where precautions can be taken to minimize the likelihood of hyperstimulation.[5] [6] Unfortunately the responsiveness of the ovaries, even in a particular patient, is not constant, and even with careful monitoring—by measuring urinary oestrogen levels—it is not always possible to avoid hyperstimulation of the ovaries and multiple conception.

The first indications in this patient that a high multiple conception had occurred were the high urinary excretion levels of oestrone and pregnanediol (Fig. 1). The uterus was large for dates and the diagnosis was confirmed by ultrasound. The main hazards that were expected were abortion or premature labour with neonatal death, placental insufficiency with intrauterine death, and pre-eclampsia. It was thought that rest would be the most helpful prophylactic treatment for these problems, and fortunately it was possible to achieve a satisfactory compromise between rest and activity. The isoxsuprine infusions used when contractions occurred may have helped to prevent abortion and premature labour.

Placental function was monitored by measuring girth and weight and the levels of oestriol and pregnanediol in 24-hour urine specimens.

Anaemia was more apparent than real and due primarily to a dilution effect. Pre-eclampsia was not a problem in this pregnancy (nor in that described by Liggins and Ibbertson.[3]), though it was in two other gonadrotrophin-induced multiple pregnancies managed in this hospital and in the sextuplet pregnancy described by Aiken.[4]

Planning for the delivery was of vital importance in ensuring that events ran smoothly when the time came. Adequate numbers of obstetric and paediatric personnel remained on call permanently for several weeks beforehand. Other preparations included preparing seven pairs of numbered clamps, blood cross-matched for the mother and for the babies, and equipment for the reception, resuscitation, and future management of seven premature babies.

Caesarean section was decided on because of possible hypoxia during labour and possible entanglement and premature placental separation during delivery. Fortunately we had easy access to the lower segment; this was not so in the case described by Aiken,[4] where a classical caesarean section had to be performed, with damage to one of the placentae and loss of a baby through haemorrhage from the placenta.

We were also fortunate that the five liveborn babies were in such good condition at birth and that none developed hyaline membrane disease. The preponderance of girls may have been partly responsible for the absence of this disease, since it occurs more often in boys. We have not, however, previously observed any evidence of hyaline membrane disease in premature babies born in this hospital after gonadotrophin therapy and possibly therefore, some factor, perhaps hormonal, is acting to mature the enzymes responsible for the synthesis of pulmonary surfactant before delivery in these fetuses.

We were successful in avoiding publicity before delivery, but subsequently arrangements had to be made for dealing with several hundred journalists. A large room was set aside for press conferences and extra telephones were installed. In general the press remained most co-operative and respected our wish to avoid personal publicity. On several occasions, however, attempts were made by journalists to force an entry into the obstetric hospital. For this reason it was necessary to post guards on the door.

We are grateful to Miss A. Stoten and Mr. H. Shah for performing the steroid assays, to Mr. Asta for preparing the Figures, to members of the Medical Research Council Human Biochemical Genetics Unit for details of the red cell antigen and enzyme studies, and to the staff of the obstetric hospital for all their help in caring for the patient and her babies.

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Clinical Endocrinology

Delayed Puberty

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British Medical Journal, 1972, **1**, 790-793

Puberty is defined as the state of having become functionally capable of procreating and in England is legally recognized to be at the age of 12 in girls and 14 in boys. In clinical practice it is an event in transition from childhood to maturity characterized by changes in somatic and sexual development that take place over a number of years. Moreover, true reproductive capability is probably not achieved, particularly in girls, until late in adolescence and not until the beginning of the third decade in some.

The onset of puberty depends on the activation of the testes or ovaries by pituitary gonadotrophin. The increased production of this hormone at this time is now believed to be due to the maturing of higher centres and the relaxing of the inhibitory influences exerted on the pituitary during childhood.

