March 23, 1973

S. Lincoln Avenue
Lebanon, PA 17042

JMEH 1181

R. C. Bacon
Director, Research and Development
R. T. Vanderbilt Company, Inc.
33 Winfield Street
East Norwalk, Connecticut 06855

Dear Mr. Bacon

RE: Talc (0) Tremolite (0), Chrysotile (2+), Anthophyllite (3+), Amosite (4+), Crocidolite (10+) etc

Thanks for consulting me about these items. As you know from my publications I have had considerable experience in decoding the biological action of the fibrous silicates. This is based both on elaborate inhalation experiments, human exposures with necropsy studies, and of course review of the literature.

The order in which I have listed these fibrous minerals represents my interpretation as to their capacity for inducing biological responses. Talc is listed first and given a zero rating since it is in pure form, practically innocuous except for overwhelming prolonged exposure. The latter is no longer permissible in the USA so, for practical purposes, this substance is harmless.

Crocidolite, by contrast, is listed last and given a 10+ or maximal rating. It can with relatively minor exposure, produce exceedingly serious and progressive changes in the lungs or wherever it becomes lodged. One of these effects is the capacity to produce neoplastic disease.

Talc, Tremolite and Chrysolite need to be discussed a little more fully.

Pure mineral talc of the non-tremolite kind, does not induce a tissue response of any clinical significance. If there is prolonged exposure the lung aleoli and some lymphatics can trap phagocytic cells which ingested the talc particles and this may block out their functions temporarily. This type of pathology is called a thesaurosis or storage effect. It is usually reversable on cessation or decrease of exposure and no significant permanent after-effects result.

The same applies for tremolite talc. It is inert like Georgia talc and induces only a thesaurosis effect when there is excessive prolonged exposure. However, Tremolite sometimes is "contaminated"

with chrysotile or other true asbestos type fibrous minerals. When this is the case, the thesaurosis becomes a thesaurismosis ie the alveolar walls and perilymphatic tissues begin to react, and fibrous tissue forms. This is due to the asbestos fibers and not the tremolite component. The fibrotic response is directly proportional to the ratio of asbestos fibers admixed with the tremolite. You will note from one of my experiments that when small quantities of chrysotile were mixed with gypsum the chrysotile effect never-the less prevailed despite dilution with the inert gypsum.

This sounds like I make chrysotile out to be a bad actor. It is true that prolonged exposure to chrysotile will produce asbestosis but of a relatively mild kind. In comparison, however, with what Crocidolite does, Chrysotile is a relatively tame beast. There are a number of persons currently making excessive propaganda about Chrysotile. Their noise tends to drown out the voices of sanity. The hullabaloo will of course go on for some time. Progressively, however, the evidence is coming in that Chrysotile causes only a fine interstitial fibrosis without blocking off the respiratory surfaces. The patient develops some disability because of stiffening of his lungs, but can survive for a long time with fairly good gas exchange. I have never yet seen a case of lung cancer caused by Chrysotile alone and no one else has ever been able to show me a case either. In mixed sequential exposure experiments with beryllium sulfate, as a potent carcinogen and Chrysotile as a potential co-carcinogen. the suprise finding was that Chrysotile acted as an anti-carcin

Of course, if one mixes Chrysotile with Amosite, Crocidolite or Silica exposures, bad effects follow - read back. Possibly this why Chrysotile got a bad name.

I hope this summary is of help to you. If I can provide more detail, please let me know.

Sincerely,

GERRIT W. H. SCHEPERS, M.D., D.Sc.

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Presented by the

DEPARTMENT OF PATHOLOGY

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JMEA #3961

An Overview of Occupational Pulmonary Diseases

Daniel E. Jenkins, M. D.

An overview of occupational lung diseases as of 1977, will be given in which the more important aspects of recent additions to the literature will be emphasized so as to keep the audience abreast of changes in the last few years, exclusive of those areas which are being highlighted in the course itself. Since the enactment of the Occupational Safety and Health Act of 1970 (OSHA/70), much of the prevailing literature has dealt with the strong impetus to improve the working conditions of the industrial employee, to quantitate hazardous influences in the industrial environment, and to relate the quantum to the control of the diseases. The continuing publication of criteria documents on specific chemical and physical agents by the National Institute of Occupational Safety and Health (NIOSH) since 1973, is one important example of the government's effort in this direction and these will also be reviewed as they relate to pulmonary problems. Key review articles will be stressed in an enlarged reference list. Acute respiratory illnesses remain the leading cause of absenteeism throughout industry and permanent impairments in the health of industrial workers which lead to total disability are largely pulmonary in origin so that the challenge to improve the health and reduce the risk of the industrial employee rightfully involves a review of relevant new industrial products and processes, a look at carcinogenic occupational exposures with special emphasis on bronchogenic neoplasms and mesotheliomas, recent studies shedding new light on established problems such as the textile and insulation industries, welding, the use of abrasives, etc. New particulate matter which may cause bronchopulmonary ailments continues to be reported in the area of organic and vegetable dusts, and other problems outside the industrial realm such as smoking continue to influence the health profile of the worker and frequently aggravate respiratory problems which are of occupational origin.

