INTERSEXUAL CAUSES OF PRIMARY AMENORRHOEA*

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Patients with primary amenorrhoea usually find their way to the gynaecologist rather than the physician. In the USA many gynaecologists are in fact physicians or endocrinologists rather than surgeons but, since this is not the case in this country, I hope I may be excused for talking about a problem which is primarily an endocrinal one. The management of such a patient is frequently a matter for nice cooperation between specialists of different disciplines, which may or may not include any actual surgery, and the natural coordinator of these efforts is the endocrinologist.

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I will divide the intersexual causes of primary amenorrhoea into those (more common) with a vagina, in which one must resist the tendency to give oestrogens without more ado and then hope for the best; and those without a vagina, where the tendency has sometimes been to get rid of the patient to the plastic surgeon as quickly as possible.

With Vagina

Gonadal Dysgenesis (*'Ovarian Agenesis'*)

There seems little doubt that the commonest cause of primary amenorrhoea seen at Groote Schuur Hospital is gonadal dysgenesis. I cannot quote exact figures, but when Dr. Muller was registrar in gynaecology we saw most of the

cases of primary amenorrhoea, and gonadal dysgenesis was outstandingly the most frequent.

The three prime features of this condition are external female appearance and body-form, internal female organs, but gonads represented by mere white streaks of tissue on the posterior aspect of the broad ligaments. Other outstanding features include shortness of stature in almost all cases (about 4 feet 8 inches when adult), and very often certain congenital anomalies, such as a webbed neck, asymmetrical face, 'shield-shaped' chest, multiple black moles, and coarctation of the aorta. Of course, no secondary sexual characters develop (although we have occasionally seen some breast growth) and the axillary and pubic hair may be scanty.

Since this condition is a variety of primary gonadal failure, the pituitary gland overacts and produces an excessive amount of gonadotropic hormone (FSH), which can be measured in the urine. Recently we have learnt that about 80% of these patients are actually genetic males*, which can be quite easily discerned by examination of the chromatin of the nuclei in stained smears of the buccal mucosa. This finding is, of course, most helpful in diagnosis and, in fact, renders a diagnosis possible at an early age if, for instance, it be suspected simply on the basis of shortness of stature. From the theoretical point of view it means that something went wrong very early in foetal development so that the gonadal tissue did not mature into testes. In the absence of foetal gonadal influence, female internal organs and female body-form developed in accordance with the known basic or neutral body-pattern.

The final diagnostic court of appeal is by laparotomy with inspection and section of the primitive gonads themselves. I have absolutely no doubt that, where the diagnosis is uncertain despite the investigations mentioned above, laparotomy is not only justified but necessary.

Management consists of explanation and encouragement, and oestrogens. We do not tell the patient about her genetic sex; but we do tell her what we can achieve with oestrogens, that we cannot add to her height, and that she will not have children. We warn her not to waste money on expensive and entirely useless injections or visits to persons of doubtful medical ethics, but we point out that many girls like herself are happily and satisfactorily married. Oestrogens we usually give simply as stilboestrol, between 0·5 and 2 mg. per day for 4 weeks, with a week's break and so on. Therapy must be continued for life. It is not good enough to produce one artificial menstrual period and then not see the patient again. Oestrogens will achieve growth of the nipples and breasts, more mature feminization of body contours, growth of the vagina and uterus, and in many patients increased energy and a feeling of well-being. They certainly look and feel 'more feminine'. Perhaps oestrogens tend to delay premature aging, atheroma and osteoporosis. Regular withdrawal bleeds are usually obtained.

At this juncture I should like to quote from a letter I recently received from an intelligent patient with gonadal dysgenesis: 'After my operation in 1955 I almost went to pieces. I wondered if it was worth while going on living if I was to be a neuter creature who would never have children.' She then says how much she appreciated our straightforward explanation of her condition, and goes on: 'Then there are the physical changes your treatment has brought about. Although I've never been a fan of Diana Dors, those extra inches certainly have made a great difference. Before 1955 I was too shy and self-conscious to appear in a bathing costume or to undress with other girls. Today I practically live in the sea during the summer. Although the periods I have are 'synthetic' and I fully realize this, it's amazing the difference it makes psychologically to be like other women'. Further, 'People who have not seen me for a long time often don't recognize me; they all say I have grown at least 8 years younger during the past few years. In the past few years I've changed from an awkward, self-conscious, self-centred introvert into a healthy, happy person who is outside as much as possible and thoroughly enjoys the company of people of both sexes—without the aid of testosterone!'

Women with Testes (Oestrogen-producing Testes)

This syndrome is not so common as gonadal dysgenesis, but is not rare—we have seen 4 cases within the past 2 years. Patients present in two main ways—either in childhood with hernia, in which case the surgeon is amazed when the odd structure he removed from the hernial sac is reported upon as testis—or as primary amenorrhoea, in which case the gonads are intra-abdominal.

The latter patient usually appears as a well-built, normally tall, female with good breast development. Two virtually diagnostic clinical features are the total absence of axillary hair and scanty pubic hair, together with lack of uterus. Then, most important, the chromatin pattern is male.