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Physiologically it is marked in boys by the differentiation and proliferation of mature Leydig cells in the testes, a rise in plasma levels of testosterone, a full maturation of the seminiferous tubules, a rapid increase in body size, deepening of the voice, and the growth of sexual hair, the penis, the prostate, and the seminal vesicles. In girls, rising oestrogen levels bring about the development of the nipples and mammary ducts, enlargement of the uterus, rounding of body contours, cornification of the epithelium of the vulva and the vagina, and the onset of menstruation. Ovulation may not occur for several menstrual cycles and may be delayed for several years. Therefore, adolescence may be followed in women by a period of physiological sterility of variable duration and maximum fertility is not achieved in some until the middle of the third decade.

Normal Adolescent Development

The first indication of puberty in boys is an increase in the size of the testes and the appearance of lightly pigmented pubic hair, together with rugosity and pigmentation of the scrotal skin. This may occur as early as 10 years or as late as 13½ years. The penis does not increase in size until a year later, when the spurt in height also begins.

In girls the first signs of puberty are an elevation of the breast papilla as a small mound, the start of the spurt in height, and a light growth of pubic hair. These may appear at any age from 8 years to 14 years, but on average 18 months to two years earlier than the boys. The menarche follows two to three years later, as early as 10 years of age or not until 16½ years.

Pubertal development lasts on average about three years in girls and four years in boys. In general, the earlier puberty begins the more rapidly it progresses, with the result that it is usually completed in some before any development has occurred in others. The range of ages over which pubertal events can begin is shown for both boys and girls in Fig. 1.

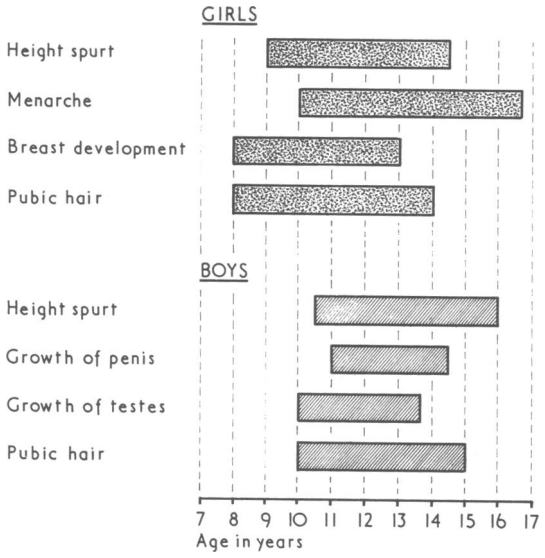

FIG. 1—Age ranges of the onset of some pubertal events (modified from Tanner, J. M., *Growth at Adolescence*, Oxford, Blackwell Scientific Publications, 1962, reproduced by permission).

Factors Influencing Timing of Puberty

The considerable range of normal in the age of onset of puberty is believed to be largely an expression of genetic variation. Thus there is a high correlation between the ages at which brothers achieve a maximum rate of growth, between the ages of menarche in mothers and daughters, and among sisters. The same is probably true of girls and their paternal grandmothers and paternal aunts.

Other factors which may contribute to a small part of the variation are the size of the sibship and the birth order. Thus the menarche occurs later in girls from large sibships, but a girl born late in a sibship may be expected to attain menarche earlier than a girl born first (in the case of the sixth in a large sibship this can be as much as a year earlier than the firstborn). When making comparisons between the age of puberty in different generations allowance must also be made for secular trends. Over the last 120 years or so puberty has been occurring earlier at the rate of about four months for every decade.

There is also a relation with physique; tall girls start adolescence earlier than shorter girls, but, as might be expected, girls in whom adolescence is late are taller on average than those who menstruate earlier. There is, at least in present times in this country, no correlation between the age at puberty and social class. This probably reflects the general levelling in social structure that has occurred in postwar years, particularly in relation to the incidence of chronic infectious diseases and nutritional status.

