A Case of Arrhenoblastoma

BY

W. KEVERALL MCINTYRE, *M.C.*, M.D. (Edin.), B.E. (Syd.), M.R.C.O.G.

CASES of arrhenoblastoma are sufficiently rare to justify publication. Moreover, I have not been able to find any published report of a case in Australia.

Reported Cases

A brief summary of reported cases is given as no résumé has been reported in recent English journals.

The first reported case was described by Pick in Germany. In a solid ovarian tumour he found a tubular arrangement of epithelial elements and noted a microscopic resemblance to seminiferous tubules in the testis. In 1907, Shickele reported similar microscopical findings in another solid ovarian tumour. Bell, in 1915, in England, described a third case and he noted that the patient had shown masculinizing changes. In addition to the tubular arrangement in microscopic sections, he described interstitial elements which contained lipoid substances. In the same year, Robert Meyer[1] collected 17 additional cases, many of which were associated with virilism. He also suggested that the number of interstitial elements present in the tumour had a direct relation to the associated virilism in the patient. The first case in America was reported by Moots in 1921, and since then Robert Meyer, Goodall,[2] Baldwin and Gafford,[3] Norris,[4] Camelo and Lisser,[5] Maxwell,[6] Dockerty and McCarty,[7] and others have reported cases in the American journals, and several of them have given complete reviews of the cases reported to date.

Origin

Robert Meyer, Goodall, Novak and others believe that these tumours arise from embryonic remnants of the seminiferous tubules in the hilus of the ovary. McLester suggests that it represents a one-sided development of a teratoma. The general opinion is that these tumours are probably derived from a primitive ovo testis, the male element being inactive until the

tumour begins to grow and form a testicular tumour, the hormone of which has masculinizing properties. Wilfred Shaw[8] states that most pathologists dislike the theory of embryonic relics as so few claim to have found them in the adult ovary. He believes that the view that embryonic relics have been present and quiescent from foetal times may be wrong and suggests that dividing cells may revert back to early cells of the foetal type. In granulosa cell tumours, which develop after the menopause, such a process must be at work, for "the new cells produced by division are anterior in type to the cells of the senile ovary." He suggests that "the same process may occur in the adult ovary, whereby adult cells revert back by division to cells which are embryonic in type." Definite conclusions have not been reached and the matter is still unsettled.

Diagnosis

There is some difference of opinion as to whether all cases reported are those of an arrhenoblastoma, as some did not reveal the masculinizing syndrome and most authorities are in agreement that it is impossible to make a diagnosis on the microscopical appearances alone.

In 1931, Robert Meyer in his classical article on "Some Species of Ovarian Tumours and their Relations to Sex Characteristics", stated his belief in the inter-relations of the various types, and divided his microscopic findings into 3 groups.

Group 1. Adenoma tubulae testiculare. This is the most mature and differentiated form and shows a regular tubular arrangement. Clinically, the majority of patients with tumours of this group do not show masculinization.

Group 2. A middle group composed of typical and atypical portions and also solid forms. This is intermediate between Groups 1 and 3, both histologically and clinically.

Group 3. A typical group composed mostly of solid forms with some atypical portions. This group does not show any true tubules, though a few areas may reveal isolated tubules or just irregular epithelial cords. These are the tumours associated with the most pronounced masculine changes.

Schiller in 1935[9] concluded that "the masculinizing effects of the arrhenoblastoma are connected with certain potentialities in the organs, and not all women possess these potentialities. They are remnants of a primary bisexual anlage which disappear in some individuals and persist in others." Evidence that there are women without such an anlage and that masculinization by

an arrhenoblastoma is dependent on the presence of such an anlage is given by the fact that there exist typical cases of arrhenoblastoma the hosts of which do not show any evidence of masculinization.

Novak, in 1938,[10] stated that "in a small minority of cases even though the tumour is clearly arrhenoblastoma, histologically, abnormal sex changes may be almost absent."

