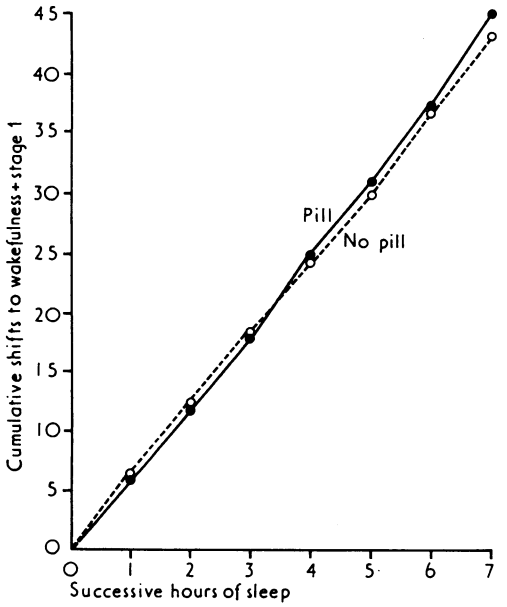


FIG 2—Mean combined numbers of times that sleep was disrupted by wakefulness and periods of drowsiness (stage 1) in the 10 volunteers on pill nights and no-treatment nights.

no-treatment nights using each person's mean score under each condition.

Results

The subjective ratings showed no change in sleep quality when the pill nights were compared with the no-treatment nights (mean scores (±SE of mean) 45·6±2·4 mm *v* 49·2±3·3 mm; NS). The volunteers knew when it was their turn to be given the placebo, but on the days when they were to take it at night their ratings of anxiety were not altered (51·8±1·8 mm *v* 52·9±2·1 mm; NS).

The electrophysiological recordings showed no significant differences between the 60 pill nights and the 60 no-treatment nights. This was true for the mean time it took to fall asleep (24·9±3·9 min *v* 21.9±4·2 min; NS) and for the accumulation of wakefulness that intervened during the night's sleep or any of its parts (fig 1). The amounts of stage 1 (drowsiness), stage 2, stages 3 and 4, and REM sleep, total sleep duration, and REM sleep latency were similarly unaffected. The numbers of times that sleep was disrupted by waking or periods of drowsiness were combined and also found to be unaffected (fig 2).

Discussion

The absence of any difference between the subjective ratings under the two conditions was not a result of insensitivity of the method. The same 10 volunteers had taken part in a cross-over study of nitrazepam 5 mg and a food drink. Their ratings showed a significant improvement in sleep quality for both substances, with a deterioration on withdrawal of the drug.[5]

In older people sleep is frequently broken by periods of wakefulness[6 7] and is thus likely to show any influence of a sedative. In a study of a food drink (Horlicks) no significant effect was found on EEG-recorded sleep of young people, whereas the sleep of a group of older people similar to those studied here became significantly less broken than when a placebo pill was given.[8] After our report on Horlicks it was proposed that suggestion could have been responsible.[9] Our present studies offer no support for this, nor for any belief that when a placebo is prescribed for those of later middle age sleep will be substantially altered.

We thank Beecham Products Ltd for their help.

References

1 Kales, J, *et al*, *Clinical Pharmacology and Therapeutics*, 1971, **12**, 691.
2 Davis, D, and Hartmann, E, *Sleep Research*, 1973, **2**, 51.
3 Hartmann, E, and Cravens, J, *Psychopharmacologia*, 1973, **33**, 153.
4 Rechtschaffen, A, and Kales, A, (editors), *Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Washington, US Government Printing Office, 1968.
5 Adam, K, *et al*, *Postgraduate Medical Journal*, 1976, **52**, 42.
6 Williams, R L, *et al*, *EEG of Human Sleep*. New York, Wiley, 1974.
7 Březinová, V, *Electroencephalography and Clinical Neurophysiology*, 1975, **39**, 273.
8 Březinová, V, and Oswald, I, *British Medical Journal*, 1972, **2**, 431.
9 Iversen, L L, and Mackay, A V P, *British Medical Journal*, 1972, **2**, 766.

SHORT REPORTS

Genetic diabetes not linked to the HLA locus

Hereditary factors appear to be of great importance in the aetiology of maturity-onset diabetes. In a series of diabetic identical twins all the pairs in which the index twin developed diabetes over 45 were concordant—that is, the co-twins were also diabetic—and nearly half had a diabetic parent.[1] As most of the twins had lived apart for most of their adult lives, diabetic concordance is more likely to have been due to genetic than environmental causes.

