ENVIRONMENTAL PULMONARY MINERAL BURDEN CORRELATED WITH SMOKING, PULMONARY EMPHYSEMA AND LUNG CANCER

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INTRODUCTION

In order to be able to identify a significant lung particle burden exceeding the background, it is necessary to know the basic pulmonary level of inhaled particles in a population. The amount of asbestos fibers in lung tissue which could originate from environmental sources would be an especially important piece of information. Numbers of asbestos fibers reported in the lung tissue of occupationally non-exposed people in the literature have varied from less than half a million to several millions per gramme of dry lung tissue.[1-3] Some of the differences may be due to inter-laboratory variation in fiber determinations, which has been reported to be vast.[4]

Environmental exposure to minerals varies at least due to local climatic conditions, the earth's crust and environmental pollution. The worst personal source of pollution is smoking. Smoking in itself, and diseases related to it, including chronic obstructive lung disease, pre-cancerous bronchial epithelial changes and cancer, may alter the deposition and retention of inhaled particles. Pulmonary emphysema is a morphological counterpart of chronic obstructive lung disease, and its severity also serves as an objective indicator for the duration of smoking in the course of the subjects life. The present paper describes pulmonary mineral content in a series of occupationally non-exposed subjects from Northern Finland and compares it with smoking history, the grade of pulmonary emphysema and the presence of lung cancer.

MATERIAL

20 cases were selected from an initial series of 42 male subjects who had died of non-malignant diseases and been autopsied and 53 male patients operated on for lung cancer. Smoking habits, measured in smoking time, pack years and time since stopping smoking, and also occupational history, were determined from the patient or from the next of kin by means of a questionnaire and/or personal interview. The effects of smoking, pulmonary emphysema and lung cancer on the pulmonary mineral content were studied in 13 pairs matched in terms of given background characteristics (Tables I–III).

METHODS

The lungs and lung lobes obtained from the autopsies and surgical operations were radiographed during continuous air inflation[5] and the severity of emphysema was graded into normal, mild, moderate and severe from these radiographs on the grounds of peripheral vascular changes, tissue defect translucencies and changes in the shape of the lung or lobe.[6] The lungs were fixed transbronchially with hyperosmolar formalin. The grade of emphysema was also estimated from gross specimens and histological sections and these data were used if grading from the radiographs did not produce an unambigious result. The histological type of cancer was determined according to the WHO classification of tumours.

A 0.5–1 g peripheral sample of fresh lung tissue containing no pleural surface or cancer tissue was taken from the (apico) posterior segment of the upper lobe and the apical segment or basal segments of the lower lobe after radiographing. The samples were ashed in aluminium cups in a low temperature asher with an oxygen plasma, after which the ash was dissolved in 1 M nitric acid to remove excess salt and then in absolute ethanol and distilled water. The residue was sonicated and various dilutions filtered onto a Nuclepore filter of pore size 0.1 μm. The filter, coated with carbon, was transferred onto a gold grid and dissolved slowly in chloroform vapour. The grid was coated again with carbon to minimize charging.

Electron microscopy was performed using a JEOL 100CX scanning transmission electron microscope (STEM) and PGT SYSTEM III energy dispersive spectrometry (EDS). At least a hundred particles (>0.1 μm) per specimen were identified using EDS analysis and electron diffraction. Two dimensions on each particle were measured on the STEM image, the thickness being assumed to be equal to the width for all minerals other than phyllosilicates ($0.2 \times$ width). Approximate volumes were calculated for the minerals, after which their masses could be determined from their known densities. To determine the number of fibers, 100 fibrous particles having the length to diameter ratio $\geq 3{:}1$ were searched and identified. Statistical comparisons were performed using paired t-tests, in which p values less than 0.05 were considered significant.

RESULTS

The pulmonary particle burden, measured as total mass, volume and surface area, showed very narrow variation depending on smoking, pulmonary emphysema or lung cancer, whereas the number of particles and the mean particle size showed some dependence on these factors. The mean total number, volume, surface area and mass of mineral particles in the material (±SD) were $155 \pm 194 \times 10^6$, 0.15 ± 0.16 mm^3, 655 ± 670 mm^2 and 0.41 ± 0.43 mg per

Table I

Characteristics of the Case-Control Pairs Chosen for Studying the Effect of Smoking on the Pulmonary Mineral Burden

