THE CLINICAL SIGNIFICANCE OF FERRUGINOUS BODIES IN SPUTA

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ABSTRACT

The clinical significance of ferruginous bodies in sputa was examined in a study of 674 former asbestos workers. Data obtained from occupational histories, smoking behavior questonnaires, chest radiographs, spirometric measurements and counts of ferruginous bodies were obtained as part of a five-year surveillance program. Statistical analysis demonstrated that ferruginous bodies found in the sputa were significantly related to radiographic findings of interstititai pulmonary disease and pleural fibrosis and to spirometric findings of restrictive lung disease. Age and cigarette smoking were also found to be factors in the presence of ferruginous bodies.

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Although ferruginous bodies have been found in the sputum of asbestos workers since 1929 (1), it is only in the past four years that the Tyler Asbestos Workers Program (TAWP) has presented the opportunity to survey former asbestos workers with multiple examinations including sputum cytology, chest roentgenograms and pulmonary function studies at six month intervals (2,3). In June, 1974, the Tyler Asbestos Workers Program was funded by the Division of Cancer Control and Rehabilitation of the National Cancer Institute to provide the latest facilities for detection and diagnosis of pulmonary disease to a cohort of 1095 former asbestos workers, 85% of whom were cigarette smokers. The amosite asbestos plant in Tyler, Texas, manufactured asbestos insulation products from 1954 to 1972, when it was closed. The amosite asbestos was mined in South Africa and shipped to Tyler in burlap sacks. A National Institute of Occupational Safety and Health study of the Tyler asbestos plant had disclosed asbestos fiber levels three to fifteen times the Occupational Safety and Health Act maximum of five fibers/cc of air (4).

For this report, the records of 674 workers examined at the TAWP were chosen for study. The former asbestos workers have been grouped according to duration of asbestos exposure, time since first exposure, time since last exposure, age and cigarette smoking history. All information has been entered into a central computer facility for analysis. The purpose of this report is to examine the significance of the ferruginous bodies in the sputum as related to occupational asbestos exposure and clinical findings.

MATERIAL AND METHODS

Both spontaneous and aerosol-induced sputum specimens are obtained for cytology. The induced sputum specimens are obtained in the clinic utilizing transoral aerosolization of 8% sodium chloride in water from a DeVilbiss 900 ultrasonic nebulizer. The spontaneous sputum specimens represent a three-day pool of early morning cough sputum collected at the worker's home and mailed to the cytology laboratory. From June, 1974, through February, 1976, sputum specimens were fixed in 60% ethyl alcohol and prepared by the "pick and smear" technique. Since March, 1976, the sputum specimens have been fixed in 50% ethyl alcohol and 2% carbowax and prepared by the Saccomanno sputum concentration technique (5). Four Papanicolaou stained slides are made from each specimen, screened by a registered cytotechnologist and are subject to review by a cytopathologist. Ferruginous bodies (See Figure 1) counted on the four slides are reported as few (1-14), moderate (15-29) and many (30 or more). Workers are classified for statistical analysis according to the highest number of ferruginous bodies found in any one specimen.

The chest roentgenograms are taken with inspiratory and expiratory posteroanterior and left lateral views utilizing a grid technique with a mean kilovoltage of 98-106 KV. In addition, a 350 KV field emission unit posteroanterior view is obtained. Radiographic findings used for this study are those from the most recent visit to the TAWP. The chest roentgenograms are interpreted by a board-certified, B-reader radiologist employing the ILO U/C classification system for pneumoconiosis.

The pulmonary function tests utilize forced vital capacity to measure restrictive pulmonary disease and are performed on an Ohio 842 spirometer with the Ohio 120 normal value indicator. The forced vital capacity is performed and recorded three times and the best results are reported. Spirometry values used for this study are those taken at the time of the most recent visit to the TAWP.

The occupational measures used for analysis include the duration of employment at the asbestos manufacturing plant and latency (the time between first or last employment dates and the date of examination). The intensity of asbestos exposure (i.e. fibers/cc of air) was not used for this analysis.

Statistical methods applied include χ^2 analysis for contingency tables, the analysis of variance (6) for correction of covariant effects with continuous response variables (e.g., forced vital capacity) and multiple logistic regression (7) for correction of covariant effects with discrete response variables (e.g., pleural thickening, yes or no).

RESULTS

The correlation between the duration of the former worker's employment in months and the presence of ferruginous bodies in both spontaneous and aerosol-induced sputum specimens is excellent (Figure 2). A positive relationship between the worker's age at examination and the presence of ferruginous bodies was also found (Figure 3). This relationship was further shown to be highly significant, controlling for the confounding factors of duration of employment, time since first exposure, and smoking behavior by multiple logistic regression. A similar relationship was found with both spontaneous and aerosol-induced sputum specimens. For purposes of brevity, only the spontaneous sputum specimen results are shown.

No latency effect was seen (Figure 4) with the presence of ferruginous bodies in the sputa specimens. The lack of correlation between the presence of ferruginous bodies and the time since first or last exposure was further verified by multiple logistic regression using latency as a continuous variable.