Norris, in 1938,[4] in a complete review of all reported cases of an arrhenoblastoma to date, criticized the diagnosis of a number of them on the grounds that the clinical syndrome was not present. He considers that in the present state of our knowledge of these rare tumours, the term arrhenoblastoma should refer to a clinico-pathologic condition and that the clinical signs and symptoms must be present as well as the pathological findings. He considers that as the microscopical picture may vary so greatly, there is no justification for classifying them as Meyer did, and one cannot make a definite diagnosis from the microscopic findings alone.

On applying this combined test to the recorded cases, Norris reduces to 29 the number then reported.

Goodall's case conforms microscopically to Meyer's third group, and yet had no defeminizing or masculinizing symptoms or signs; while Phelan's case showed a definitely tubular arrangement and conformed to Meyer's Group 1, but had a typical defeminizing and masculinizing syndrome. Norris would not agree that Goodall's case was an arrhenoblastoma; indeed, its derivation implies that if a case has not revealed masculine changes the tumour should not be called an arrhenoblastoma. The case I am about to describe conformed both clinically and microscopically to Meyer's third group.

These brief references to the views held by some pathologists show that the classification, as well as the origin of these tumours, is still unsettled.

Signs and Symptoms

The profound biologic changes caused by the tumour have striking and characteristic effects on the patient and the results of its removal are dramatic. The tumour produces defeminization and masculinization in the host. Amenorrhoea, loss of fat in the breasts and thighs, and atrophy of the mammary glands, are among the former signs, while masculine changes are shown in the growth of hair over the face (distributed as in the male beard), abdomen, forearms and thighs, a deepening of the voice

and hypertrophy of the clitoris. The uterus and the uninvolved ovary become hypoplastic.

The tumour usually occurs in young women who have matured normally and who then develop amenorrhoea. Hair begins to grow on the face and abdomen, with definite male distribution, and they usually consult a doctor about these signs and perhaps because they have noticed a swelling of the abdomen.

Malignancy

Most authorities agree that these tumours are usually benign. Wilfred Shaw[8] states that they are almost always innocent in type and for this reason removal of the affected ovary with the tumour is all that is considered necessary. On the other hand, Norris refers to the ' arrhenoblastoma ' as " a small but highly interesting group of malignant tumours, in which, through the actions of the hormone produced by the tumour, defeminizing or masculinizing effects become manifest in the host." He considered that all arrhenoblastoma are malignant. Dockerty and McCarty in a report on 4 cases of arrhenoblastoma in the Mayo Clinic records[7] state " these tumours are of a low grade of malignancy and in most cases respond well to local surgical removal."

Differential Diagnosis

A masculinizing syndrome may be caused by:

1. Cushing's Disease—Basophilic adenoma of the anterior pituitary.
2. Adrenal cortex tumour.
3. Arrhenoblastoma of the ovary.
4. Thymic tumour.

1. *Cushing's Disease.* A polyglandular disease of pituitary origin with hyperplasia of the cortices of the suprarenal glands and over-activity of the thyroid. This condition causes amenorrhoea; increase in weight due to fat on the trunk, neck and head, but not on the limbs; hypertrichosis of the face and loss of hair on the scalp. There is a characteristic kyphosis and often a raised blood-pressure which may cause headaches. Glycosuria develops in some cases and occasionally the clitoris hypertrophies. Signs and symptoms common to Cushing's and arrhenoblastoma are amenorrhoea, hirsutism and (occasionally in the former) an enlarged clitoris. Blood-pressure is not

raised, and glycosuria is not a characteristic sign. An X-ray of the sella turcica and a diabetic glucose tolerance test, with increase rather than loss of fat, should make the diagnosis clear.

2. *Adrenal cortex tumour.* These are more difficult to differentiate since they cause a masculinizing syndrome, and in the absence of a pelvic tumour or a palpable renal tumour, examination of the blood for the hormones might be the only way of arriving at a decision. If the adrenal tumour were large enough, a urogram might be useful, or a perirenal air injection for outline of the adrenals.

