# PAPERS AND SHORT REPORTS

## Silica exposure and rheumatoid arthritis: a follow up study of granite workers 1940-81

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**Abstract**

**The incidence and prevalence of subjects awarded disability pensions and the prevalence of subjects receiving free medicines because of rheumatoid arthritis were studied in a Finnish cohort of 1026 granite workers hired between 1940 and 1971 and followed up until 31 December 1981. The incidence of awards of disability pensions because of rheumatoid arthritis during 1969-81, the prevalence of rheumatoid arthritis on 31 December 1981, and the prevalence of subjects receiving free medicines for rheumatoid arthritis at the end of 1981 were significantly higher among the granite workers than in the general male population of the same age. Retrospective analysis of the records of all patients with rheumatoid arthritis in the cohort showed a predominance of a severe, serologically positive and erosive form of rheumatoid arthritis, usually with an age at onset of 50 or over.**

**The possible aetiological or pathophysiological role of granite dust in rheumatoid arthritis may be based on the effects of quartz on the immune system.**

### Introduction

The pathophysiological manifestations of exposure to silica depend on both environmental factors and intrinsic differences in those exposed. Exposure to silica and silicosis have been suspected of being associated with some extrapulmonary diseases such as systemic sclerosis,[1] systemic lupus erythematosus,[2] rheumatoid arthritis,[3] renal disease,[4] and pulmonary as well as digestive tract carcinoma.[5] The mechanisms of these associations are not clear, but disorders of humoral (autoantibodies, immune complexes, decreased resistance to infection) and cellular (prolonged graft rejection, macrophage toxicity) immunity are induced in laboratory animals and man by exposure to silica.[6]

In 1972 a follow up study of disability and mortality among 1026 Finnish granite workers disclosed an excess of disability caused by diseases of the musculoskeletal system, mainly osteoarthritis and rheumatoid arthritis.[7] The present study was therefore undertaken to investigate morbidity from rheumatoid arthritis in the cohort of granite workers hired between 1940 and 1971 and followed up until the end of 1981.

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### Subjects and methods

The study group comprised 1026 Finnish granite workers employed in quarries and processing yards in three regions of central and south western Finland (Vehmaa, Viitasaari, and Kuru) and hired for at least three months between 1940 and 1971. The ages of the workers ranged from 15 to 72 years (median 27) at the time of entry into the cohort. The mean exposure time to quartz dust was about 12 years (in 1971).

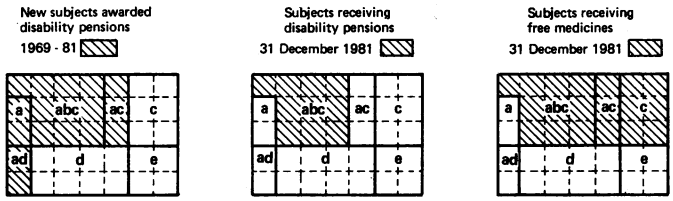
Workers' names, dates and places of birth, and work history at the different firms were collected from the employers' personnel records. All the workers were traced through the Population Data Register. The whole cohort was then compared with national registers on death, disability, and free medicines for chronic diseases.

New disability pensions awarded to granite workers between 1969 and 1981 were studied and the prevalent number of people receiving these pensions calculated at the end of 1981. The causes of disability, coded according to the International Classification of Diseases, were obtained from the Finnish Social Insurance Institution. People with diseases for which medicines were free under the national sickness insurance law were followed up until the end of 1981; these data were also obtained from the Social Insurance Institution.

Lifelong occupational histories of the whole cohort of granite workers were sought by postal questionnaire at the end of 1985 (from those still alive or from the next of kin). The response rate was 73%.

#### PATIENTS WITH RHEUMATOID ARTHRITIS

The patient oriented study included all registered cases of rheumatoid arthritis in the cohort—that is, 35 (see figure). These were distributed as




Origins of 35 cases of rheumatoid arthritis detected retrospectively by perusal of Social Insurance Institution registers. Each square represents one patient.

a=New subjects awarded disability pensions for rheumatoid arthritis during 1969-81 (n=17; table II).

b=Subjects receiving disability pensions for rheumatoid arthritis on 31 December 1981 (n=10; table I).

c=Subjects receiving free medicines for rheumatoid arthritis on 31 December 1981 (n=19; table III).

d=Subjects who died during 1940-81 with rheumatoid arthritis mentioned on death certificate (n=10).

e=Subjects who died during 1940-81 known to have been receiving free medicines for rheumatoid arthritis (n=4).