In studying the association of cigarette smoking with the presence of ferruginous bodies in the sputum (without considering possible confounding factors), a significant correlation was found for spontaneous sputum specimens but not for aerosol-induced sputum specimens (Table 1). Controlling for duration of employment and age at examination, the cigarette smoking/ferruginous body relationship was once again shown to be significant for spontaneous specimens but not for aerosol-induced specimens (Figures 5 and 6).

Figure 7 shows the correlation between ferruginous bodies in the sputum and irregular small opacities in the chest roentgenograms. The irregular small opacities are defined according to the ILO U/C pneumoconiosis classification (8) for chest radiographs as types s, t or u. A significant correlation is found between the presence of ferruginous bodies and the presence of irregular small opacities (sometimes called linear opacities), even after correcting for age, smoking and duration of employment by the multiple logistic regression technique.

The correlation between ferruginous bodies and pleural thickening is seen in Figure 8. For this purpose, pleural thickening is defined by the ILO U/C pneumoconiosis classification as obliteration of the costophrenic angle or pleural thickening of either the diaphragm or chest wall. A significant relationship is shown between the presence of ferruginous bodies and pleural thickening, even after correcting for confounding factors by multiple logistic regression.

For this report, restrictive lung disease is defined as a forced vital capacity of less than 80% of the expected value. Expected spirometry measurements were standardized by age, race and sex before analysis. Figure 9 shows a positive correlation between the presence of ferruginous bodies in the sputum and the presence of restrictive lung disease. This relationship was found to be significant ($p <.02$) after correcting for smoking and employment factors by the analysis of variance. For a further comparison between the varying degrees of severity of the restrictive lung disease and ferruginous bodies in the sputum, the restrictive lung disease was categorized according to the forced vital capacity (FVC) as normal (more than 80% expected), mild (65-80% expected), moderate (50-65% expected), and severe (less than 50%). Figure 10 demonstrates that the severity of restrictive lung disease is also related to the presence of ferruginous bodies.

DISCUSSION

Previous investigations of ferruginous bodies in the sputum of asbestos workers include the early reports of Stewart and Haddow, 1929 (1), Simpson and Strachan, 1931 (9), Page, 1935 (10), and a later report of Stumphius and Meyer, 1968 (11). These former studies were not structured to include periodic sputum examinations of workers with known asbestos exposure. The TAWP provides for repeated sputum examinations at six month intervals, and by the laboratory methods described approximately one-third of the former asbestos workers have shown ferruginous bodies in their sputum specimens (2,3). On the other hand, autopsy lung specimens studied elsewhere by various laboratory techniques have yielded ferruginous bodies from the majority of the adult urban population, most of whom were not asbestos workers (12,13,14,15). It is important to note that the routine cytopathology techniques employed in our laboratory do not include special techniques for the detection of asbestos fibers or ferruginous bodies. Thus, the results are comparable to what might be obtained by routine sputum examination in a competent cytopathology laboratory. It is likely that more diligent search by special techniques (iron stain, electron microscopy or digestion) would yield a much higher percentage of workers showing ferruginous bodies in their sputum. Interpretation of the clinical significance of the ferruginous bodies in sputum should consider the extent of the laboratory methods employed.

In small laboratory animals such as the guinea pig and hamster, intra-pulmonary instillation of asbestos has resulted in the formation of ferruginous bodies within two months (16). Even after two years the majority of the asbestos fibers in the animals' lungs remain uncoated or free (17).

From our previous study (3), it was evident that the presence of ferruginous bodies in the sputum of former asbestos workers is strongly related to their duration of employment. In the present report, it has also been shown that the presence of ferruginous bodies is significantly related to smoking behavior and to age at examination. Therefore, any correlation of ferruginous bodies with other clinical findings, such as chest roentgenograms or pulmonary function studies, must be corrected for the influence of these factors. After correcting for duration of employment, age at time of clinical examination and smoking history, significant correlations are still found between the presence of ferruginous bodies in the sputum, chest roentgenographic and spirometric findings. These positive correlations between ferruginous bodies in the sputum, small irregular parenchymal opacities, pleural thickening and a decrease in the forced vital capacity indicate that with time the ferruginous bodies are related to restrictive (or interstitial) pulmonary disease.

Aerosol-induced sputum specimens contained more ferruginous bodies than did spontaneous specimens. However, spontaneous specimens correlated more strongly in every test of clinical factors (lower p values) than did the induced specimens. One can speculate that the aerosolized hypertonic (8%) saline solution acts as a bronchial irritant, resulting in increased secretions of the bronchial glands. These abundant bronchial secretions in turn serve to deliver (or "float out") increased numbers of ferruginous bodies in the sputum. Conversely, spontaneous sputum specimens, with less bronchial secretions, yield fewer ferruginous bodies. The more significant statistical correlations for the presence of ferruginous bodies in spontaneous sputum specimens suggest that they are more relevant physiologically than the artificially induced specimens.

