Using a cDNA subclone of the Hep G2-type glucose transporter gene, we have studied an *Xba*1 restriction fragment length polymorphism in three separate diabetic populations. The two Caucasian and the Japanese diabetic groups showed a higher frequency of the X1 allele than did their control subjects. That the association was observed in all three diabetic populations suggests the X1 allele may be within 0·5% recombination fraction from a putative diabetogenic locus.[14] Mapping experiments will be required to identify such a locus, and if it lies within an exon sequence of the glucose transporter gene it may possibly be a major genetic determinant for the disease. Alternatively, it may be in linkage disequilibrium with other abnormalities adjacent to the glucose transporter gene that impair carbohydrate metabolism. From our studies it is apparent that DNA polymorphisms of the glucose transporter gene will be useful in the elucidation of the inherited defects of this common metabolic disorder.

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Preliminary Communication

SEVERE PREMENSTRUAL EXACERBATIONS OF ASTHMA: EFFECT OF INTRAMUSCULAR PROGESTERONE

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Summary Three patients with severe premenstrual exacerbations of asthma are reported. None had responded to conventional treatment, including high-dose corticosteroids. In all cases there was a striking fall premenstrually in peak flow rate. The addition of intramuscular progesterone (100 mg daily in two cases and 600 mg twice a week in one) to the regimen eliminated the premenstrual dips in peak flow, and daily doses of prednisolone were reduced in the three patients.

INTRODUCTION

IT has long been recognised that premenstrual exacerbations of asthma occur in about a third of affected women but the fall in the peak flow expiratory flow rate is usually modest.[1-3] The effect of corticosteroid hormones on asthma is well established but the effects of other steroid hormones has not been much investigated, despite circumstantial evidence that they might be beneficial. We report three patients with recurrent life-threatening premenstrual exacerbations of asthma who did not respond to conventional treatment, including high-dose corticosteroids, but who responded to intramuscular progesterone.

CASE HISTORIES

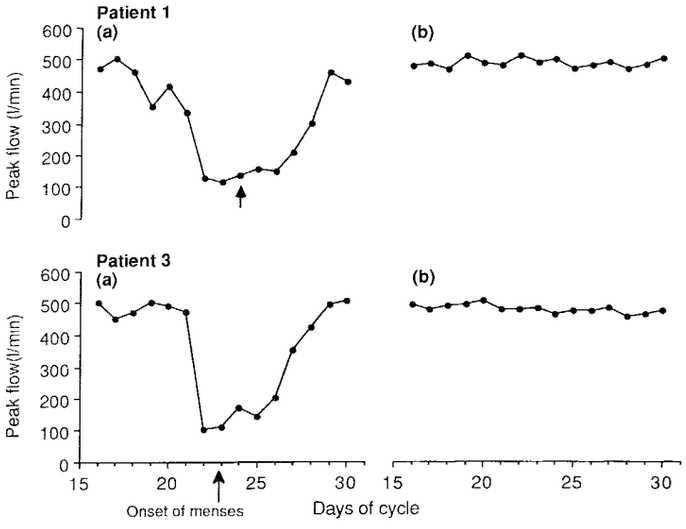
Case 1

A 23-year-old woman who was a non-smoker had had asthma from age 7 years; she also had eczema and seasonal hay fever. Her asthma was initially well controlled with inhaled β_2-agonists but at the onset of puberty her asthma deteriorated. No symptoms characteristic of premenstrual tension were reported. Regular peak flow readings showed striking falls before her menstrual period, with the peak flow dropping from a baseline of 400–500 l/min to below 100 l/min. These premenstrual exacerbations were resistant to full conventional treatment including high-dose oral corticosteroids, which made her grossly cushingoid. She received 20 mg of prednisolone daily which was increased to 40 mg in the premenstrual week in an attempt to maintain a normal peak flow rate. The severity of the premenstrual exacerbations was such, however, that monthly admissions to hospital were necessary, and on three occasions ventilation was needed. Intermittent use of the low-dose oestrogen contraceptive pill 'Microgynon 30' for dysmenorrhoea did not improve asthma control.

At age 23 she was started on a high-dose progesterone preparation ('Depo-Provera' 600 mg) given twice weekly by intramuscular injection. During follow-up for six months, premenstrual dips in peak flow did not occur and her daily dose of prednisolone was reduced to 7·5 mg daily (figure).

Case 2

A 33-year-old woman who did not smoke had had atopic asthma from age 5 years. She had remained well until age 22 when her asthma increased in severity. Peak flow rate varied from day to day, with pronounced early morning dips from 400 l/min to 280 l/min. The most striking feature of her asthma, however, was the consistent symptomatic deterioration mirrored by a drop in the peak flow rate to 150 l/min that occurred 48 h before menses and continued for the first 2 days of a 5-day menstrual flow. The pattern of her asthma did not change when her family practitioner prescribed the oral contraceptive pill 'Eugynon 30'. In an attempt to control her symptoms, she was given oral corticosteroids up to



Peak flow recordings for patients 1 and 3 before (a) and during (b) progesterone therapy.