TABLE I—*Observed and expected numbers of subjects receiving disability pensions for rheumatoid arthritis on 31 December 1981. Expected numbers based on age specific disability figures for Finnish male population at same date*

| | Age (years)* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 16- | 35- | 40- | 45- | 50- | 55- | 60-64 | Total |
| No expected | 0 | 0·1 | 0·1 | 0·2 | 0·4 | 0·4 | 0·4 | 1·6 |
| No observed | 0 | 0 | 0 | 0 | 3 | 5 | 2 | 10*** |

*Age group as defined in national disability statistics.
***p<0·001 (Poisson distribution).

tions were high in several phases of the work. The highest concentrations were noted during drilling, the recommended standard for quartz being exceeded 10-fold on average during drilling (standard for total inorganic dust 10 mg/m³, and for quartz (particles under 5 μm diameter) 0·2 mg/m³). During drilling total dust concentrations ranged from 12 to 116 mg/m³ (geometric mean 39·8 mg/m³), during surfacing of blocks with a pneumatic hammer from 4 to 94 mg/m³ (24·9 mg/m³), and in other phases of the work from 0·3 to 90 mg/m³ (1·7-28·1 mg/m³). The corresponding quartz concentrations ranged from 0·3 to 4·2 mg/m³ (geometric mean 1·47 mg/m³), 0·2 to 4·9 mg/m³ (0·82 mg/m³), and 0·02 to 3·6 mg/m³ (0·12-1·44 mg/m³), respectively.[7] Of the 1026 men in the cohort, 170 (17%) were working in quarrying and drilling; 119 (11%) in sawing; 160 (16%) in cutting, dressing, and polishing; 452 (44%) were general stone workers (that is, not in any specific category); and 125 (12%) were labourers. The proportions of workers with rheumatoid arthritis in the various occupational categories did not differ essentially from that in the total cohort.

The aetiology of rheumatoid arthritis is unknown. Hence potential confounders could not be controlled for, except for age and regional distribution of the disease. Important confounders with special reference to cancer, such as exposures to radon, asbestos, and smoking, were controlled for in the study population.[5]

The decision on eligibility for a disability pension and free medicines for rheumatoid arthritis within the Social Insurance Institution is centralised and based on thorough clinical examination and radiological and laboratory investigations generally performed at hospital level.

### STATISTICAL ANALYSIS

The age specific and cause specific observed and expected numbers of subjects receiving disability pensions on 31 December 1981 were calculated. The incidence rates of awards of new disability pensions were calculated for the period 1 January 1969 to 31 December 1981. The observed prevalent numbers and incidence rates were compared with figures for the male population of working age for the same period.[9] The Poisson distribution

TABLE II—*Incidence rates of awards of disability pensions for rheumatoid arthritis among granite workers and in general male population during 1969-81*

| Age (years) | Granite workers | | | General male population | | |
|---|---|---|---|---|---|---|
| | Person years | No observed | Incidence rate/1000 person years | Person years | No observed | Incidence rate/1000 person years |
| 16-24 | 885 | 0 | 0·00 | 4 500 990 | 152 | 0·03 |
| 25-34 | 2 969 | 0 | 0·00 | 4 647 769 | 300 | 0·06 |
| 35-44 | 2 540 | 1 | 0·39 | 3 436 419 | 706 | 0·21 |
| 45-54 | 1 977 | 8 | 4·05 | 2 800 201 | 1 388 | 0·50 |
| 55-64 | 1 714 | 8 | 4·67 | 1 715 269 | 1 624 | 0·95 |
| Total | 10 085 | 17 | 1·69*** | 17 100 648 | 4 170 | 0·24 |

***p<0·001 (Mantel-Haenszel $\chi^2$ test for incidence data). Mantel-Haenszel estimate for rate ratio=5·08, 95% confidence limits 3·31 and 7·79.

(*a*) new subjects awarded disability pensions (incidence study; n=17); (*b*) subjects receiving these pensions at the end of 1981 (prevalence study; n=10); (*c*) subjects receiving free medicines at the end of 1981 (prevalence study; n=19); (*d*) subjects who had died during 1940-81 with rheumatoid arthritis mentioned on the death certificate (n=10); and (*e*) subjects who had died during 1940-81 who were known to have been receiving free medicines for rheumatoid arthritis (n=4). The patients' records were evaluated retrospectively for diagnostic accuracy by using the criteria of the American Rheumatism Association[8] and noting the presence or absence of rheumatoid factor (Waaler-Rose or latex test) and joint erosions. The records also provided information on the chest *x* ray appearances at onset of the disease.

