EXHIBIT E

August 1988, Volume 30, No. 8
ISSN 0096-1736

Journal of Occupational Medicine

DOES SEASONAL EMPLOYMENT IN GRAIN ELEVATORS INCREASE NONSPECIFIC AIRWAYS RESPONSIVENESS?

Grain handling and increased airways responsiveness have been independently associated with a decline in FEV_1. This study did not support the hypothesis that seasonal exposure to grain dust increases airways responsiveness.

DEGREE OF CONFOUNDING BIAS RELATED TO SMOKING, ETHNIC GROUP, AND SOCIOECONOMIC STATUS IN ESTIMATES OF THE ASSOCIATIONS BETWEEN OCCUPATION AND CANCER

The authors examined the extent to which three confounders—smoking, ethnicity, and socioeconomic status—influenced estimates of odds ratios for three types of cancer in 26 occupations.

LUNG VOLUME REFERENCE VALUES FOR BLUE COLLAR WORKERS NOT EXPOSED TO OCCUPATIONAL RESPIRATORY HAZARDS

The authors present prediction equations for total lung capacity (TLC), residual volume (RV), and the ratio RV/TLC% for four combinations of race and gender.

FACTORS ASSOCIATED WITH ENROLLMENT IN AN EMPLOYEE FITNESS CENTER

Persons participating in a company fitness program were more likely than non-participants to have engaged in prior fitness activity, to assign fitness a high priority, and to have more positive attitudes about keeping fit.

Official publication of AMERICAN OCCUPATIONAL MEDICAL ASSOCIATION
and of AMERICAN ACADEMY OF OCCUPATIONAL MEDICINE

Journal of Occupational Medicine

Official Publication of AMERICAN OCCUPATIONAL MEDICAL ASSOCIATION and of AMERICAN ACADEMY OF OCCUPATIONAL MEDICINE

ORIGINAL ARTICLES

DEPARTMENTS

JOURNAL OF OCCUPATIONAL MEDICINE (ISSN 0096-1736) is published monthly by the American Occupational Medical Association, 428 East Preston Street, Baltimore, Maryland 21202. Second-class postage paid at Baltimore, Maryland, and additional mailing offices. POSTMASTER: Send address changes to JOM JOURNAL OF OCCUPATIONAL MEDICINE, 428 East Preston Street, Baltimore, Maryland 21202. Subscriptions per year, individuals $55.00 ($70.00 foreign, $87.00 Japan), institutions $80.00 ($95.00 foreign, $112.00 Japan), in-training $45.00 ($60.00 foreign, $77.00 Japan) and single copies $8.00 ($10.00 foreign). Subscription prices subject to change.

'B-Readers' and Asbestos Medical Surveillance

Alan M. Ducatman, MS, MD; CDR William N. Yang, MD, MPH; and Samuel A. Forman, MD, MPH

"B-readers" certified in International Labor Office methodology interpret large numbers of randomly distributed asbestos medical surveillance roentgenograms of US Navy employees. Analysis of 23 participating observers, interpreting more than 105,000 radiographs, demonstrated a 300-fold prevalence range of perceived "definite" pulmonary parenchymal abnormalities. There was an evident geographic component to interpretation habits, with East and West Coast observers more likely to interpret films as abnormal than observers from the midcontinent. The most expert observers, a group who instruct the course leading to National Institute for Occupational Safety and Health certification in International Labor Office methodology, also perceived fewer abnormalities than other readers or coastal observers. Instructors still exhibited a sevenfold prevalence range of positive interpretation. Under usual surveillance conditions, the habits of B-readers appear to have a major impact upon the diagnosis of asbestosis from roentgenograms. Certification in B-reading should not be the only quality assurance for radiographic surveillance programs, medical decision-making, epidemiologic comparisons, nor related legal activities.

A uniform standard for the classification of radiologic changes of the pneumoconioses has been published[1] and updated[2] by the International Labor Office (ILO). ILO designations, intended for descriptive epidemiologic purposes,[3] have also taken on increasing socioeconomic importance in compensation programs and legal arenas.