	Age	Smoking	Smoking time	Grade of emphysema	Occupation	Lung cancer	Site of sample*
1.	75	Non-smoker	0	No	Farmer	No	BLL
	71	Smoker	25	Mild	Unknown	No	AUL
2.	79	Non-smoker	0	Mild	Unknown	No	BLL
	75	Smoker	44	No	Roadman	No	BLL
3.	73	Non-smoker	0	Mild	Car driver	No	AUL
	61	Smoker	46	Mild	Road scraper driver	No	AUL
4.	77	Non-smoker	0	No	Unknown	No	BLL
	72	Smoker	25	No	Salesman	No	BLL

* AUL= apical upper lobe, ALL= apical lower lobe, BLL= basal lower lobe

Table II

Characteristics of the Case-Control Pairs Chosen for Studying the Effect of Pulmonary Emphysema on the Pulmonary Mineral Burden

	Age	Smoking	Smoking time	Grade of emphysema	Occupation	Lung cancer	Site of sample*
1.	72	Smoker	25	No	Salesman	No	BLL
	71	?	?	Severe	Unknown	No	BLL
2.	71	Smoker	25	Mild	Unknown	No	AUL
	60	Ex-smoker	25	Moderate	Clerk	No	BLL
3.	75	Non-smoker	0	No	Farmer	No	BLL
	68	Ex-smoker	25	Moderate	Farmer	No	AUL
4.	77	Non-smoker	0	No	Unknown	No	BLL
	73	?	?	Severe	Roadman	No	AUL
5.	75	Smoker	44	No	Roadman	No	BLL
	69	Smoker	50	Moderate	Caretaker	No	AUL

* AUL= apical upper lobe, ALL= Apical lower lobe, BLL= Basal lower lobe

Table III
Characteristics of the Case-Control Pairs Chosen for Studying the Effect of Lung Cancer on the Pulmonary Mineral Burden

	Age	Smoking	Smoking time	Grade of emphysema	Occupation	Lung cancer	Site of sample*
1.	68	Ex-smoker	25	Moderate	Farmer	No	AUL
	65	Ex-smoker	35	Moderate	Farmer	Yes	BLL
2.	71	Smoker	57	Moderate	Mason	No	ALL
	60	Smoker	40	Moderate	Sawer	Yes	AUL
3.	71	Smoker	25	Mild	Unknown	No	AUL
	63	Ex-smoker	40	Mild	Surveyor technician	Yes	ALL
4.	74	Smoker	50	Moderate	Caretaker	No	AUL
	73	Ex-smoker	25	Moderate	Roadwork foreman	Yes	ALL

* AUL= apical upper lobe, ALL= apical lower lobe, BLL= basal lower lobe

gramme of dry lung tissue respectively. In individual cases the number of particles varied from 10×10^6 to 670×10^6, and the number of fibers from less than a hundred thousand to 10×10^6 per gramme of dry weight. The asbestos fibers were mostly anthophyllite and crocidolite, but not many amosite and chrysotile were found.

Smoking

The number of particles, including every particle type except fibers, aluminium, plagioclase and talc, was greater in the lung tissue of the smokers than in their matched non-smoking counterparts. Kaolinite particles were especially numerous in the lungs of the smokers as compared with the non-smokers. The differences in the number and type of particles between the non-smokers and smokers were not statistically significant, however. The mean particle size (mean volume of single particles) was larger in the non-smokers than in the smokers ($p=0.065$) (Table IV).

Pulmonary Emphysema

The total number of particles in patients with moderate or severe pulmonary emphysema was lower than in their matched pairs with mild or no emphysema. Plagioclase was the only particle type which was more numerous in the emphysematous lungs. The mean size of single particles was significantly larger in the patients with moderate or severe emphysema as compared with controls who had mild or no emphysema ($p<0.05$) (Table V).

Lung Cancer

All the cancers included in the material were histologically of the squamous cell type. The total number of particles did not differ significantly between the patients with lung cancer and their matched controls, but the numbers of fibers, plagioclase, and particles containing aluminium, iron or titanum only, were higher in the lung cancer patients, the difference in the number of fibers being statistically significant ($p<0.05$) (Table VI).

DISCUSSION

The pulmonary mineral particle burden was measured here in terms of total number, mass, volume and surface area. The number of particles varied from case to case and due to smoking and pulmonary emphysema more than the other parameters did. The total number of particles found in the lung tissue of the patients without known occupational exposure to minerals is in a fairly good agreement with the findings of Churg and Wiggs.[7] In the present study smokers' lung tissue contained more particles than that of the non-smokers, although the difference was not statistically significant. The total volume of particles did not differ between the smokers and matched non-smokers, but the average volume of the individual particles was smaller in smokers, the difference approaching statistical significance. Churg and Wiggs[7] found more particles in the lungs of heavy smokers than in those of light smokers. It is not known whether the numerous small particles such as kaolinite in smokers' lung tissue originate from the tobacco smoke or whether their additional presence is due to a deterioration in mucociliary clearance in smokers.