In 33 of the 35 cases of rheumatoid arthritis the lifetime occupational histories were verified, in 26 from the responses to the questionnaire and in seven either from the medical records or from our questionnaire study in 1972.

### EXPOSURES

A survey of dust exposure in the Finnish granite industry (quarrying, crushing, and block processing) was performed by the Institute of Occupational Health in 1970-2. Dust measurements were taken in 28 quarries and processing yards and four crushing plants. Dust concentra-

model was used to test observed numbers against expected. The Poisson model was chosen as an approximate method to compare a small population against a large comparison group—that is, a national population. Incidence rates were tested by the Mantel-Haenszel $\chi^2$ test for incidence data.[10]

The age specific and cause specific observed numbers of subjects receiving free medicines were calculated at the end of 1981 and compared with the expected numbers at the same date for the general male population of Finland.[11] The Poisson distribution was used to compare observed and expected numbers.

## Results

### DISABILITY

At the end of December 1981, 10 subjects were receiving disability pensions for rheumatoid arthritis compared with 1·6 expected (table I).

The incidence rates of awards of disability pensions during 1969-81 showed no essential differences between granite workers and the Finnish male population of working age (table II). Nevertheless the overall incidence of rheumatoid arthritis was significantly higher in the granite workers (p<0·001), the excess occurring in subjects aged 45 to 64.

FREE MEDICINES

At the end of follow up 189 granite workers were receiving free medicines for chronic diseases—for example, diabetes, schizophrenia, congestive heart failure, bronchial asthma, arterial hypertension, chronic pyelonephritis, and rheumatoid arthritis—compared with an expected 181·3. Of these 189 cases, 19 subjects were receiving free medicines for rheumatoid arthritis as compared with an expected 7·5. This difference was significant ($p \leq 0{\cdot}001$). Table III shows the age specific observed and expected numbers of patients receiving free medicines for rheumatoid arthritis.

TABLE III—*Observed and expected numbers of subjects with rheumatoid arthritis receiving free medicines by national sickness insurance on 31 December 1981. Expected numbers based on age specific and cause specific figures for Finnish male population at same date*

| | Age (years)* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 15- | 35- | 40- | 45- | 50- | 55- | 60- | 65- | ≥70 | Total |
| No expected | 0·4 | 0·6 | 0·9 | 0·8 | 1·0 | 1·0 | 0·8 | 1·0 | 1·0 | 7·5 |
| No observed | 0 | 2 | 0 | 1 | 2 | 5 | 3 | 4 | 2 | 19*** |

*Age groups as defined in national statistics on free medication.
***$p<0{\cdot}001$ (Poisson distribution).

CASE ANALYSIS OF WORKERS WITH RHEUMATOID ARTHRITIS

Table IV gives the individual clinical and laboratory details of the 35 registered cases of rheumatoid arthritis among the cohort of granite workers. Among these cases the median age at the beginning of silica exposure was 23 (range 15-49), the median age at onset of rheumatoid arthritis was 50 (range 35-62), and the median duration of exposure was 18 years (range 0·9-38). The median interval between first exposure to silica and the onset of rheumatoid arthritis was 25 years (range 1-47).

Of the 15 subjects who were dead by the end of 1981 (cases 1-15; table IV), 13 (87%) had classic or definite rheumatoid arthritis and one had probable rheumatoid arthritis based on our retrospective analysis using American Rheumatism Association criteria. One patient had shown a rapidly progressive connective tissue disease with features of periarteritis nodosa. Thirteen patients were positive for rheumatoid factor and 10 had an erosive polyarthritis. Only three patients showed signs of simple silicosis of the lung at the onset of rheumatoid arthritis and four had a history of pulmonary tuberculosis.

Among the 20 patients still alive at the end of 1981 and receiving disability pensions or free medicines, or both (cases 16-35; table IV), 17 (85%) had classic or definite rheumatoid arthritis and two probable rheumatoid arthritis. The remaining patient had a wrong diagnosis of osteoarthritis owing to an error in classification at registration. Fifteen patients were positive for rheumatoid factor and 15 had erosive polyarthritis. Five patients had a history of pulmonary tuberculosis with mild pulmonary fibrosis seen in their chest radiographs. One patient had pulmonary silicosis at the onset of rheumatoid arthritis.