Late Puberty

More often than not it transpires that "delayed puberty" is a term that has been applied to boys and girls who develop later and more slowly than most, but who eventually develop fully. This late appearance of pubertal changes may, however, cause severe social embarrassment for young persons and considerable concern for parents. Unfortunately it is not possible to give unqualified reassurance except in retrospect but an inquiry about the pattern of adolescence in other members of the family, including previous generations, and consideration of the other factors known to affect the timing of puberty may provide grounds for justified optimism. In the absence of generalized disease or evidence of a developmental disorder, the possibility of a normal outcome can be expected up to the age of 20 years in boys and 18 years in girls. If there are pressing social and psychological reasons for accelerating puberty this may be achieved in boys by administering chorionic gonadotrophin for a short period and in girls by cyclic oestrogen therapy, which should be interrupted at intervals to determine if development can be maintained spontaneously.

PUBERTY DELAYED BY GENERALIZED DISEASE

Prepubescent disease and malnutrition followed by recovery or correction before the time of puberty has been shown to have little or no effect on the timing of this stage of development. This runs counter to the popular belief that dietary deprivation in infants during war years leads to diminished adult size or late menarche. Malnutrition and chronic disease persisting into adolescent years do, however, delay and prolong puberty when not adequately controlled or treated. The diagnosis of such diseases as malabsorption, malnutrition, diabetes mellitus, asthma, etc., is more likely to be suspected on other grounds than their effect on adolescent development, but chronic infection such as tuberculosis may account for nothing more specific than fatigue and debility and may not be brought to the attention of the doctor until there is concern over retarded adolescent development. Anorexia nervosa may present as a failure in the normal growth spurt, and primary amenorrhoea and the symptom of anorexia may be concealed by the patient. Continuous observation may be necessary to make the correct diagnosis.

Sexual maturation may also be delayed in hypothyroidism and in hyperthyroidism, but skeletal development in thyro-

toxicosis is more likely to be advanced for the age of the patient.

DEVELOPMENTAL DISORDERS IN BOYS

Disorders which interfere with normal adolescent development are very rare. In boys it is usual for sexual development alone to be affected, the increase in height occurring normally, and often continuing for longer, with the result that on average they are taller. Muscle development, on the other hand, is likely to be impaired, and the habitus does not assume male proportions, the shoulders remaining narrower than the hips. Facial hair growth is also delayed and if and when it does occur it is very sparse. It is exceptional, however, for the voice not to "break."

There may be more than the usual degree of pubertal gynaecomastia and on occasions this can be extreme. This clinical picture was first described by Klinefelter and subsequently the majority were found to be chromatin-positive, owing to the presence of an extra X chromosome. Some boys with this syndrome, however, have a normal chromosome complement and males with extra X chromosomes do not always have the features described by Klinefelter.

Klinefelter's Syndrome

The most consistent feature of males with extra X chromosomes is the shrinking of the testes which occurs at adolescence in place of the usual increase in size; they become pea-sized and soft in consistency. The penis and scrotum develop normally but the scrotum does not become pendulous because of the small size of the testes. A testicular biopsy shows a characteristic hyaline degeneration of the seminiferous tubules and hypertrophy of the interstitial cells, but the diagnosis is established simply by examining cells scraped from the inside of the buccal mucosa with a wooden spatula, spread on to a glass slide, fixed with absolute alcohol and stained with cresyl violet.

The chromatin body which indicates the presence of the second X chromosome is seen under the nuclear membrane, as it is in all normal females (Fig. 2). Very exceptionally

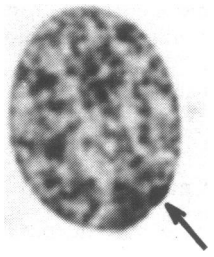

FIG. 2—Chromatin positive nucleus of a buccal mucosal cell.

there may be two or even three chromatin bodies, in which case they are due to an XXXY or XXXXY sex chromosome complement, respectively. These are invariably associated with considerable degrees of mental retardation, and in the case of the XXXXY condition with various skeletal and other somatic abnormalities. The treatment of chromatin-positive males consists of administering testosterone, usually by subcutaneous implantation at intervals of 6 to 9 months—though the new oral androgen Mesterolone may prove to be a satisfactory substitute.