Normally, the mucociliary clearance of the lung is an effective defense mechanism against inhaled materials (18). The airways of the chronic cigarette smoker, however, have increased goblet cells and islands of squamous metaplasia, neither of which have cilia (19). Thus, these individuals have impairment in the mucociliary transport mechanism

(20). Ferruginous bodies may be increased in the sputum of cigarette smokers because the less effective bronchial clearance of the asbestos fibers allows more retention of fibers for ferruginous body formation. Similarly, decreases in pulmonary clearance mechanisms as related to age at exposure may account for the increase in ferruginous bodies found in the sputum of older asbestos workers (20).

CONCLUSION

Statistical analysis has shown that the presence and number of ferruginous bodies in the sputum of former asbestos workers are significantly related to the duration of their occupational exposure. Additionally, probably because of less effective bronchial clearance, more of the older workers and cigarette smoking workers have ferruginous bodies in their sputum. The time since the former workers' asbestos exposure was not shown to be related to ferruginous bodies in the sputum. Clinically, ferruginous bodies in the sputum were found to be significantly related to radiographic findings of interstitial pulmonary and pleural fibrosis and spirometric findings of restrictive lung disease.

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Figure 1. High magnification photomicrograph of a ferruginous body in a sputum specimen. Note at either end the attached free alveolar macrophages (FAM's). (Papanicolaou stain; X600).

18-0000110

001529

Figure 2. Percentage of workers with ferruginous bodies and the duration of employment. The ordinate represents the percent of workers in each duration group with ferruginous bodies ($p < .001$ for both spontaneous and aerosol-induced specimens).

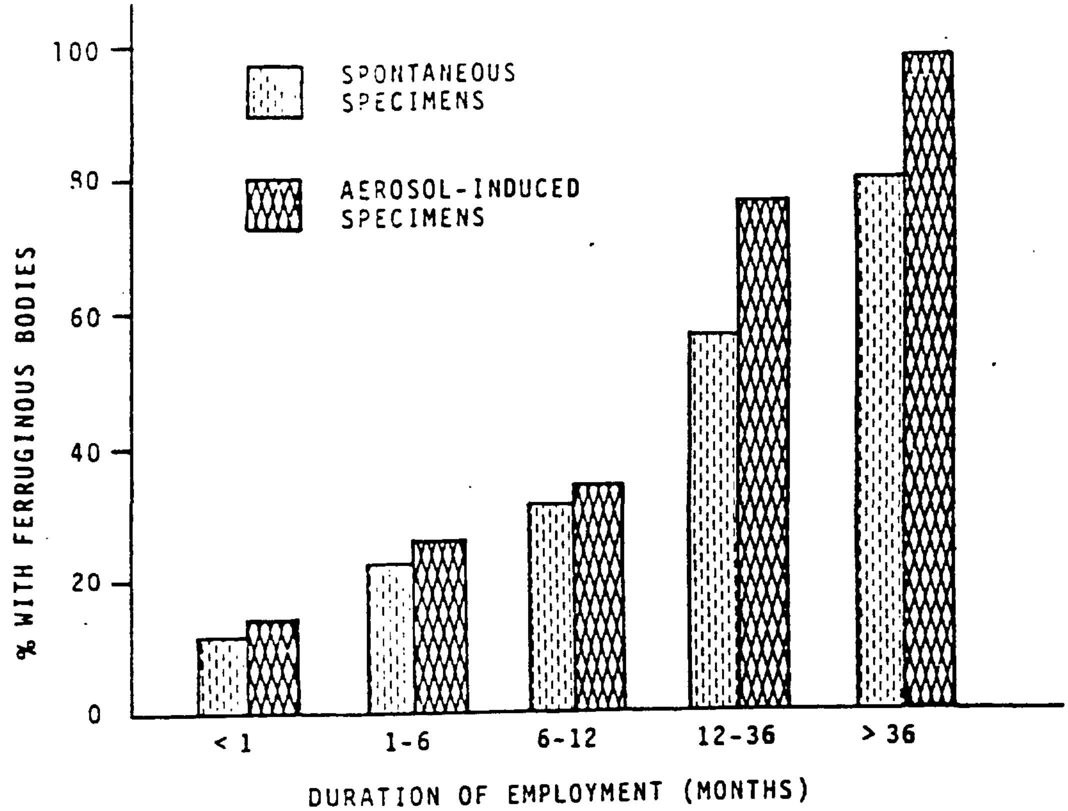

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Figure 3. Percentage of workers with ferruginous bodies and age at testing, correcting for duration of employment ($p < .001$).

