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Dear Ted

GENETIC SUSCEPTIBILITY TO SCLERODERMA-LIKE SYNDROME INDUCED BY VC

You may have come across the paper in Lancet by Dr Ann Walker etc. This relates to Vinatex workers at the Staveley Factory now taken over by Norsk Hydro. I enclose a copy of the paper, January 1 1983, pages 53-55. Ann Walker likes to keep the pot boiling but I don't think she really manages to prove anything. However, Dr Brian Bennett who noticed the paper first, got our experts Dr Ted Davies in our Immunology Section and Geoff Paddle to comment. I know you like to have critiques on your file. You are welcome to have a copy of our critiques for what they are worth.

With best wishes.

Yours sincerely

J Stafford
Health & Environment Protection

John,
We would like to
have the comments
of Davies & Paddle
Ted Torkelson
29 March 1983

patients typed in the present study also showed an increased association between B8 and DR3 and a significantly increased frequency of DR5. The VC group A and the scleroderma group are remarkably similar in terms of HLA-antigen frequencies. There is therefore a striking similarity in both the clinical symptoms and in the HLA-region genetic markers in VC disease and scleroderma. Autoantibody responses, however, are totally different: in none of the VC-disease patients could we detect any evidence of either anti-centromere or anti-Scl-70 antibodies. The anti-centromere result is significant, because such antibodies are generally found only in the CREST form of scleroderma, and both the CREST form and VC disease are limited forms of scleroderma. Thus anti-centromere antibody is unlikely to be involved in any disease limitation process.

VC disease is unusual in that (i) the causative agent is known; (ii) only some members of the population exposed to the agent develop the symptoms; and (iii) the total population exposed to the causative agent are numerically known, and documented medical histories are available for study. We know that approximately 150 people in the work population from which the patients came were exposed to VC and that symptoms later attributed to severe VC disease developed in 28 of these. A further 27 were classified as having mild symptoms of VC disease. Of this total of 55, 44 were available for follow-up—21 with severe and 23 with mild disease. Although increased awareness of the problems associated with acute exposure to vinyl chloride and better safety precautions have almost prevented new cases of VC disease, the question of what happens after chronic exposure to low levels remains to be answered.

That 11 of the 21 patients classified as having severe disease were DR3 positive (8 of these were also B8 positive) is difficult to explain. If the VC is more likely to affect B8, DR3 positive workers, then the frequency of the antigens in the mildly affected patient group should be also raised. In fact no-one in the latter group was either B8 or DR3, and the disparity in the frequency of these antigens is highly significant ($p = 0{\cdot}0006$, corrected $p = 0{\cdot}004$). The most likely explanation is that B8 and DR3 are associated not with the susceptibility to the disease but to its progression from mild symptoms to a more severe form. This is an important point, because it might apply to the group of autoimmune diseases which are B8-DR3-linked.

In contrast DR5, which has a raised frequency in the whole patient group, might be associated with a susceptibility marker. The influence of genetic factors on the susceptibility to industrial or related chemicals has not been widely investigated. There are very close associations between susceptibility to some drug complications and HLA markers,[9,10] and a weak association has been reported between HLA markers and susceptibility to Kaplan's syndrome.[11]

We thank the staff of the tissue typing laboratory at Guy's Hospital for technical assistance and Dr P. J. Maddison and Prof. M. I. V. Jayson for reading the script.

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References continued at foot of next column

Child Health

AN APPEAL AND A PROGRAMME FROM UNICEF

THE obviously starving child is the extreme tip of the mountain of malnutrition. Most of the 40 000 children who die daily throughout the world succumb to infections superimposed on the seldom visible undernourishment caused by repeated bouts of diarrhoea. The 1982–83 report[1] by UNICEF's executive director, James P. Grant, proffers four strategies by which to break the cycle of malnutrition and disease. In his estimate, the lives of 20 000 children a day could be saved by these relatively inexpensive measures.

Oral rehydration therapy (ORT) permits the mother to make up her own oral rehydration solution (one teaspoonful of salt to eight teaspoonfuls of sugar per litre of boiled, cooled water) or to buy cheap packets of ready-made salts and administer the mixture in her own home to the child dehydrated by diarrhoea. The discovery that adding glucose to a salt solution increases the body's rate of absorption of fluid by 2500% has meant that dehydrated children seldom have to be treated intravenously by trained personnel—if such facilities even exist. In Narangwal, India, the death-rate among young children has been halved by community workers using oral rehydration salts and penicillin. Grant writes: "The need for ORT is clear, the technology is known, the means of dissemination are available. The receptiveness of parents has been demonstrated. The cost is small. And only an inexcusable lack of national and international will can now prevent the bringing of its benefits to the vast majority of children in need".

The development of more stable and effective vaccines and the reduction in their cost has made the second plan of *mass initial and booster immunisation* feasible. Measles, diphtheria, tetanus, whooping-cough, poliomyelitis, and tuberculosis account for about a third of all child deaths. The malnourished child is susceptible to disease and disease provokes malnutrition.

