ORIGINAL ARTICLE

Clinical and histopathological changes of the nasal mucosa induced by occupational exposure to sulphuric acid mists

S S Grasel, V A F Alves, C S da Silva, O L M Cruz, E R Almeida, E de Oliveira

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See end of article for authors' affiliations

Correspondence to: Dr S S Grasel, Depto de Oftalmologia e Otorrinolaringologia, Hospital das Clínicas, Av. Dr. Enéas de Carvalho Aguiar, 255 sala 6021, 05403-000 São Paulo SP, Brazil; cfgrasel@uol.com.br

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Aims: To assess potential alterations of the nasal mucosa by clinical and histopathological evaluation of workers exposed to sulphuric acid mists at anodising plants, correlating the findings with duration of exposure and sulphuric acid concentrations in the air, and comparing them with a control group.
Methods: Fifty two workers from five plants underwent a clinical evaluation (standard questionnaire, clinical, and ear, nose, and throat examination including nasal endoscopy). For the histopathological study, 20 of the 52 subjects (study group) were randomly selected, as well as 11 unexposed subjects (control group), matched by sex, age, and smoking habits. Nasal biopsy specimens were obtained from the anterior septum mucosa and the anterior curvature of the middle turbinate in each individual. A total of 56 nasal mucosa specimens (37 in the study group and 19 in the control group) were evaluated with regard to normal respiratory epithelium or metaplastic epithelium, atypia or dysplasia, and alterations of the lamina propria.
Results: The histopathological study revealed squamous metaplasia in 29 (79%) and atypia in 13 (35%) of the 37 study group samples. No association was found between exposure duration and the clinical and histopathological variables, but a significant association was found between sulphuric acid concentrations higher than 200 μg/m^3 and pale mucosal patches and ulcerations in the exposed subjects. Logistic regression analysis showed that the exposed subjects had a fivefold risk of developing atypia compared with the unexposed subjects.
Conclusions: Workers exposed to sulphuric acid mists presented with a high incidence of nasal symptoms, and macroscopic and microscopic changes of the nasal mucosa, including squamous atypia and dysplasia. The risk for these histopthological lesions increased with higher sulphuric acid concentrations in the air, revealing an exposure-response relation.

Sulphuric acid mist is a widespread air pollutant and a common environmental contaminant in industrial settings. Occupational exposure to sulphuric acid mists may lead to several nasal symptoms such as epistaxis, nasal discharge, itching, and irritation.[1] Clinical and epidemiological studies have shown a significant association of workplace exposure to this agent with respiratory tract cancer (cancer of the nose and paranasal sinuses, laryngeal and lung cancer).[2–5] According to the World Health Organisation, occupational exposure to strong inorganic acid mists containing sulphuric acid is carcinogenic to humans.[6]

At anodising plants, sulphuric acid is the main air contaminant. During the electrolytic reaction, sulphuric acid mists are released from the tanks. The mists are inhaled by the workers who operate the tanks, especially when proper protection is missing. Metallic agents are not involved, unlike in the electroplating industry. Hence, the anodising plant appears to be a reasonable workplace environment for studying the effects of sulphuric acid mists on the nasal mucosa.

The effects of sulphuric acid mists on the lower airways are well known, but there is very little information about nasal symptoms.[7]

The aim of this study was to assess potential alterations of the nasal mucosa by clinical and histopathological evaluation of workers exposed to sulphuric acid mists at anodising plants, correlating these findings to the exposure duration and sulphuric acid concentrations in the air, compared to a control group.

SUBJECTS AND METHODS

A multidisciplinary cross sectional study was conducted among 461 workers of 22 galvanic plants in the metropolitan area of São Paulo, Brazil. The baseline survey was carried out from 1993 to 1996 during working days. The study was approved by the Ethics Committee of the Hospital das Clínicas, University of São Paulo School of Medicine. Written, informed consent was obtained from all workers.

Study population

The present study reports on the clinical findings in all 52 process workers from five anodising plants exposed to sulphuric acid mist as the main air contaminant. The workers included in this study were exposed to sulphuric acid mist without co-exposure to any other vapours or metals (inclusion criteria). Excluded were 409 workers from 17 plants who were exposed to other agents (chromium, nickel, zinc, copper) or to multiple agents, and the non-process workers. The average age of the 52 male workers was 33 years. Twenty two (42.3%) were smokers, 30 (57.7%) non-smokers.

As the operational routine of the small anodising plants did not permit sending all exposed workers to the Hospital das Clínicas for biopsy, we randomly selected 20 of the 52 subjects for the histopathological study group. The mean age was 35 years. Nine (45%) were smokers, 11 (55%) non-smokers. Subjects who quit smoking at least one year before evaluation were considered non-smokers.

The control group consisted of 11 male subjects, with no known exposure to industrial airway irritants. Age of the control subjects was in the range of ±5 years of the study group individuals; the proportion of smokers and non-smokers was the same in each group.