In our case, a salpingogram confirmed the diagnosis that the swelling was an ovarian or broad ligament tumour.

4. *Thymic tumour.* A rare condition which may give rise to a polyglandular syndrome caused by change in the activity of the suprarenal cortex, pancreas and thyroid gland.

Treatment

This is necessarily surgical and consists in the removal of the affected ovary only, in the majority of cases.

The results are usually dramatic. The menses reappear, the breasts enlarge and the figure develops normal feminine curves again. The voice remains more or less baritone and as a rule the clitoris does not return to its normal size. While there is a decrease in the growth and distribution of hair, some degree of hirsutism usually remains. The uninvolved ovary and the endometrium again function normally as is proved by the return of regular monthly periods, and by pregnancy, which in some cases has followed the removal of the tumour.

The following history is of interest, because the syndrome was typical of that associated with a masculinizing tumour. The diagnosis was suggested by the junior resident in the ward, Dr. D. Alexander, when he reported that the case had been admitted under my care, and subsequent investigations proved that his diagnosis was correct.

Case History

Miss L.D., aged 26 years. She consulted a doctor about a swelling in the abdomen, which she first noticed about a year ago. The swelling gradually increased in size, but did not cause any discomfort. She was admitted to the Launceston General Hospital under my care with a diagnosis of a probable ovarian tumour, or, alternatively, a pedunculated fibroid of the uterus.

Previous history. The patient has always been a healthy girl and has not had any serious illnesses. She lives in the country and has led a healthy out-door life. Her periods began at 14 years and were regular until 2 years ago. Four years ago she became pregnant and had an illegal operation at 2 months. Two years later she noticed that her periods were progressively becoming scantier and 18 months ago they ceased altogether. She has not menstruated since then, nor had any vaginal discharge. Since she was 18 years of age she has had a slight growth of hair on the upper lip and under her chin. She states that her mother and her two sisters have more hair on their faces than is usual, but not enough to disfigure them. About a year ago, she noticed that the hair on her face was growing coarser and spreading over her cheeks. She began to shave herself, and now has a strong beard and has to shave every day. (Fig. 1.) She also noticed that the pubic hair was spreading. This now covers the whole abdomen. Quite lately she noticed that her forearms and thighs had become hairy. She has not noticed any change in her breasts. Her health has been satisfactory and her only reminder of her periods is a regular, rather severe headache, which occurs at monthly intervals.

She admits that she had regular coitus for years up to about 6 months ago. She always had normal libido and her only reason for ceasing such relations was that pressure on the tumour hurt her. She almost always has an orgasm and the loss of her periods made no difference whatever to this. Her feelings towards men apparently have not been affected in any way by the masculinizing tumour.

Heart and lungs—clear.

Urine—no albumin or sugar.

Blood-pressure—130/88.

Abdomen—there is a large firm tumour about the size of a small football lying to the right side. It is somewhat kidney-shaped and the surface is irregular but smooth. It is freely mobile and does not extend into the pelvis. It seems a solid rather than a cystic tumour. Its shape suggests an enlarged prolapsed right kidney.

Vaginal examination. The labia majora are flat and hardly to be identified as such. The clitoris (Fig. 2) is greatly hypertrophied, having a well-marked glans, and has the size and appearance of a 12-months infant's circumcised penis, about $1\frac{1}{2}$ inches long. The frenum of the clitoris hangs like a curtain and is grossly enlarged. Bimanually, the vagina and cervix are normal

