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***** EXPERIMENTAL DESIGN *****

TO DETERMINE IF A HIGHER FREQUENCY OF CHROMOSOME ABERRATIONS OCCURRED IN VC POLYMERIZATION WORKERS THE PERIPHERAL LYMPHOCYTES OF 7 OCCUPATIONALLY EXPOSED AND 3 NON-EXPOSED CONTROL SUBJECTS, ALL EMPLOYED IN THE SAME FACTORY, WERE STUDIED. THE AIR CONCENTRATION OF VC IN THE POLYMERIZATION DEPARTMENT WAS ESTIMATED TO BE AROUND 20 TO 30 PPM. THE DURATION OF EMPLOYMENT IN VC WORK RANGED FROM 9 TO 29 YEARS. NONE OF THE WORKERS HAD ABNORMAL CLINICAL EXAMINATIONS, EXCEPT FOR CASE A WHO HAD THROMBOCYTOPENIA AND ALPHA 1 - ANTITRYPSIN DEFICIENCY. CHROMOSOMAL ANALYSES WERE MADE ON 48 AND 72 HOUR CULTURES WHICH WERE CODED AND ANALYZED BLINDLY. THE DATA FROM THE CONTROL SUBJECTS (566 CELLS) WERE HOMOGENOUS AND THEREFORE POOLED. IN CELLS FROM THE EXPOSED GROUP THERE WAS NOT FOUND IN ANY CASE A STATISTICALLY SIGNIFICANT DIFFERENCE IN THE FREQUENCY OF ABERRATIONS BETWEEN 48 AND 72 HOURS CULTURES, AND THEREFORE THEY WERE POOLED.

***** KEYWORDS *****

VINYL CHLORIDE; HUMAN STUDY; OCCUPATIONAL EXPOSURE;
CHROMOSOME ABERRATIONS; THROMBOCYTOPENIA; ALPHA 1 -
ANTITRYPSIN DEFICIENCY; PERIPHERAL LYMPHOCYTES; X RAYS;
CHROMATID GAPS; ISOCHROMATID GAPS; CHROMATID BREAKS;
CHROMATID EXCHANGES; ISOCHROMATID BREAKS; DICENTRIC
CHROMOSOMES; RING CHROMOSOMES.

***** ABSTRACTS *****

THE RESULTS OF THIS ANALYSIS ON A SMALL GROUP OF VC EXPOSED WORKERS INDICATES THERE IS AN INCREASED FREQUENCY OF CHROMOSOMAL ABERRATIONS. IN 566 CELLS OF CONTROL WORKERS THERE WERE 11 ABNORMAL CELLS (1.94%) AND IN 1450 CELLS, COMBINING THE DATA FROM THE 7 CASES OF EXPOSED VC WORKERS THERE ARE 318 ABNORMAL CELLS (9.52%). THE FOLLOWING FREQUENCY OF ABERRATIONS IN THE CONTROL POPULATION CORRESPONDED TO THAT FOUND IN THE GENERAL POPULATION. IN THE EXPOSED POPULATION THE FREQUENCY OF CHROMOSOME ABERRATION WERE FOUND HIGHER IN CHROMOTID AND ISOCHROMATID GAPS AND BREAKS, BUT NOT FOR THE OTHER TYPES TESTED. THE HIGHEST FREQUENCY OF ABNORMAL CELLS WERE FOUND IN THE TWO INDIVIDUALS WITH THE SHORTEST DURATION OF EXPOSURE (9 YEARS) AND TWO INDIV-

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IDUALS, ONE WITH 12 YRS. AND THE OTHER 20 YRS. EXPOSURE, DID NOT DIFFER SIGNIFICANTLY FROM THE CONTROLS. A TEST OF HETEROGENEITY GAVE A CHI SQUARED= 47.72 P LESS THAN 0.001. HIS NEGATIVE CORRELATION OF THE FREQUENCY OF ABNORMAL CELLS WITH THE TIME OF EXPOSURE WAS NOT SIGNIFICANT.

NOTE: THE AUTHORS MENTION PREVIOUS DIAGNOSTIC X-RAYS AS A POSSIBLE EXPLANATION OF CHROMOSOMAL ABERRATIONS IN THE CONTROL GROUP. SUBJECTS WITH CURRENT DRUG INTAKE OR PREVIOUS X-RAYS ARE NOT INDICATED AS EXCLUDED FROM THESE STUDIES. THERE IS ALSO A THIRD EXPOSED SUBJECT, CASE E, THAT DOES NOT APPEAR TO DIFFER SIGNIFICANTLY FROM CONTROLS.

release of low concentrations of proteolytic enzymes in the skin due to the non-specific cytotoxic effects of bile salts could account for both the pigmentation and the pruritus of patients with chronic obstructive jaundice.