US regulations require periodic chest roentgenograms as part of asbestos medical surveillance and recently stipulated ILO interpretations.[4] Most asbestos medical surveillance programs have long followed scientific recommendations[5] for ILO methodology. Within the ILO system, roentgenograms were historically classified as follows: category 0, normal; category 1, abnormal, few opacities; category 2, numerous opacities but lung markings visible; category 3, lung markings obscured. Each category determination is followed by consideration of a possible alternative so that 1/0 could alternatively be normal but 1/1 and 1/2 are certainly and progressively abnormal.[1] Category classifications are now properly based upon comparisons to standard films distributed by the ILO.

In the United States, certification examinations are administered by the National Institute for Occupational Safety and Health (NIOSH). Those who pass have been called "B-readers," and the proficiency examination process has been generally described.[6] ILO methodology has received excellent quality assurance testing in a number of settings, particularly for coalworkers' pneumoconiosis. Studies have characterized intra- and inter-observer variability with multiple blinded readings of the same roentgenograms,[7] but have not characterized how variability affects a large medical surveillance program. The US Navy's Asbestos Medical Surveillance Program (AMSP), employing civilian B-readers for more than 30,000 radiographs yearly, permits investigation of interpreter habits in a practical surveillance setting.

Methods

Three-year contracts have been awarded since 1978 to independent, certified civilian B-readers based on

From the Occupational Health Department, Navy Environmental Health Center, Norfolk, VA 23511-6695.

Dr Ducatman is now Director, Environmental Medical Service, Massachusetts Institute of Technology, 77 Massachusetts Avenue, 20B-238 Cambridge, MA 02139 (address reprint requests to Dr Ducatman). CDR Yang is Head of the Occupational Preventive Medicine Department, Naval Medical Clinic, Norfolk, VA 23508-1296. Dr Forman is Medical Consultant at the Health and Safety Division, Proctor and Gamble Company, Cincinnati, OH 45217.

The views presented are those of the authors and do not reflect the official position or policy of the Department of the Navy, Department of Defense, nor the US Government.

0096-1736/86/3006-0644$02.00/0

competitive bids. No B-reader was removed from participation by the Navy during the study period, although several either participated in only one of the contracts or else removed themselves from participation during a contract. This is reflected in the numbers of roentgenograms interpreted by each reader.

Single view radiographs were taken according to specifications designed for the detection of pneumoconioses.[8] Radiographic techniques of individual clinics were reviewed by an experienced B-reader. Roentgenographs received initial interpretations at site clinics in order to rule out acute processes. The Navy Environmental Health Center then assigned, on a random sequential basis, packets of 50 to 200 radiographs from local clinics to B-readers. Films were distributed without regard to geographic convenience, so that observers were as likely to interpret films from distant as from nearby sources. Available data do not permit analysis of initial film randomization. Randomization can be shown to have worked adequately for persons who have remained in the program long enough to obtain more than one roentgenogram; follow-up films of enrollees through the years of the study were not more likely to be sent to the initial interpreter. Each film was read by only a single B-reader, who was deliberately blinded from demographic information and from the results of previous radiographs.

B-readers could reject technically flawed roentgenograms. Of the submitted films, 5.4% were rejected; these were repeated and randomly reassigned. Interpretations coded in ILO format were checked for completeness and internal inconsistencies. Incomplete or internally inconsistent forms were reinterpreted by the same B-reader. This study dealt only with coded parenchymal findings; 1/1 was taken to mean that the B-reader was certain of a parenchymal abnormality.

Summary data pertaining to each worker's most recent radiograph were collected for each participating B-reader and assigned to geographic areas depending on reader residence in a state with a Pacific or Atlantic coastal border. Residence in other states was termed "midcontinent." "Instructors" were defined as individuals who teach the course leading to NIOSH "B-reading certification" in ILO methodology.

Results

Table 1 summarizes B-readers' categorization of parenchymal findings on the most recent radiograph of 105,029 individuals. There is a more than 300-fold prevalence range of "definite" (≥1/1) parenchymal opacifications (0.02% to 7.55%). One outcome of this variation is shown in Table 2. This summarizes data with and without the contributions of a single observer (H, who read 4.4% of all submitted roentgenograms, yet contributed 33% of films categorized ≥1/1 and more than half of those classified as ≥2/1). Similar comparisons for other readers can be simply performed and give less dramatic results.