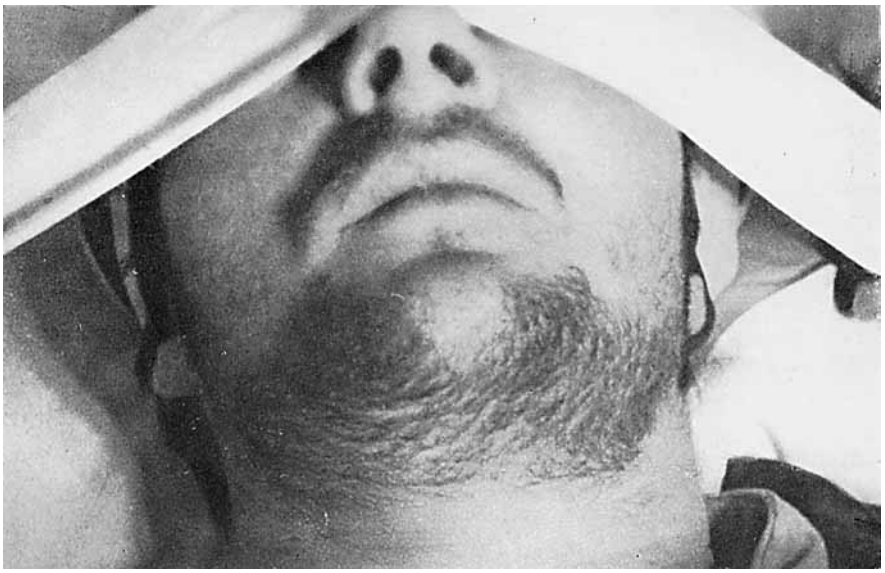

FIG. 1

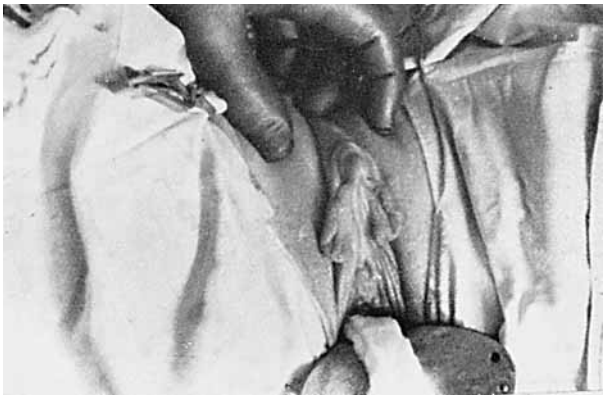

FIG. 2

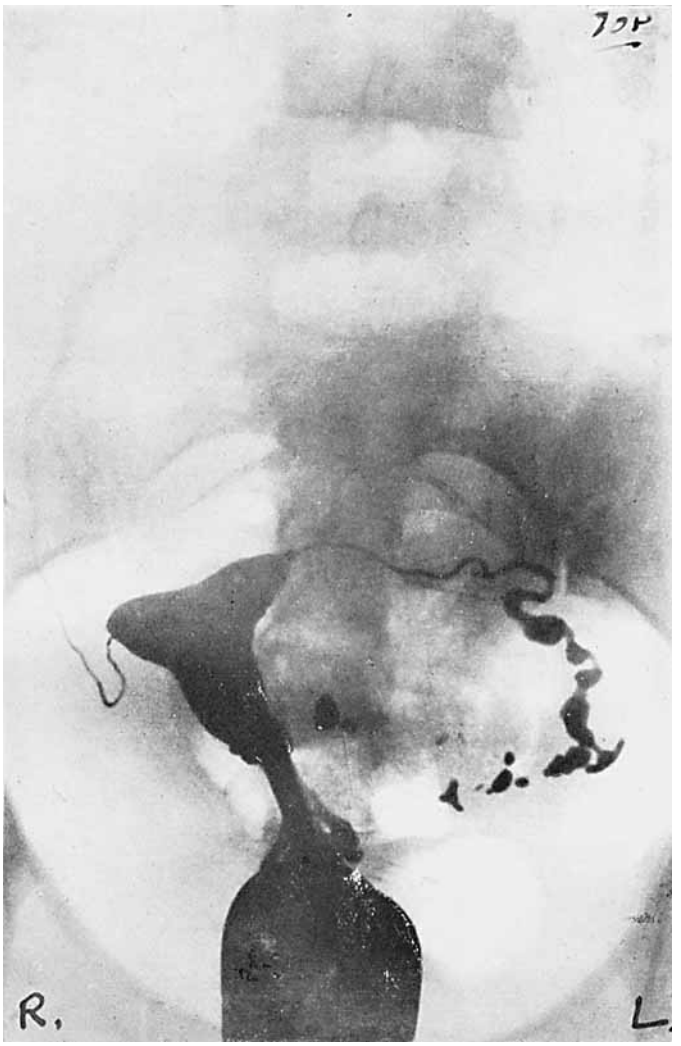

FIG. 3

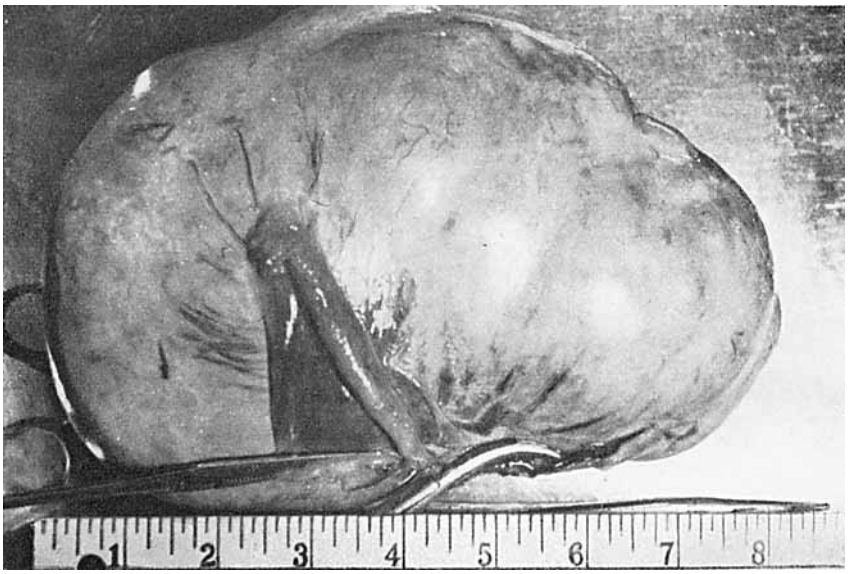

FIG. 4

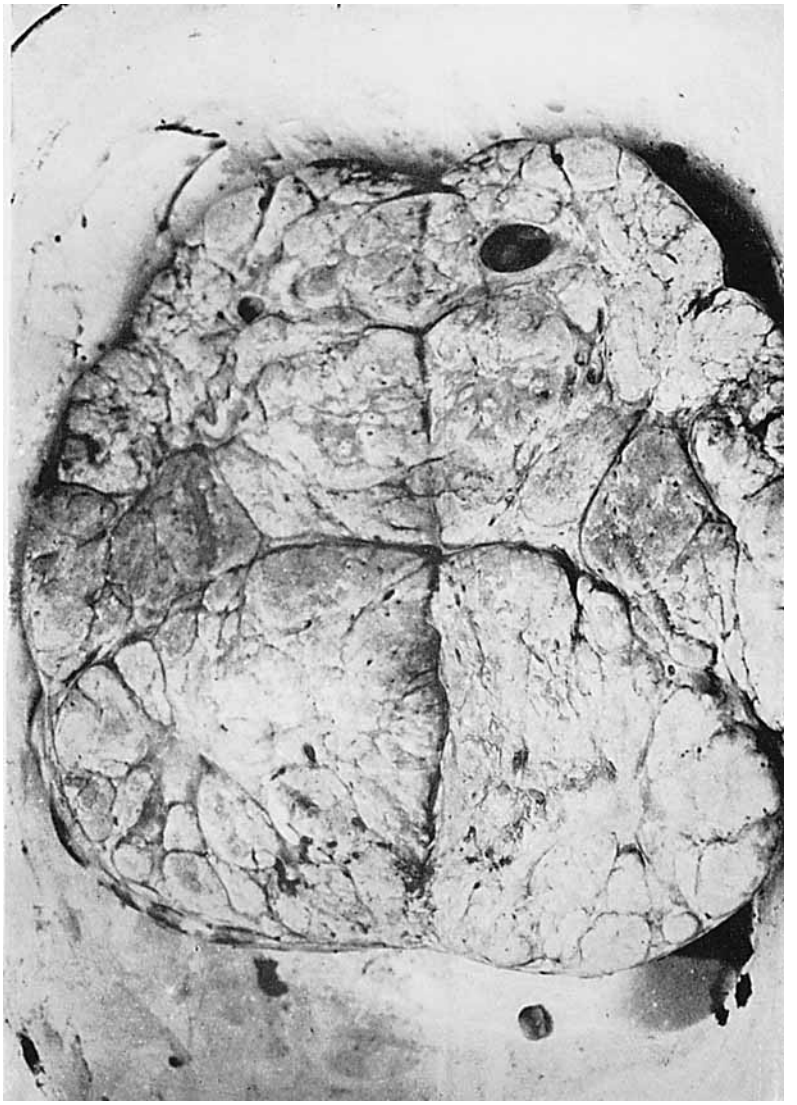

FIG. 5

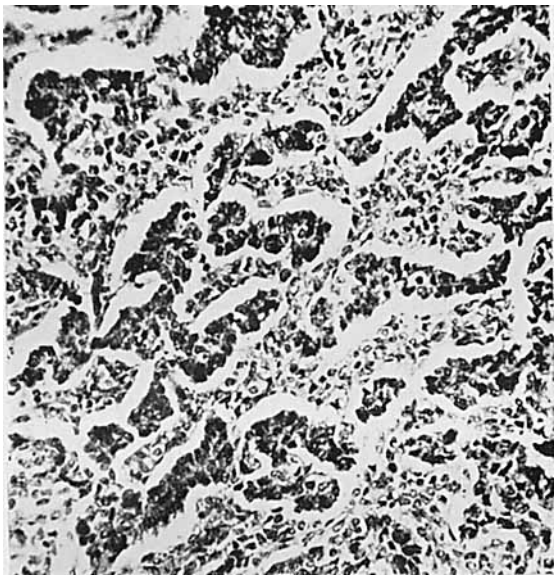

FIG. 1A

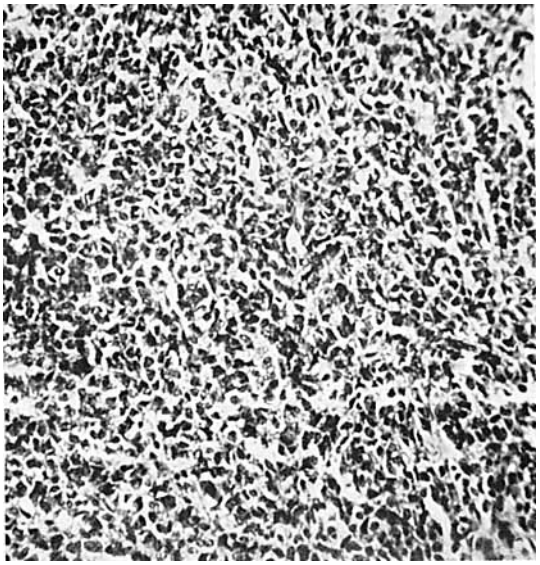

FIG. 2A

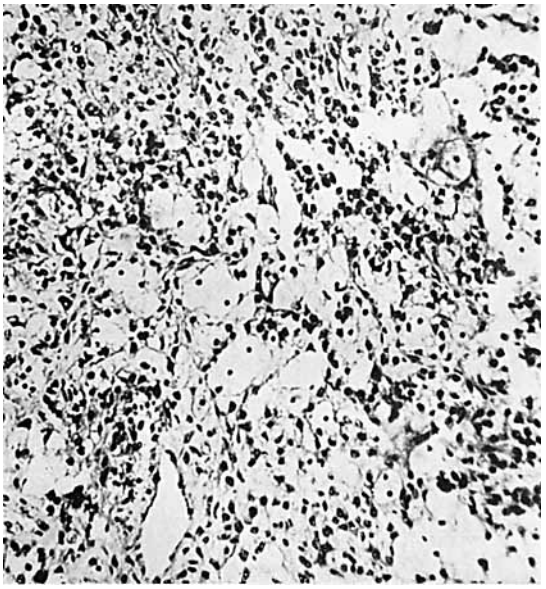

FIG. 3A

and the uterus seems a little enlarged, and lying to the left side, slightly retroverted. The tumour is not in the pelvis. From its shape it might be a solid ovarian tumour with a long pedicle, a pedunculated fibroid of the uterus, or less likely, a prolapsed grossly enlarged right kidney.

A salpingogram (Fig. 3) assisted in the diagnosis. This showed the lengthened right Fallopian tube passing upwards so that the fimbria was at the level of the 4th lumbar vertebra and near the midline. It was apparently closed at the fimbriated end. The left tube was normal in shape and position and was patent. The uterus seemed to be a little enlarged and lying to the left