Approxi]mately half of the patients studied had well-established hypertension, and only 13.6 were newly diagnosed hypertensives at the time of entry into the trial. Before the study the majority of patients had been on a combination of 2, 3 or more drugs, whereas during the study 1 THA tablet per day achieved satisfactory control in most. The advantage of dosage simplicity carried the bonus of patient compliance. No new or unexpected adverse effects emerged during phase 2 of the trial.

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REFERENCES

Chromosomal Aberrations in Occupation-Associated Progressive Systemic Sclerosis
RENEE BERNSTEIN, I. PRINSLOO, S. ZWI, M. J. A. ANDREW, B. DAWSON, T. JENKINS

SUMMARY
An occupational association between progressive systemic sclerosis (PSS) and workers in the goldmining industry in South Africa was first documented in 1957. We investigated the chromosomes of 18 goldminers suspected to be suffering from PSS. Eight patients were classified as definite cases of PSS, and a highly significant increase in unstable (C-) cells and random aneuploidy was found in this group compared with control subjects (P<0.001). Ten patients had some of the features of the disease, and in this group there was a significant increase in the number of C- cells (P<0.05) and a highly significant increase in the number of aneuploid cells (P<0.001). There was a significant increase in the number of sister chromatid exchanges per cell in the 6 patients screened. These findings are similar to those reported in PSS sufferers who have not had occupational exposure.


An environmental occupational association has been reported between progressive systemic sclerosis (PSS) and silicates, vinyl chloride and welding. The potential hazard of this collagen disease to workers in the goldmining industry in South Africa was first noted by Erasmus, and prompted further investigation of South African goldminers suspected to be suffering from PSS. Several of these patients were recently referred to the National Research Institute for Occupational Diseases (now the National Centre for Occupational Health) for assessment of a possible occupational aetiology.

Cytogenetic studies were undertaken as part of their investigation because of reported chromosome breakage in patients with PSS.

PATIENTS AND METHODS
Eighteen patients with symptoms and signs suggestive of PSS were entered into the cytogenetic study. They were all male Caucasian goldminers. In 8 of these 18 patients (group 1) a definitive diagnosis of PSS, based on the cri-
teria specified by Medsger and Masi, was established. Their ages ranged from 37 to 66 years, with a median age of 55 years. In the remaining 10 patients (group 2) investigations failed to confirm a diagnosis of PSS based on Medsger and Masi’s criteria, but some of them may develop more convincing features of the disease in the future. The median age of group 2 patients was 59 years, their ages ranging from 57 to 68 years.

Cytogenetic Methods

Peripheral blood cultures were established by a standard wholeblood microculture technique in all but 2 patients in group 1 and 2 patients in group 2; in these cases a modified synchronized cell culture technique was used. The control series comprised 62 patients referred for cytogenetic investigation of a variety of conditions, whose blood was cultured at the same time and by the same method as that of the study group; all patients with haematological disorders, suspected chromosome breakage syndromes or suspected viral disease were excluded from the controls. Identical culture conditions, using the same batches and concentrations of TC 199 culture medium, AB or fetal calf serum, phytohaemagglutinin, colchicine (and methotrexate and thymidine in the synchronized cultures) pertained for each study patient and the control subjects cultured at the same time. The same technologist was responsible for the initiation and termination of cultures and the preparation of slides for each batch. One individual screened the slides of the whole study group and all the controls; the classification of the study patients into groups 1 or 2 was not known at the time of screening. A minimum of 20 unselected, consecutive and apparently complete unbanded metaphases from each study patient were analysed for chromosome aberrations. Fifty cells from control subjects of the same culture batch as the study subject were similarly screened; the number of control subjects in each culture batch ranged from 2 to 5. At least two Giemsa-banded metaphases per subject were karyotyped to exclude any stable abnormality.

Sister chromatid exchanges (SCEs) were demonstrated by the incorporation of 5-bromo-deoxy-uridine (30 μg/ml culture) through two cycles of replication by slight modification of a previously described technique. The frequency of SCE in study subjects was expressed as the mean number of SCEs per cell and compared with the mean number of SCEs per cell in 13 normal control subjects.

Statistical Methods

The number and type of aberrations in the two study groups were compared with those in their controls and submitted to statistical analysis. The χ² test (1 degree of freedom) with Yates’s continuity correction was used for all comparisons. The significance of the difference between the mean number of SCEs per cell in the affected individuals and the control subjects was assessed by determining the standard error of the difference between the two means.