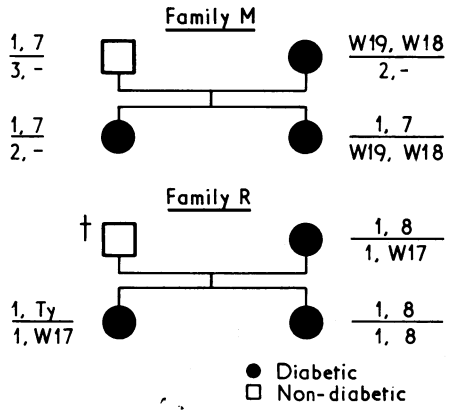
By contrast, the genetic contribution to classical juvenile-onset diabetes (JOD) is much less clear. In the twin study[1] half the pairs in which diabetes was diagnosed in the index twin under 45 were discordant (only one twin affected), and remained so on repeated glucose tolerance testing, and few had a family history of diabetes. In these pairs the diabetes must be largely of environmental origin. This is consistent with the view that viruses may damage the pancreatic islets.

Studies of histocompatibility antigens in patients with JOD suggest a possible mechanism for genetic susceptibility to infections. The frequency of the antigens HLA-8 and W15 is increased in insulin-dependent but not in maturity-onset diabetics.[2 3] Furthermore, in families in which two or more sibs have JOD there is a highly significant increase in the number with one or both HLA haplotypes identical.[4] Both these findings suggest the presence of an important gene predisposing to this type of diabetes near the HLA locus on the 6th chromosome.

There is one kind of diabetes—maturity-onset diabetes of young people (MODY)—of which 3 families have been described from this department[5] which appears to be purely genetic in origin. Diabetes appears in early life; is and remains mild, insulin seldom, if ever, being needed; and complications are conspicuously rare. The evidence for a dominant pattern of inheritance is overwhelming—three successive generations affected in direct line, all (or nearly all) cases having an affected parent and half of the offspring of affected individuals being themselves affected. It was of interest to discover whether this type of diabetes whose inheritance is clearly distinct from that in other types of the disease (insofar as we understand it) was also associated with specific HLA types.

We have HLA-typed 13 diabetic and nine non-diabetic members of these families. All the non-diabetics have had oral glucose tolerance tests with results in the normal range. Three of 13 diabetics (23%) and two of the nine non-diabetics (22%) were HLA-8 positive, both figures being the same as the control frequency for this antigen (20-31%)[4]; in classical JOD the frequency of this antigen is approximately twice normal. So far, the W15 antigen has not been found in these families (control frequency 5-14%).[4]

The figure illustrates the pattern of inheritance of HLA haplotypes



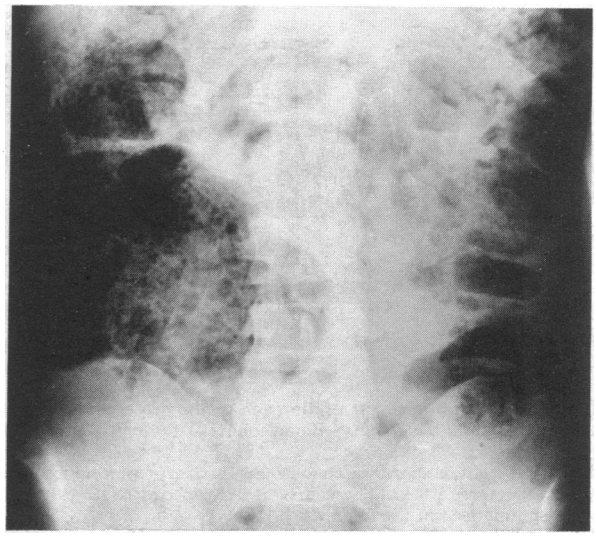
HLA haplotypes in eight members of two families with MODY.

in two branches of the families. The most striking feature is that the diabetics in each family do *not* share a common HLA haplotype. This is thus clear evidence that the gene in MODY is not linked to the HLA-B locus. This study provides further evidence that more than one gene predisposes to, or causes, diabetes.

Dr P G Nelson is supported by the Nuffield Foundation.