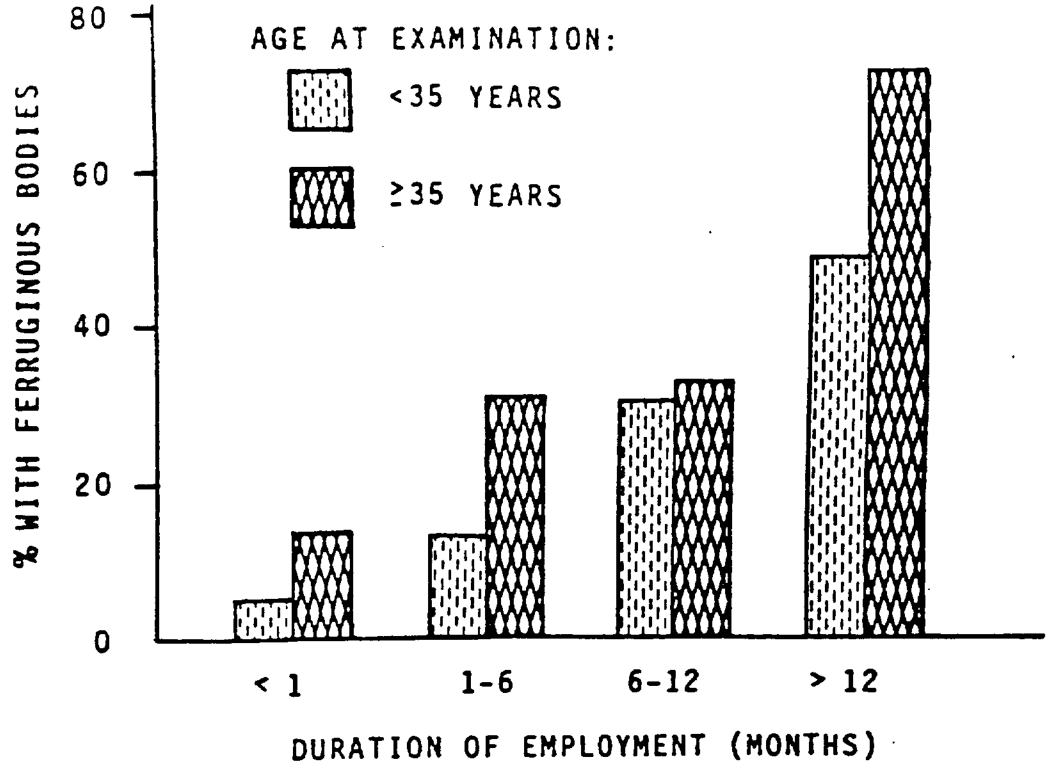
AGE AT EXAMINATION:
<35 YEARS
≥35 YEARS
% WITH FERRUGINOUS BODIES
80
60
40
20
0
< 1
1-6
6-12
> 12
DURATION OF EMPLOYMENT (MONTHS)

Figure 4. Percentage of workers with ferruginous bodies and latency, the time elapsed between first employment and the date of testing, correcting for duration of employment ($p > .2$, not significant).

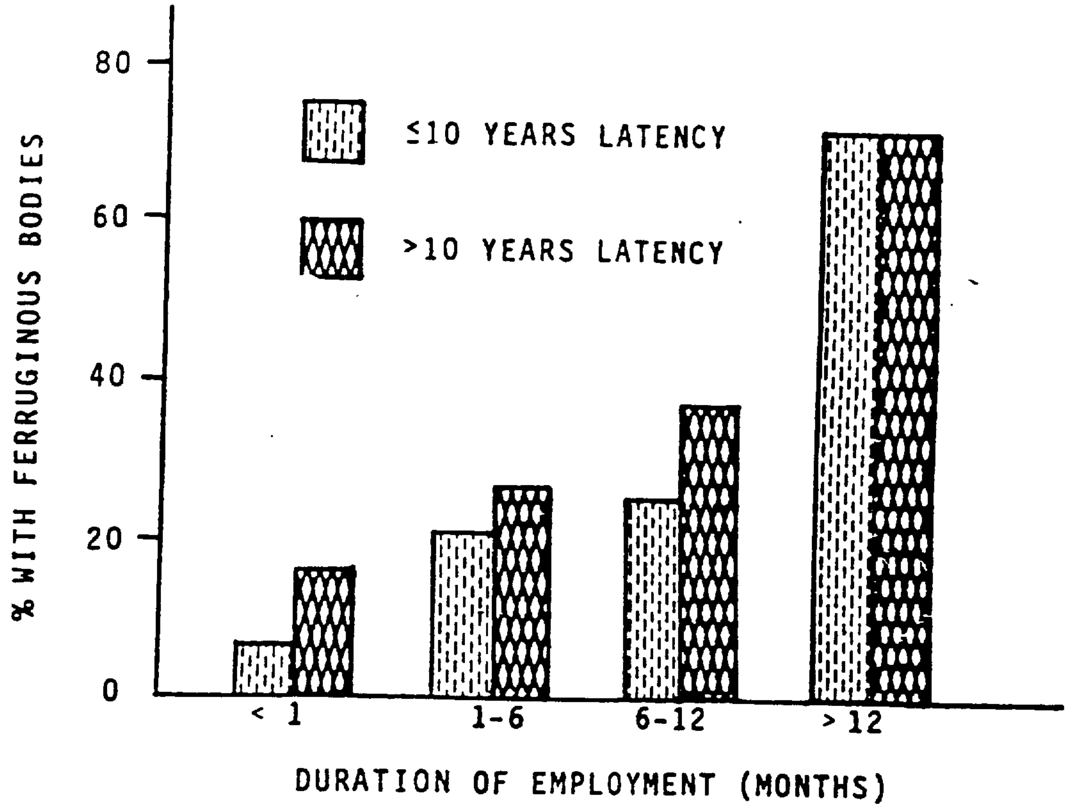
80
60
40
20
0
% WITH FERRUGINOUS BODIES
≤10 YEARS LATENCY
>10 YEARS LATENCY
< 1
1-6
6-12
> 12
DURATION OF EMPLOYMENT (MONTHS)