The effect of pulmonary emphysema on the total number of particles and the mean volume of single particles seemed to be the opposite of that of smoking. The small number of particles in the emphysematous lungs may be attributable firstly to tissue destruction, and secondly by a reduction in the inhalation of particles from tobacco smoke, since many people with marked emphysema stop or cut down their smoking because of dyspnoea.

The lung cancer patients did not differ significantly from their matched controls in terms of pulmonary particle burden. Churg and Wiggs[2] found a greater number of particles in lung cancer patients than in controls without cancer, but this could not be found here. On the other hand, the number of fibers was significantly higher in the lungs of the present lung cancer patients than in those of the controls, even though none of them had any known occupational exposure to asbestos. The same observation is recorded by Churg and Wiggs,[2] but the number of fibers they found in both the lung cancer and control patients was about ten times higher than we could detect. Similarly, ten to fifteen times higher pulmonary concentrations of fibers are reported in lung cancer patients in another study from Great Britain[8] than we found in our patients. The difference may be due to the slightly different methods used, but it is also possible that the finding is real and reflects the degree of local environmental outdoor pollution or an unrecognized presence of asbestos materials in buildings.

Table IV

Mean Number and Type of Particles in Lung Tissue from Non-Smokers and Smokers

	Non-smoker (4 pairs)	-	Smoker	t	p
Total number ($x10^6$/g dry w.)	106	-	214	- 0.6	NS
Total volume (mm^3/g dry w.)	0.2	-	0.2	- 0.2	NS
Total surface (mm^2/g dry w.)	736	-	798	- 0.1	NS
Total mass (mg/g dry w.)	0.4	-	0.5	- 0.2	NS
Mean particle volume (um^3)	1.5	-	0.8	2.5	<0.07
Numbers of particles ($x10^6$/g dry w.):					
Fibers	3.2	-	1.2	0.6	NS
Al	0.9	-	0.5	0.5	NS
Fe	8.1	-	14.8	- 0.4	NS
Kaolinite	7.6	-	29.9	- 0.8	NS
K-feldspar	18.2	-	27.8	- 0.5	NS
Mica	23.4	-	60.5	- 0.7	NS
Plagioclase	15.4	-	9.6	1.0	NS
Quartz	14.8	-	27.8	- 0.5	NS
Talc	2.1	-	2.0	0.1	NS
Ti	5.5	-	10.0	- 0.4	NS
Others	10.5	-	29.0	- 0.8	NS

Table V
Mean Number and Type of Particles in Lung Tissue from Patients with and without Pulmonary Emphysema

	No emphysema	-	Emphysema (5 pairs)	t	p
Total number ($x10^6$/g dry w.)	194	-	50	1.1	NS
Total volume (mm^3/g dry w.)	0.2	-	0.2	0.1	NS
Total surface (mm^2/g dry w.)	718	-	453	0.5	NS
Total mass (mg/g dry w.)	0.5	-	0.4	0.1	NS
Mean particle volume (um^3)	1.0	-	2.8	- 2.8	<0.05
Numbers of particles ($x10^6$/g dry w.):					
Fibers	0.9	-	0.3	0.9	NS
Al	0.9	-	1.0	- 0.1	NS
Fe	15.4	-	0.1	1.5	NS
Kaolinite	26.2	-	3.6	1.1	NS
K-feldspar	25.7	-	10.5	1.0	NS
Mica	50.4	-	6.0	1.1	NS
Plagioclase	11.1	-	13.4	- 0.6	NS
Quartz	27.3	-	5.4	1.3	NS
Talc	2.2	-	0.6	1.5	NS
Ti	11.5	-	2.0	1.2	NS
Others	22.8	-	7.5	0.8	NS

Table VI

Mean Number and Type of Particles in Lung Tissue from Patients with and without Lung Cancer