Table 1 Sulphuric acid air concentrations at five anodising plants as measured by ambient and personal samples

Plant	Ambient air samples		Personal samples	
	Geometric mean ($\mu g/m^3$)	Range ($\mu g/m^3$)	Geometric mean ($\mu g/m^3$)	Range ($\mu g/m^3$)
A	580.2	108.5–1469.8	396.5	245.1–865.6
B	34.7	7.2–220.2	39.8	27.2–49.5
C	60.5	40.5–80.9	12.7	5.3–30.5
D	338.9	173.1–1530.2	–	–
	190.5	120.0–302.5	–	–
E	1582.2	1056.3–2667.0	–	–
	2133.6	1523.0–2780.0	–	–

The geometric mean was the result of sequential samples on five consecutive workdays.

Exposure measurements

Exposure measurements were carried out on five consecutive workdays, taking several samples over the eight hour work shift. Our team's chemical staff determined fixed places near the tanks from where the ambient air samples were collected. Personal air samples were obtained from the respiratory area of the worker, at about 35 cm from the nose. At all plants except D and E, where it was not possible to obtain personal samples, both ambient and personal samples were collected. The samples were aspirated at a low flow rate of 2 l/min and collected on 0.8 μm cellulose ester filters (Millipore AAWP). Sulphuric acid was recovered from the filters by three 6.0 ml distilled water washes and analysed by liquid chromatography with an ion conductivity detector at the Institute of Chemistry, University of São Paulo. The geometric mean of the sequential samples was used for statistical analysis as the best estimate for overall exposure evaluation.

Clinical evaluation

Data on work history, workplace exposure, and respiratory work related symptoms, as well as allergic complaints were collected by means of a standardised questionnaire.

Length of employment at the anodising department was calculated in months. Previous exposure periods at the same or another plant were added to determine the overall exposure time to sulphuric acid mists.

Symptoms were considered work related if the subjects experienced unusual itching or running nose, sneezing, obstruction, bleeding, or hyposmia, or if these symptoms appeared only after starting at the anodising plant.

All subjects underwent a general and ear, nose, and throat evaluation, including nasal endoscopy (Machida 3.2 mm flexible endoscope or Storz 0^0 rigid endoscope). Nasal findings were classified as follows: 1 = normal, 2 = hyperplastic turbinates, 3 = hyperaemia (with or without crusts or secretion), 4 = pale mucosal patches, 5 = ulceration, 6 = septum perforation, 7 = other (pigment deposition, septum deviation, polyps, signs of acute or chronic sinonasal infection, etc). When several lesions were present, the most prominent finding was chosen for evaluation.

Nasal biopsy and histopathological evaluation

After infiltration with lidocaine (2%)/adrenaline (1/120 000), biopsy samples were obtained from the anterior septum mucosa and the anterior curvature of the middle turbinate in each subject. A total of 56 nasal mucosa specimens were evaluated—37 from the study group (20 from the anterior septum mucosa and 17 from the middle turbinate), and 19 from the control group (10 from the anterior septum mucosa and 9 from the middle turbinate)—with regard to normal respiratory epithelium or metaplastic epithelium (immature or mature squamous epithelium), ulceration, squamous atypia or different degrees of dysplasia,[8 9] and alterations of the lamina propria. Six specimens (three from the study group and three from the control group) were not suitable for analysis and were excluded.

Squamous dysplasia (mild, moderate, or severe) was defined as an architectural disturbance in squamous cell maturation, either in original or metaplastic squamous epithelium. Besides basal cell hyperplasia, dysplasia encompassed alterations in nuclear/cytoplasmic volume ratio, nuclear enlargement, and basophilia. Mitoses were seen more frequently than in normal epithelium, and not restricted to the basal cell layer. A diagnosis of squamous cell atypia was applied when minor forms of some of the above mentioned criteria were found in isolated cells, not really amounting to an architectural disturbance of the epithelium, following the WHO definition for squamous cell lesions for the uterine cervix.[9]

The specimens were immersed in a 10% buffered formaldehyde solution and processed for routine haematoxylin-eosin staining. All cases were analysed blindly by two independent observers. In cases of disagreement (four slides or less than 8% of the specimens), a consensus was reached by joint examination.

Statistical analysis

The continuous variables age, exposure duration, and sulphuric acid air concentration were analysed using the following categories:

- Age: group 1, subjects under 30 years of age; group 2, subjects 30 years or older.
- For exposure duration, the workers were divided into three groups: group 1, subjects with exposure from 0 to 5 years; group 2, subjects with exposure from 5 years 1 month to 10 years; group 3, subjects exposed for more than 10 years.
- For exposure levels, the workers were divided into two groups: group 1, mean exposure $\leqslant 200$ $\mu g/m^3$ sulphuric acid air concentration; group 2, mean exposure >200 $\mu g/m^3$.

For smoking status, the subjects were divided into smokers and non-smokers (subjects who quit smoking at least one year before evaluation were considered non-smokers).

The clinical scores were reduced to three groups: group 1 (normal); group 2 (hyperplastic turbinates and/or hyperaemia); and group 3 (pale mucosal patches and/or ulceration and/or septum perforation).

SAS 6.11 software was used to perform the Mann-Whitney test to assess histopathological parameters between cases and controls. A χ^2 test and Fisher's exact test were used to study associations of the clinical and histopathological parameters with age, smoking habits, exposure duration, and sulphuric acid air concentration. Statistical significance was set at $p < 0.05$. Logistic regression analysis was performed to estimate the risk ($e^{coefficient}$) of atypia/dysplasia among the exposed ($n = 20$) versus the unexposed subjects ($n = 11$). The influence of the following variables was assessed: exposure (+/−), exposure time, sulphuric acid air concentration. Significance was set at $p \leqslant 0.30$.