TABLE 1
B-Readers' Classification of Most Recent Radiograph

B-Reader	No. of Roentgenograms	≥1/0 (%)	≥1/1 (%)	≥2/1 (%)
A	1,885	100 (5.30)	31 (1.64)	2 (0.11)
B	5,475	33 (0.60)	12 (0.22)	5 (0.09)
C	5,701	3 (0.05)	1 (0.02)	0 (0.00)
D	6,056	175 (2.89)	80 (1.32)	14 (0.23)
E	4,475	44 (0.98)	23 (0.51)	4 (0.09)
F	4,621	73 (1.51)	45 (0.93)	13 (0.27)
G	4,137	13 (0.31)	11 (0.27)	2 (0.05)
H	4,648	508 (10.93)	351 (7.55)	120 (2.58)
I	5,691	130 (2.28)	29 (0.51)	1 (0.02)
J	5,779	57 (0.99)	10 (0.17)	1 (0.02)
K	4,457	46 (1.03)	13 (0.29)	5 (0.11)
L	4,747	81 (1.71)	42 (0.88)	6 (0.14)
M	5,331	107 (2.01)	52 (0.97)	15 (0.28)
N	1,777	19 (1.07)	5 (0.28)	1 (0.06)
O	5,015	17 (0.34)	9 (0.18)	1 (0.02)
P	5,922	276 (4.66)	46 (0.78)	5 (0.08)
Q	4,533	8 (0.18)	4 (0.09)	2 (0.04)
R	4,383	150 (3.42)	53 (1.21)	12 (0.27)
S	4,627	30 (0.65)	15 (0.32)	0 (0.00)
T	4,262	190 (4.46)	54 (1.27)	3 (0.07)
U	4,686	130 (2.77)	36 (0.77)	5 (0.11)
V	4,685	242 (5.16)	119 (2.54)	12 (0.26)
W	1,936	48 (2.48)	25 (1.29)	3 (0.15)

TABLE 2
Summary Classification Outcomes and Effect of a Single B-Reader on Asbestos Medical Surveillance

Reader	No. of Roentgenograms	≥1/0 (%)	≥1/1 (%)	≥2/1 (%)
H	4,648	508 (10.93)	351 (7.55)	120 (2.58)
Others	100,381	1,972 (1.97)	715 (0.71)	112 (0.11)
TOTAL	**105,029**	**2,480 (2.36)**	**1,066 (1.01)**	**232 (0.22)**

Geographic variations are shown in Table 3. Observers from Pacific states read (≥1/1) parenchymal abnormalities four times more often than readers from the midcontinent; this ratio dropped from 4.5:1 to 1.8:1 when the outlying B-reader's contributions were discarded. Eastern seaboard B-readers read definite parenchymal abnormalities about twice as often as midcontinent readers (2.1:1). Comparison between a single Pacific Coast city (25,118 roentgenograms) and a midcontinent city (15,235 roentgenograms) reveals 1.97% and 0.20% ≥1/1, respectively (not shown in tables) for a ratio of 9.9:1.

Instructors of the NIOSH certifying examination were heavily represented among the sample. Six instructors classified from 0.17% to 1.29% of roentgenograms as having definite opacifications. Table 4 shows that non-instructors categorized films as ≥1/1 substantially more often than instructors. Geographic variation is not due to maldistribution of films to the more conservative instructors in any region; their film interpretations were distributed in the three regions in proportions very close to all readers.

Differences among regions are far less marked for

TABLE 3
Geographic Summary of Classification Outcomes

Reader	No. of Roentgenograms	≥1/0 (%)		≥1/1 (%)		≥2/1 (%)	
East	41,294	962	(2.33)	376	(0.91)	51	(0.12)
Midcontinent	36,736	321	(0.87)	161	(0.44)	32	(0.09)
Pacific	26,999	1,197	(4.43)	529	(1.96)	149	(0.55)
	(22,351)*	(689)*	(3.08)	(178)*	(0.80)	(29)*	(0.13)

* Pacific B-readers without the contributions of a single reader.

