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The Tyler Asbestos Workers Program. I. A Medical Surveillance Model and Method

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ABSTRACT. An asbestos-exposed worker who smokes cigarettes has a high risk of developing cancer of the lung. One thousand ninety-five former workers at a plant manufacturing asbestos (amosite) insulation products were exposed to high levels of asbestos dust concentrations in the atmosphere. The workers have been identified and located. A semi-annual medical surveillance program has been developed with National Cancer Institute support. Examination of the worker includes the following: history (questionnaire), physical examination, sputum cytopathology, chest roentgenogram, pulmonary function studies, and other tests. Emphasis has been placed on understanding the role of sputum cytopathology in a cancer control program in former asbestos workers.

THE HAZARD of pulmonary fibrosis in asbestos workers in Great Britain was demonstrated by Merewether and Price in 1930.[1] In 1949, Merewether reported a more ominous association of cancer of the lung with asbestos exposure.[2] Lung cancer as the cause of death of persons certified as having asbestosis rose from 7% in 1935 to 17% in 1947. Sixty-one cases of lung cancer had been recorded in persons with asbestosis prior to 1955.[3-5] In that year, Doll reported that mortality from lung cancer was a specific industrial hazard of certain asbestos workers.[5] Buchanan, in 1965, reported that lung cancer caused the death of 54% of workers with asbestosis.[6]

Cigarette smoking has been demonstrated by Selikoff et al.[7] to greatly increase the risk of death from lung cancer among asbestos insulation workers. It was calculated that these workers with a history of cigarette smoking had eight times the risk of cancer death compared with cigarette smokers who had no asbestos exposure. Further, the smoking asbestos insulation worker had approximately ninety-three times the risk of men who neither worked with asbestos nor smoked cigarettes.

In addition, Selikoff showed that workers exposed to asbestos dust for 3 months or less died of lung cancer at a higher rate than expected based upon white male age-specific death rate data of the U.S. National Office of Vital Statistics.[8] Amosite, which accounts for less than 5% of asbestos fiber consumption in the United States, has a carcinogenic potential which is similar to other asbestos materials.[9]

Consumption of asbestos materials in the United States was 725,000 short tons in 1976. Approximately 55,000

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individuals are currently in occupations related to the manufacture of products containing asbestos. Several times this number have had significant exposure to asbestos in the utilization of over 3,000 products containing this mineral.

The present paper describes a protocol for the serial health examination, including cytology, of a large group of former asbestos workers. A subsequent report will outline the worker characteristics and participation and the preliminary results of the examination.

Historical Background

An extensive review of the history, operation, and environmental survey of the plant at Tyler, Texas was published by Brodeur.[10]

The Plant

The plant manufactured asbestos insulation products from 1954 through February 1972, when it closed. A predecessor installation in Paterson, New Jersey operated from 1941 to 1954 using some of the same equipment and raw materials.[11] The amosite asbestos was transported from Transvaal in South Africa in burlap sacks. The sacks were removed from railroad boxcars and transferred to the plant for storage. Insulation material was manufactured from the amosite asbestos (approximately 90%) mixed with varying amounts of diatomaceous earth, sodium silicate, and mineral wool.[11] Plant operations were housed in a rectangular army barrack-type building with an open ceiling, and management offices were separated from the plant by a door which remained closed much of the time.

Medical and Environmental Studies

The University of Texas Health Center at Tyler (UTHCT) conducted medical and laboratory studies in August 1971, on sixty-two workers at the request of the medical director of the parent firm. A medical and environmental team from the Division of Field Studies and Clinical Investigations of the National Institute for Occupational Safety and Health (NIOSH) conducted a separate survey in October 1971. At this time, employment records at the plant were microfilmed and efforts were begun to locate the former asbestos workers.