Table 2 Nasal symptoms, clinical score of the nasal mucosa, and exposure status of 52 workers exposed to sulphuric acid mists

No.	Age (y)	Smoking (1)	Nasal symptoms (2)	Allergic symptoms (3)	Clinical score (4)	ExpoT (5)	ExpoV (μg/m³) (6)	Plant
1	39	S	N	N	5	13 y 11 m	580.2	A
2	23	NS	Itching, epistaxis, rhinorrhoea, sneezing	N	5	1 y 6 m	580.2	A
3	42	NS	N	N	4	2 y 8 m	338.9	A
4	22	S	Epistaxis	N	5	2 y 6 m	580.2	A
5	27	NS	Epistaxis	N	4	5 y 9 m	580.2	A
6	42	S	Itching, sneezing	Y	5	5 y	580.2	A
7	42	NS	N	N	4	3 y 9 m	580.2	A
8	43	S	N	N	5	6 y	580.2	A
9	40	NS	N	N	4	2 y 2 m	2133.6	E
10	29	NS	Itching, rhinorrhoea	N	1	7 y 9 m	580.2	A
11	27	NS	N	N	3	14 y 4 m	580.2	A
12	57	S	N	N	4	7 y 8 m	580.2	A
13	39	NS	Itching	N	4	15 y	580.2	A
14	31	NS	Epistaxis	N	3	13 y	580.2	A
15	29	NS	Epistaxis	Y	4	2 y 10 m	580.2	A
16	39	S	N	N	4	7 y 1 m	338.9	D
17	21	NS	N	N	3	1 y 4 m	2133.6	E
18	39	S	N	N	3	3 y 2 m	34.7	B
19	30	S	Itching	Y	1	7 y 9 m	60.45	C
20	34	S	N	N	1	6 y	60.45	C
21	26	S	N	N	3	2 y 1 m	60.45	C
22	27	NS	Itching, rhinorrhoea	N	3	5 y 10 m	60.45	C
23	30	NS	N	N	1	6 y 8 m	60.45	C
24	29	S	Itching, rhinorrhoea	N	3	4 m	60.45	C
25	34	NS	N	N	2	6 y 5 m	60.45	C
26	25	NS	N	N	1	4 m	60.45	C
27	31	S	N	N	1	1 y 5 m	60.45	C
28	38	NS	N	N	2	4 y 11 m	60.45	C
29	46	NS	N	N	2	2 y 2 m	60.45	C
30	30	NS	N	N	3	5 y 8 m	34.7	B
31	30	S	Epistaxis	N	3	3 y 8 m	34.7	B
32	59	S	N	N	1	12 y 8 m	34.7	B
33	23	NS	N	N	1	2 y 8 m	580.2	A
34	30	NS	N	N	4	8 y 2 m	580.2	A
35	54	NS	N	N	1	9 m	580.2	A
36	25	NS	Itching, rhinorrhoea, epistaxis	Y	5	1 y 4 m	580.2	A
37	19	NS	Itching, obstruction	N	4	1 y 4 m	580.2	A
38	27	S	N	N	4	6 y 4 m	580.2	A
39	21	NS	Epistaxis	N	3	unknown	580.2	A
40	34	S	N	N	1	1 y 9 m	580.2	A
41	25	NS	Itching, rhinorrhoea, sneezing, burning	N	2	5 y 1 m	580.2	A
42	27	S	Itching, epistaxis	N	4	14 y 11 m	580.2	A
43	25	S	Itching, hyposmia, epistaxis, rhinorrhoea	Y	4	4 y 9 m	580.2	A
44	27	S	N	N	3	8 y 2 m	580.2	A
45	39	NS	N	N	6	14 y 7 m	580.2	A
46	20	S	Itching, obstruction	N	3	1 y 8 m	580.2	A
47	33	NS	Itching, epistaxis	N	3	7 y 11 m	580.2	A
48	40	S	Itching, sneezing	N	3	1 y 3 m	338.9	D
49	46	NS	N	N	3	10 y 3 m	338.9	D
50	39	NS	N	N	3	9 y 7 m	2133.6	E
51	30	NS	N	N	4	1 y 4 m	2133.6	E
52	46	NS	N	N	4	16 y	2133.6	E

No. 1–20: workers selected for the histopathological study.
(1) S, smoker; NS, non-smoker.
(2) N, no symptom.
(3) N, no; Y, yes.
(4) 1 = normal, 2 = hyperplastic turbinates, 3 = hyperaemia, 4 = pale mucosal patches, 5 = ulceration, 6 = septum perforation.
(5) Exposure duration in years and months.
(6) Sulphuric acid air concentration.

RESULTS

Exposure measurements, nasal symptoms, and clinical findings of the study group subjects

Table 1 details sulphuric acid air concentrations in personal and ambient air samples. Exposure duration varied from 4 months to 16 years (mean 6 years) and was similar for the whole study group (n = 52) and the histopathological study group (n = 20).