TABLE 4
Instructors' and other B-Readers' Categorization of Asbestos Surveillance Radiographs

Reader Group	No. of Roentgenograms	≥1/0 (%)	≥1/1 (%)	≥2/1 (%)
Instructors	27,732	531 (1.92)	159 (0.57)	26 (0.09)
Others	77,297	1,949 (2.52)	907 (1.17)	206 (0.27)

category 2 and 3 parenchymal opacities. Readers from different regions more closely resembled each other and the instructors in perception of these more serious categories, particularly when the contributions of one B-reader (H) were discounted.

The cutoff chosen for comparisons among observers is arbitrary. Table 1 shows that decreasing the degree of severity from 1/1 to 1/0 decreases the prevalence range of perceived abnormalities. The range diminishes from 377-fold (≥1/1) to 219-fold (≥1/0). The same change increases the perceived prevalence range among instructors from seven-fold to 15-fold, however. It also increases the apparent differences among regions, with Eastern Seaboard readers viewing 2.66 times and Western Seaboard readers viewing 5.1 times more films with parenchymal changes ≥1/0 than midcontinent readers (Table 3).

Discussion

These are inferential data. No two observers were interpreting the same film, and the findings do not directly measure interobserver variability. The very large size of the distributed pool and its randomization scheme minimize the possibility that individual B-readers were regarding populations with different risks or groups of roentgenograms of substantially different quality. Follow-up films were adequately randomized; initial films were distributed by the same mechanism. Although the data lack some precision, the range of findings document a distressing impact of B-reader habits.

Controlled studies of interobserver variability in roentgenographic surveillance for pneumoconioses have shown up to threefold variations in ILO classification in abnormal categories.[9-12] The actual effect under routine medical surveillance conditions appears far larger. To summarize, 23 B-readers evaluated randomly distributed roentgenograms of more than 100,000 people and perceived parenchymal abnormalities ≥1/1 between 0.02% and 7.55% of the time, a 377-fold range. Arbitrary exclusion of the outermost readers (C and H) reduces the range to 28-fold, still striking for a surveillance procedure. Although the inferred habits of 23 B-readers may not be representative of the more than 450 currently on the approved NIOSH list, the outer range of interpretation outcomes could only widen if more readers were included.

Interpreter geography appears to play a role in surveillance outcomes. East and West Coast readers perceived definite (≥1/1) abnormalities an average of three times as often as their colleagues from the midcontinent. Comparison between two cities, involving more than 40,000 roentgenograms, showed a ninefold average difference in positive interpretations. An evident question is whether local or regional habits may supercede the standardization efforts of B-reader training and certification.

Decreasing the degree of certainty for abnormalities from 1/1 to 1/0 does little to improve the picture. The range of habits is still inferred to give positive interpretations over a 200-fold prevalence range. The apparent differences among regions actually enlarge slightly.

There is no gold standard for B-reading in surveillance settings. Instructors of the NIOSH certification examination are presumably the most expert; their habits may constitute a relative standard for the evaluation of surveillance outcomes. Instructors read 26.4% of Navy films but found only 14.9% of definite (≥1/1) parenchymal abnormalities. Among geographic groups, midcontinent observers most closely resembled instructors for these definite interpretations. The relatively conservative habits of the most expert observers has been previously documented in controlled interreader comparisons of coal miner films,[13] and is again confirmed in this large sample. Among instructors, there is still a sevenfold range of definite (≥1/1) positive findings, which increases to 15-fold at the ≥1/0 threshold.

Surveyed workers and their physicians, attorneys and others interested in legal aspects of radiography, and epidemiologists all need to understand some present limitations of the B-reading art. Physicians and workers need to distinguish between the numerical precision of the ILO classification system, a valuable epidemiologic tool, and the subjective nature of what constitutes an abnormal reading. Legal proceedings need to account for the apparent wide range of certified observer thresholds for the perception of abnormalities. Epidemiologists need to consider that the lack of independent readings in this inferred study of reader habits also mimics the common study design in population research pertaining to the radiography of asbestosis. Comparing outcomes for populations using different observer(s) may be more problematic than previously supposed.