In January 1972, the following data from the studies were reviewed: history (questionnaire), physical examination, chest roentgenogram findings, and pulmonary function tests. At the review the following were present: medical director of the parent firm, UTHCT staff, and staff of NIOSH. Eighty-five percent of the workers indicated a history of smoking cigarettes. Among those seen were seven patients who fulfilled Murphy's epidemiologic criteria for the diagnosis of asbestosis.[12]

Three environmental surveys of plant operations conducted by the Department of Health, Education, and Welfare are depicted in Table 1.[11] The five plant operations revealed a mean fiber count of three to eighteen times as many fibers as allowed by OSHA Standards (maximum of five fibers longer than 5 μ in length per ml air). Deficient housekeeping practices were also cited.

The Biometry Branch of NIOSH, using employment records, developed a computer master file of 878 workers. Information on the workers included the following: employee's name, sex, race, vital status, address, spouse, birth information, death information (person to notify, etc), and employment history (i. e., duration of employment, sequence, department, and operation).

On June 6, 1974 the Tyler Asbestos Workers Program (TAWP) was established with National Cancer Institute support. The purpose was to develop and evaluate a Cancer Control Model in a group with significant occupational exposure. Since receiving information of the 878 workers from NIOSH in June 1974, fifty-two individuals who were not on the computer master file have been identified as being former employees of the plant. In addition, 165 workers employed by Manpower Incorporated had intermittent asbestos exposure unloading the amosite from the railroad freight cars and have been added to the cohort. As of May 31, 1978 the total known cohort was 1,095 workers.

Methods

Rationale and Method of Surveillance

Lung cancer may be a frequent and usually fatal health problem in asbestos workers. The 5-yr survival of patients with lung cancer presenting to the health delivery system is between 7 and 8%. Doctors Doucot and Weiss have con-

Table 1.–Tyler Asbestos Plant Mean Fiber Concentrations by Operation and Year

Operation	1967	1970	1971	Mean of 3 yr
		(Fibers/ml)		
Milling	163.5	36.2	74.4	91.4
Forming	33.3	25.7	50.6	36.5
Curing	2.5	31.0	14.4	15.9
Finishing	44.6	34.8	39.5	39.6
Packing	16.7	17.9	22.8	19.1
Miscellaneous	–	13.8	16.6	–

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cluded that routine twice-a-year roentgenograms failed in a random population to improve this unfortunate frequency of survial.[13,14] Selikoff, reporting on the follow-up of 1,249 asbestos workers from January 1, 1963 to December 31, 1974 found that clinical surveillance including serial chest X-rays was insufficient to appreciably improve the prognosis among such individuals.[15] Fifty-nine instances of bronchogenic carcinoma occurred during the interval of observation. Fifty-seven of fifty-nine men were dead by January 1, 1975, and Dr. Selikoff stated that "far more effective measures of preclinical diagnosis are needed if anticipated disease in this group at high risk of cancer is to be effectively treated."[15] Preliminary reports by Fontana indicate that lung cancer can be detected early using sputum cytopathology.[16,17] In addition, localization by fiberoptic bronchoscopy and surgical resection appears to increase the survival of patients with squamous lung cancer.[16] Dr. Marsh has reported the localizing of seventeen consecutive radiologically occult carcinomas discovered in the sputum of fifteen patients.[18] Two had simultaneous second primary lesions in the opposite lung, and detailed examination of the upper respiratory tract revealed occult tumors in two patients.

Serial sputum cytopathology is an untried method for cancer surveillance in occupationally high-risk groups such as asbestos workers. It seemed reasonable that sputum cytopathology should be a prominent feature of a prospective surveillance of these workers. Further, it seemed appropriate to make the following modifications to the Mayo Early Lung Cancer Detection Project.

1) Screening would be carried out very 6 months instead of every 4 months. It was deemed impractical to have the workers who were, for the most part, well and employed submit to examinations more frequently than every 6 months.

2) It was determined that cytopathology examination should be performed on aerosol-induced secretions in addition to the 3-day pooled specimens collected spontaneously. This would allow a comparison of the yield of these two methods of sputum collection for cytology and ferruginous body examination.[19]

3) It was decided to include a group (smokers and nonsmokers) of nonasbestos-exposed individuals in the surveillance primarily as a control for cytopathology.