## Discussion

This paper reports an association between occupational exposure to silica and a severe chronic disease of unknown aetiology—namely, rheumatoid arthritis. The excess of rheumatoid arthritis in the cohort of granite workers was evident from two partly independent sources—namely, registers of people receiving disability pensions and registers of people granted free medicines for rheumatoid arthritis. Possible confounding factors were not likely to explain our findings. The observed rates of rheumatoid arthritis were not influenced by the regional distribution of the disease across Finland. Regional statistics on disability pensions[9] and use of free medicines[12] and survey data on rheumatoid arthritis showed that the study cohort worked in areas where the prevalence of rheumatoid arthritis was low or medium.[13 14]

TABLE IV—*Case analysis of granite workers registered as having rheumatoid arthritis*

| Case No | Age at beginning of silica exposure (years) | Age at onset of rheumatoid arthritis (years) | Interval (years) | Length of exposure before onset of rheumatoid arthritis (years) | Chest x ray appearances at onset of rheumatoid arthritis | Rheumatoid factor | Joint erosions | Source of information on rheumatoid arthritis, and comment on diagnosis after re-evaluation† |
|---|---|---|---|---|---|---|---|---|
| | | | | *Patients dead by 31 December 1981* | | | | |
| 1 | 27 | 56 | 29 | 28 | Silicosis | + | Yes | d |
| 2 | 20 | 58 | 38 | 33 | Normal | + | Yes | a, d |
| 3 | 24 | 60 | 36 | 26 | Silicosis | + | ?* | d |
| 4 | 28 | 47 | 19 | 19 | Normal | ?* | Yes | d |
| 5 | 18 | 57 | 39 | 34 | Emphysema | + | Yes | d |
| 6 | 42 | 49 | 7 | 1·8 | Emphysema, local fibrosis (tuberculosis) | + | Yes | d |
| 7 | 27 | 44 | 17 | 5·5 | Normal | + | Yes | d |
| 8 | 33 | 56 | 23 | 11 | Normal | + | Yes | a, d |
| 9 | 15 | 62 | 47 | 38 | Silicosis | + | Yes | d |
| 10 | 20 | 43 | 23 | 1·8 | Normal | + | No | e, Periarteritis nodosa |
| 11 | 37 | 59 | 22 | 2·5 | Normal | − | No | a |
| 12 | 36 | 53 | 17 | 1 | Normal | + | Yes | e |
| 13 | 38 | 56 | 18 | 5 | Normal | + | No | e |
| 14 | 41 | 48 | 7 | 1·5 | Normal | + | No | d, Probable rheumatoid arthritis |
| 15 | 38 | 42 | 4 | 4 | Local fibrosis | + | Yes | e |
| | | | | *Patients with disability or granted free medicines (1969-81) and alive on 31 December 1981* | | | | |
| 16 | 18 | 49 | 26 | 20 | Normal | + | Yes | a, b, c |
| 17 | 21 | 51 | 30 | 11 | Emphysema | + | Yes | a, b, c |
| 18 | 20 | 46 | 26 | 25 | Normal | + | Yes | a, b, c |
| 19 | 18 | 50 | 32 | 32 | Emphysema, local fibrosis (tuberculosis) | + | Yes | a, b, c |
| 20 | 30 | 56 | 26 | 16 | Normal | + | Yes | a, b, c |
| 21 | 15 | 49 | 34 | 31 | Normal | + | Yes | a, b, c |
| 22 | 22 | 46 | 24 | 24 | Normal | − | Yes | a, b, c |
| 23 | 39 | 44 | 5 | 5 | Normal | + | Yes | a, b, c |
| 24 | 18 | 41 | 23 | 19 | Silicosis | + | Yes | a, b, c |
| 25 | 16 | 48 | 32 | 18 | Normal | + | No | a, b, c |
| 26 | 22 | 61 | 39 | 5 | Mild fibrosis, emphysema | − | No | a, c, Probable rheumatoid arthritis |
| 27 | 25 | 55 | 30 | 27 | Mild fibrosis | + | ? | c |
| 28 | 22 | 60 | 38 | 32 | Normal | + | Yes | a, c |
| 29 | 23 | 53 | 30 | 26 | Emphysema | + | Yes | a, c |
| 30 | 18 | 36 | 18 | 18 | Local fibrosis | + | Yes | c |
| 31 | 23 | 35 | 12 | 2 | Normal | − | Yes | c |
| 32 | 19 | 61 | 42 | 24 | Local fibrosis (tuberculosis) | + | Yes | c |
| 33 | 35 | 43 | 8 | 1·2 | Local fibrosis | + | Yes | c |
| 34 | 49 | 50 | 1 | 0·9 | Normal | − | ? | c, Probable rheumatoid arthritis |
| 35 | 43 | — | — | — | Normal | − | No | a, Osteoarthritis |

*?=Not studied.
†Cases were distributed as: a=new subjects awarded disability pensions for rheumatoid arthritis during 1969-81 (n=17; table II); b=subjects receiving disability pensions for rheumatoid arthritis on 31 December 1981 (n=10; table I); c=subjects receiving free medicines for rheumatoid arthritis on 31 December 1981 (n=19; table III); d=subjects who died during 1940-81 with rheumatoid arthritis mentioned on death certificate (n=10); e=subjects who died during 1940-81 known to have been receiving free medicines for rheumatoid arthritis (n=4).