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CHROMOSOME ABERRATIONS IN WORKERS EXPOSED TO VINYL CHLORIDE

SIR,—Epidemiological evidence suggests that the risk of malignancy is increased in workers chronically exposed to vinyl chloride (V.C.).¹⁻⁵ The carcinogenicity of V.C. has been demonstrated in animal experiments.⁶ In-vitro⁷ and in-vivo⁸ experiments suggest that the carcinogenicity of V.C. probably depends on the formation of an alkylating compound, presumably chloroethylene oxide. Since carcinogenic chemicals are often mutagenic,⁹ we wondered if V.C. is also mutagenic. In fact V.C. has been reported as inducing mutations in *Salmonella typhimurium* in the presence of metabolically active liver homogenates.¹⁰ If alkylation of D.N.A. by V.C. metabolites also produces chromosomal aberrations in man, chromosomal analyses could be used as an indicator of risk and also possibly be helpful in establishing a genetically meaningful maximum allowable concentration of V.C. We report an increased frequency of chromosomal aberrations in workers exposed to V.C.

Seven occupationally exposed male workers and three non-exposed control subjects, all employed in the same factory, were studied. The level of exposure to V.C. had continuously decreased during past years. In the weeks preceding the collection of blood-samples for chromosomal analysis (before the summer holidays in 1974) the air concentration in the polymerisation department was estimated to be 20-30 p.p.m. Workers had been exposed

to V.C. for 9-29 years. Clinical examinations had been carried out at regular intervals. None of the workers had showed disturbed liver function, signs of atherosclerosis or haematological changes, except for case A in which there was slight thrombocytopenia and an α_2 -antitrypsin deficiency. Chromosomal analyses were made on cells from conventional lymphocyte-cultures incubated for 48 and 72 hours. All blood specimens and slides were coded and analysed blindly.

The result of the chromosome analysis is given in the accompanying table. The data for the control subjects were homogenous and therefore pooled. Altogether they comprised 566 cells, 11 of which (1.94%) contained chromosomal aberrations. This finding might be explained by previous diagnostic X-rays. The frequency of aberrations nevertheless accorded with that of a male population selected at random.¹¹

1450 cells from the group exposed to V.C. were analysed, 800 in the 48-hour cultures and 650 in the 72-hour cultures. In none of the cases was there a statistically significant difference in the frequency of aberrations between the 48 and 72 hour cultures. Therefore these data were pooled. The frequency of abnormal cells in the group exposed to V.C. (9.52%) was significantly greater than in the controls ($P < 0.001$). This was also true for chromatid and isochromatid breaks when analysed separately, but not for the remaining types of aberrations.

The highest frequency of abnormal cells was found in those subjects who had the shortest duration of exposure (see table), and two cases (C and F) did not differ significantly from the controls. A χ^2 test of the frequencies of abnormal cells also revealed a significant deviation from homogeneity ($P < 0.001$). The negative correlation of the frequency of abnormal cells with the time of exposure was not significant. Therefore, on the basis of the present data it is not possible to discuss the biological background of this heterogeneity.

We thank the staff at KemaNord, Stockviksverken, for cooperation and Miss Anita Tillberg for technical assistance. The expenses for the present study were covered by grants from the Swedish Medical Research Council (3681) and the Swedish Board of Occupational Safety and Health.

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Subjects	Duration of exposure (yr.)	No. of cells analysed	Gaps		No. of different types of aberrations							No. of abnormal cells	
			Chromatid	Isochromatid	Chromatid breaks	Chromatid exchanges	Isochromatid breaks	Dicentric chromosomes	Ring chromosomes	Other types	Total	Total	%
Controls (3)	0	566	5	4	4	1	4	2	1	0	12	11	1.94
Exposed:													
A	9	200	22	8	19	2	19	0	0	1	41	36	18.00
B	9	250	15	14	24	1	17	3	1	2	48	37	14.80
C	12	250	4	6	5	1	5	2	1	0	14	12	4.80
D	18	200	8	5	12	1	9	0	0	2	24	22	11.00
E	19	150	3	2	4	0	5	0	0	2	11	11	7.33
F	20	200	1	1	0	0	1	0	0	2	3	3	1.50
G	29	200	9	12	7	0	9	1	1	1	19	17	8.50
Total (A-G)	...	1450	62	48	71	5	65	6	3	10	160	318	9.52*

* A test of heterogeneity gave $\chi^2 = 47.72$, 6 d.f., $P < 0.001$.

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