4) Other details of the surveillance routine are related to their unique occupational exposure and the ventilatory function studies to evaluate the development of pulmonary fibrosis in the workers. Plasma and serum were collected for 4½ yr and stored for possible future use for clinical or investigative studies.

The surveillance is as follows:

1) Each worker is given an appointment every 6 months by mail. The first worker was examined on June 24, 1974.

2) Each worker is interviewed utilizing a 9-page health questionnaire requiring 40 to 50 min to administer. Approximately 60% of the questions are derived from a questionnaire on respiratory symptoms utilized by Ferris in a survey of a New Hampshire town.[20] Fifteen percent of the questions are taken from the Mayo Lung Project questionnaire. The remaining questions were developed by TAWP to obtain additional social, smoking, occupational, past, and family history, and a review of systems. The follow-up questionnaire is less than 2 pages in length and can be administered in about 10 min. Approximately 55% of these questions are from the Mayo Lung Project questionnaire and the remaining questions were prepared by TAWP.

3) The physical examination is performed by a physician and careful attention is given to the examination of the chest (for rales), abdomen (for masses), and extremities (for clubbing). The worker is counseled about the findings and questions are answered.

4) Chest roentgenograms are obtained as follows: inspiratory postero-anterior (PA), left lateral views, and an expiratory PA utilizing a grid technique with a mean kilovoltage (KV) of 98 to 106. In addition, a 350 KV field emission unit PA is obtained. Thus, the higher and the lower KV technique may be compared for effectiveness in early detection of peripheral lesions. The roentgenograms are read independently by two board-certified radiologists. A conventional report is dictated and additional findings are recorded utilizing the ILO-U/C classification system for pneumoconiosis.

5) Forced vital capacity (FVC) and maximum voluntary ventilation (MVV) are performed on the Ohio 842 spirometer with the Ohio 120 normal value indicator. The instrument is calibrated and maintained in accordance with the manufacturer's recommended procedures. The FVC procedure is performed and recorded three times and the MVV two times. The best result is reported, but the data on all the strip charts are maintained. From the FVC procedure the following parameters are obtained: peak flow (PF), forced expiratory volume in one second ($FEV_{1.0}$), forced expiratory flow between 25 and 75% of total (FEF 25-75), and forced expiratory flow between 200 and 1200 ml (FEF .2-1.2). The $FEV_{1.0}$ is reported in ml and the other parameters in *l*/min. The ventilatory tests are interpreted by the program director. A complete pulmonary function profile, including carbon monoxide diffusion capacity is not done at the time of the routine visits. A pulmonary profile is done if the patient is seen in the UTHCT outpatient clinic or admitted to the medical service. It is desirable to streamline the screening process and eliminate a visit to the cardiopulmonary laboratory.

6) The following specimens are processed by the cytopathology laboratory:

a) sputum obtained at the clinic utilizing aerosol of 8% sodium chloride in water generated by DeVilbiss 900 ultrasonic nebulizer;
b) 3-day pooled early morning sputum collected at home and mailed to the laboratory.

The sputum is collected in 50% alcohol and 2% carbo wax. From June 1974 through February 1976, specimens were prepared by the "pick and smear" technique.[21] Cell blocks were prepared when adequate material remained. Since March 1976 the Saccomanno sputum concentration technique[22] has been used for smear preparations and cell

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locks have not been prepared. All smears are stained by e routine Papanicolaou technique, screened by cotoechnologists, and reviewed by a cytopathologist.

The following additional laboratory procedures are performed utilizing standard written protocols: a) electrocardiograph utilizing an American Optical Model 3200 instrument; (b) hemoglobin and hematocrit; (c) carcinoembryonic antigen (CEA) performed by Hoffman-La-Roche Laboratory; (d) urinalysis; (e) additional blood is drawn, where half is anticoagulated using EDTA and the plasma separated. Approximately 5 ml of plasma are mailed to Hoffman-LaRoche for CEA determination. The remaining plasma is divided into two aliquots and stored. The stored plasma and serum are kept in a Revco ultralow freezer at −70°F.