[1] Tattersall, R B, and Pyke, D A, *Lancet*, 1972, **2**, 1120.
[2] Nerup, J, *et al*, *Lancet*, 1974, **2**, 864.
[3] Cudworth, A G, and Woodrow, J C, *Diabetes*, 1975, **24**, 345.
[4] Cudworth, A G, and Woodrow, J C, *British Medical Journal*, 1975, **2**, 133.
[5] Tattersall, R B, *Quarterly Journal of Medicine*, 1974, **43**, 339.

Diabetic Department, King's College Hospital, Denmark Hill, London SE5 9RS
P G NELSON, MB, MRCP, research registrar
D A PYKE, MD, FRCP, consultant physician



X-ray picture of abdomen in case of pseudo-obstruction.

Pseudo-obstruction due to clonidine

Pseudo-obstruction of the large bowel is characterised by signs and symptoms of bowel obstruction without any demonstrable mechanical cause for them.[1 2] We report a case of this disorder that may have been secondary to antihypertensive therapy with clonidine.

Case report

A 26-year-old man received a cadaveric renal transplant after three years of haemodialysis for chronic renal failure. Hypertension persisted post-operatively and was eventually controlled with hydrallazine 400 mg/day, propranolol 400 mg/day, methyldopa 2 g/day, frusemide 40 mg/day, and clonidine 2 mg/day. During the third to fourth weeks after transplantation the patient developed abdominal distension and obstipation unresponsive to bulk laxatives, mineral oil, and cathartics. Colonoscopy to 60 cm revealed only large amounts of soft, bulky stool. Colonic lavage temporarily lessened the distension but obstipation continued. Thirty days after transplantation the patient developed abdominal pain and vomiting. There were high-pitched, tinkling bowel sounds and radiographic evidence of gross faecal distension of bowel with air-fluid levels (fig). Clonidine was discontinued and, despite continued therapy with other antihypertensive agents, the gastrointestinal signs and symptoms disappeared and bowel function returned to normal within 36 hours.

Comment

The efferent pathway of the defaecation reflex is parasympathomimetic and cholinergic. The reflex, however, can be modulated (for example, voluntarily) by the central nervous system. In view of its effects on the central nervous system clonidine, either alone or with other centrally active antihypertensive drugs, may cause bowel dysfunction. Alternatively, a direct effect of clonidine on the enteric neuromuscular complex cannot be ruled out. The manufacturers state that clonidine may cause constipation. An informal survey of our patients taking this drug shows that constipation is surprisingly common. The present report suggests that constipation due to clonidine may occasionally progress to complete pseudo-obstruction.

[1] Bardsley, D, *British Journal of Surgery*, 1974, **61**, 963.
[2] *British Medical Journal*, 1975, **2**, 105.

Department of Nephrology, St Michael's Hospital, University of Toronto, Toronto, Canada
R BEAR, MD, FRCPC, assistant professor of medicine
K STEER, MD, senior resident in urology

Polycythaemia in androgen-dependent aplastic anaemia

Androgenic steroids—in particular, oxymetholone—have been used to treat aplastic anaemia,[1] but their value is still debated.[2 3] We desribe a patient with phenylbutazone-induced marrow aplasia who responded so well to oxymetholone that she became ill with polycythaemia. Yet whenever oxymetholone was stopped, aplastic anaemia recurred.

Case report

A 65-year-old woman was prescribed a four-week course of phenylbutazone, 200 mg daily, in September 1970 for phlebitis associated with varicose ulceration. It was her only medication apart from thyroxine. She was admitted to hospital in April 1971 with a history of five months' increasing breathlessness, lethargy, and abnormal bruising, and had symptoms and signs of severe anaemia, heart failure, and purpura.

Investigations showed haemoglobin (Hb) = 6·7 g/dl, white cell count (WBC) = 2·70 × 10^9/l (2700/mm^3) (neutrophils 0·35 × 10^9/l (350/mm^3)), platelets $\leqslant$10 × 10^9/l ($\leqslant$10 000/mm^3), and $\leqslant$1% reticulocytes. Sternal marrow showed reduced haemopoietic cell lines and relatively increased lymphocytes and plasma cells. A chest *x*-ray film showed changes characteristic of heart failure. The results of the following investigations have remained normal throughout her illness: liver function, neutrophil alkaline phosphatase, uric acid level, and tests for paroxysmal nocturnal haemoglobinuria. She was treated with repeated blood transfusions, corticosteroids, and oxymetholone,