MATTERS ARISING

Exposure to chemicals and systemic sclerosis

Occupational exposure to various chemicals, including vinyl chloride, silica dust, epoxy resin, benzene, trichloroethylene, perchloroethylene, and other solvents, has been described as a potential provoking factor of systemic sclerosis (SSc) and scleroderma like disorders.¹ However, the precise contribution made by occupational environmental factors to the occurrence of scleroderma remains unknown.²

Susceptibility to these agents may differ widely in distinct areas of Europe, as a result of both genetic and environmental differences, as the following examples indicate.

Several cases of exposure to solvents have been described, including that reported by Garcia-Zamalloa and colleagues in the *Annals*.³ Predominantly male workers have been described,^{4,5} except in the study by Yamakage and Ishikawa.⁶ In the Hungarian population, a remarkable predominance of women has been found among patients with SSc who were previously exposed to chemicals.^{7,8} 23 of our 180 patients with SSc had exposure to solvents in their case history; only three of them were men. During the epoch of 'socialist industrialisation' in the 1950s and 60s, a large number of unskilled female workers from rural areas were employed to do menial jobs in the urban areas, with a concomitant higher risk of exposure to solvents and other chemicals. After a latent period of several years, these patients developed SSc indistinguishable from 'true' systemic sclerosis. Now, with the improvement of working conditions in Hungary, the number of cases with exposure to chemicals seems to be decreasing.

Vinyl chloride disease seems to be relatively frequent among British workers exposed to this agent.^{9,10} Conversely, in Hungary, vinyl chloride disease has been found to be extremely rare, in spite of the presence of well detectable exposure to this chemical: 464 workers were exposed to vinyl chloride in Kazincbarcika (north eastern Hungary) for more than 10 years on average, but only one case of vinyl chloride disease has been described, despite regular and well documented screening for the presence of this disorder. Another group of 60 workers has long been exposed to trichloroethylene without any signs of scleroderma related disease.

Genetic markers are useful tools for relating chemically induced SSc-like vinyl chloride disease.⁹ Susceptibility to this disorder is increased in the presence of HLA-DR5 or a gene in linkage disequilibrium with it and an antigen associated with the haplotype A1 B8, while DR3 favours the progression of the disease,¹⁰ as seen among the British workers.

The heterogeneity of clinical symptoms, distribution of major histocompatibility complex alleles, and autoantibody profiles in SSc suggest that this disorder may represent a group of distinct diseases, and that the characteristic genetic and environmental pre-

disposing risk factors can be totally different in these subgroups. The environmental contribution to scleroderma is unknown, raising the need for a European multicentre case-control study to determine the groups at risk.

LÁSZLÓ CZIRJÁK
ZOLTÁN CSIKI
ZOLTÁN NAGY

3rd Department of Internal Medicine
University Medical School of Debrecen
4004 Debrecen, Hungary

ERZSÉBET TÓTH
City Health Service, Kazincbarcika
Hungary

- 1 Silman A J. Epidemiology of scleroderma. *Ann Rheum Dis* 1991; 50 (suppl 4): 846–53.
- 2 Silman A J, Jones S. What is the contribution of occupational environmental factors to the occurrence of scleroderma in men? *Ann Rheum Dis* 1992; 51: 1322–4.
- 3 Garcia-Zamalloa A M, Ojeda E, Gonzales-Beneitez C, Goni J, Garrido A. Systemic sclerosis and organic solvents: early diagnosis in industry. *Ann Rheum Dis* 1994; 53: 618.
- 4 Bottomley W W, Sheehan Dare R A, Hughes P, Cunliffe W J. A sclerodermatous syndrome with unusual features following prolonged occupational exposure to organic solvents. *Br J Dermatol* 1993; 128: 203–6.
- 5 Brasington R D J, Thorpe Swenson A J. Systemic sclerosis associated with cutaneous exposure to solvent: case report and review of the literature. *Arthritis Rheum* 1991; 34: 631–3.
- 6 Yamakage A, Ishikawa H. Generalized morphea-like scleroderma occurring in people exposed to organic solvents. *Dermatologica* 1982; 165: 186–93.
- 7 Czirkák L, Bokk A, Csontos G, Lőrincz G, Szegedi G. Clinical findings in 61 patients with progressive systemic sclerosis. *Acta Derm Venereol Stockh* 1989; 69: 533–6.
- 8 Czirkák L, Nagy Z, Szegedi G. Survival analysis of 118 patients with systemic sclerosis. *J Int Med* 1993; 234: 335–7.
- 9 Black C, Briggs D, Welsh K. The immunogenetic background of scleroderma—an overview. *Clin Exp Dermatol* 1992; 17: 73–8.
- 10 Black C, Pereira S, McWhirter A, Welsh K, Laurent R. Genetic susceptibility to scleroderma-like syndrome in symptomatic and asymptomatic workers exposed to vinyl chloride. *J Rheumatol* 1986; 13: 1059–62.