One or more work related nasal symptoms were referred by 21 workers (40%) (table 2, fig 1). Eleven workers (21%) had at least one episode of nasal bleeding while working at the anodising plant. Although workers with shorter exposure duration (<5 years) reported a higher number of nasal symptoms than workers with longer exposure time (>10 years) (fig 2), this difference did not reach statistical significance (p = 0.8).

The major clinical findings were hyperaemia in 16 subjects (30%) and pale mucosal patches in 15 (29%). Ulcerations were found in six cases (12%), hyperplastic turbinates in four (8%), and normal mucosa in 10 (19%). One subject had a non work-related septum perforation (prior nasal surgery) (table 2).

Histopathological findings (study group versus control group samples)

The histopathological evaluation showed that in workers exposed to sulphuric acid mists, squamous metaplasia of the

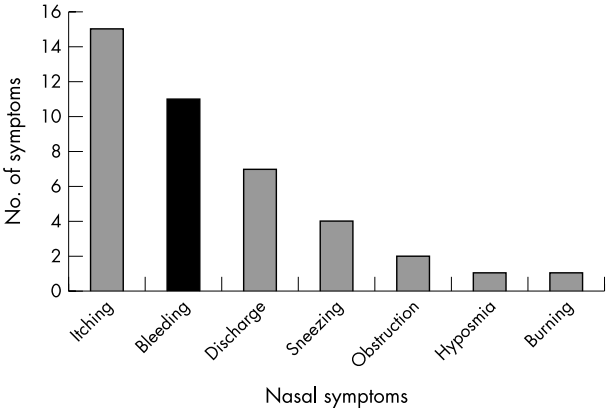

Figure 1 Nasal symptoms referred by 52 workers of five anodising plants.

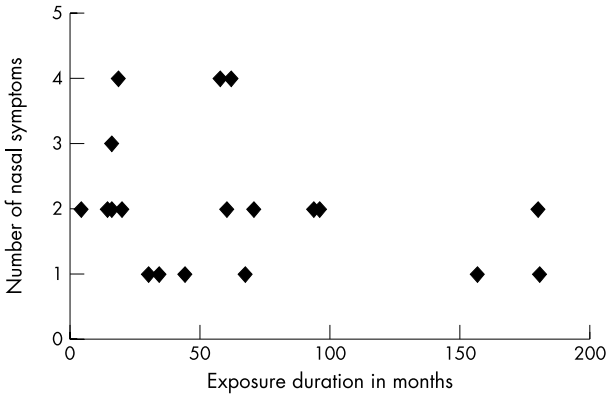

Figure 2 Nasal symptoms of 21 workers in relation to exposure duration.

nasal mucosa (immature and mature squamous epithelium) was more frequent than in the unexposed group ($p = 0.01$) (tables 3 and 4, figs 3 and 4). Significant differences between both groups were also found for squamous atypia (10 cases in the study group and one case in the control group) (fig 5) and mild dysplasia (three cases in the study group, none in the control group) ($p = 0.01$) (fig 6), thickness of the basal membrane ($p = 0.007$), inflammatory infiltrate in the lamina propria ($p = 0.02$), and infiltration by neutrophils ($p = 0.01$). Thirteen (35%) study group samples showed cellular atypia or dysplasia, although none of them showed high grade lesions.

Analysis of the variables age, smoking habits, exposure duration, and sulphuric acid air concentration (study group)

There was no association of age, smoking habits, or exposure duration with the clinical and histopathological parameters. Exposure level was seen to be strongly related to the clinical findings: only workers with mean exposure >200 $\mu g/m^3$ of sulphuric acid air concentration had pale mucosal patches or ulcerations ($p = 0.0003$), which were absent in workers with lower exposure.

Logistic regression analysis (study group versus control group)

Logistic regression analysis revealed that the exposed workers had a fivefold risk of squamous atypia or dysplasia when compared with the unexposed ($e^{1.82}$). The risk for these lesions was found to parallel increasing sulphuric acid air concentrations: workers exposed to up to 60.5 $\mu g/m^3$ of sulphuric acid mist had a risk comparable to the unexposed ($e^{0.0007\times60.5}$), while workers exposed to 580.2 $\mu g/m^3$ had a 50% greater risk ($e^{0.0007\times580.2}$) and workers exposed to 2133.6 $\mu g/m^3$ had a threefold risk for squamous atypia/dysplasia ($e^{0.0007\times2133.6}$). Exposure duration was not found to be significant in this statistical model, not even correlating with an increased risk for atypia/dysplasia.

DISCUSSION

Exposure to air pollutants at the workplace is still a major health problem in developing countries like Brazil. In this study, exposure to sulphuric acid mists was significantly associated with clinical and histopathological changes of the nasal mucosa. Exposure levels above 200 $\mu g/m^3$ of sulphuric acid air concentration showed a significant association with ulcerations and white mucosal patches, most prominently on the anterior septum mucosa. Immature and mature squamous epithelium, squamous atypia and dysplasia, and inflammatory infiltrate by neutrophils were the major histopathological findings among the exposed workers. These subjects had a fivefold risk for squamous atypia/dysplasia, parallel to the concentration of sulphuric acid mist at the workplace, revealing an exposure-response relation.