RESULTS

None of the 18 patients in the study group showed any stable chromosomal abnormality. There was, however, a highly significant increase in unstable (C') cells in the group 1 patients with a definite diagnosis of PSS (P < 0,001), whereas in the patients in group 2 the numbers of C' cells and C cells showing more than one aberration per cell were significantly greater than in the control subjects (P < 0,05).

There was a significant increase in chromatid and isochromatid gaps and isochromatid breaks (P < 0,05) in group 1 patients, and group 2 patients showed a significant increase in the number of isochromatid breaks (P < 0,05). Comparison of the number of random aneuploid cells as a possible indicator of in vitro metaphase instability showed a highly significant increase in the number of aneuploid cells (P < 0,0001) in both group 1 and group 2 patients (Table I).

The mean number of SCEs per cell in 3 patients from group 1 was 11,7 ± 3,97 in 30 cells screened, and 3 patients from group 2 showed 13,16 ± 4,62 SCEs per cell in 31 cells. The standard error of difference between the two means in group 1 and 2 was 1,101 which is not significant. The combined data of the 6 study patients from groups 1 and 2 showed 12,44 ± 4,34 SCEs per cell in 61 cells screened, whereas 13 normal control subjects had a mean number of 9,57 ± 3,11 SCEs per cell in a total of 138 cells screened. The difference between the two means (2,87) is 4 times greater than the standard error of their difference (0,616), indicating significance at the 5% level.

DISCUSSION

Chromosome studies in workers exposed to occupational hazards were first reported in 1964 in individuals exposed to benzene. Since that time chromosome surveys have been carried out on industrial populations exposed to vinyl chloride, ethylene oxide, epichlorhydrin, arsenic, mercury, lead, spray adhesives, cadmium and DDT (reviewed by Purchase in 1978). The findings in the present study add yet another relationship between chromosome damage and occupation, viz. individuals in the goldmining industry who develop PSS. Although many of the chemicals studied cause chromosome damage in vitro, the exact relationship of these clastogenic effects to the induction of mutagenesis, carcinogenesis and teratogenesis is not yet fully elucidated. The problem is further compounded by the difficulty in interpreting the results of chromosome studies and other epidemiological surveys, owing to confounding factors such as age, the effects of other unrecognized environmental agents, and the difficulty in controlling and standardizing the technical screening procedures used.

With regard to our findings in patients with features of PSS, possibly occupationally induced, the significant increase in chromosome instability in the 8 goldminers with PSS confirms the finding of increased chromosome breakage in vitro and in vivo in patients with this disease in whom there is no known occupational association. Rodnan et al. found no difference in the clinical features of
The demonstration of similar chromosomal aberrations indicates that the manifestations of this collagen disease are similar whether it is occupationally induced or not.

Most cases of scleroderma are sporadic, but rare familial association and even immunological disturbances in asymptomatic family members have been reported. The finding of increased chromosome breakage in 86% of siblings and 68% of children of PSS patients lends support to the concept of an inherited predisposition to PSS. The precipitating factors in the aetiology of non-occupational PSS are as yet unknown, but a study of occupationally associated PSS could possibly elucidate the relative roles of the genetic and environmental components.

Although the 10 patients in group 2 did not fulfil the criteria for a definitive diagnosis of PSS, as defined by Medsger and Masi, some of the chromosomal abnormalities noted in this group, such as an increase in C cells and the number of C cells with more than one aberration and increased isochromatid breaks, were significant (P < 0.05) and the rate of random aneuploidy was increased to a highly significant extent (P < 0.001). This suggests that a prospective serial follow-up study of this group of patients could prove informative in assessing the value of monitoring chromosomal aberrations as a diagnostic and prognostic indicator of PSS in subjects whose occupations are known to be associated with a high incidence of PSS.

Latt demonstrated that a variable of chemicals induce large numbers of SCEs at doses far lower than those required to produce ordinary chromosomal aberrations, and the sensitivity and ease of scoring SCEs have led to the widespread use of this technique as a sensitive assay of clastogenic agents (reviewed by Wolff, 1977). The significant increase in SCEs in our small sample of 6 patients with PSS warrants further investigation because, if this is confirmed in larger numbers of patients, it could form the basis of a relatively simple screening procedure for individuals at risk of developing PSS due to occupational exposure to silicates or other noxious environmental agents. A case could even be made for screening all such individuals at risk of chromosome breakage and SCE frequency. This would be of value from the diagnostic and prognostic point of view, and the laboratory techniques involved are already available in most large medical centres.

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