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JMEA #3962

Diffuse Pulmonary Parenchymal Changes In New Orleans Asbestos-Cement Workers

Hans Weill, M.D.

A description of the asbestos dust exposure characteristics in the asbestos-cement industry will be provided. Methods for reconstructing the past dust exposures both qualitatively and quantitatively will be described and the use of these reconstructed dust exposure indices in developing dose-response relationships will be illustrated.

Techniques and problems in the detection of a biologic response in exposed workers of this industry will be discussed. Cross-sectional and longitudinal readings of chest x-ray films using the ILO U/C International Classification have provided results which have been analyzed in a variety of ways. Problems to be discussed include inter-observer variability, interpretation of pleural shadows, the role of silica in producing a "mixed-dust pneumoconiosis" and independent randomized versus side-by-side reading of paired films taken serially. The use of median readings in generating dose-response curves will be illustrated.

Attention will be directed toward those measurements of pulmonary function which are useful in detecting an adverse dust-related functional effect in exposed workers. Again, dose-response relationships will be shown using pulmonary function as the indicator of a biologic response. Results of these studies will be compared with those of other investigators.

Finally, evidence will be presented suggesting differing severity of effects associated with fiber-type (chrysotile versus crocidolite) when total estimated dose of fiber exposure is similar.

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JMEM #3963

THE TYLER ASBESTOS WORKERS PROGRAM

George A. Hurst, M. D.

The association of cancer of the lung and asbestosis was reported by Merewether in Great Britain in 1949. Lung cancer as the cause of death in persons certified as having asbestosis in Great Britain rose from 7% in 1935 to 17% in 1947. Buchanan, in 1965, reported that lung cancer caused the death of 54% of workers with asbestosis. Cigarette smoking was shown by Selikoff to greatly increase the risk of death of lung cancer among asbestos insultation workers. In addition, Selikoff showed that workers exposed for three months or less also had a significantly higher risk of developing malignancy of the lung.

An asbestos production plant, which manufactured thermal pipe insultation, operated in Tyler from 1954 to 1972, at which time it closed. Medical studies on sixty-two employees of the plant were done in August, 1971, by the East Texas Chest Hospital. Medical and environmental studies were done by a team from the National Institute of Occupational Safety and Health in October, 1971. Among sixty-two employees surveyed, eighteen men had been employed for ten years or longer and among this group, eight cases had findings compatible with an epidemiologic diagnosis of asbestosis. Workers in this plant were exposed to high concentrations of amosite asbestos fibers.

In June, 1974, the Tyler Asbestos Workers Program was initiated to provide health surveillance, early cancer detection and diagnosis to the former workers. Funding was secured by means of contract from Cancer Control and Rehabilitation Division of the National Cancer Institute No. 1-CH-45066. Through November 30, 1976, 908 asbestos workers have been identified who had been employed by the plant and 169 workers who were employed by Manpower to work on a temporary basis. The Manpower workers were utilized to unload raw asbestos fibers in burlap sacks from boxcars and transport the sacks to the plant.

Among the plant workers, 75 are known to be deceased, 73 are lost to follow-up and 760 are available for examination. Of these, 588 or 77% have been seen on one occasion.

Among the Manpower workers, five are deceased, seven are lost to follow-up and 157 are available for examination. Seventy-five or 47.7% have been seen on one occasion.

Workers are given an appointment every six months. With each visit, the worker is interviewed utilizing Standard Health Questionnaire and a physical examination is performed. The following laboratory procedures are performed: chest roentgenograms, sputum cytopathology, routine ventilatory function tests, CBC, urinalysis, CEA. In addition, aliquots of plasma and serum are collected, frozen and stored for subseuqent biological marker studies.

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The East Texas Chest Hospital provides the services regarding localization, diagnosis and treatment of cancer of the lung.

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JMEA #3964

Chrystallography and Mineralogy of Occupational Pulmonary Diseases

Arthur M. Langer, Ph.D.

The inhalation, retention and subsequent interaction of inorganic particles in parenchymal tissues may give rise to a number of pulmonary diseases. These may include the pneumoconioses and in some instances malignant neoplasms. Although the lung parenchyma is considered the primary target organ, pleural involvement may be a complication (fibrosis and diffuse malignant mesothelioma). A number of inorganic mineral species have now been identified as agents involved in the etiology of pulmonary diseases: the various forms of silica, i.e., quartz, tridymite, and cristobalite, with silicosis; the various forms of asbestos, i.e., amosite, anthrophyllite, chrysotile, crocidolite, tremolite, with asbestosis and malignant noeplasms; the mineral talc, in its platy and fibrous form, by itself and contaminated with asbestiform amphiboles, with talcosis and malignant neoplasms; coal dust, and its associated mineral contaminants, with coal workers pneumoconiosis. Other active mineral dusts are also known.

