—are well known to occur in athletes who train hard.[4] It may be that exercise simply unmasks a pre-existing heart disorder and that those with unrecognised coronary artery disease simply die rather sooner. Perhaps this might account for early death in a handful of athletes. Any suggestion that Russian athletes are more likely to drop dead than their American counterparts remains, however, highly speculative —drugs or no drugs.

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Management of delayed puberty

Most doctors are inadequately briefed to deal with the problems that may arise in the pubertal development of boys and girls. Mismanagement may lead to hypogonadal patients in their late teens being treated too late with large doses of sex steroids in order to bring about the changes of puberty quickly. These patients have suffered from waiting in vain to mature before a diagnosis is made, from then facing the physical changes of adolescence more quickly than they can accommodate emotionally, and from an end result of their sexual development which is often cosmetically unsatisfactory.

The key to the proper management of pubertal delay is early recognition of a problem. Half of all children show the first signs of puberty before their 12th birthdays, and in 97% of normal children signs of puberty, usually breast development in the girl and enlargement of the testes in the boy, have appeared by the 14th birthday.[1] If no such signs have appeared by that age investigation is required. Doctors should be cautious in offering a wait and see approach to such a patient; delayed puberty is a physical sign and not a diagnosis. Once it has started, progress through puberty should be orderly with a succession of physical changes taking place over about three years; arrest at any stage requires explanation as much as does a failure to enter puberty.

Some clinicians believe that delaying the induction of puberty in a hypogonadal patient leads to a final taller stature. In fact, since the extent of the adolescent growth spurt decreases the older a patient becomes what is gained by waiting is lost in the growth spurt; delay will not be beneficial. Indeed, patients with multiple pituitary hormone deficiencies who have received maintenance treatment with growth hormone without sex steroids in their teens end up not only short but disproportionately short, having inadequate growth of the spine.[2]

Puberty results from pulsatile secretion of gonadotrophin releasing hormone.[3] Secretion of this hormone begins in utero, and the hypothalamopituitary gonadal axis in the prepubertal child is far from quiescent. Examination by ultrasound shows that ovarian follicles in normal prepubertal girls wax and wane over long periods, and a girl who has gonadal dysgenesis shows signs of oestrogen deficiency before the conventional age of puberty. Concentrations of gonadotrophin progressively rise as puberty advances, and this may be due to a change in amplitude or frequency of the pulses of gonadotrophin releasing hormone (and experimental evidence shows both of these to be critical in reproductive terms) or to a release of the pituitary gonadotrophes from an inhibiting influence. Whichever of these possibilities turns out to be the case the endocrine and physical changes of puberty may be entirely mimicked by pulsatile administration of gonadotrophin releasing hormone.[4]

In a patient with delayed puberty measuring the serum gonadotrophin concentration may help: a raised concentration indicates gonadal failure, but there are problems in diagnosing the prime cause of pubertal delay due to diminished secretion of gonadotrophin. A response of secretion of gonadotrophin to acute administration of gonadotrophin releasing hormone is not helpful: a satisfactory response may be seen with a deficiency of endogenous gonadotrophin releasing hormone secretion, but a negative response may be reversed by repeated administration of gonadotrophin releasing hormone. A more promising approach is to examine the spontaneous pulsatility of gonadotrophin secretion, but unfortunately this means taking samples at frequent intervals throughout the night. A useful non-invasive assessment of gonadotrophin secretion in girls is available through the interpretation of pelvic ultrasound examination, but a similar welcome short cut is not available for boys.

Treatment should take account of the fact that while the fastest maturing girls and boys take about two years to complete all the physical changes of puberty half will have done so over about three years and most over five years.[1] For replacement purposes, therefore, therapeutic agents should be used in small but gradually increasing amounts over a physiological time scale. This time scale requires an early diagnosis and recognition of a problem.

The pulsatile administration of gonadotrophin releasing hormone, at present a research procedure, seems likely to become the treatment of choice since it is the only one likely to confirm long term reproductive capability in a hypogonadotrophic patient. Until this method of treatment becomes routine most hypogonadal patients will continue to be treated by conventional regimens: human chorionic gonadotrophin or testosterone is used in boys followed by a preparation containing follicle stimulating hormone to induce spermatogenesis. In girls only oestrogens are available, since the long term administration of preparations containing gonadotrophins leads to the formation of large ovarian cysts and dysfunctional uterine bleeding.