TABLE 1

FERRUGINOUS BODIES AND SMOKING

SPECIMEN TYPE	SMOKING STATUS	FERRUGINOUS BODIES PRESENT	SIGNIFICANCE
SPONTANEOUS	SMOKERS	163 (30%)	$p < .02$
	NONSMOKERS	19 (18%)	
AEROSOL	SMOKERS	191 (34%)	$p > .30$
	NONSMOKERS	32 (29%)	

Figure 5. Percentage of workers with ferruginous bodies (from spontaneous specimens) and smoking, correcting for duration of employment ($p < .02$).

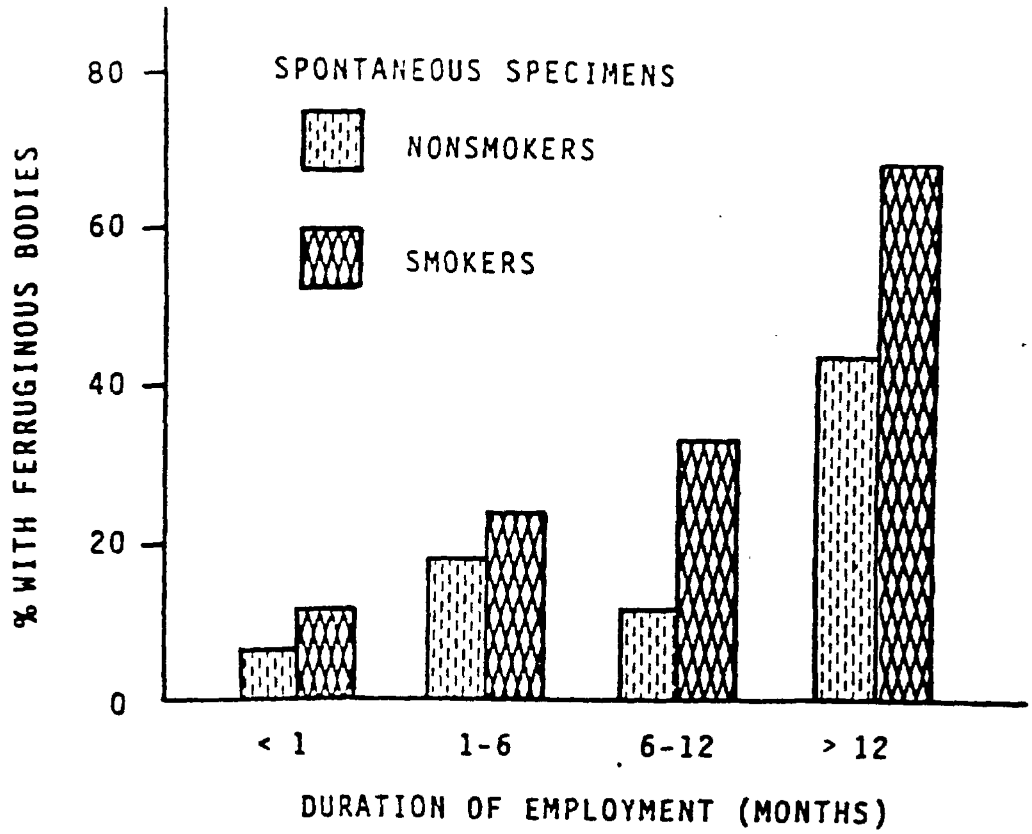
SPONTANEOUS SPECIMENS
NONSMOKERS
SMOKERS
% WITH FERRUGINOUS BODIES
80
60
40
20
0
< 1
1-6
6-12
> 12
DURATION OF EMPLOYMENT (MONTHS)

Figure 6. Percentage of workers with ferruginous bodies (from aerosol-induced specimens) and smoking, correcting for duration of employment ($p > .3$, not significant).