	No cancer	-	Lung cancer	t	p
	(4 pairs)				
Total number (x10^6/g dry w.)	218	-	164	0.3	NS
Total volume (mm^3/g dry w.)	0.3	-	0.1	1.5	NS
Total surface (mm^2/g dry w.)	1098	-	541	0.8	NS
Total mass (mg/g dry w.)	0.9	-	0.3	1.4	NS
Mean particle volume (um^3)	2.7	-	0.9	2.0	NS
Numbers of particles (x10^6/g dry w.):					
Fibers	0.2	-	1.2	- 2.9	<0.05
Al	0.6	-	5.3	- 0.8	NS
Fe	13.2	-	16.2	- 0.1	NS
Kaolinite	29.5	-	9.5	0.7	NS
K-feldspar	29.3	-	23.6	0.3	NS
Mica	58.9	-	13.7	0.9	NS
Plagioclase	12.7	-	26.4	- 1.4	NS
Quartz	30.0	-	16.6	0.5	NS
Talc	0.2	-	0.0	1.0	NS
Ti	11.4	-	41.2	- 0.8	NS
Others	32.1	-	11.9	0.9	NS

REFERENCES

1. Churg, A., Warnock, M.L.: Asbestos Fibers in the General Population. *Am. Rev. Resp. Dis.* 122:669-679 (1980).
2. Churg, A., Wiggs, B.: Mineral Particles, Mineral Fibers and Lung Cancer. *Environ. Res.* 37:364-372 (1985).
3. Warnock, M.L., Wolery, G.: Asbestos Bodies or Fibers and the Diagnosis of Asbestosis. *Environ. Res.* 44:29-44 (1987).
4. Gylseth, B., Churg, A., Davis, J.M.G. et al.: Analysis of asbestos fibers and asbestos bodies in tissue samples from human lung. *Scand. J. Work. Environ. Health* 11:107-110 (1985).
5. Sutinen, S., Lohela, P., Pääkkö, P., Lahti, R.: Accuracy of Post-Mortem Radiography of Excised Air-inflated Human Lungs in Assessment of Pulmonary Emphysema. *Thorax* 37:906-912 (1982).
6. Sutinen, S., Pääkkö, P., Lahti, R.: Postmortem Inflation, Radiography, and Fixation of Human Lungs: A Method for Radiological and Pathological Correlations and Morphometric Studies. *Scand. J. Respir. Dis.* 60:29-35 (1979).
7. Churg, A., Wiggs, B.: Types, Numbers, Sizes, and Distribution of Mineral Particles in the Lungs of Urban Male Cigarette Smokers. *Environ. Res.* 42:121-129 (1987).
8. Wagner, J.C., Newhouse, M.L., Corrin, B., Rossiter, C.E.R., Griffiths, D.M.: Correlation between fibre content of the lung and disease in east London asbestos factory workers. *Br. J. Ind. Med.* 45:305-308 (1988).

ELEMENT ANALYSES IN HUMAN LUNG TISSUE CORRELATED WITH SMOKING, EMPHYSEMA AND LUNG CANCER

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INTRODUCTION

The results of recent investigations have shown that several heavy metals accumulate in the lung tissue after inhalation of relatively insoluble compounds.[3] The quantitative detection of the heavy metals in samples of pulmonary tissue hence permits the amount of postexposure to be estimated.[5] Recently, there are many possibilities for occupational and environmental exposures to several trace elements and heavy metals. In addition to organic compounds tobacco contains metals such as As, Cd, Cr and Ni.[2] Chromium and cadmium are toxic and carcinogenic elements.

Fragmental knowledge has been published on the tissue levels of major and minor trace elements in the human lungs in relation, e.g., to the exposure to cigarette smoke and pulmonary tissue reactions.[7] Modern analytical instrumentation reveals new possibilities for detecting a number of elements in the same sample.

The aim of this study is to determine the concentrations of light elements derived mainly from minerals, heavy metals and essential trace elements in human lung tissue. The elemental concentrations found in lung tissue are related to smoking, emphysema and lung cancer.

MATERIAL

The lung specimens were collected from subjects without any malignant disease and from the lung cancer patients. The group without malignancies consisted of 41 lungs (alternatively the right or the left lung) from consecutive autopsies of male subjects with or without emphysema (Table I). Because emphysema is an indicator of smoking, the subjects without lung cancer were selected to include cases with different grades of emphysema (Table II). Smoking habits and occupational history were ascertained from the next of kin. The lungs or lung lobes have been obtained from 52 male patients operated for lung cancer (Table I). Smoking habits and occupational history have been acquired by personal interview.