Following each examination the worker receives a written medical report including positive findings regarding history, physical examination, and laboratory data. When abnormal sputum cytology and/or chest roentgenogram findings are noted, the patient may be seen again immediately, or may be placed on a 3 month surveillance schedule, depending upon the clinical significance of the findings. Most of the workers requiring 3 month visits have shown moderate to severe atypia in the sputum.

When a worker fails to keep an appointment, he is contacted by telephone within the next week. The reason(s) for the missed appointment is ascertained and another appointment is scheduled. If the worker cannot be reached by telephone or is not seen after a reasonable me interval, he is placed in a category requiring special ttention. A letter is written to encourage attendance and a decision is made regarding the need for additional telephone contacts and/or a home visit.

Eighty-seven percent of the workers are seen at the UTHCT clinic with appointments being scheduled each day from 8:00 A.M. to 5:00 P.M. Clinic sessions are also held periodically on Thursday evenings and Saturday mornings for those who cannot attend during regular hours. Satellite clinics have been conducted in East Texas utilizing a mobile clinic trailer owned by the Texas Department of Health for use in the Tuberculosis Control Program. Clinics have also been held at regular intervals in Dallas and Houston with the cooperation of the health departments in these cities and at the Texas Department of Corrections in Huntsville. Twelve percent of the workers have been screened at satellite clinics which are staffed largely by TAWP personnel. Approximately 1% of the workers have been examined by contractual arrangements with health facilities located out of state.

Patient Care and Other Support

Workers who require additional diagnostic services and/or treatment may be seen in the UTHCT outpatient clinic or admitted to the inpatient service. Eighty-three workers have the majority of their health needs met at the UTHCT clinic and approximately 217 additional workers are seen occasionally for health-related services. One thousand, five hundred and ninety-six outpatient clinic visits have been recorded from June 1974 through May 31, 1978. One hundred and two workers have been admitted 251 times to the medical and surgical inpatient service during the same time interval. Eleven patients were admitted for diagnosis and treatment of known or suspected respiratory malignant disease. Bronchoscopic localization of radiographically occult lung cancer is done utilizing a protocol similar to that reported by Sanderson.[23] The following are some of the additional services provided to the workers as needed: financial (for medical care including drugs and equipment), social, dietary (obesity), psychological, spiritual, and vocational rehabilitation counseling.

For the large number of workers who are cigarette smokers, health education has been accomplished on an individual basis by the interviewer, the physician, and other members of the staff.

A collaborative relationship between the UTHCT and the University of Texas System Cancer Center (UTSCC) in Houston was established, and on June 14, 1976 staff were employed by UTSCC to coordinate smoking cessation and health education activities. A smoking cessation clinic and instructional aids have been developed but emphasis is placed on one-on-one counseling. Other health needs such as hypertension, obesity, and diabetes are addressed by the staff which is oriented toward prevention of disease. As of September 1, 1978 smoking cessation and health education were reorganized and unified with the program conducted by the UTHCT staff.

In November 1976, a contract with the University of Texas System Cancer Center was implemented to provide statistical support services for TAWP. Work has begun to develop programs, enter a large backlog of data into the computer, and keep the data entry on a current basis. The staff of UTHCT has access to current information through interactive cathode ray tube CRT) and printing terminals.

Discussion

There are at least two avenues of possible help for workers who are at risk of developing cancer of the lung: 1) smoking cessation, and 2) early detection and treatment of cancer. In this report we deal with aspects of early detection of lung cancer.

A preliminary report of the cytology aspect of early diagnosis of TAWP workers has been published.[24] The first year cytopathology findings in 554 workers have shown two workers (.04%) with squamous carcinoma. Although localization was accomplished in one, neither individual (ages 78 and 74 yr) had resectional surgery and both have expired. Since that report, one worker (RS, age 58 yr) and one smoker control (CS, age 67 yr) with positive cytologies have had localization and surgical resection for radiologically occult carcinoma. Chest roentgenograms revealing no evidence of malignant changes may be seen in Figures 1 and 2. The smoking history of RS and CS was 60 and 50 packs/yr, respectively; however, CS quit in 1970.