AEROSOL-INDUCED SPECIMENS

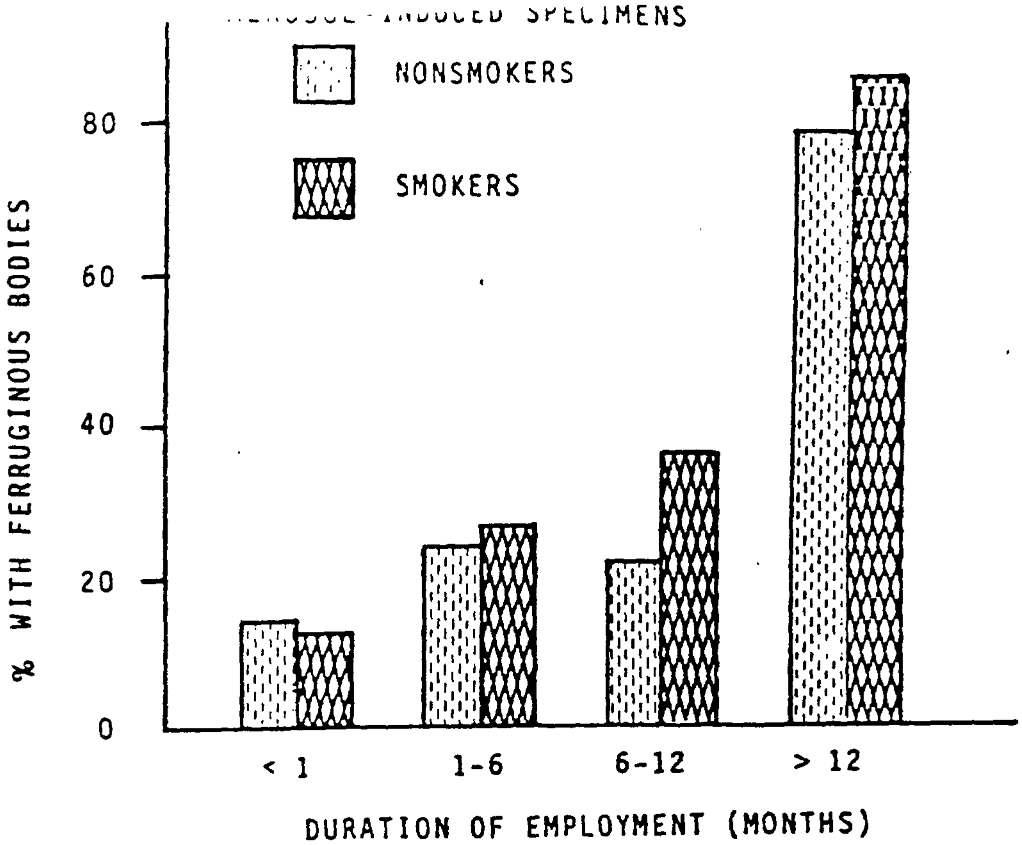

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Figure 7. Percentage of workers with ferruginous bodies and irregular small opacities ($p < .001$).