The third proposal is the promotion of *breastfeeding*. UNICEF sponsored a four-year study of over 10 000 newborn infants in a hospital in the Philippines. After two years, its director of paediatrics declared: "I closed the door of the nursery to the milk companies. We stopped giving our babies the standard dose of infant formula. Down came the colourful posters and calendars. In their place, we hung the 'baby-killer' posters which show an emaciated baby inside a dirty feeding bottle. Everything that was conducive to bottle feeding was removed not only from the nurseries but from everywhere else in the hospital. I myself rejected samples and donations from the milk companies". Over the next two years, the incidence of infection, diarrhoea, and death among the

C. M. BLACK AND OTHERS. REFERENCES—*continued*

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Of the data obtained on the VC-disease patients the HLA types and the anticentromere and anti-Scl-70 results are directly comparable to our previous findings in a study on patients with classical scleroderma.[6]

PATIENTS AND METHODS

Patients

44 of the 53 patients with symptoms of VC disease originally described and classified by Ward et al.[7] were available for this 5-year follow-up. The patients were divided into two groups. Group A consisted of 21 patients moderately or severely disabled with arthralgias, Raynaud's phenomenon (symptomatic or clinically observed), dyspnoea, and scleroderma-like skin lesions; 3 of these had radiological evidence of acro-osteolysis. Group B consisted of 23 mildly disabled patients who presented with miscellaneous symptoms that were not confirmed by visible abnormalities or overt clinical signs. These clinical findings are compared with the results obtained in 50 scleroderma patients (see table I). The most notable abnormality on serial lung-function tests was the reduction of diffusion capacity to below 70% of normal.

HLA Typing

All patients were typed for HLA A, B, and DR locus antigens with sera standardised against 8th histocompatibility workshop sera. Lymphocytes were prepared from 10 ml blood taken into an equal volume of 0·5% EDTA. Separation of B and T cells and the HLA typing methods used have been described previously.[8] The statistical significance of the HLA associations with VC disease were determined with the χ^2 test with Yates' correction. Multiplication of the p value by the number of DR antigens tested for was used to allow for the possibility that the difference in DR3 frequency between groups could have occurred by chance because of the number of observations made. This correction may not be necessary, however, because the DR3 difference is paralleled by the B8 difference, and these two antigens are in close linkage disequilibrium. Such corrections need not be applied when previous studies have shown a similar association. It is a matter of debate whether or not VC disease and idiopathic scleroderma are similar enough to meet this criterion.

Anti-centromere Antibodies

These were detected with an indirect immunofluorescence technique. The antibodies were observed as discrete granular immunofluorescence on the interphase nuclei, with characteristic localisation on mitotic figures.[6]

Scleroderma-70 Antibodies

Antibody to nuclear antigen Scl-70 was detected by means of double immunodiffusion in 0·4% agarose gel with a freshly prepared extract of rabbit thymus powder (Pel-freeze Biologicals Inc., Rogers A & K) as the source of antigen.[6] A prototype serum was provided by Prof. E. M. Tan.

TABLE I—CLINICAL FEATURES (%) IN VC DISEASE AND SCLERODERMA

Symptom	VC disease			
	Total (n=44)	Group A (n=21)	Group B (n=23)	Scleroderma (n=50)
Diffuse scleroderma	4·7	9·5	0	32·0
Raynaud's phenomenon	74·4	85·7	60·9	96·0
Sclerodactyly	9·3	19·0	0	94·0
Calcinosis	0	0	0	50·0
Acrosclerosis	7·0	14·3	0	72·0
Telangiectasia	9·3	19·0	0	60·0
Digital pitting scars	0	0	0	80·0
Arthralgia	81·4	95·2	65·2	72·0
Arthritis	18·6	28·6	8·7	30·0
Myalgia	55·8	66·7	43·5	26·0
Abnormal lung function	55·8	95·2	19·1	46·3

RESULTS

16 (36·4%) of the 44 patients were DR5 positive, compared with 22 (14·9%) of the 148 controls. This difference is significant with $p<0·05$, and the observation is an exact parallel of the finding that DR5 frequency is raised in scleroderma (table II).

The frequency of DR3 in the VC-disease patients was less than that in the controls, but on further analysis we were surprised to find that the 11 VC-disease patients who were DR3 positive were all in group A—i.e., they had the more severe symptoms. Thus 11 of the 21 group-A patients were DR3 positive, compared with none of the 23 group-B patients ($p=<0·001$, corrected p value = 0·004). The group-A patients thus had raised DR3 (table II), and both the group-A and the scleroderma patients had raised B8, DR3. Indeed the group-A patients were very similar to the scleroderma patients in terms of HLA antigen frequencies. Apart from the B8, DR3, and DR5 there was also a raised frequency of B7 and a lowered frequency of DR2 in both disorders—a surprising observation, because these antigens, like B8 and DR3, are in linkage disequilibrium.

The frequencies of HLA Bw35 and DR1, which are raised in scleroderma, especially the CREST form (calcinosis, Raynaud's oesophagus, sclerodactyly, telangiectasia), were marginally lowered in VC disease. In scleroderma these antigens tended to be associated with autoantibody production, and such antibodies were not observed in VC disease.