In boys with evidence of hypogonadism during adolescence but in whom the nuclear sex is chromatin-negative, primary testicular failure will be indicated by raised pituitary gonadotrophin levels in a 24-hour collection of urine. These patients will be indistinguishable on clinical grounds from chromatin-positive males and treatment will be the same.

Pituitary Failure

Male hypogonadism which is secondary to pituitary failure is difficult to distinguish before the age of 20 years from the normal prepubertal state of a normal but late developing boy. The testicular histology is similar and the urinary gonadotrophin excretion is low in both. When this situation persists after the age of 20 a diagnosis of hypogonadotrophin eunuchoidism should be made. It sometimes occurs in several members of the same family and it is believed to be due to a mutant gene that is inherited as an X-linked trait. It is sometimes associated with an absent or impaired sense of smell, hair lip, cleft palate, or asymmetry of the face and the skull. Treatment consists of stimulating Leydig cell activity with chorionic gonadotrophin. After three to six months' treatment development may progress and be maintained spontaneously.

Failure of adolescent development due to lesions involving the anterior pituitary or the hypothalmus almost invariably present earlier because of severely retarded preadolescent growth, and may be accompanied by evidence of impaired thyroid and adrenal function.

DEVELOPMENT DISORDERS IN GIRLS

Failure of pubertal development is less common in girls than in boys. When it does occur it is usually due to primary ovarian failure, and at laparoscopy or laparotomy the ovaries are seen to be replaced by streaks of fibrous tissue, in which histological examination may show a little identifiable ovarian stroma but no follicles. This condition is described as female gonadal dysgenesis, and in the form known as pure gonadal dysgenesis the sexual infantilism is usually not associated with any other somatic abnormalities. Because of the persistent low oestrogen levels the epiphyses close late and growth continues, so that there is often a degree of eunuchoidism. The delayed epiphyseal closure can be seen on an *x*-ray film of the hands. Other evidence of diminished oestrogen production is provided by a vaginal smear. Oestrogen excretion rates are similar to those found in postmenopausal women. Chromosome analysis may show a normal male or female sex chromosome complement but there is no clinical distinction discernable between the two on clinical grounds.

Turner's Syndrome

A better known form of gonadal dysgenesis is associated with numerous somatic abnormalities and is usually referred to as Turner's Syndrome. These girls do not grow taller than 5 feet (152 cm) in height. In addition to this growth retardation the syndrome also includes webbing of the neck, an increased carrying angle at the elbow, short fourth and fifth metacarpals, vascular naevi, lymphoedema, dystrophy of the hair and nails, ptosis, strabismus, a tapering of the anterior chest wall sometimes referred to as a shieldlike chest (Fig. 3) widely separated nipples, congenital heart disease—particularly coarctation of the aorta or pulmonary stenosis—and congenital renal abnormalities.

All these features, however, are extremely variable, and only the peristent sexual infantilism and small stature are always present. Most girls who have this condition have an abnormality of the sex chromosomes. The most common is a complete absence of the second X, so that the total chromosome complement is only 45. The others usually have some structural chromosome abnormality which has led to the loss of part of one the X's. The total absence of one X chromosome may be deduced from the finding of a chromatin-negative buccal smear; occasionally a structural abnormality of one of the X chromosomes can be suspected from an abnormal size of a chromatin boy—but usually this diagnosis can be made with certainty only by examining the chromosomes.

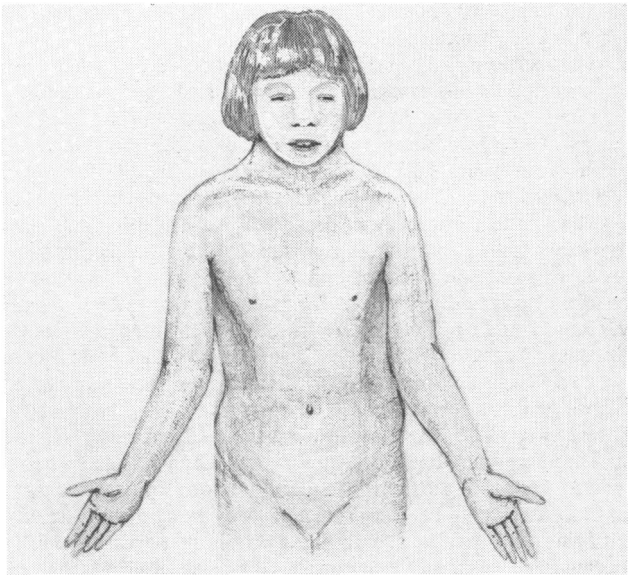

FIG. 3—Turner's Syndrome. A schematic drawing to show ptosis, neck webbing, "shield-like" chest, and increased carrying angle.