While dysplasia is considered a preneoplastic lesion, squamous atypia might be related to an inflammatory process induced by an irritating or toxic agent. Mild nuclear and cellular anomalies such as hyperchromasia, multiple nucleoli, and basophilic cytoplasm have been described in nasal mucosa specimens in association with a toxic inflammatory process.[10] Since most of our specimens revealed some inflammation, squamous atypia might be related to the very irritating and toxic nature of sulphuric acid. Yet, the dysplastic lesions may be the result of low pH induced changes of cells, alterations in mitotic and enzyme regulation, which are thought to be involved with a possible genotoxic action of sulphuric acid.[11]

Higher exposure to sulphuric acid has been associated with the development of respiratory tract cancer, particularly with laryngeal cancer.[4 5 12 13] An exposure-response relation, as found in several case-control studies, furthers the belief that sulphuric acid causes laryngeal cancer.[4 12 13] In our study, with a reduced sample size and short average exposure duration, we did not expect to find any nasal cancer. Even so, logistic regression analysis showed an increasing risk for atypia and for dysplasia with increasing concentrations of sulphuric acid at the workplace. This finding supports the existence of an exposure-response relation as previously suggested, though on rather scant evidence. The irritant action of sulphuric acid is discussed as an initial event in carcinogenesis,[11] and squamous atypia and mild dysplasia could be early changes related to this process. Molecular cytogenetic studies are necessary to corroborate the supposed genotoxic action of sulphuric acid.

A fact of major interest in the present study was the finding of 11 of 13 samples with atypia from workers exposed to sulphuric acid concentrations up to 580 $\mu g/m^3$, well below the ACGIH threshold limit value (TLV) of 1000 $\mu g/m^3$.[14] If this finding is confirmed in larger populations of workers, this TLV should possibly be reassessed as the threshold for a "safe" exposure level. Indeed, the limited nature of TLVs is widely acknowledged. Some authors have already suggested replacing the numerical values by a more appropriate industrial hygiene evaluation and exposure assessment.[15 16]

Clinical evaluation was not able to detect lesions with the most significant histopathological changes, such as squamous atypia and dysplasia, found in 35% of the study group specimens. This finding should raise the question of whether a clinical evaluation, the cornerstone of industrial hygiene inspections, is effective in assessing all the health risks of workers exposed to sulphuric acid mists. In this study, clinical evaluation alone would have ignored and thus underestimated the more important microscopic changes. Since these lesions are more frequently related to squamous cell lineage,

Table 3 Histopathological scores of 37 nasal mucosa specimens from 20 exposed workers.

No.	Age (y)	Smoking (1)	ExpoV (µg/m³) (2)	ExpoT (3)	Bx no. (4)	Epithel (5)	Ulcer (6)	Atypia (7)	Basal (8)	Oedema (9)	Fibro (10)	Ves (11)	Int. (12)	Infl. inf. (13)	Lymph (14)	Plas (15)	Eos (16)	Neut (17)	Glands (18)
1	39	S	580.2	13y11m	2788A	3	0	0	0	3	2	3	1	2	1	1	1	2	1
					2788B	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2	23	NS	580.2	1y 6m	2789A	3	0	1	2	1	3	1	1	1	1	0	0	1	0
						–	–	–	–	–	–	–	–	–	–	–	–	–	–
3	42	NS	338.9	2y 8m	3271A	2	1	0	2	3	0	3	0	3	3	3	2	2	0
					3271B	1	0	0	0	3	0	2	0	2	1	2	1	2	0
4	22	S	580.2	2y 6m	3272A	2	1	2	0	2	1	2	0	2	1	2	1	1	1
					3272B	1	0	0	0	3	0	4	0	1	1	1	1	1	0
5	27	NS	580.2	5y 9m	3432A	2	1	1	0	2	1	2	0	3	2	3	2	1	0
					3432B	2	1	0	0	2	1	2	0	2	2	2	1	1	0
6	42	S	580.2	5y	3433A	2	0	0	0	2	1	2	0	2	2	1	2	1	0
					3433B	2	0	0	0	2	0	2	0	3	3	3	1	1	0
7	42	NS	580.2	3y 9m	3434A	2	0	1	0	2	1	1	0	3	2	2	1	3	0
					3434B	1	0	0	0	2	1	1	0	2	2	1	1	2	0
8	43	S	580.2	6y	0235A	3	1	1	0	2	0	1	0	3	3	3	2	2	2
					0235B	2	0	1	0	3	1	4	0	2	2	1	0	1	2
9	40	NS	2133.6	2y 2m	0633A	2	0	2	0	2	1	3	0	3	2	2	1	2	0
					0633B	3	0	0	0	2	1	1	0	2	2	2	2	1	0
10	29	NS	580.2	7y 9m	0801A	3	1	1	0	2	0	1	0	2	2	2	1	2	0
					0801B	2	0	0	0	3	0	3	0	2	3	2	1	0	0
11	27	NS	580.2	14y 4m	0802A	2	0	0	–	–	–	–	–	–	–	–	–	–	0
					0802B	2	0	0	1	1	0	3	0	3	3	3	1	1	0
12	57	S	580.2	7y 8m	0909A	3	0	0	0	2	2	2	0	2	2	2	1	1	0
					0909B	2	0	2	1	3	1	3	0	2	2	2	2	3	0
13	39	NS	580.2	15y	0910A	2	1	1	0	2	1	2	0	2	2	1	1	0	1
					0910B	1	0	0	0	3	0	3	0	2	1	2	2	1	0
14	31	NS	580.2	13y	0911A	2	1	0	1	2	1	2	0	3	2	3	1	1	0
					0911B	–	–	–	–	–	–	–	–	–	–	–	–	–	–
15	29	NS	580.2	2y10m	0959A	2	1	0	1	2	2	2	0	4	3	2	1	2	2
					0959B	1	0	0	1	2	2	1	0	2	2	1	1	1	0
16	39	S	338.9	7y 1m	0960A	2	0	1	1	2	2	3	0	3	3	2	2	3	3
					0960B	2	0	1	0	2	2	3	1	3	2	2	1	1	0
17	21	NS	2133.6	1y 4m	0961A	2	1	1	0	2	2	2	0	3	3	2	3	1	1
					0961B	1	0	0	1	3	2	2	0	2	1	1	2	2	0
18	39	S	34.7	3y 2m	1104A	3	1	0	0	2	4	0	0	2	2	2	1	1	2
					1104B	3	1	0	1	3	2	3	0	3	3	2	2	1	4
19	30	S	60.45	7y 9m	1105A	1	0	0	2	1	2	1	0	2	2	2	1	1	0
					1105B	2	0	0	1	2	1	2	0	2	2	2	2	2	0
20	34	S	60.45	6y	1106A	3	0	0	0	3	2	1	0	1	1	1	1	1	2
					1106B	1	0	0	0	2	1	1	0	1	1	1	0	1	0