METHODS

The lungs and lobes of lungs were radiographed during continuous air-inflation, and the severity of emphysema was graded from the radiographs into normal lung and mild, moderate and severe emphysema.[6] In addition, the grade of emphysema[4] and the histological types of cancer were determined from histological sections.[1]

A piece of fresh lung tissue was taken after radiographing from the (apico) posterior and anterior segment of the upper lobe and from the superior (apical) segment and basal segment of the lower lobe.[1,4] The sample, measuring 0.5–2 g, contained no pleural surface or cancer tissue. Equal portions of samples representing left and right lungs were analyzed of the nonmalignant and cancer material. The fresh sample was weighted, dried for three hours in vacuum, and ashed in glass cups with a blank and NBS Bovine Liver (SMR 1577) for

Table I
Age, Smoking Habits and Grade of Emphysema of the Subjects without Cancer (Autopsy Lungs) and of the Lung Cancer Patients

	Autopsy lungs (N = 41)	Lung cancer patients (N = 52)
Age, years	68 ± 9	62 ± 10
Smoking time, years	36 ± 15	39 ± 11
Stopped, years ago	7 ± 10	5 ± 8
Grade of emphysema	2.5 ± 0.9	2.6 ± 0.8

Table II

Age and Smoking Habits of the Subjects without Cancer (a) and the Lung Cancer Patients (b) Grouped as a Function of Emphysema

a)	Autopsy lungs (N = 43)			
	Grade I (normal) (N = 4)	Grade II (mild) (N = 20)	Grade III (moderate) (N = 9)	Grade IV (severe) (N = 8)
Age, years	75 ± 2	64 ± 9	65 ± 8	75 ± 5
Smoking time, years	26 ± 9	32 ± 12	37 ± 13	49 ± 13
Stopped, years ago	6 ± 12	6 ± 11	6 ± 10	10 ± 5
Stopped	(N = 4)	(N = 16)	(N = 9)	(N = 6)
b)	**Lung cancer patients (N = 52)**			
	Grade I (normal) (N = 3)	Grade II (mild) (N = 18)	Grade III (moderate) (N = 20)	Grade IV (severe) (N = 6)
Age, years	53 ± 14	59 ± 13	65 ± 6	63 ± 7
Smoking time, years	38 ± 16	34 ± 12	44 ± 9	42 ± 8
Stopped, years ago	0	6 ± 9	4 ± 7	3 ± 3
Stopped	(N = 0)	(N = 10)	(N = 7)	(N = 4)

Table III

The Element Concentrations in Lung Tissue of the Subjects without Malignant Disease and in Surgical Specimens from Lung Cancer Patients

Element	µg/g dry weight				
	Autopsy lungs		Surgical specimens		
	Mean	Geometric SD	Mean	Geometric SD	P
Mg	380	2.0	430	1.8	0.007
Ca	630	1.7	740	1.6	
Ti	8.3	2.6	14	3.3	0.031
Cr	2.5	3.2	4.5	2.5	0.006
Fe	1100	1.6	980	2.5	
Cu	12	1.5	13	1.8	
Zn	47	1.5	50	1.2	
Cd	1.2	3.5	2.5	2.6	0.012

48–72 hours in a low temperature oxygen plasma asher (100–120°C).

Tissue residue was digested in a mixture of 3 ml concentrated nitric acid (supra pure grade) and 0.2 ml of perchloric acid at 150°C for 2 hours, after which the solution was allowed to stand over night and diluted in 3–6 ml of high quality water. The plasma emission (DCP-AES) spectrometer (Spectra-Span IIIB) was used to determine trace elements (Ca, Mg, Cu, Zn, Fe) and heavy metal (Ti, Cr, Cd). The validity of the overall procedure and the effective control of contamination were checked by analyzing the blank throughout the procedure in each test series and employing the NBS Bovine Liver (SMR 1577) standards.

RESULTS AND DISCUSSION

The concentrations of eight elements in lung tissue were analyzed (Table III). The mean and geometric standard deviations of most of the elements studied lie between those published in present papers.[7]

The concentrations of Mg, Ti, Cr and Cd were higher in the surgical specimens of lung cancer patients than in autopsy lung tissue of non-malignant subjects. Table IV reveals that the severity of emphysema is related to the increase of the concentrations of Ca, Cd and Cr. The moderate and severe emphysema is related to the decrease of the concentrations of Cu and Fe. In lung tissue of non-malignant autopsy lungs the effect of severity of emphysema was more prominent (Table IV).