At present, individual diagnoses, legal decisions, and population assessments ought to rely on multiple readings. Apparent differences between cities and regions may indicate that the choice of additional readers also requires some thought. Selecting observers whose habits are continually monitored for approximation to a stand-

rd for "relative truth" may give additional standardization. An "asbestos board" model comes to mind; this would require the participation of far fewer than the hundreds of presently certified readers in the United States. A smaller number of tightly monitored readers would greatly increase confidence in the B-reading process and, perhaps, eliminate some expensive logistical problems of multiple readings.

There have been previous indications that B-readers may disagree under controlled study or medical surveillance[14] conditions. Insightful articles and editorials[15,16] have cautioned about the need for informed skepticism and continued improvements regarding legal and epidemiologic use of B-reader data. The data presented here show the probable scope of the problem and underline a need for new quality assurance in the B-reading process.

References

1. Jacobson G, Lainhard WS (eds): ILO U/C 1971 International classification of radiographs of the pneumoconioses. *Med Radiogr Photogr* 1972;48:55–110.
2. Classification of radiographs of the pneumoconioses. *Med Radiogr Photogr* 1981;57:2–17.
3. Bohlig H, Bristol LJ, Cartier PH, et al: UICC/Cincinnati classification of the radiographic appearance of pneumoconioses: A cooperative study by the UICC committee. *Chest* 1970;58:57–67.
4. US Dept of Labor, Occupational Safety and Health Administration. General Industry Standards (29 CFR 1910.1001), Revised 1986.
5. National Institute for Occupational Safety and Health: *Criteria for a Recommended Standard—Occupational Exposure to Asbestos.* Dept of Health, Education, and Welfare, HSM 72-10267, 1972.
6. Morgan RH: Proficiency examination for classifying pneumoconiosis chest films. *Am J Radiol* 1979;132:803–808.
7. Rossiter CE: Initial repeatability trials of the UICC/Cincinnati classification of the radiographic appearances of pneumoconioses. *Br J Ind Med* 1972;29:407–419.
8. Sargent EN (ed): *Technique for Chest Radiography for Pneumoconiosis. Task Force on Pneumoconiosis.* Chicago, American College of Radiology, 1982.
9. Musch DC, Higgins ITT, Landis JR: Some factors influencing interobserver variation in classifying simple pneumoconiosis. *Br J Ind Med* 1985;42:346–349.
10. Musch DC, Landis JR, Higgins ITT: An application of kappa-type analysis to interobserver variation in classifying chest radiographs on the categorization of coalworkers' pneumoconiosis. *Stat Med* 1984;3:73–83.
11. Reger RB, Morgan WKC: On the factors influencing consistency in the radiologic diagnosis of pneumoconiosis. *Am Rev Respir Dis* 1970;102:905–915.
12. Shears G, Rossiter CE, Gilson JC, et al: UK naval dockyards asbestos study: Radiological methods in the surveillance of workers exposed to asbestos. *Br J Ind Med* 1978;35:195–203.
13. Felson B, Morgan WKC, Bristol LJ, et al: Observations on the results of multiple readings of chest films in coal miners' pneumoconiosis. *Radiology* 1973;108:19–23.
14. McMillan GHG, Rossiter CE: Development of radiological and clinical evidence of parenchymal fibrosis in men with non-malignant asbestos-related pleural lesions. *Br J Ind Med* 1982;39:54–59.
15. Greenberg M: The ILO international classification of radiographs of pneumoconiosis 1980: Where do we go from here? *Am J Ind Med* 1984;6:405–406.
16. Weill H, Jonwa E, (eds): The chest roentgenogram as an epidemiologic tool: Report of a workshop. *Arch Environ Health* 1975;30:435–439.

Critical Medical Devices List

The Food and Drug Administration's 1988 list of critical medical devices includes 182 products. The number of these devices—which are intended to be surgically implanted in the body or to support or sustain life, and whose failure could cause significant injury to a patient—is up from 75 on the original 1978 list. The list is "only illustrative" and does not necessarily include all devices that fall under the critical device definition.

—From "The Notebook," *FDA Consumer*, 1988;22(5):30.