(1) S, smoker; NS, non-smoker.
(2) Exposure level.
(3) Exposure duration in years.
(4) Biopsy number: A = anterior septum mucosa, B = middle turbinate.
(5) Epithelium: 1 = pseudostratified cylindric ciliated epithelium, 2 = immature squamous epithelium, 3 = mature squamous epithelium.
(6) Ulceration: 0 = absent, 1 = present.
(7) Atypia: 0 = absent, 1 = squamous atypia, 2 = mild dysplasia.
(8) Basalm = thickness of basal membrane from 0 to 3.
(9) Oedema: varying from 0 to 4.
(10) Fibrosis: varying from 0 to 4.
(11) Vessels: vasocongestion varying from 0 to 4.
(12) Intima: hypercellularity of endothelial cells varying from 0 to 4.
(13) Intensity of global inflammatory infiltrate varying from 0 to 4.
(14) Intensity of lymphohistiocytic infiltrate varying from 0 to 4.
(15) Intensity of plasmocytic infiltrate varying from 0 to 4.
(16) Intensity of eosinophilic infiltrate varying from 0 to 4.
(17) Intensity of neutrophilic infiltrate varying from 0 to 4.
(18) Glands: 0 = normal, 1 = dilatation, 2 = metaplasia, 3 = dilatation and metaplasia, 4 = hyperplasia, 5 = calcification.

Table 4 Histopathological scores of 19 nasal mucosa specimens from 11 control subjects

No.	Age (y)	Smoking (1)	ExpoV (μg/m^3) (2)	ExpoT (3)	Bx no. (4)	Epithel (5)	Ulcer (6)	Atypia (7)	Basal (8)	Oedema (9)	Fibro (10)	Ves (11)	Int (12)	Infl. (13)	Lymph (14)	Plas (15)	Eos (16)	Neut (17)	Glands (18)
1	31	S	–	–	2014A	3	0	0	0	1	3	1	0	1	1	1	0	0	0
					2014B	–	–	–	–	0	2	0	0	1	1	1	0	0	0
2	39	S	–	–	2242A	2	0	0	0	2	2	1	0	1	1	1	0	0	0
					2242B	1	0	0	1	2	1	2	0	3	3	3	1	1	2
3	33	S	–	–	3918A	3	1	0	3	1	3	1	0	1	1	0	0	0	0
					3918B	–	–	–	2	1	3	2	0	1	1	1	0	0	0
4	29	S	–	–	0165A	2	0	0	2	1	4	1	0	1	1	1	0	0	0
					0165B	1	0	0	2	2	1	2	2	2	2	2	2	1	0
5	21	NS	–	–	0192A	1	1	0	0	3	2	3	0	2	2	1	2	1	0
					0192B	1	0	0	0	3	3	2	0	3	2	2	3	1	0
6	40	NS	–	–	0207A	2	1	0	1	1	2	1	0	2	2	3	1	1	0
					0207B	1	1	0	1	3	2	1	0	2	2	1	2	2	5
7	39	S	–	–	0206A	1	0	0	2	1	1	1	3	1	1	1	1	0	0
					0206B	1	0	0	0	3	1	3	2	1	1	1	1	0	0
8	39	NS	–	–	0259A	1	0	0	1	2	2	3	0	2	2	2	1	1	0
					0259B	1	0	0	0	3	2	2	0	2	2	1	1	1	0
9	25	NS	–	–	0406A	2	0	0	1	3	2	0	0	3	2	3	1	2	0
					0406B	2	1	0	1	3	1	2	0	3	3	3	1	1	0
10	57	NS	–	–	0407A	1	1	0	1	1	3	1	0	2	2	2	1	1	0
					0407B	2	0	1	1	2	1	1	0	2	2	2	1	1	0
11	44	NS	–	–	0429A	–	–	–	–	–	–	–	–	–	–	–	–	–	–
					0429B	1	0	0	1	2	1	3	0	2	2	2	2	1	0