as found by the vaginal examination. A definite diagnosis was now made of a solid right ovarian or broad ligament tumour, probably in view of the age of the patient, its being unilateral, and the associated syndrome, an arrhenoblastoma. Unfortunately, we were unable to have any hormonal tests carried out.

Operative findings. Curette. Length of uterus, 9 cm. Very little endometrium and very free bleeding from the curetted surface. Laboratory report on the scrapings was as follows: "tubular glands present in normal stroma, a good deal of haemorrhage present."

Abdominal section. The findings conformed to what was expected from the salpingogram. The left ovary (3·75 cm. × 2.5 cm. × 1.25 cm.) was hypoplastic and looked like a senile post-menopausal ovary. The left Fallopian tube was normal. The right ovary was replaced by a large solid tumour (20 cm. × 15 cm. × 10 cm.). (Fig. 4.) Omentum was adherent to a small area of the posterior surface. The tumour was greyish in colour, with a smooth but somewhat bossy surface, and had a thick varicose pedicle. The right tube was lengthened and spread over the tumour. The cut surface was bright yellow and lobulated in some areas, some of these lobules having a stellate arrangement. It had the consistence of freshly cut spleen. Some areas were a paler yellow and softer, almost suggesting degeneration. Only one or two cysts were to be seen. Throughout the tumour, there was a remarkable absence of blood vessels, but a few were visible here and there between the lobules. (Fig. 5.)

The tumour was submitted to Dr. Rupert A. Willis, pathologist to the Baker Institute, Prince Alfred's Hospital, Melbourne, who reported as follows:

"The material submitted for examination consisted of four blocks of tissue preserved in formalin solution. These were

embedded in paraffin, sections were cut and stained by haemalum and eosin and by Ehrlich's acid-haematoxylin and eosin.

"The tumour consists of masses of epithelial cells, most of which are polyhedral in shape and 12 to 15 mm. in average diameter. Each cell contains a single rounded or oval vesicular nucleus 8 or 10 mm. in diameter, usually without a distinct nucleolus. Mitotic figures are fairly numerous. The cytoplasm is finely granular or foamy, and the cell outlines in most places indistinct. The cells are arranged partly in clumps or anastomosing cords (Fig. 1a) and partly diffusely (Fig. 2a). Some of the cell clumps contain central extra-cellular vacuolated or honeycombed spaces, but nowhere are there distinct lumina of glandular character. The stroma of the tumour is not abundant, consisting of scanty strands of connective tissue between the groups of tumour cells; in many places these strands themselves contain scattered tumour cells. Blood vessels are few in number. In places there are collections of large rounded phagocytic foam-cells, lying both in the interstitial framework, and within the tumour clumps. (Fig. 3a.) These no doubt correspond with the yellow degenerate-looking areas seen on the cut surfaces of the tumour with the naked eye. The histological characters of the tumour are in accord with the clinical diagnosis of arrhenoblastoma as described by Meyer and others."