Selikoff has shown that increased mortality from lung cancer and pleural mesothelioma in asbestos insulation workers became apparent after 10 yr from onset of exposure.[25] Tumor doubling time studies by Spratt and by Garland revealed a mean doubling time for squamous cell cancer of the lung of 93 and 126 days, respectively.[26,27]

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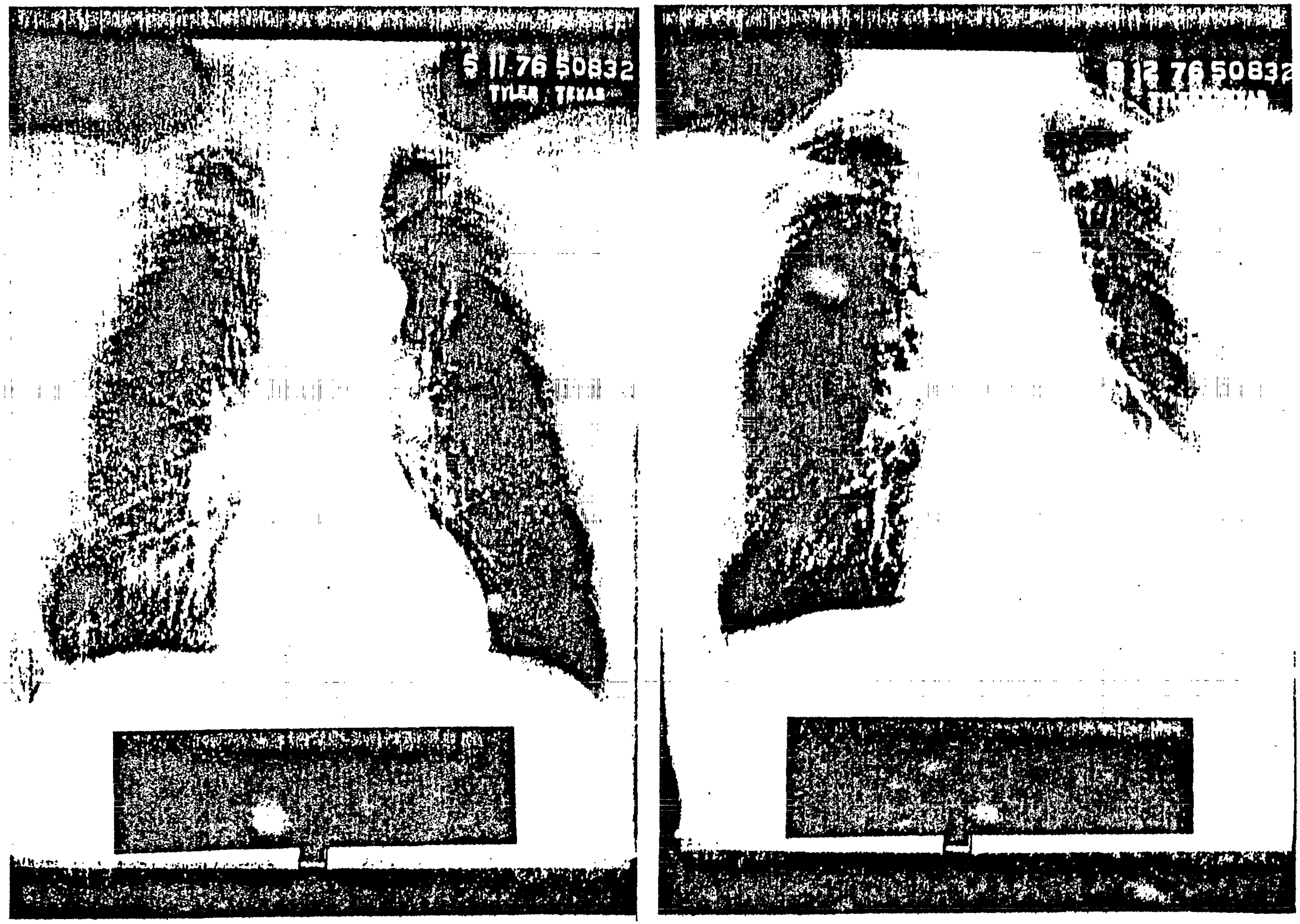

Fig. 1. (Case 1, RS, 58 yr of age.) (*A*) Chestroentgenogram was negative for malignancy at a time when numerous malignant cells were noted in the sputum with cytopathological features of squamous carcinoma. (*B*) Chest roentgenogram following left upper lobe resection for carcinoma in situ.