Charts 1a and 3a show typical falls in the peak flow before menses; progesterone eliminates these falls and prevents normal menses (1b and 3b).

60 mg daily but the premenstrual exacerbations were unresponsive. The introduction of intramuscular progesterone (100 mg daily) eliminated the premenstrual dips and stabilised her asthma, allowing her daily maintenance dose of prednisolone to be reduced to 5 mg.

Case 3

A 48-year-old mother of two who did not smoke and who did not have atopic features had asthma for the first time at the age of 41 following an upper respiratory tract infection. She needed daily oral corticosteroids in addition to full conventional treatment to control her symptoms. Premenstrually, over 24 h, her peak flow rate consistently fell from 500 l/min to below 100 l/min. The premenstrual dips were resistant to high-dose corticosteroids given both orally (60 mg prednisolone daily) and intravenously (200 mg of hydrocortisone 4-hourly). With the onset of the menopause treatment became difficult because of the irregularity of her periods and the unpredictability of her attacks. The addition of intramuscular progesterone (100 mg daily) to the regimen eliminated premenstrual dips and allowed a reduction in her corticosteroid dose to 5 mg prednisolone daily (figure).

DISCUSSION

Dawson et al[4] reported the median age of onset of asthma to be later in girls than boys. At age 10 years the ratio of asthma in girls:boys was 1:3, whereas at 14 the ratio had become 1:1. It has been suggested that the later onset in girls could be attributed to the menstrual cycle.

Exacerbations in asthma during the premenstrual and menstrual periods were first described by Claude and Allemany Vall[5] and have subsequently been well documented. Eliasson et al[6] reported that of 57 women who showed menstrual exacerbations of their asthma, 10% were worse during the premenstrual period, 16% were worse during the menstrual period, and 74% were worse during both. Gibbs et al[3] reported that 40% of their 91 female patients had premenstrual deteriorations in their peak flow—the falls being only of borderline significance. They showed no relation between premenstrual exacerbations of asthma and symptoms of premenstrual tension, consumption of aspirin, use of the contraceptive pill, cycle length, or behaviour of asthma during pregnancy. These findings contrast with those of Rees[1] and Eliasson et al[6] who reported positive correlations between the severity of premenstrual tension symptoms and premenstrual asthma. In Eliasson and colleagues' series, 33% of women showed worsening of their asthma before or during menses, 68% of women with such exacerbations required admittance to hospital, compared with 26% of those who did not have premenstrual problems. In one patient premenstrual peak flow fell to such a low level that she was admitted to hospital on ten occasions and was ventilated three times in 2 years. Sudden death from asthma during the premenstrual period has been reported in two sisters just after the onset of puberty.[7]

In the three cases we have reported, there was a pronounced deterioration in the peak flow rate premenstrually; these falls were not controlled with conventional therapy, but administration of high-dose progesterone throughout the menstrual cycle prevented this deterioration. The two regimens (100 mg intramuscular progesterone daily or 600 mg intramuscular depro-provera twice a week) were equally effective. In our three cases there was no relation between the presence of symptoms of premenstrual tension and the premenstrual exacerbations of asthma.

The mechanism of progesterone action is unknown. In the normal menstrual cycle progesterone reaches a peak 7 days before menses and then rapidly decreases before the onset of menstruation. Progesterone has immunosuppressive actions and also decreases the contractility of smooth muscle. In vitro investigations have shown that sex hormones, including progesterone, can potentiate the relaxation effect of isoprenaline on bronchial smooth muscle.[8] Progesterone could act as a bronchodilator in its own right or achieve an action through its potentiation of other bronchodilators, and it may be that in a susceptible subgroup of asthmatic patients the sudden premenstrual decrease in plasma progesterone triggers bronchoconstriction. Another possibility is that progesterone is important in the regulation of microvascular leakage in airways and that the falling plasma concentration leads to airways mucosal oedema.

Weinmann et al[9] and Juniper et al[10] have investigated airway responsiveness during the menstrual cycle in asthmatic patients. Neither group was able to show an increase in bronchial wall reactivity, but they studied an unselected sample of asthmatic women and only 1 of Juniper's 17 subjects had premenstrual asthma.

