quiescent for 18 months. Her drug treatment consisted of oral mesalazine 800 mg twice daily, which she had been taking for the past eight months. She had previously taken sulphasalazine for several years but had stopped this after developing arthralgia.

On examination there was decreased air entry at both lung bases and no other abnormality. Investigations showed a white cell count of $11.3 \times 10^9/l$ with 16% eosinophils and a high plasma viscosity; she was negative for rheumatoid factor, weakly positive for antinuclear factor, and strongly positive for antibody to neutrophil cytoplasm (titre 1/400). The pattern of staining of the antibody to neutrophil cytoplasm was cytoplasmic, and the neutrophils were negative for antibodies to myeloperoxidase, lactoferrin, and cathepsin G. Initial urine testing showed microscopic haematuria, an isotope lung scan did not show any abnormality, and an electrocardiogram was normal. She was unable to perform lung function tests because of coughing. A chest x ray film showed bilateral lung infiltrates, especially at the apexes, and bilateral small pleural effusions.

In view of the picture of pulmonary eosinophilia, haematuria, and strongly positive titre of antibodies to neutrophil cytoplasm a thorascopic lung biopsy specimen was taken from the right upper lobe. It showed no evidence of Wegener's granulomatosis or pneumonia due to bronchiolitis obliterans: appearances were those of a chronic eosinophilic pneumonia. Mesalazine was stopped, and the patient refused steroid treatment. Her condition improved over the next few weeks, and the abnormalities in the chest x ray film and blood eosinophilia resolved. The titre of antibody to neutrophil cytoplasm was still 1/400 three weeks after she stopped taking mesalazine but had fallen to 1/25 a few months later.

This patient's illness was probably caused by mesalazine. Pulmonary side effects from this drug are rare and may occur soon after the drug is started, as in the case described by Lim and Hine, or after many months of exposure,² as in this case. One report mentions a strongly positive titre of antinuclear antibody, which fell after mesalazine was stopped.³ Ulcerative colitis may cause a positive result in a test for antibodies to neutrophil cytoplasm, but the staining is usually perinuclear.⁴ The high titre of antibody to neutrophil cytoplasm with a cytoplasmic staining pattern, which fell when mesalazine was stopped, raises the possibility of a link with the drug.

D HONEYBOURNE

Department of Thoracic Medicine,
Dudley Road Hospital,
Birmingham B18 7QH

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Safety of tamoxifen

EDITOR,—V Craig Jordan reports some of the preclinical toxicological findings on tamoxifen in his editorial.¹ Though he states that tamoxifen "promotes hepatic tumours in rats," he fails to note that tamoxifen is a strong liver carcinogen by itself in rats, producing tumours within six months and a high incidence by one year at doses that yield blood concentrations comparable to those in treated women.² In addition to causing the formation of DNA adducts in the liver of rats, which Jordan mentions, tamoxifen causes the formation of DNA adducts in the liver of hamsters

and mice. This feature is characteristic of human carcinogens. In fact, tamoxifen is associated with increases in cancers of the endometrium^{3,4} and possibly liver⁵ in treated patients.

In answer to the question "Is tamoxifen safe?" Jordan compares the risk of tamoxifen with that of use of oral contraceptives on the basis of his conclusion that it is the oestrogenic properties of tamoxifen that result in the assumed, but not proved, ability of tamoxifen to promote hepatic tumours in rats. This conclusion fails to take into account other aspects of the toxicology of tamoxifen, as noted above, which are different from the effects of oestrogens. The weakness of the comparison with oestrogens is further illustrated by the fact that toremifene, which is related to tamoxifen and has comparable oestrogenic properties in liver, is not hepatocarcinogenic.²

It is important to ascertain whether breast cancer can be prevented without the potential risks of tamoxifen being imposed. Considerable evidence supports the view that breast cancer can be substantially prevented by reduction of dietary consumption of fat,⁶ which entails no risk and affords other benefits. If chemical intervention is deemed necessary the antioestrogen toremifene could be used.

GARY M WILLIAMS

American Health Foundation,
Valhalla,
NY 10595, USA

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Genetic susceptibility to non-insulin dependent diabetes

EDITOR,—Eva Tuomilehto-Wolf and coworkers have presented the interesting hypothesis that genetic susceptibility to non-insulin dependent diabetes mellitus is located in the HLA region. Their conclusions are based on findings in 157 elderly Finnish men (age 70-89), in whom HLA haplotypes associated with insulin dependent diabetes could explain 98% of non-insulin dependent diabetes and 79% of impaired glucose tolerance. This association depended strongly on the presence of HLA-DR4, which was observed in 57% (56/98) of patients with non-insulin dependent diabetes but only 13% (3/23) of controls ($P=0.003$). The frequency of HLA-DR4 in the patients with non-insulin dependent diabetes is in the same range as that previously reported from Finland² and the United States³ (table). The frequency in the control population is considerably lower than that previously reported, but this is most probably due to the small number of control subjects studied.