(1) S, smoker; NS, non-smoker.
(2) Exposure level.
(3) Exposure duration in years.
(4) Biopsy number: A = anterior septum mucosa, B = middle turbinate.
(5) Epithelium: 1 = pseudostratified cylindric ciliated epithelium, 2 = immature squamous epithelium, 3 = mature squamous epithelium.
(6) Ulceration: 0 = absent, 1 = present.
(7) Atypia: 0 = absent, 1 = squamous atypia, 2 = mild dysplasia.
(8) Basalm = thickness of basal membrane from 0 to 3.
(9) Oedema: varying from 0 to 4.
(10) Fibrosis: varying from 0 to 4.
(11) Vessels: vasocongestion varying from 0 to 4.
(12) Intima: hypercellularity of endothelial cells varying from 0 to 4.
(13) Intensity of global inflammatory infiltrate varying from 0 to 4.
(14) Intensity of lymphohistiocytic infiltrate varying from 0 to 4.
(15) Intensity of plasmocytic infiltrate varying from 0 to 4.
(16) Intensity of eosinophilic infiltrate varying from 0 to 4.
(17) Intensity of neutrophilic infiltrate varying from 0 to 4.
(18) Glands: 0 = normal, 1 = dilatation, 2 = metaplasia, 3 = dilatation and metaplasia, 4 = hyperplasia, 5 = calcification.

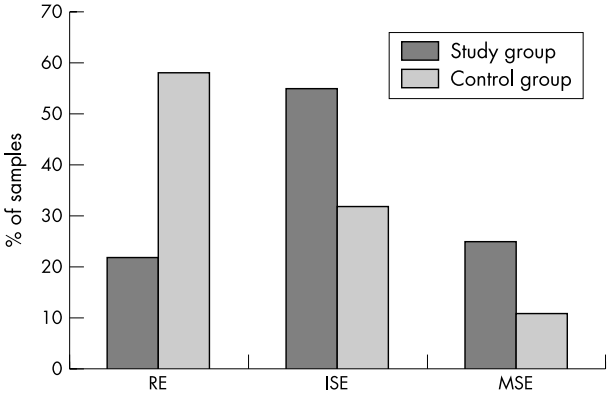

Figure 3 Distribution of different epithelial types among the study group (n = 37) and the control group samples (n = 19) of nasal mucosa. RE, respiratory epithelium; ISE, immature squamous epithelium; MSE, mature squamous epithelium.

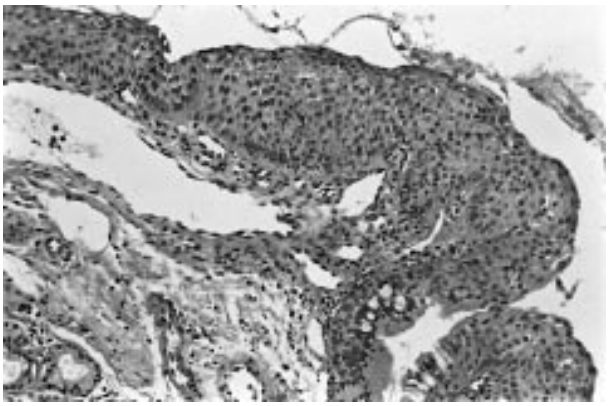

Figure 4 Minor inflammatory changes. Normal pseudostratified epithelium is still present in the right inferior quarter of the picture. Moderate oedema and inflammatory infiltrate are present in the corion. Early squamous epithelial metaplasia is the major finding (H&E, ×150) (B94-2789).

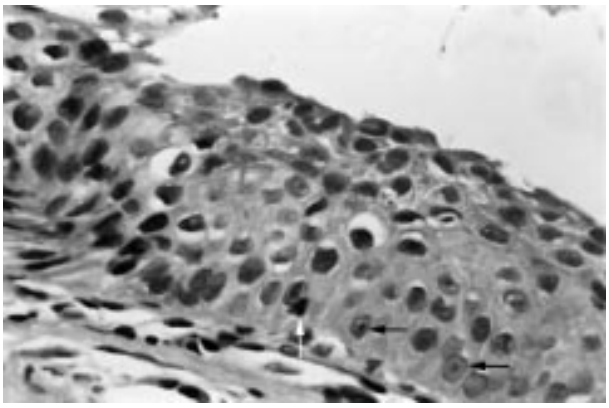

Figure 5 Squamous atypia in an area of squamous metaplasia. Basal-like cells are seen up to the 1/3 superficial layer with a moderate rise in nuclear-cytoplasmic ratio, nuclear hyperchromasia (white arrow), and prominent nucleoli (black arrows). Maturation towards the superficial layer is preserved (H&E ×600) (B95-3432A).