Although worsening of asthmatic symptoms in relation to the menstrual cycle is common, there seems to be a small subset of female patients with asthma who show severe life-threatening premenstrual drops in peak flow that are resistant to standard treatment with high-dose corticosteroids but who respond to high-dose intramuscular progesterone therapy. This form of treatment seems safe but local problems can arise from repeated intramuscular injections. The intramuscular route is more efficacious than oral or vaginal routes because of the high plasma concentrations achieved which mimic progesterone concentrations during pregnancy. We recommend a gynaecological assessment before regular therapy is begun. We are unaware of any published reports of the use of progesterone in such patients and feel that a formal prospective trial is now warranted.

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Reviews of Books

Cecil: Textbook of Medicine

18th Edition. Edited by J. B. Wyngaarden and L. H. Smith. Philadelphia: W. B. Sanders. 1988. Pp 2402. £59.95 single volume: £73 two volumes. ISBN 0-721618480.

IT is 61 years since Dr Russell Cecil first produced this book and the preface to the latest edition reminds us that the original aim was to provide "authoritative clinical guidance and a reasoned scientific basis for the pursuit of medicine". Seventeen editions later this objective continues to be maintained despite the facts that today's authors have infinitely more science with which to pursue the subject. Much of the strength of the book rests with the distinguished group of only six editors who have been associated with its publication over the years. This edition represents another tour de force with no fewer than 339 contributors. The policy of changing authors has been continued with approximately one-third of them being replaced since the last edition, and several innovations have appeared. The introduction of eight colour plates at the front is perhaps the most obvious example. Classic ophthalmic and haematological disorders are beautifully illustrated, as are some less usual conditions. The pictures of the cutaneous appearance of Lyme disease will for many readers be the first colour illustrations of the condition they have seen. The inclusion of new chapters appropriately reflects recent advances; contributions on AIDS have increased substantially while a short but very relevant chapter entitled The Health of the Physician is to be welcomed.

The standard of individual contributions remains as high as ever, and each is followed by a short bibliography. Serious students will welcome this as an opportunity to read in greater depth, for clearly no single textbook today can be expected to include every detail. Here the reader may be disappointed since the selection of references is often parochial and patchy. Coronary angioplasty, for example, is referred to on several occasions but no references to this new and important development are cited.

How does this book rate in comparison with other texts? Clearly for English readers it had to be compared with the *Oxford Textbook of Medicine*. The American textbook is not quite so massive and it seems less "user-friendly" than its English counterpart in that the text retains the formal, almost severe, print of previous generations. Nevertheless, I found it much easier to dip into for information—at least partly because of its simpler indexation. While both books are well illustrated, biochemical pathways predominate in North America while clinical illustrations are the major feature in Oxford. Perhaps this reflects differences in teaching on the two sides of the Atlantic.

Wyngaarden and Smith intend their book for the undergraduate as well as the postgraduate reader. I suspect that most English medical students would be intimidated by both the cost and the content of this book, but for postgraduates working for a higher examination or seeking a reference textbook I would recommend them to give serious consideration to its purchase. For those who can afford the extra few pounds I would advise the two volumes rather than one. Not only is the 4·2 kg volume more suited for weightlifting than for browsing but the cover is clearly not strong enough to withstand the frequent consultation that the book deserves.

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Textbook of Uncommon Cancer

Edited by L. J. Williams, J. C. Krikorian, M. R. Green, and D. Ragnavan. Chichester: Wiley. 1988. Pp 1064. £110. ISBN 0-471909688.

UNCOMMON cancers collectively are commonplace. They tend to get short shrift in reference texts of formidable weight so this volume with 4 editors and 93 contributors sets out to redress the balance. The choice of what is uncommon is inevitably somewhat arbitrary but properly includes common tumours at uncommon sites. The text is liberally supplied with illustrations, mainly microphotographs, with reproduction ranging from mediocre to good.

Material has been assembled on an anatomical basis, which is convenient when the primary site is known and when the clinician wants a quick rundown on an unfamiliar tumour. But anatomical grouping carries a penalty of textual reduplication, since tumours with similar morphology and behaviour arise at various anatomical sites. Pineal tumours get double treatment and germ cell tumours crop up several times but only get an up-to-date therapeutic review in relation to the ovary. The absence of cross-referencing in such situations is lamentable. Some reviews, such as that of placental site trophoblastic tumour, are too cursory to be useful and fail to make the important points.

Despite its shortcomings the book should find a useful place. It is no substitute for the standard texts on tumour pathology but in general it is more informative about clinical manifestations and management than either pathology texts or the comprehensive textbooks on clinical oncology. More than anything else the volume highlights the deficiencies in our knowledge of many of these tumours and it is a pity that the opportunity of discussing how progress might be made has not been seized. Multicentre trials, which are often essential in determining the best management of common tumours, are no substitute for establishing and supporting referral centres where experience can be established for the 200 or so different types of uncommon cancer.

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