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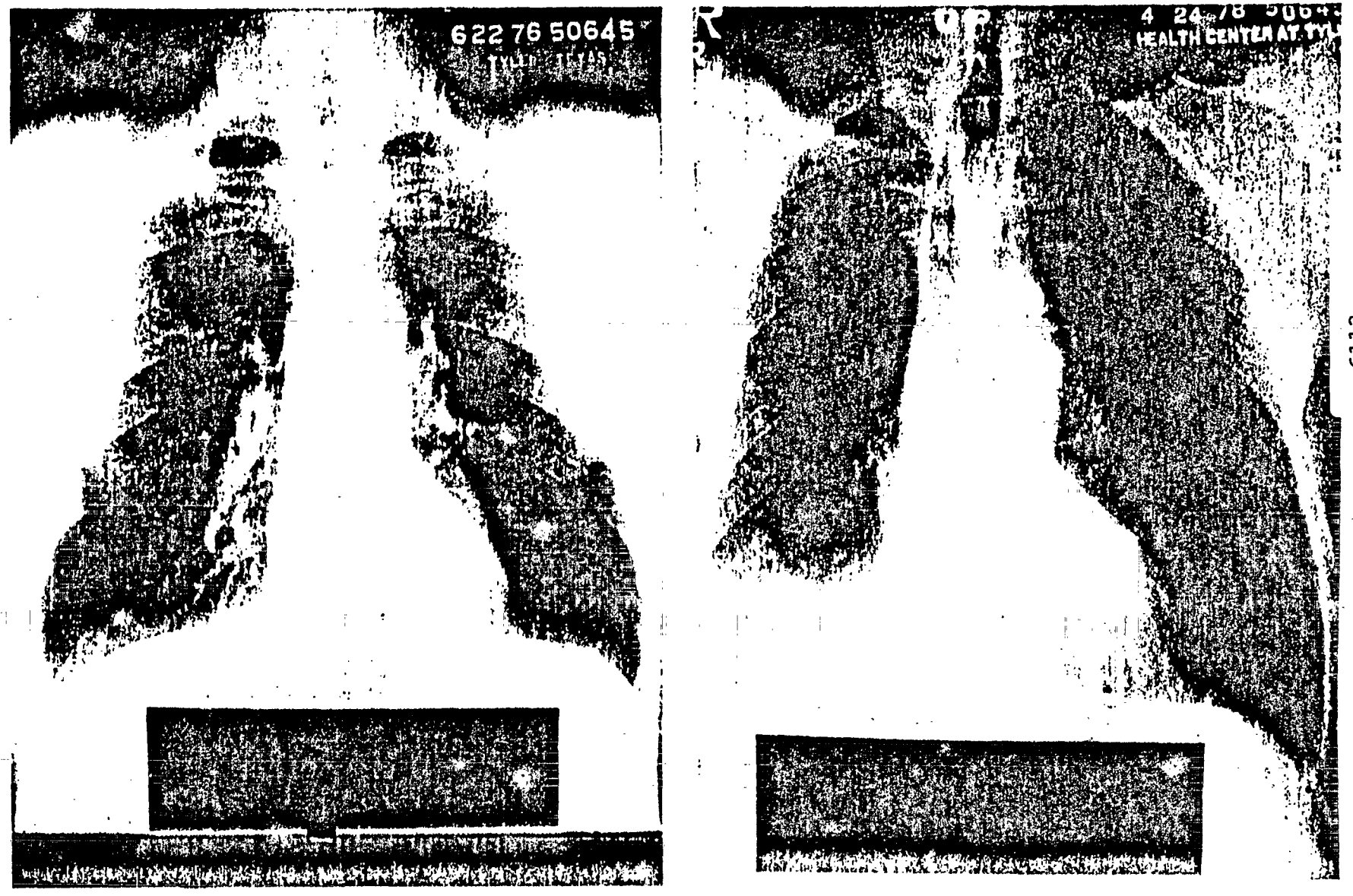

Fig. 2. (Case 2, CS, 67 yr of age.) (*A*) Chest roentgenogram reveals no evidence of malignancy. Sputum cytology was positive for squamous cell carcinoma. (*B*) Chest roentgenogram following right middle and lower lobe lobectomy. Carcinoma in situ was found at the bronchial margin of both lobes.