We look upon these patients as examples of male pseudo-hermaphrodites with complete sex reversal—their testes produce oestrogens rather than androgens and their hormonal abnormality allows female anatomical development and later breast development. (It is possible that it is the absence of androgen, rather than an actual excess of oestrogen, which is really responsible for the intersexual state since, as we saw in gonadal dysgenesis, a lack of male hormone leads to the 'neuter' or female type of development.) Such patients should, of course, continue to live as females, and may marry happily (their libido appears to be extremely healthy). We usually recommend removal of the gonads because of their liability to malignant change, (±10%), after which oestrogens are necessary to prevent menopausal symptoms!

Female Pseudo-hermaphrodites (Congenital Adrenal Hyperplasia)

It is extremely important to recognize these patients, since appropriate treatment may be highly successful (though it should really start soon after birth). Undiagnosed patients may be thought to be males with extreme hypospadias and undescended testes, or females with large clitoris and primary amenorrhoea who become masculinized and hairy at puberty. Actually they are genetic females (nuclear chromatin is female), with ovaries, whose adrenals are producing too much androgen. The final diagnostic feature is the presence of a great excess of 17-ketosteroids (and particularly pregnantriol) in the urine. They possess uterus and vagina, and in fact if the adrenal activity can be suppressed, they can develop breasts, menstruate normally and even bear children.

The treatment is with cortisone or an analogue, such as prednisone, which will successfully suppress the adrenal overactivity. The only surgical procedure which may be

* Recent work has shown abnormal chromosome numbers to exist in gonadal dysgenesis, so that the term 'genetic male' is not correctly applied here. (This matter is discussed in an Editorial article on page 743 of this issue.—*Editor.*)

necessary is reduction of the size of the hypertrophied clitoris. If, however, the patient has been brought up as male, it may be best to do nothing, certainly once male-type puberty has occurred.

True Hermaphrodites

These patients, whose gonads contain both ovarian and testicular tissue, are not as rare as you might think. Here we are really only interested in those with sufficiently feminine form to have been brought up as female and then to be seen for lack of menses. There is great variety in this form of intersexuality, but all have some kind of ambiguous sexual development and almost all have a uterus and vagina. One or both gonads may have descended into the labial region (in which case the relevant gonad must be either a testis or an ovotestis). The genetic sex may be male or, more commonly, female. There is a single perineal orifice, which may be shown by catheterization and radio-opaque dye studies to lead to a urogenital sinus which drains both a female genital tract and the urinary system.

Secondary sexual characters of either sex may develop with maturity. Breast growth and menstruation may occur, or the menstrual flow may be obstructed to produce a haematometria or haematocolpos, or appear as periodic 'bloody urine'. The person usually continues to assume the role in which he has been brought up. In some instances both male and female roles may be adopted in sexual relationships, provided the environment and circumstances of the moment call for such virtuosity.

Treatment in general consists of full investigation, with laparotomy if necessary, followed by such surgical, plastic or hormonal therapy as may be suited to furthering the patient's life in the sex to which he feels he belongs.

Male Pseudo-hermaphrodite (Intermediate Cases)

These patients have a phallus of variable size, and persistence of Mullerian-duct structures with a vagina into which the urethra opens—really a urogenital sinus. The scrotum is bifid and neither gonad may be descended, so that the patients may be mistakenly regarded as female. The gonads, of course, are testes, and the genetic sex male. If the diagnosis is not made early, the advent of a male type of puberty will come as a shock.

It may be right to continue to deal with some of these patients as females, but each one deserves careful investigation and individual consideration.

Without Vagina

Male Pseudo-hermaphrodites (some cases)

These patients, again, have a phallus of variable size, with extreme hypospadias, a bifid scrotum and, usually, undescended testes. There is no vagina, or only a rudimentary one.

Left alone, a male puberty will ensue, or the patient may become eunuchoidal if the gonads are incapable of producing male hormone. Catheterization and dye injection discloses no Mullerian-duct structures, the nuclear chromatin pattern is male, and gonadal biopsy reveals only testicular tissue.

Congenital Lack of Vagina

These patients appear normally female in all ways except that they lack a vagina and often uterus as well. Before an artificial vagina is constructed it is advisable to check that the nuclear sex is really female and that no Mullerian-duct structures open into the urethra. This is particularly important since the 'women-with-testes' syndrome or the true hermaphrodite may, rarely, lack a vagina—and the diagnosis in these instances would be completely missed if special investigations were not performed.

A lesser degree of abnormality, of course, is the incomplete canalization of the vagina—really an overgrowth of the labioscrotal folds, which may be combined with a rather large clitoris. Catheterization of the single perineal opening will readily separate these cases from those where no vagina is present at all.

CONCLUSION

Unless there is an obvious cause for primary amenorrhoea, such as tuberculous endometritis, all patients presenting with this complaint should be submitted to certain definitive investigations. These may include:

1. Examination under anaesthesia.
2. Catheterization of perineal orifice(s) with injection of radio-opaque dye. (Further examination by a urologist may be necessary.)
3. Nuclear sexing, by examination of buccal smear or other tissue.
4. Urinary output of 17-ketosteroids.
5. Urinary output of FSH.
6. Biopsy of accessible gonad.
7. Laparotomy, with biopsy of intra-abdominal gonad.
8. Psychological appraisal of the patient's own sexual orientation, which may be extremely useful in helping to decide upon the final lines of treatment.

I am pleased to acknowledge the value of my discussions with Dr. R. Hoffenberg, who has always worked with me on this subject.