The effect of cigarette smoke upon the elements in the lungs was estimated (Table V). A positive correlation, but not statistically significant, between the concentrations of Cr and Cd and smoking time was found in the non-malignant autopsy lungs of the current smokers. The surgical specimens revealed no significant trend in the concentrations of any element as a function of smoking time. The concentration of Cd was significantly decreased in lung tissue of ex-smokers in both groups (Table V). A relative correlation was observed between non-smoking years and the Cd lung content among ex-smokers. The biological half-time for Cd in human lung was estimated to be about 9 years.[4] The concentration of Cr was slightly higher in the lung tissue of ex-smokers than in that of current smokers.

REFERENCES

1. Anttila, S., Kokkonen, P., Pääkkö, P., Kerola, T., Rainio, P., Kalliomäki, P.-L., Sutinen, S.: *Extended Abstracts: Trace Elements in Human Health and Disease*. pp. 173-176 (2nd Nordic Symposium, Odense, Denmark, 17-21 August 1987).
2. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Tobacco Smoking.* Vol. 38. International Agency for Research on Cancer, Lyon (1986).
3. Kollmeier, H., Leeman, J.W., Muller, K.M., Rothe, G., Wittig, P., Schejbal, V.B.: Increased Chromium and Nickel Content in Lung Tissue and Bronchial Carcinoma. *Am. J. Ind. Med.* 11:659-669 (1987).
4. Pääkkö, P., Anttila, S., Kokkonen, P., Kalliomäki, P.-L.: Cadmium in Lung Tissue as Marker for Smoking. *Lancet* 1:477 (1988).
5. Raithel, H.J., Schaller, K.H., Reith, A., Svenes, K.B., Valentin, H.: Investigations on the Quantitative Determination of Nickel and Chromium in Human Lung Tissue. *Int. Arch. Occup. Environ. Health* 60:55-66 (1988).
6. Sutinen, S., Pääkkö, P., Lohela, P., Lahti, R.: Pattern Recognition in Radiographs of Excised Air-Inflated Human Lungs in Emphysema Alone and with Other Common Lesions. *Eur. J. Resp. Dis.* 62:297-314 (1981).
7. Vanoeteren, C., Cornelis, C., Sabbioni, E.: *Critical Evaluation of Normal Levels of Major and Trace Elements in Human Lung Tissue.* Commission of the European Communities, Luxemburg (1986).

Table IV

Effect of the Severity of Emphysema upon the Element Concentration in Non-Malignant Autopsy Lungs (a) and in the Lungs of Lung Cancer Patients (b)

Mean, µg/g dry weight

a) Autopsy lungs (N = 41)

	Grade I	Grade II	p	Grade III	Grade IV	p	Trend; T[1]
Mg	250	400	0.007	390	390		N.S.
Ca	440	560		710	870		/ ;-2.7*
Ti	7.6	7.2		12	8.3		
Cr	1.6	1.3		3.4	7.1		_/ ;-5.2*
Fe	830	1300	0.09*	1200	790		Λ ;N.S.
Cu	5.9	13	0.001*	13	9.3	0.1*	Λ ;N.S.
Zn	25	52	0.01*	50	42		/ ;-2.8*
Cd	0.3	1	0.16	1.7	1.8		/ ;-1.9*

b) Lung cancer patients (N = 51)

	Grade I	Grade II	p	Grade III	Grade IV	p	Trend; T[1]
Mg	390	430		430	450		N.S.
Ca	490	760		790	870		/ ;N.S.
Ti	4.0	26	0.04*	10	14		N.S.
Cr	2.7	5.4		4.4	3.4		N.S.
Fe	760	1000		1100	870		Λ ;N.S.
Cu	9.6	14	0.07*	14	15		N.S.
Zn	48	49		50	56		N.S.
Cd	-	2.1		2.0	3.7		/ ;N.S.

[1] Student's t-test value

Table V

Effect of Smoking Habits upon the Element Concentrations in Lung Tissue of the Subjects without Cancer and of Lung Cancer Patients

Element	Mean, µg/g dry weight					
	Autopsy lungs		p	Surgical specimens		p
	Smokers	Ex-smokers		Smokers	Ex-smokers	
Mg	390	340		420	450	
Ca	630	660		650	960	0.005
Ti	11	7		11	18	
Cr	1.5	3.5	0.03	4.3	5.4	
Fe	1320	930	0.05	980	930	
Cu	13	10	0.03	13	13	
Zn	48	41		48	52	
Cd	2.6	0.8	0.001	3.5	1.6	0.042