Prevalence of HLA-DR4 in patients with non-insulin dependent diabetes. Figures are numbers (percentages) of patients

Study	Controls	Non-insulin dependent diabetes	P value
Groop <i>et al</i> ²	86/322(28)	51/121(51)	0.02
Rich <i>et al</i> ³	62/221(27)	36/86 (42)	0.02
Tuomilehto-Wolf <i>et al</i> ²	3/23 (13)	56/98 (57)	0.03

If patients with non-insulin dependent diabetes are divided into insulin requiring and non-insulin requiring on the basis of a glucagon stimulated C peptide concentration <0.6 nmol/l, however, only the insulin requiring patients show an increased frequency of HLA-DR4 (54% (37/69) compared with 32% (41/127) in patients whose condition was controlled with oral antidiabetic agents).⁴ Patients with DR4 had lower C peptide concentrations than patients with other HLA-DR antigens.²

Since high insulin and C peptide concentrations are associated with an increased risk of cardiovascular disease we propose that these patients represented a subgroup of patients with non-insulin dependent diabetes protected against cardiovascular disease. Therefore, the increase in frequency of HLA-DR4 is due to an admixture of patients with genes conferring susceptibility to insulin dependent diabetes rather than a general feature of patients with non-insulin dependent diabetes. In the search for genes for non-insulin dependent diabetes correct definition of the phenotype is critical, since the disease is likely to be heterogeneous.

LEIF GROOP

Department of Endocrinology,
University of Lund,
Malmö General Hospital,
S-214 01 Malmö, Sweden

GIAN FRANCO BOTTAZZO

Department of Immunology,
London Hospital Medical College,
London E1 2AD

- 1 Tuomilehto-Wolf E, Tuomilehto J, Hitman GA, Nissinen A, Stengård J, Pekkanen J, et al. Genetic susceptibility to non-insulin-dependent diabetes mellitus and glucose intolerance are located in HLA region. *BMJ* 1993;307:155-9. (17 July.)
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Breast feeding and diabetes mellitus

EDITOR,—K G M M Alberti briefly mentions that "breast feeding has been shown to protect against the development of insulin dependent diabetes mellitus."¹ Two papers have strongly suggested that infants born into families with a family history of diabetes have a lesser chance of developing insulin dependent diabetes if they are breast fed up to the age of 9-12 months.^{2,3} This breast feeding must be exclusive of top up formula milk feeds as these initiate the autoimmune process that may result in insulin dependent diabetes in later life. This message seems not to be getting across to diabetic people in the community. Doctors, health visitors, and midwives must try to make breast feeding the norm in diabetic families.

Alberti mentions a possible link between consumption of bovine serum albumin and the development of insulin dependent diabetes. Karjalainen *et al* found raised antibodies to bovine serum albumin in most newly diagnosed insulin dependent diabetic patients.⁴ More importantly, Dahl-Jørgensen *et al* showed a close correlation between the amounts of cows' milk consumed per head of the population in various countries and the incidence of insulin dependent diabetes.⁵ This leaves little doubt that consumption of cows' milk is a trigger for diabetes mellitus. Bovine serum albumin is 97% denatured by ultraheat treatment of milk. We are assessing data to see whether ultraheat treated milk is less diabetogenic than pasteurised milk.

We question whether children born to diabetic families should ever consume cows' milk. Breast milk and goats' milk are readily available in Britain, and their use should be encouraged for infants, children, and adolescents at risk of developing diabetes mellitus.

M R KILN

Paxton Green Health Centre,
London SE21 8AU

DORA HENSCHER

London SE13 7JD

LAURA KILN

Beckenham,
Kent BR3 4JB

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Genetic prediction of adult onset disease

EDITOR,—Genes for an increasing number of adult onset disorders are being defined, and in this era of budgetary restriction and planning by contract we wonder how long doctors can afford to ignore lessons learnt from predictive testing for Huntington's disease. After the localisation of the locus for Huntington's disease in 1983¹ caution was initially exhibited by transatlantic colleagues, who wanted patients and their families legally to exonerate them from the consequences of giving bad news and from the predictable errors inherent in the use of linked genetic markers. In the United States and Britain extensive counselling programmes were developed.² People could decide to be tested only after a period of reflection and after receiving accurate information about the limits of the test, the implications for other family members, and the problems of living with good and bad news.

The results of several hundred tests have now been given out in Britain,^{2,3} and the counselling programmes are accepted as the minimum for good practice in participating clinical genetics centres.⁴ This is in contrast to the situation in other centres in Europe and the United States, where appreciable problems have resulted when inadequate support was provided.

Counselling programmes may be expensive in clinical time, but follow up of the people who have had predictive testing for Huntington's disease in Britain has shown that over half are free of risk and its associated morbidity, while those who receive high risk results cope well with no appreciable changes to their lifestyle.⁵ These programmes save the NHS money as well as providing a good service for patients. People at high risk can be followed up so that their problems are dealt with promptly and they may benefit from current research into the disease. Patients find this reassuring, and some visit their general practitioner less frequently than before testing (personal communications from general practitioners).