Rheumatoid pneumoconiosis (Caplan's syndrome)—that is, the association between nodular fibrosis of the lung and rheumatoid arthritis in coal workers—is the best known association between dust exposure and rheumatoid arthritis.[15] In an epidemiological study of an entire community in south Wales there was no increased prevalence of rheumatoid arthritis among miners and ex-miners and it was concluded that neither exposure to dust nor the lung changes of complicated pneumoconiosis were of any aetiological importance in the disease.[16 17] In our study none of the patients had a history of Caplan's syndrome. That only a few patients had evidence of simple silicosis at the onset of rheumatoid arthritis does not suggest that established pulmonary fibrosis is a prerequisite for rheumatoid arthritis.

In most diseases of unknown aetiology we are not certain of the relative importance of environmental and hereditary factors.[18] Rheumatoid arthritis is closely associated with the HLA antigens DR4.[19] Exposure to silica may facilitate entry of bacterial and viral particles by way of the respiratory tract. Exposure to silica decreases resistance to infection, especially by predominantly intracellular organisms. For instance, macrophages exposed to silica lose their ability to restrict the multiplication of virulent intracellular tubercle bacilli,[20] and infections with normally non-pathogenic agents, including fungi and other opportunistic organisms, have also been noted in patients with silicosis.[21] Exposure to silica is well known to increase susceptibility to tuberculosis. Cross reactivity between microbial antigens and tissue components has been detected in autoimmune conditions. Clones of anti-*Mycobacterium tuberculosis* T lymphocytes have been shown to cross react with an epitope of joint cartilage,[22] and patients with early rheumatoid arthritis have such increased T lymphocyte reactivity.[23] High responsiveness to mycobacterial antigens has been linked with HLA-DR4 histocompatibility antigens.[24] Interestingly in this respect a comparatively high proportion of patients with rheumatoid arthritis in our cohort had a history of pulmonary tuberculosis.

Silica is a selective macrophage toxin in all species examined.[25] Even macrophages that resist killing will survive with modified biochemistry and may also alter the function of lymphocytes[26] and contribute to a disturbed T lymphocyte-macrophage immune regulation in lungs and rheumatoid joints. Quartz particles have also been shown to absorb proteins into their surfaces, perhaps denaturing them and rendering them antigenic,[27 28] resulting in unknown immunological consequences.

Besides affecting the lungs, inhalation of quartz may facilitate the entry of potentially infectious agents through the gastrointestinal tract. The proportion of inhaled silica which is cleared by the mucociliary escalator of the lung will reach the gut and probably interfere with the gastrointestinal milieu. Arthropathies have been suggested to be indirect consequences of an alteration in the resident bacteria in the gut. Abnormal gut flora with high counts of *Clostridium perfringens* and high antibody titres to *Proteus mirabilis* have been found in patients with rheumatoid arthritis.[29 30]

Exposure to silica, pulmonary silicosis, and rheumatoid arthritis are characterised by very similar, measurable disturbances of the immune system—for example, the frequent presence of rheumatoid and antinuclear factors, presence of circulating immune complexes, and decreased resistance to infectious diseases.[21 31 32] The exact pathophysiological role of these various autoantibodies in rheumatoid arthritis is not known. Nevertheless, their function in perpetuating the inflammatory reaction, together with their unfavourable effect on the progression and severity of silicosis if present, is probably of clinical importance.[6]

Alveolar macrophages with phagocytosed material (including quartz) may translocate to regional lymph nodes, and macrophages may transport inhaled dust from the lung into the circulation.[33 34] Thus silica is not deposited only in the lungs; cells with phagocytic activity belonging to the mononuclear phagocyte system of the liver, spleen, and bone marrow may contain silica.[35] We do not know whether type A synoviocytes—that is, cells with the characteristics of phagocytising fixed tissue macrophages—deposit silica within joint cavities. Interestingly, in addition to the secretion of a factor that stimulates proliferation of lymphocytes and fibroblasts (interleukin 1),[36] macrophages exposed to silica also secrete a factor(s) that stimulates deoxyribonucleic acid synthesis of human synovial cells in vitro.[37]

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