LUNG FIBROSIS ASSOCIATED WITH RARE EARTH EXPOSURE

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Diffuse interstitial lung fibrosis (DILF) with the most prominent clinical sign of progressive restriction of respiratory function may have a variety of causes. The spectrum of disorders in this category is very large and still growing.[1] Besides cases with known etiology — viral, bacterial, environmental etc. — the group of so called cryptogenic or idiopathic interstitial pulmonary fibrosis deserves special attention. Among these primarily obscure cases those originating from unrecognized inhalation of organic or inorganic particles may be hidden. In recent years the application of sophisticated methods for the search of inorganic noxious particles often has been most successful in finding the true cause of pulmonary fibrosis, for instance in workers exposed to hard metals[2] or in asbestosis mimicking interstitial pulmonary fibrosis induced by mica.[3]

Presently we wish to concentrate on diffuse interstitial lung fibrosis (DILF) observed in reprophotographers. Until 1960 in Switzerland in large printing laboratories carbon arc lamps have been used as powerful light sources for reproducing photographs. The carbon rods contain coal and a wick of rare earth metal compounds such as Lanthanum, Cerium, Praseodymium, Neodymium and also Thorium. The reprophotographers have been exposed to fumes occurring during burning of the carbon rods.

After years of exposure the workers developed a slowly progressive dyspnoea. Radiographs showed a diffuse interstitial pulmonary fibrosis. From the 9 patients reported only three were diagnosed during life by lung biopsy as suffering from rare earth exposure. The majority of the cases were diagnosed as "idiopathic" interstitial pulmonary fibrosis, since etiology and relation to occupational fume exposure were not recognized during life.

The average exposure time was about 31 years, the latency period (interval between onset of exposure to time of analysis) was on the average 43 years. Data on the concentration of fume and dust at the workplace are not available. The first cases were traced and shown to be related to reprophotographer occupation more than ten years after cessation of the use of carbon rod lamps. We analyzed our first case in 1972, the last of our series in 1987 (Table I). Because of that, for the recognition of the lung disorder as due to occupational injury the histopathological and mineralogical examination of the diseased lung tissue with a variety of modern methods and a careful occupational history is crucial.

The techniques applied were: histology, transmission elektronmicroscopy, energy dispersive X-ray analysis (EDXA), selected area electron diffraction (SAED), and X-ray spectroscopy.[4,5,6]

PATHOLOGY

Gross pathology in all autopsied cases of interstitial pulmonary fibrosis was similar and sometimes difficult to assess. Extensive severe bilateral involvement occurred in only one case. Focal irregular scarring resembling honeycombing was also observed. Emphysematous areas were seen in all cases.

Microscopically the prominent features were marked interstitial fibrosis with mild interstitial infiltration. Lobular and interlobular septa were fibrosed and occasionally showed proliferation of smooth muscle cells. Interstitial infiltrates of macrophages containing small non birefringent particles less than 10 micrometer were present and there was perivascular accumulation of small deposits of dust particles. Granulomas were absent. Some alveolar spaces contained groups of macrophages with dust inclusions. The type II pneumocytes were proliferating in some areas. There was focal honeycombing with septal retraction. The pulmonary vessels showed mild hypertensive changes with muscularization of arterioles.

ELECTRON MICROSCOPY

In alveolar macrophages as well as in extracellular interstitial spaces electron dense irregular deposits ranging from 0.1 to 10 micrometer were seen. They consisted of densely packed rodlike mineral particles 0.01 micrometers in diameter and 0.1 micrometer in length.

Energy dispersive X-ray analysis (EDXA) revealed elements of the lanthanides series. Lanthanum, Cerium were regularly found, less often Praseodymium and Neodymium were noted. Selected area electron diffraction (SAED) of the aggregates resulted in diffraction patterns characteristic of brockite and rhabdophane respectively according to the ASTM Standards. Brockite and rhabdophane are carbonates and phosphates of the lanthanides.[7]

X-ray spectroscopy (Debye-Scherrer) revealed Samarium, Holmium and Thorium in one case and Ytrium in another. The results are summarized in Table II.

DISCUSSION

Although Lanthanides are widely used in industry, (nowadays also in superconductivity material Bednorz & Müller Nobelprize 1987) little is known about their effects on human health. The first radiological report on the lung disease of workers exposed to rare earth was published in 1955 by Scheppers.[8] As in our material most of the diseased persons were engaged in reprophotographic work, and worked for years with carbon arc lamps producing fumes containing Lanthanides and root.[9] Unfortunately no data are available concerning concentration and particle size of the original fumes. Retrospectively the patients or their relatives described the working place as dusty and covered with a fine white powder.