It is estimated that 7 yr may be required for a squamous tumor to reach a size of 1 cm from the time of malignant cell (clone of cells) transformation. Pulmonary carcinomata less than 1 cm in diameter are very rarely recognized by chest roentgenography.[28] The mean doubling time for adenocarcinoma was 219 and 269 days, respectively.[26,27] Thus, the estimated preclinical incubation time for cancer of this cell type is 20 yr. It appears that ample time is available for diagnosis of preinvasive or early invasive lung cancer by means of cytopathology. Once lung cancer has become symptomatic, nine out of ten patients are dead within 8 months.

Because of the latent period for development of lung cancer, it is preferable for a group undergoing prospective medical surveillance to be young. Eighty-six percent of the TAWP workers were less than 40 yr of age at the onset of their employment. About 25% of the Tyler workers are approaching 23 yr from the onset of employment. The greatest yield from early detection efforts is expected to occur in the next 13 yr, at which point 88% of the workers will have 20 or more yr since beginning employment.

Routine sputum cytology has been most effective in the detection of squamous carcinomas which generally are centrally located in the tracheobronchial tree. Fifty to 55% of lung cancers in cigarette smokers are of this cell type. This appears to be the most favorable group of carcinomas which can be detected early by means of cytopathology.

Kannerstein found that the cell type of carcinoma of the lung in fifty patients occupationally exposed to asbestos was the same as matched controls.[29] He reported the following lung cancer cell types in asbestos-associated patients: eleven squamous (22%), eleven anaplastic small cell (22%), eleven adenocarcinoma (22%), six anaplastic large cell (12%), eight combined (16%), and three unclassified (6%). Whitwell, however, has reported that the histological cell types of lung cancer in workers suffering from asbestosis in the United Kingdom show a higher percentage (34%) of adenocarcinoma than would be expected in a group of cigarette smokers.[30]

Fontana has suggested that the radiological and cytopathological screening are complimentary in the early detection of lung cancer.[16] Chest roentgenogram is said to be more effective in the early diagnosis of peripheral lesions such as adenocarcinoma. The value of having a chest roentgenogram every 6 months as an early screening technique for lung cancer has been the subject of debate. The present serial study may help to answer this question and to clarify the role of cytology in a group at risk for environmentally related cancer.

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Occupational Lead Exposure and Renin Release

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ABSTRACT. Hypertension may result from chronic lead exposure. Lead poisoning arising from "moonshine whiskey" drinking has been associated with a rise in plasma renin activity. In the present study, plasma renin concentration following intravenous administration of frusemide was measured in eleven subjects with moderate or severe lead poisoning of industrial origin. The results were compared with those obtained for seven normal, control subjects. There was no significant difference in response obtained in the two groups. Industrial lead poisoning does not appear to affect renin release. The combined insult of lead and alcohol may explain the findings in the previous study.

CHRONIC or repeated exposure to toxic amounts of lead (Pb) gives rise to a chronic nephropathy characterized by renal tubular damage[1,2] and cortical atrophy with interstitial fibrosis.[3] Hypertension in itself may not be a feature of acute Pb poisoning[4] but during the last century when industrial hygiene was poor, a high incidence of renal disease, hypertension, and vascular disease was noted.[5,6] In a recent epidemiological study, an association was demonstrated between chronic low-grade Pb exposure and elevation of blood pressure.[7] The authors were interested to know whether plasma renin, which may be high, normal, or low in hypertensives and is released from the juxta-glomerular apparatus of the kidney, could be affected by Pb poisoning.

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