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 $11{\cdot}3 \times 10^9$/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 thoracoscopic 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 anbitody, 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.

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1 Lim AG, Hine KR. Fever vasculitic rash, arthritis, pericarditis, and pericardial effusion after mesalazine. *BMJ* 1994;**308**:113. (8 January.)
2 Reinoso MA, Schroeder KW, Pisani RJ. Lung disease associated with orally administered mesalazine for ulcerative colitis. *Chest* 1992;**101**:1469-71.
3 Welte T, Hamm H, Fabel H. Mesalazine alveolitis. *Lancet* 1991;**338**:1273.
4 Cambridge G, Rampton DS, Stevens TRJ, McCarthy DA, Kamm M, Leaker B. Anti-neutrophil antibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut* 1992;**33**:668-74.

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 liver[3] 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,[5] which entails no risk and affords other benefits. If chemical intervention is deemed necessary the antioestrogen toremifene could be used.

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1 Jordan VC. How safe is tamoxifen? *BMJ* 1993;**307**:1371-2. (27 November.)
2 Hard GC, Iatropoulos MJ, Jordan K, Radi L, Kaltenberg O, Imondi AR, *et al.* Major difference in the hepatocarcinogenicity and DNA adduct forming ability between toremifene and tamoxifen in female crl:CD(BR) rats. *Cancer Res* 1993;**53**:4534-41.
3 Fornander T, Rutqvist LE, Cedermark B, Glas V, Mattsson A, Silfverswärd C, *et al.* Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1989;**i**:117-20.
4 De Muylder X, Neven P. Tamoxifen and potential adverse effects. *Cancer Journal* 1993;**6**:111-5.
5 Cohen LA, Rose DP, Wynder EL. A rationale for dietary intervention in postmenopausal breast cancer patients: an update. *Nutrition and Cancer* 1993;**19**:1-10.

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 ($P = 0{\cdot}003$). The frequency of HLA-DR4 in the patients with non-insulin dependent diabetes is in the same range as that previously reported from Finland[2] and the United States[5] (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 *et al*[2]	86/322(28)	51/121(51)	0·02
Rich *et al*[5]	62/221(27)	36/86 (42)	0·02
Tuomilehto-Wolf *et al*[1]	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 $< 0{\cdot}6$ 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 heterogenous.

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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.)
2 Groop L, Groop P-H, Koskimies S. Relationship between B-cell function and HLA antigens in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1986;**29**: 757-60.
3 Rich SS, French LR, Sprafka JM, Clements JP, Goetz FC. HLA-associated susceptibility to type 2 (non-insulin-dependent) diabetes mellitus: the Wadena City health study. *Diabetologia* 1993;**36**:234-8.
4 Groop L, Miettinen A, Groop P-H, Meri S, Koskimies S, Bottazzo GF. Organ-specific autoimmunity and HLA-DR antigens as markers for ß-cell destruction in patients with type II diabetes. *Diabetes* 1988;**37**:99-103.

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.