When puberty is delayed in girls on account of gonadal dysgenesis oestrogen replacement therapy is required to bring about breast development and maturation of the external genitalia. Treatment is started with ethinyl oestradiol but can be conveniently maintained with one of the proprietary preparations of the contraceptive pill. It is administered cyclically to allow for withdrawal bleeding, which may also have a beneficial psychological effect. Such treatment should be withheld until the optimum or maximum height has been achieved as it will accelerate epiphyseal closure and arrest any further growth. In girls with Turner's Syndrome there is very little growth beyond the age of 15 years. In pure gonadal dygenesis it may be desirable to start treatment early so as to avoid eunuchoidism.

In a girl with dysgenetic gonads who also has a cell line with a Y chromosome there is a risk of developing a gonadoblastoma, which may become malignant. The vestigial gonads should therefore be removed.

Testicular Feminization

Primary amenorrhoea associated with absent or diminished pubic hair but a normal growth spurt and feminization of body configuration, including breast enlargement, occurs in the very rare condition of testicular feminization. These girls, however, have no ovaries, Fallopian tubes, or uterus, and the vagina is short and ends blindly. Instead, they have testes and male ducts either intra-abdominally or in a hernial sack, and they have a male sex chromosome constitution. This condition is due to a mutant gene which may be inherited through the mother as an X-linked recessive or an autosomal sex-limited dominant. There may therefore be similarly affected "sisters" or maternal "aunts." Incomplete forms of this disorder are also thought to occur. Treatment should be aimed at first at enlarging the vagina. After "puberty" the testes should be removed because of the risk of malignancy, and this introduces the need for replacement oestrogen therapy. There is, of course, no prospect of inducing "menstruation."

Conclusions

"Delayed puberty" is most often due to physiological late development in girls and boys who will eventually undergo full sexual maturation. The delay may occasionally be due to generalized disease and very rarely may be the mode of presentation for a number of genetically determined disorders of sexual differentiation. Treatment and advice should be aimed at minimizing the social embarrassment and psychological trauma. When necessary normal adolescent changes should be accelerated or simulated as far as possible by hormonal treatment.

Scientific Basis of Clinical Practice

Clinical Psychology and the General Practitioner

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British Medical Journal, 1972, 1, 793-795

Clinically trained psychologists are now sometimes employed as community psychologists rather than as hospital clinical psychologists. Whatever their employment or financial support, more and more of them are working in the community in, for example, citizens' advice bureaux, prisons, schools, health centres, and rehabilitation units. Traditionally the clinical psychologist has had a great deal to offer in connexion with the disorders of behaviour that find their way into mental hospitals and psychiatric clinics. Nevertheless, in addition to the trend towards treating mental patients in general hospitals, there is also a growing realization that disorders of behaviour are certainly not confined to such psychiatric patients. There is a disorder of behaviour when a child falls behind his classmates in schoolwork; when a discharged prisoner blatantly steals and is returned to prison; when parents complain that their lad is surly and rude at home, though he may conform to social norms when away from home; when a married couple rouses the neighbourhood with quarrelling and breaking of crockery. Although these are already fairly extreme examples, they are not all likely to come to the psychiatrist.

Disorders of behaviour are in fact all around us and this should come as no surprise when we remember that behaviour is all around us. The ubiquity of behaviour is what makes psychology such an interesting study. Moreover, none of us can avoid observing behaviour—our own and others'—and making predictions from our observations. Psychology is about just this. Psychology, the scientific study of behaviour, starts,

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