the time of her operation, prompted the author to look back at the X-ray which included the upper third of the chest and both shoulders taken when the child had fractured her clavicle 9 months previously to see if any evidence could be detected of increased radiological bone-age at that time. Unfortunately the shoulder has so few epiphyses and metaphyses in the process of ossification and there is so little reliable statistical information about their rate and mode of development that it was only possible to estimate the skeletal age from this plate as between 3 and 4 years (I. R. S. Gordon, 1966 personal communication).

The question of the management of children with granulosa-cell tumours of the ovary is a

difficult one mainly because, by virtue of the rarity of the condition, there is inadequate reliable statistical information about the prognosis. Formerly it was believed that such tumours were relatively benign or of low grade malignancy, and Seckel (1946) and Seckel, Scott & Benditt (1949) noted only two deaths in thirty-one proven cases while Pedowitz, Felmus & Mackles (1955) reported eight deaths in forty-nine cases. In 1954 a 5-year follow-up from the Ovarian Tumour Registry (Busby & Anderson, 1954) revealed a mortality rate of 21% unrelated to age. A few years later Novak's evaluation of current data from the Ovarian Tumour Registry (Novak & Novak, 1958) indicated a 28% mortality rate. Recurrences have been observed as late as 25 years by Diddle (1952) and 33 years by Aimes, Guibert & Galvaing (1946) and prognosis should therefore be guarded and the patients should have a careful and prolonged follow-up.

Varying opinions, therefore, have been expressed on the management of these cases. Groeber (1963) discusses this question at some length pointing out that 'the dominant attitude should be unwillingness to accept the risk of overtreatment' and that intelligent conservation of ovarian function and fertility should be accomplished whenever feasible even if this occasionally entails a calculated risk which would not be acceptable in the adult. He states that if malignancy is found a partial operation, viz. unilateral salpingo-oophorectomy, is acceptable only if the tumour is unilateral, if the capsule is intact, if there is no evidence of local spread and if there is no lymph-node involvement. In our case all these conditions were fulfilled and at the time of operation the contralateral ovary was inspected and palpated and appeared to be normal. Marshall (1965) expresses the opinion that since granulosa cell tumours are bilateral in 15% of large series (Traut & Marchetti, 1940) and in 40% of his own series, bisection of the contralateral ovary and, if involved, possible oophorectomy would seem warranted.

It frequently happens that the true diagnosis is not established pre-operatively. The case reported by Litton *et al.* (1965) which presented with acute abdominal pain went to operation with the pre-operative diagnosis of acute appendicitis. In our case a malignant tumour was suspected and a short course of actinomycin-D was therefore administered pre-operatively. If at laparotomy there is still doubt about the diagnosis but the question of malignancy is raised, Groeber (1963) advocates the adoption of the 'second look' attitude, that is the taking of material for permanent sections and proceeding

to operation at a later date depending on the diagnosis obtained from the sections. He considers that frozen section in the operating room may not be reliable enough in ovarian tumours to dictate a radical operation in a child.

Obviously the choice of treatment will depend on the merits of each individual case and on the amount of experience available. For these reasons it was considered worthwhile to report the present case. It would seem that Groeber's list of requirements for partial operation form a useful basis on which to make a decision bearing in mind also the statement by Niswander *et al.* (1965) that 'there is no proof that more radical procedures will decrease the possibility of recurrence'.

Postscript: One-half of the tumour removed from our case can be seen at the Museum of the Royal College of Surgeons.

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References

- AIMES, A., GUIBERT, H.L. & GALVAING (1946) Retroperitoneal recurrence of a granulosa cell tumour following removal of a right ovarian tumour at the age of 8 years. *Gynec. Obstet.* **48**, 801.
- BUSBY, T. & ANDERSON, G.W. (1954) Feminizing mesenchymomas of the ovary. *Amer. J. Obstet. Gynec.* **68**, 1391.
- DIDDLE, A.W. (1952) Granulosa and theca cell ovarian tumors: prognosis. *Cancer*, **5**, 215.
- EBERLEIN, W.R., BONGIOVANNI, A.M., JONES, I.T. & YAKOVAC, W.C. (1960) Ovarian cysts and tumors associated with sexual precocity. *J. Paediat.* **57**, 484.
- GROEBER, W.R. (1963) Ovarian tumors during infancy and childhood. *Amer. J. Obstet. Gynec.* **86**, 1027.
- LITTON, M.A., LITTON, E.W. & FOX, T.C. (1965) Haemorrhage from a granulosa-theca cell tumour of the ovary: An unusual case of acute abdominal pain in a child. *Wis. med. J.* **64**, 282.
- MARSHALL, J.R. (1965) Ovarian enlargements in the first year of life: review of 45 cases. *Ann. Surg.* **161**, 372.
- NISWANDER, K.R., COUREY, W.G. & WOODWARD, T. (1965) Precocious puberty caused by ovarian tumours: report of 3 cases. *Obstet. and Gynec.* **26**, 381.
- NOVAK, E. & NOVAK, E.R. (1958) *Gynecologic and Obstetric Pathology*. Saunders, Philadelphia.
- PEDOWITZ, P., FELMUS, L.B. & MACKLES, A. (1955) Precocious pseudopuberty due to ovarian tumors. *Obstet. Gynec. Survey*, **10**, 633.
- SECKEL, H.P.G. (1946) Precocious sexual development in children. *Med. Clin. N. Amer.* **30**, 183.
- SECKEL, H.P.G., SCOTT, W.W. & BENDITT, E.P. (1949) Six examples of precocious sexual development. I. Studies in diagnosis and pathogenesis. *Amer. J. Dis. Child.* **78**, 484.
- TRAUT, H.F. & MARCHETTI, A.A. (1940) A consideration of so-called 'granulosa' and 'theca' cell tumors of the ovary. *Surg. Gynec. Obstet.* **70**, 632.