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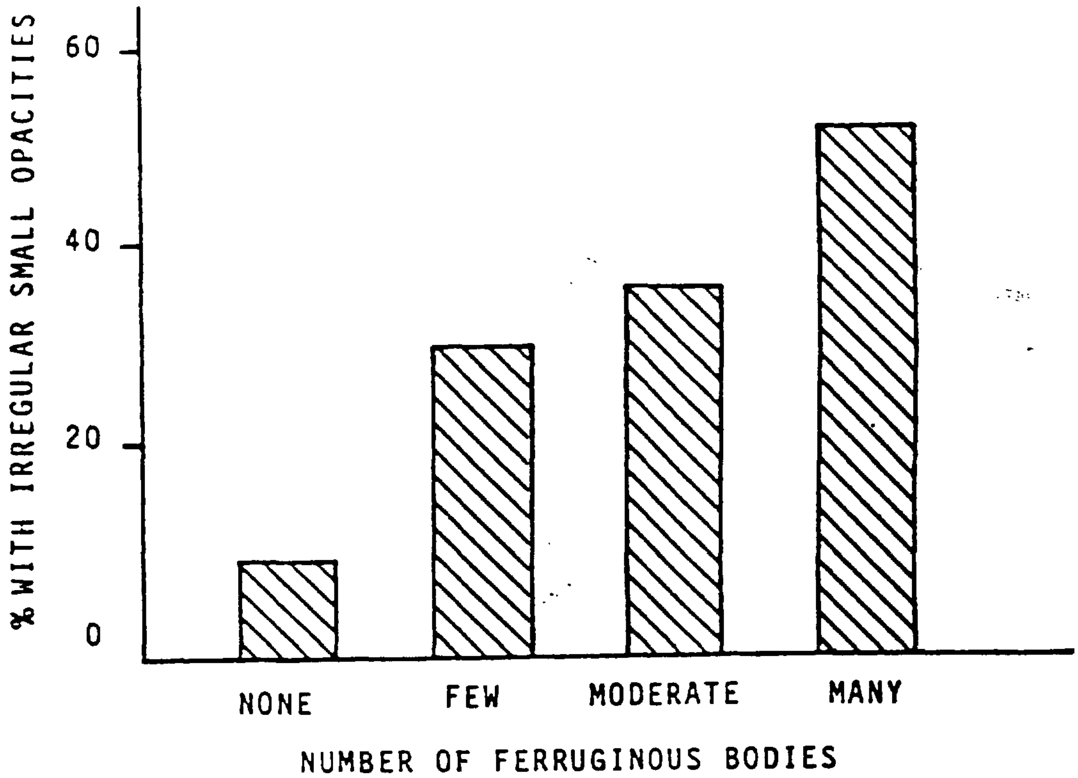
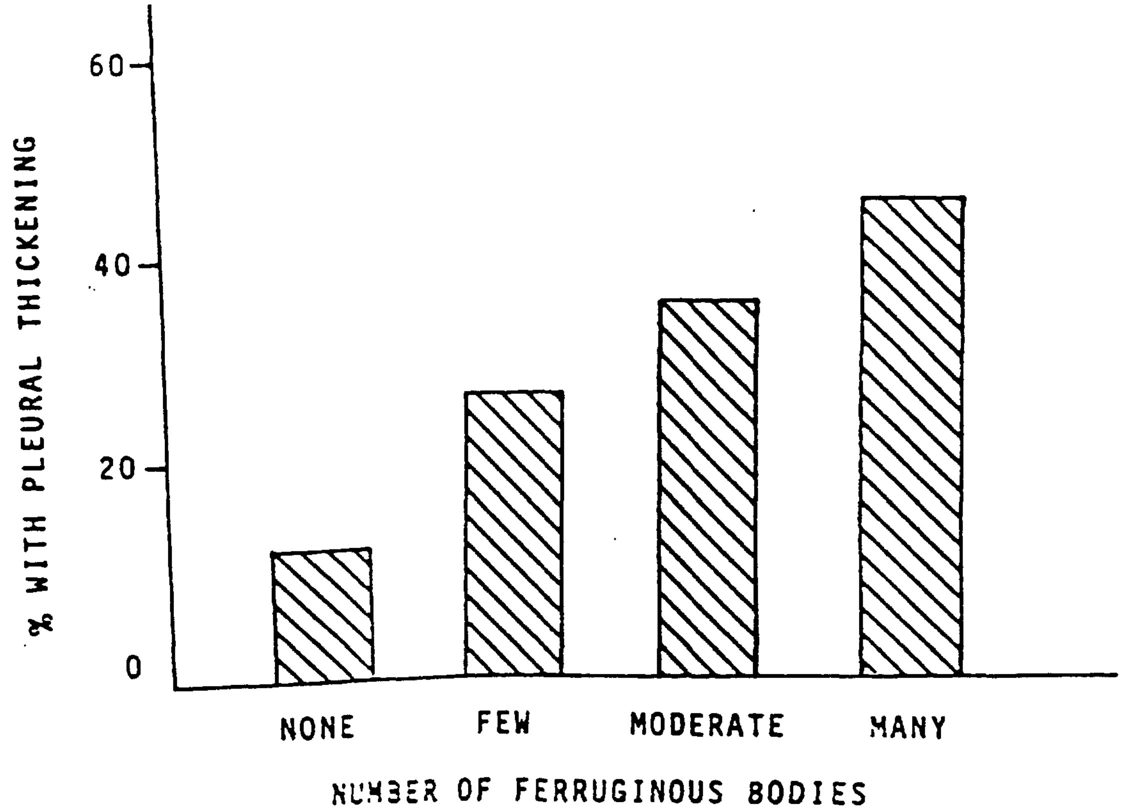

% WITH IRREGULAR SMALL OPACITIES
60
40
20
0
NONE
FEW
MODERATE
MANY
NUMBER OF FERRUGINOUS BODIES

Figure 8. Percentage of workers with ferruginous bodies and pleural thickening ($p < .03$).



60
40
20
0
% WITH PLEURAL THICKENING
NONE
FEW
MODERATE
MANY
NUMBER OF FERRUGINOUS BODIES

Figure 9. Percentage of workers with restrictive lung disease and ferruginous bodies ($p < .02$).