No anti-centromere or anti-Scl-70 antibodies were found in any of the VC patients (table III). Although these were not looked for in the original study, only 3 of the 44 patients had changed groups in the 5 years before follow-up. These antibodies persist for many years in scleroderma patients.

TABLE II—HLA ANTIGEN FREQUENCIES (%) IN VC DISEASE, SCLERODERMA, AND CONTROLS

Antigen	Controls (n=148)	Scleroderma (n=50)	VC disease		
			Total (n=44)	Group A (n=21)	Group B (n=23)
A1	21·6	36·0	27·3	38·1	17·4
B7	20·3	30·0	25·0	28·6	21·7
B8	22·3	30·0	18·2	38·1	0·0*
DR1	14·9	20·0	18·2	14·3	21·7
DR2	21·6	12·0	22·7	14·3	30·4
DR3	28·4	36·0	25·0	52·4	0·0†
DR4	33·8	30·0	25·0	23·8	26·1
DR5	14·9	30·0*	36·4*	28·6	43·5
DR6	20·9	20·0	16·3	33·3	13·6
DR7	26·4	14·0	25·0	19·0	30·1
B8 and DR3	19·6‡	12·0‡	18·2	38·1	0·0

*p<0·05, †p<0·001, ‡p<0·01, for the data values B4, B8 and DR1 are in greater linkage disequilibrium in the scleroderma patients and in the patients with severe VC disease than in the control populations.

TABLE III—AUTOANTIBODIES IN VC DISEASE AND SCLERODERMA

Disease	No. of patients	No. with anti-centromere antibodies	No. with anti-Scl-70 antibodies
VC disease	44	0	0
Scleroderma	50	18	17
CREST	18	17	7

DISCUSSION

This is the first report on the frequency of genetic markers in patients with VC disease, but an increased association between antigens B8 and DR3 and an increased frequency of DR5 in scleroderma have already been described.[4-6] The

complications after elective termination before 16 weeks' gestation. One was performed by suction evacuation, the other by hysterotomy.

If the pregnant EDS IV patient is first seen late in pregnancy, she must be cared for as a high-risk patient. Vaginal delivery and delivery by elective caesarean section have both been advocated for such patients. However, on the basis of the experience of patients in our group there does not appear to be a mode which has fewer complications. We suggest that all patients should be carefully monitored during labour and for several days post partum so that prompt intervention can be initiated in the event of vessel or uterine rupture.

We cannot emphasise too strongly that EDS IV is a distinct type of EDS which differs in clinical and biochemical features from all other forms. Those complications which affect women with EDS IV are not to be expected in patients with other forms of EDS.[24]

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Industrial Medicine

GENETIC SUSCEPTIBILITY TO SCLERODERMA-LIKE SYNDROME INDUCED BY VINYL CHLORIDE

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Summary Vinyl chloride (VC) monomer can induce a scleroderma-like syndrome in a proportion of workers exposed to it during production of polyvinyl chloride. As part of a 5-year follow-up study HLA A, B, and DR antigens and anti-centromere and anti-scleroderma-70 antibodies were determined in 44 such workers. 21 of these had severe and 23 mild forms of vinyl-chloride disease. 50 patients with "classical" scleroderma and 148 healthy hospital workers acted as controls. 11 of the 21 patients classified as having severe VC disease were DR3 positive, and 8 of these had both B8 and DR3 antigens. None of the 23 patients with mild disease carried either antigen. The HLA-antigen frequencies in VC disease mirrored those found in scleroderma (raised DR5 frequency and increased linkage disequilibrium between B8 and DR3). There were, however, significant differences in the frequency of autoantibodies in the two conditions.

INTRODUCTION

VINYL chloride (VC) was first polymerised to polyvinyl chloride (PVC) in Germany in the 1930s, but it was many years before reports of liver changes[1] and acro-osteolysis[2] in workers involved in PVC production began to appear. These and many subsequent reports[3] indicate that exposure to vinyl chloride can lead to a syndrome characterised by sclerotic changes in the skin, skin nodules, clubbing of the fingers, osteolysis, Raynaud's phenomenon, thrombocytopenia, portal fibrosis and impaired hepatic function, and pulmonary fibrosis. Excessive fatigue, muscle and joint pains, central nervous system symptoms, and impotence have also been described. Although only some workers who had been in contact with vinyl chloride developed symptoms, no studies on genetic markers in those affected have been reported. Vinyl-chloride disease is, however, clinically very similar to scleroderma, and the observations by ourselves and others that susceptibility to scleroderma is linked, albeit weakly, to HLA markers[4-6] led us to study 44 of the 53 patients with symptoms of vinyl-chloride disease originally described by Ward et al.[7] These patients are men who had developed either mild or severe forms of the disease after exposure to vinyl chloride. They were studied, as part of a 5-year follow-up, for HLA-region allotypes, Gm allotypes, complement allotypes, and autoantibodies to centromere, Scl-70, and collagen subtypes. In addition we were able to determine the number of workers from the same factories who had been exposed to vinyl chloride but had no symptoms of vinyl-chloride disease.