Clinical symptoms occurred in most cases many years after cessation of exposure. At the time of the clinical diagnosis of a restrictive lung disorder with the radiologic feature of pulmonary fibrosis neither the patients nor the physicians were aware of a rare earth exposure.

The slowly progressive restrictive lung disease and its unknown origin led to the diagnosis of "idiopathic" pulmonary fibrosis.

Pathological findings were not specific. The search for exogenous particles proved to be successful and diclosed fume particles consisting of rare earth compounds. Microscopically it was difficult to visualize them. Electron microscopy, however, led to the discovery of particles of ultramicroscopic size in places where their presence was unsuspected. The size of the particles ranged from 0.1 to 10 micrometer. They were aggregates of crystals measuring approximately 0.01 micrometer in diameter and 0.1 micrometer in length.

Pathogenetically rare earth pneumoconiosis resembles the pulmonary fibrosis of hard metal workers which is similarly caused by very small dust particles. Rare earth interstitial lung fibrosis is another example of a lung disorder formerly called cryptogenic and ultimately elucidated by mineralogic analysis of the diseased lung tissue. The correlation with a careful occupational history is also a prerequisite for precise diagnosis.

REFERENCES

1. Colby, T.V., Carrington, C.B.: Infiltrative Lung Disease in *Pathology of the Lung*, Ed. Thurlbeck, W.M., New York, 1988, 424-517.
2. Rüttner, J.R., Spycher, M.A., Stolkin, I.: Inorganic particulates in pneumoconiotic lungs of hard metal grinders. *Brit. J. Ind. Med.* 44:657-660 (1987).
3. Rüttner, J.R., Spycher, M.A., Sticher, H.: Diffuse "Asbestosis-like" interstitial fibrosis of the lung. *Path. & Microbiol.* 31:250-257 (1972).
4. Abraham, J.L.: Analysis of particulates in tissue. in. *Environmental Pathology*, Ed. Hill, R.B., Terzian J.A., New York 1982, 229-241.
5. Rüttner, J.R., Spycher, M.A., Sticher, H.: The detection of etiologic agents in interstitial pulmonary fibrosis. *Hum. Pathol.* 4: 497-512 (1974).
6. Ehrenreich, T., Mackler, A.D., Langer, A.M.: Identification and characterization of pulmonary dust burden in pneumoconiosis. *Ann. Clin. Lab. Sci.* 3:118-135 (1973).
7. Sticher, H., Spycher, M.A., Rüttner, J.R.: Crystallization in vivo of Rhabdophane in human lungs. *Nature* 241:49 (1973).
8. Scheppers, G.W.H.: The biological action of rare earths. *Arch. Industr. Health* 12:301-316 (1955).
9. Vogt, P., Spycher, M.A., Rüttner J.R.: Pneumokoniose durch "Seltene Erden" (Cer-Pneumokoniose). *Schweiz. med. Wschr.* 116: 1303-1308 (1986).
10. Menz, E., Kaufmann, E.: Lungenveränderungen durch "Seltene Erden". *Z. Unfallmed. Berufskr.* 65: 62-73 (1972).
11. Kappenberger, L., Bühlmann, A.A.: Lungenveränderungen durch "seltene Erden". *Schweiz. med. Wschr.* 105: 1799-1801 (1975).

COAL WORKERS' PNEUMOCONIOSIS LESIONS AND THEIR CORRELATION TO DUST LOAD

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ABSTRACT

The relationship between the development, type, and severity of CWP and the concentration and composition of dust burden in the lung has been a subject of great interest. Several studies have shown that the concentration of quartz was the most important factor in the development of severe forms of CWP and pure silicosis. Since coal mine dust contains several minerals, it is important to know the relationship between these minerals and the development of various pulmonary lesions. Therefore, this study was undertaken to investigate the relationship between the type and severity of CWP with silica concentration, total mineral load, and coal dust load. We studied 120 coal miners and 21 non-coal miner autopsy lungs collected from Beckley, West Virginia, during 1960 to 1972 through consecutive autopsies. Whole lung sections prepared according to standard Gough procedure were reviewed and graded using NIOSH/CAP criteria. Concentrations of silica, total mineral dust load, and coal dust burden were determined in freeze-dried samples of the lung using standard protocols. Our findings indicate a good correlation between the type and severity of CWP and the concentration of total dust load. In addition, we also found that the proportions of silica and other mineral dust burden is an important factor in reducing the effects of quartz.

No Paper provided.