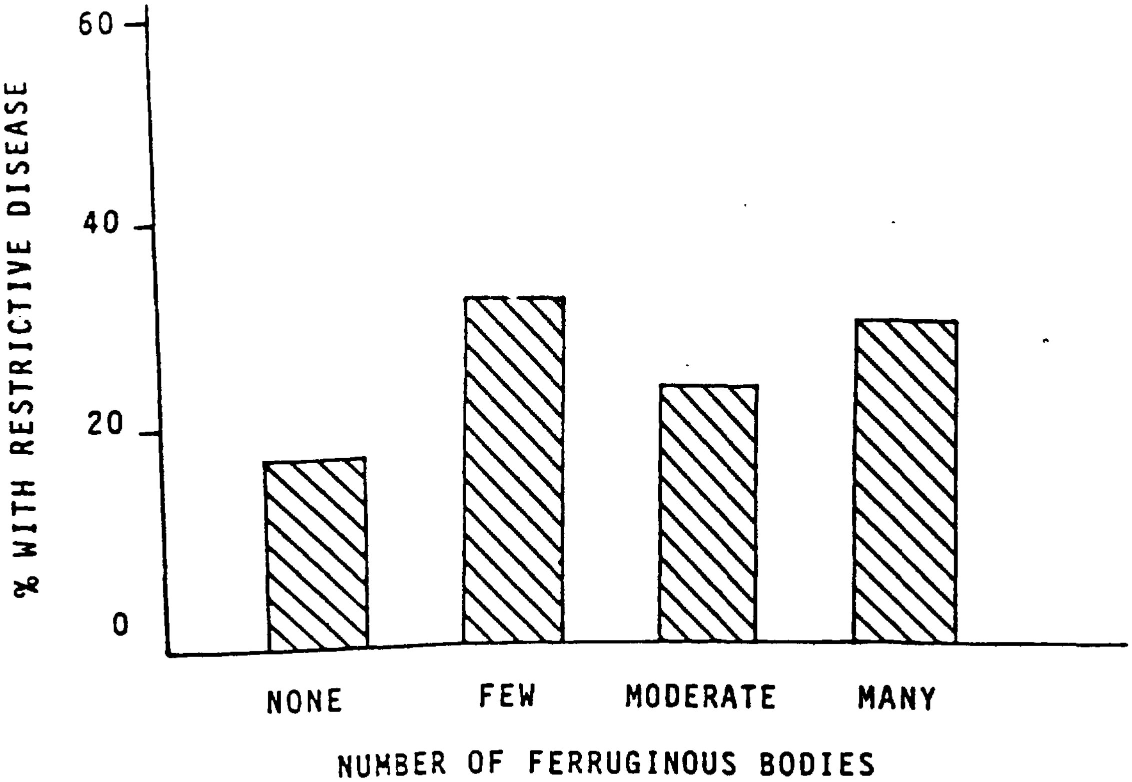
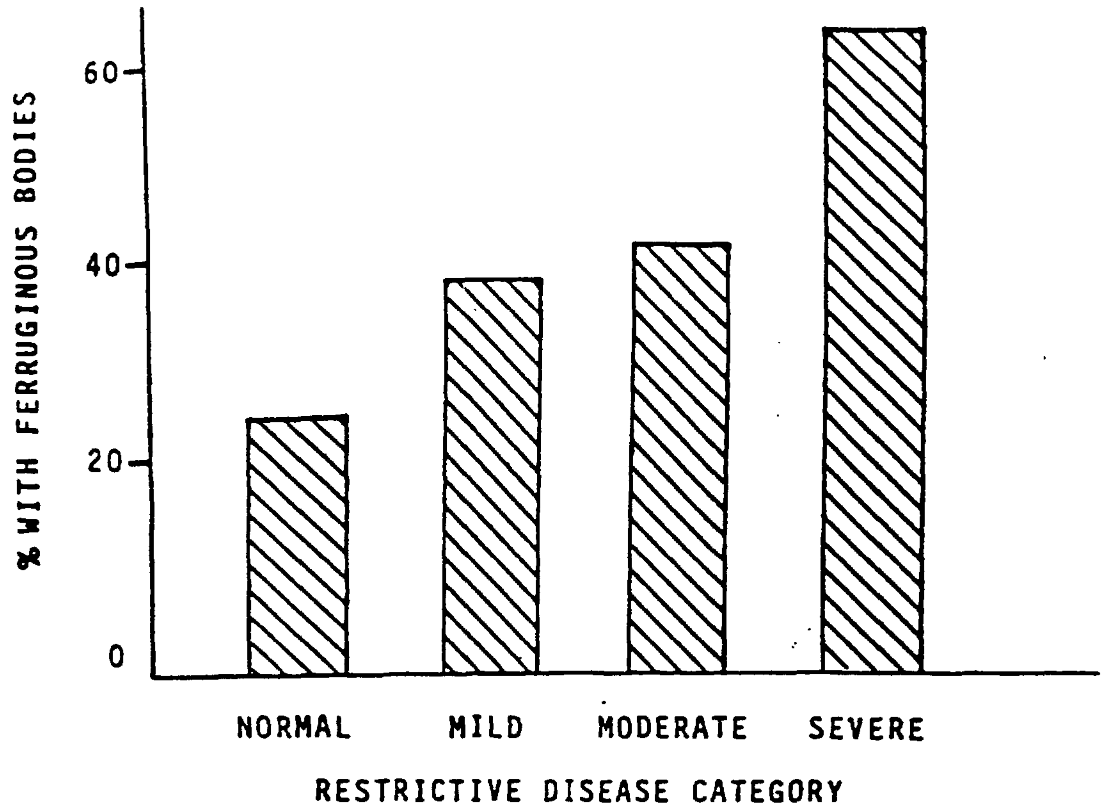

60
40
20
0
% WITH RESTRICTIVE DISEASE
NONE
FEW
MODERATE
MANY
NUMBER OF FERRUGINOUS BODIES

Figure 10. Severity of restrictive lung disease and ferruginous bodies ($p < .02$).


% WITH FERRUGINOUS BODIES
60
40
20
0
NORMAL
MILD
MODERATE
SEVERE
RESTRICTIVE DISEASE CATEGORY