Subsequent History

The patient made a normal and uneventful convalescence, and a fortnight after the operation she was given 2 c.c. of Antuitrin S. at 3-day intervals. She menstruated normally after the fourth injection, which were then discontinued. A month later she again had a normal 4-day period. By this time, the hair on her cheeks was definitely less, but she still had a strong growth on her upper lip and chin. There was no reduction in the size of the clitoris, but her breasts were larger and tender. The areolae were brighter in colour and increased in area. There was still a strong growth of hair on the abdomen, with the same male distribution.

She has reported at 2-monthly intervals, the last being 10 months since her operation. She still has to shave, but less frequently, and there is a decided improvement in her appearance. She has less hair on her face, thighs and upper abdomen, but the male distribution has not anywhere disappeared. She has gained weight—most of this being due to an increase in the

breasts and thighs, which have now normal feminine curves The clitoris has not changed.

She is now married to her former lover, and it is interesting to note that though she is in excellent health and full of energy, she has now a complete absence of libido. She says she has no desire and has not experienced orgasm since the operation. I had hoped she might enable me to complete the case by reporting that she had become pregnant, but unfortunately this is not so, and her husband has recently gone abroad with the Australian Imperial Force.

Discussion

The presence of a palpable abdominal tumour, which had first been noticed by the patient soon after amenorrhoea began, and which steadily increased in size, together with the obvious masculinizing syndrome, made the differential diagnosis comparatively simple in this case.

The morphology of the tumour is in appearance similar to the group termed arrhenoblastoma; and would, in Meyer's classification, conform with his third or atypical group. The pronounced masculine changes which Meyer associated with this group were present.

It is a matter of conjecture whether the rapid reappearance of the menses while she was still in hospital was due to the administration of Antuitrin S. Grant Baldwin and James Gafford in the report of their case suggest that the male hormone secreted by the tumour renders the anterior pituitrin hormones inactive either directly or indirectly. In this case, the uninvolved ovary looked so shrivelled and inactive that one would not have expected any immediate hormonal activity on its part. Possibly the extra stimulus from the injected hormone hastened its recovery.

Her earlier gratitude for the results of the operation is now somewhat tempered by the loss—temporary, I hope—of libido. I have not read of this loss in other case reports.

Summary

A case is described which is believed to be the first reported in Australia of an arrhenoblastoma of the ovary, in which typical microscopic findings were associated with a classical defeminizing and masculinizing syndrome. Since the surgical removal of this

tumour, the patient has menstruated normally and has made a gradual return to feminism.

I am indebted to Dr. R. Y. Mathew, of the Commonwealth Health Laboratory, and to my son, Flight-Lieutenant A. K. McIntyre, M.B., B.Sc. (Syd.), R.A.A.F., for assistance in the preparation of this paper. Also to Sister Tucker, of the Radiological Department of the Launceston Public Hospital, for the preparation of the photographs.

REFERENCES

1. Meyer, Robert, *Amer. Journ. Obstet. and Gynecol.*, 1931, xxii, 697.
2. Goodall, J. R., *Amer. Journ. Obstet. and Gynecol.*, 1934, xxvii, 748.
3. Baldwin and Gafford, *Endocrinology*, 1936, xx, 373.
4. Norris, E. H., *Amer. Journ. Cancer*, 1938, xxxii, 1.
5. Camelo and Lisser, *Endocrinology*, 1938, xxiv, 39.
6. Maxwell, A. F., *West Journ. Surg.*, 1937, lxv, 134.
7. Dockerty and McCarty, *Mayo Clinic Vol.*, 1939, 14–24.
8. Shaw, Wilfred, " Recent Advance in Obstetrics and Gynaecology," 1939, 4th edition.
9. Schiller, *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1935.
10. Novak, *Amer. Journ. Obstet. and Gynecol.*, 1938.