To give predictive information about other incurable disorders of adult onset to asymptomatic people without such support may well be considered to be negligent. Genetics centres are receiving requests for predictive testing for motor neurone disease, Alzheimer's disease, and some cancers. We believe that clinicians must become aware urgently of the impact of the information

that can be produced for these people and that these people should receive the benefit of the experience of the programmes concerned with Huntington's disease.

SHEILA A SIMPSON

JOHN C S DEAN

NEVA E HAITES

Department of Medical Genetics,
Aberdeen Royal Infirmary,
Aberdeen AB9 2ZZ

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Clusters of anophthalmia

EDITOR,—Eduardo E Castilla states that the reported prevalence of anophthalmia and microphthalmia at birth in England and Wales (0.22/10 000) is less than a quarter of the figure for the other populations for which the International Clearinghouse for Birth Defects Monitoring Systems receives data.¹ He also states that anophthalmia is the diagnosis in more than half the cases in England and Wales but in one quarter of those reported elsewhere.¹

The data for England and Wales come from the nationwide system centred on the Office of Population Censuses and Surveys, which covers only malformations notified soon after birth. In the experience of local English registries, which ascertain malformations from multiple sources, the prevalence of anophthalmia and microphthalmia at birth is much higher (1.3/10 000 in both Birmingham and Liverpool) and at least two thirds of affected subjects have only microphthalmia.^{2,3} These findings strongly suggest that the differences reported by Castilla are due (as he hinted that they might be) to incomplete ascertainment, especially of less severe cases, by the nationwide system for England and Wales. This and earlier evidence of the limitations of the nationwide system⁴ shows the need for caution when data from this source are used to explore possible clusters of malformations.

IAN LECK

Woodstock,
Oxford OX20 1UW

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Tuberculous pericarditis

EDITOR,—The patient reported on by C P Clifford and G J Davies, who had tuberculous pericarditis that rapidly progressed to constriction, was Sri Lankan.¹ Tuberculosis is the commonest cause of pericardial effusions in Sri Lanka. We recently prevented constrictive pericarditis in a boy in our unit by using steroids.

A 13 year old boy was admitted with fever and cough of two weeks' duration. He was febrile with a pulse of 96 beats/min and a jugular venous pressure of 5 cm water. He had a remarkable pericardial rub in the left sternal edge. A chest x ray film showed severe cardiomegaly, and echocardiography confirmed a large pericardial effusion. A pericardial aspirate contained many red cells and lymphocytes but was repeatedly negative for acid fast bacilli. A Mantoux test yielded a negative result. He was given a course of antituberculosis treatment, and the fever settled completely in five days. Steroid treatment (prednisolone 10 mg three times a day) was started one week after the start of antituberculosis treatment. An echocardiogram at one month showed a mild pericardial effusion with good contractility of ventricles and a normal ejection fraction.

A controlled clinical trial has shown that adding steroids increases the rate of recovery from tuberculous pericarditis compared with that with standard antituberculosis treatment alone.² It also reduced the risk of death due to pericarditis and the need for pericardectomy. Furthermore, the highly potent antituberculosis regimen of streptomycin, rifampicin, isoniazid, and pyrazinamide daily for 14 weeks followed by rifampicin and isoniazid for six months is believed to be associated with a lower death rate than the less potent regimen of rifampicin, isoniazid, ethambutol, and pyrazinamide for two months followed by rifampicin and isoniazid for four months.^{3,4}

It is our practice to start steroids for all patients with tuberculous pericarditis only after the fever has responded to antituberculosis drugs. Thus antituberculosis drugs can be a diagnostic aid in pericardial effusions when the result of a Mantoux test is negative and acid fast bacilli cannot be isolated from pericardial fluid or sputum.

ANULA WIJESUNDERE

S H SIRIBADDANA

Sri Jayewardene General Hospital,
Nugegoda,
Sri Lanka

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Imaging methods used in acute aortic dissection

EDITOR,—Our experience as radiologists in a large cardiothoracic centre does not lead us to support the imaging policy put forward by C M Francis and colleagues.¹ Because aortic dissection requires rapid and accurate diagnosis since early surgery may be lifesaving² we disagree with the suggestion that transoesophageal echocardiography is the best imaging method. The decision to intervene surgically and the type of operation depend on whether any part of the ascending aorta or vessels of the head and neck are affected. Francis and colleagues themselves state that transoesophageal echocardiography has a restricted view at this site, and it may result in an inaccurate diagnosis. This is supported by results of a study by Nienaber *et al.*, which found a specificity of only 68% for transoesophageal echocardiography largely because of false positive findings in the ascending aorta.³ In addition, none of the useful information on aortic branch vessels, which are easily seen on angiography, can be obtained with transoesophageal echocardiography. We have also found