LETTERS TO THE EDITOR

Acquired sideroblastic anaemia associated with penicillamine therapy for rheumatoid arthritis

Penicillamine has been successfully used in the treatment of rheumatoid arthritis since 1964.^{1,2} Most of the serious reactions have been haematological and include agranulocytosis, thrombocytopenia, and aplastic anaemia.^{2–5} The incidence of some adverse side effects, such as thrombocytopenia, rashes and proteinuria, has been shown to be unacceptably high with high dose treatment.⁴

We report a case of acquired sideroblastic anaemia following treatment with penicillamine for rheumatoid arthritis.

A 50 year old man with a five year history of rheumatoid arthritis and non-insulin-dependent diabetes mellitus developed more active joint disease associated with rheumatoid nodules and erosive changes revealed by

radiography. His joint disease had been controlled on ibuprofen 600 mg three times daily, but in June 1988 penicillamine 125 mg once daily was added to his regimen. The dose was gradually increased, by 125 mg at monthly intervals, to 500 mg once daily. At no stage was he taking phenacetin or paracetamol.

Before he commenced taking the penicillamine, the patient's full blood count had been stable, with a haemoglobin concentration of 13.2 g/dl, platelet count $351 \times 10^9/l$, leucocyte count $9.3 \times 10^9/l$ and erythrocyte sedimentation rate 35 mm/1st h. The film was mildly microcytic (mean cell volume (MCV) 76 fl) and hypochromic. The white cell differential was normal.

Two months after he started treatment, his haemoglobin had decreased to 9.9 g/dl and showed hypochromia and microcytosis (MCV 68 fl). He then began a course of iron therapy and the haemoglobin temporarily increased to 12 g/dl in November 1988. By January 1989 his haemoglobin decreased again, to 10.8 g/dl with a hypochromic, microcytic picture (MCV 70 fl) and by February 1989 it had decreased further, to 7.0 g/dl. At this stage, the film showed a dimorphic picture with some hypochromia, basophilic stippling, and poikilocytosis. There were some nucleated red cells and the white cells and platelets were normal. Because of the appearance of the blood film, the possibility of sideroblastic anaemia was raised.

Clinically, there was no evidence of blood loss and an endoscopy was normal. His arthritis was considered to be well controlled on therapy, with a C reactive protein 29 mg/l (normal range (NR) <20 mg/l) and C3 degradation product 15 U/ml (NR 5–12 U/ml); vitamins B-12 and folate levels were normal, serum iron 33 $\mu\text{mol/l}$ (NR 14–34 $\mu\text{mol/l}$), and iron binding capacity 34 $\mu\text{mol/l}$ (NR 43–72 $\mu\text{mol/l}$). Bone marrow aspirate and trephine revealed a hypocellular marrow with markedly reduced erythropoiesis, gross dyserythropoiesis and 24% ringed sideroblasts. The karyotype was normal. The appearance of the myeloid and megakaryocytic series were normal. During the period of investigation the haemoglobin decreased to a minimum of 4.9 g/l. The patient's penicillamine regimen was discontinued and he began taking pyridoxine 100 mg twice daily. He required a blood transfusion to control his symptoms, but subsequently maintained his haemoglobin at about 12.5 g/dl, with a normal MCV (81 fl). A repeat bone marrow aspirate at two months was hypercellular, and although there was mild dyserythropoiesis, ringed sideroblasts were not present.

During subsequent follow up, the patient's joint disease flared. In view of the previous problem, it was decided initially to treat him with prednisolone 5 mg once daily and, more recently, with hydroxychloroquine.

Patients with acquired idiopathic sideroblastic anaemia show abnormalities of all three haemopoietic cell lines. The changes are most marked in the red cell lineage, with at least 15% of nucleated erythroid cells in the marrow being ringed sideroblasts.⁶ The peripheral blood shows a dimorphic picture with poikilocytosis, basophilic stippling and some hypochromic features, although the overall MCV is often slightly increased. The karyotype may be abnormal and there is a predisposition to develop acute leukaemia.⁶

Secondary sideroblastic change occurs in a wide variety of conditions, but the number of