If human chorionic gonadotrophin is to be used in a boy it should be given in small amounts—say, 500 units a week in the first instance—and gradually increased as plasma concentrations of testosterone rise. Each incremental step should take not less than six months; proceeding more quickly seriously risks overtaking the emotional development of adolescence. If oral preparations of testosterone are to be used similar considerations apply. Injections of testosterone depot preparations should start at a low dose (say, 100 mg at six weekly intervals) or possibly even less than this to achieve an adult plasma testosterone concentration over two years.

In girls ethinyloestradiol should be introduced in a small dose, probably less than 5 μg daily, for about six months. There should be no question of introducing cyclical oestrogen

replacement for at least a year, and even then conventional adult hormone replacement should not be contemplated for at least another year. To move more quickly than this causes development of the breasts which is almost entirely confined to the nipple and areola—which causes great unhappiness. Whether in such patients history can be rerun with advantage is far from clear.

The problem with the medical care of patients in their teens is that in the hospital service such patients fall between the spheres of knowledge of physicians, including endocrinologists and oncologists, of gynaecologists, and of paediatricians. Family doctors may be more directly concerned, but unfortunately the education which most of us had on this difficult topic was woefully inadequate. Puberty is of such great importance to patients that abnormalities of it deserve early recognition and skilled, if not complex, management.

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Regular Review

Graft versus host diseases: new versions of old problems?

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Bone marrow transplantation is now an accepted part of medical treatment. For example, chemotherapy achieves remissions in few adults with acute non-lymphocytic leukaemia and in virtually none in relapse. In contrast, bone marrow grafts from HLA compatible sibling donors have substantially improved the outlook for such patients.[1] The grafted cells take on the function of the recipient's own bone marrow which has been destroyed by total body irradiation and high dose cyclophosphamide. Bone marrow grafts are also being used increasingly to replace the non-functioning bone marrow of patients with aplastic anaemia. In addition, marrow transplantation is the treatment of choice in severe combined immunodeficiency and is being tried in other forms of inherited defects of bone marrow function.[2]

Siblings who are HLA identical are still the preferred donors, but unrelated donors are being selected more often, usually with the proviso that at least they have one HLA haplotype in common with the recipient and possess identical HLA-D determinants. These grafts from imperfectly matched donors require more immunosuppression to be successful—and are more likely to induce graft versus host disease.

Graft versus host disease has long been recognised as a major obstacle to successful transplantation. Its acute form, occurring within 100 days of transplantation and manifested by rash, hepatitis, diarrhoea, and delayed restoration of haemopoiesis and lymphopoiesis, was observed in 30-70% of patients in early transplantation programmes. Several factors have reduced its incidence, some concerned with the selection of donors and others with the management of the procedure itself and the aftercare of patients. With growing experience in ensuring the survival of grafts and in overcoming acute graft versus host disease the chronic disease has become increasingly common, with an incidence varying between 15% and 40% in different centres.

The clinical and pathological features of graft versus host disease are of interest not only for their practical importance to transplantation practice but as models of immunopathological processes which may operate in several spontaneous diseases of unknown aetiology. Indeed, this possibility was foreseen in pioneering studies in animal models of graft versus host disease in the 1960s.[3]

Chronic graft versus host disease appears between 70 and 400 days after transplantation and has well defined clinical features. Skin lesions are almost invariably present. At first these are inflammatory but later they take the form of subcutaneous fibrosis with telangiectasia and joint contractures; oral lesions resembling lichen planus, oesophageal strictures, and the sicca syndrome are common, while polymyositis and serositis are occasionally encountered.[4,5] Severe obstructive airways disease has also been reported.[6] There are definite similarities with diseases such as scleroderma—but there are also differences and, in particular, a virtual absence of renal abnormalities of the kind characteristic of scleroderma and systemic lupus erythematosus.[7]

Detailed histological analysis has confirmed the clinical distinction between the acute and chronic forms of graft versus host disease.[8] Many features of the lesions in the acute form suggest that the target cells may be damaged by the products of donor lymphocytes and by natural killer cells and not simply by donor T lymphocytes. In contrast, chronic graft versus host disease is marked by florid cellular infiltration and vascular reactions resembling the lesions of primary connective tissue diseases.

Pathogenesis

In essence graft versus host disease in all its forms stems from an attack on host cells by T lymphocytes in the donor