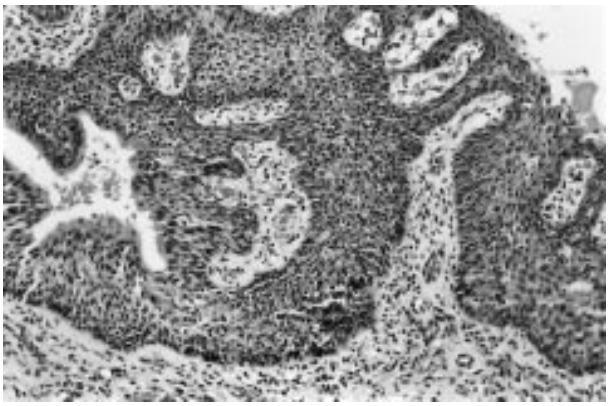

Figure 6 Squamous epithelium with mild dysplasia showing marking infoldings, akanthosis, major basal cell hyperplasia, and some mitoses. Increased nuclear cytoplasmic ratio and nuclear hyperchromasia are present up to the superficial layer (H&E ×150) (B95-3272A).

analogous to other squamous epithelium such as uterine cervix, oesophagus, and metaplastic bronchial epithelium, we would suggest that a screening cytological examination, which is not invasive and is more cost effective than the classical histopathological examination, should be included as a periodic routine evaluation of workers exposed to sulphuric acid mists. The combined clinical and cytological assessment has proved to be a reliable screening method among workers exposed to nickel dust and soluble nickel compounds, which are known respiratory tract carcinogens.[17 18]

In the present study, exposure duration was probably not long enough (mean 6 years) to detect more severe histopathological lesions. Maximum exposure duration was 16 years, yet the risk for respiratory cancer seems to increase significantly after 20 years of exposure to sulphuric acid.[19] A long term survey of the exposed individuals is underway and may be helpful to determine whether longer exposure duration is associated with more severe histopathological changes. Steenland *et al* failed to show a relation between excess risk of laryngeal cancer and exposure duration (average exposure 9.5 years). They suggest that exposure duration may be a poor surrogate for dose if men with higher exposures worked less time.[20]

Like exposure duration, age and smoking habits showed no relevant association with the clinical and histopathological parameters and were consequently excluded as possible confounders.

As a practical result, this study has contributed to improvement of working conditions in the electroplating and anodising industries of the State of São Paulo, Brazil. In March 1999, the employers association, union representatives, and the Labour Secretary signed an agreement which requires proper exhaust systems, a minimum height, and appropriate ventilation at these factories.

CONCLUSION

In the current study, workers exposed to sulphuric acid mists presented with a high incidence of nasal symptoms, and macroscopic and microscopic changes of the nasal mucosa, compared to the control group. Logistic regression analysis showed that the exposed subjects had a fivefold risk of acquiring cellular atypia or dysplasia compared with unexposed subjects. Higher exposure levels were associated with increasing risk of developing atypia, whereas exposure duration, age, and smoking habits were not.

To our knowledge, this is the first study using a combined approach of exposure measurement, clinical, and histopathological techniques to assess potential effects of sulphuric acid on the nasal mucosa. Follow up of the study population will provide more data about the evolution of cellular atypia and dysplasia.

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Authors' affiliations
S S Grasel, E R Almeida, Dept of Otorhinolaryngology, University of São Paulo School of Medicine, Brazil
V A F Alves, Dept of Pathology, University of São Paulo School of Medicine
C S da Silva, Fundacentro, Secretary of Work, São Paulo
O L M Cruz, Dept of Otorhinolaryngology, Federal University of São Paulo School of Medicine
E de Oliveira, Dept of Chemistry, University of São Paulo

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ECHO

Breathing dust can trigger Wegener's granulomatosis too

Please visit the Occupational and Environmental Medicine website [www.occenvmed.com] for link to this full article.

Doctors would do well to remember that dust exposure can trigger Wegener's granulomatosis, as a case of Wegener's granulomatosis with chronic rhinosinusitis has shown.

The case was in a 54 year old man who presented with chronic nasal symptoms and crusting and bloody inflammation lasting eight years. Over 20 years before he had worked for 15 years as a carpenter, when he had suffered with constant nose pain; soreness; bloody nasal discharge; and chronic obstruction when planing wood, stripping paint, and doing tasks generating dust. He had never worn a mask. He had been a heavy smoker but had not used cocaine.

Clinical examination and follow up tests plus a nasal biopsy showed a strong positive reaction to antineutrophil cytoplasmic antibodies (ANCA) and histological evidence of chronic inflammation of the nasal mucosa and around the vessel walls with necrosis, indicating Wegener's granulomatosis.

The symptoms almost all resolved after a year of oral steroid and trimethoprim-sulphamethoxazole with four intravenous cyclophosphamide pulses every four weeks.

Carpenters have an increased risk of chronic respiratory diseases, sinusitis, and sinus cancers, which can occur decades after original exposure to the trigger. This patient had 10 years before presented with chronic rhinosinusitis and presented again with recurrence of symptoms. A decline in woodworking means that dust exposure may easily be overlooked—recent publications fail to mention such exposure as an environmental trigger for Wegener's granulomatosis.

▲ *Annals of the Rheumatic Diseases* 2002;**61**:1113.