As naturally occurring inorganic species, minerals possess properties which enables the investigator to uniquely identify them. Their crystalline character, specifically crystal structure and associated symmetry elements, and their bulk chemistry may be used to unequivocally establish their presence in tissues. These two basic properties control numerous other measurable parameters, e.g., characteristics observable by light microscopy.

A number of instruments are available for the study of inorganic dusts in human tissues:

The pathologist routinely utilizes a light microscopic technique for the examination of lung parenchyma, for the determination of the nature and extent of the disease state and for the identification or confirmation of the agents responsible for it. Bright field illumination, with phase contrast or polarized light optics, normally allows the investigator to determine the relative amounts of exogenous dusts associated with the tissues, their distribution, and some limited characteristics which might by used for identification purposes. However, often the agents involved are small, optical properties altered by tissue preparation techniques, and the resolution insufficient for proper dust characterization.

Techniques have been developed whereby 5μ tissue sections may be prepared for examination with electron beam instruments. Utilizing transmission electron microscopy, selected area

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electron diffraction, and an electron microprobe technique, the morphology, structural character and the chemical composition of the particles may be determined. The advantages in utilizing electron beam instrumentation to characterize particles in tissues is that relative amounts of particles, their identities, morphologies, size distribution characteristics, etc., may be determined and the nature of the exposure determined. However, the tissue areas scanned with beam instruments are small and so may not be representative of the total distribution of particles; the agents involved may be multiple so that a large number of analyses are required for statistical validation of the exposure. Scanning, utilizing an electron beam instrument, is time-consuming and a great deal of expertise is required for interpretation of data.

Currently, a combination of pathological and mineralogical examination of the same tissue block is required for a firm establishment of disease state and implicated agent. Utilizing a range of staining techniques, the maturity and extent of fibrosis may be determined. A number of special stains are also required for the evaluation of some tumors, e.g., mesotheliomas. In addition to these techniques, materials are sectioned from the same specimen, prepared by the carbon extraction technique, and examined with electron beam instruments. Utilizing transmission electron microscopy the inorganic dusts are characterized. On the basis of joint investigations between the pathologist and mineralogist, a more accurate clinical diagnosis may be approached, or a more correct ascertainment of cause of death.

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IMEA #3965

Physiologic and Radiographic Abnormalities In Asbestos Workers

Charles G. Spivey, M.D.

A plant manufacturing asbestos pipe insulation was located in Tyler, Texas from 1954 to 1972. This plant used amosite in the production of insultation. Almost 900 workers were employed at this plant for varying lengths of time during the years that it was in production.

Under the sponsorship of the National Cancer Institute a medical surveillance program for this group of workers was initiated in 1974, and has been in operation for over two years. During this time over 2,000 examinations of former workers have been carried out. These examinations consist of a health questionnaire, physical examination, hemoglobin and hematocrit, urinalysis, spirometric studies, chest films, and sputum specimens for cytology. About 80% of these workers have a history of cigarette smoking. The workers are seen at intervals of six months. Among the problems faced by individuals with significant exposure to asbestos are those of pulmonary insufficiency due to both pleural and parenchymal changes, and the development of malignant disease. Several authors have noted reduction in lung volumes and a decrease in diffusion capacity. Decreased diffusion studies may occur with a declining arterial oxygen saturation and reduced pulmonary compliance. Vital capacity has been shown to be a more sensitive index of early dysfunction than the diffusion sutdies. Recently evidence has been presented supporting a dose response relationship between dust exposure and lung function. It has been noted that pulmonary function studies do not always correlate with x-ray abnormalities and that frequently, there is a decline in pulmonary physiologic studies before x-ray abnormalities are noted. In some workers, especially those who have been non-smokers, flow rates are well preserved.

Various authors have noted pleural disease in asbestos or former asbestos workers. Pleural effusion in asbestos workers has been described and occassionally may be the precursor of a mesothelioma. A significant number of workers have been found to have thickened pleura, sometimes associated with calcification in both the pleura and the diaphragm. Asbestos plaques have been found in the parietal pleura. Pleural calcification has been noted in workers with long exposure. Becklake has mentioned two types of pleural reaction: 1) an exudative reaction involving the parietal and visceral pleura and the lung parenchyma with obliteration of the pleural space, and 2) a discrete reaction involving the parietal

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pleura with formation of a pleural plaque. The pathogenesis of pleural plaques is unknown. The characteristic lesion of pleural asbestosis is the plaque, described as a fibrotic process in the parietal pleura with late calcification. A shaggy pericardial shadow is sometimes seen also. The patients may also be found to have diffuse ground glass fibrosis with fine stipling or larger parenchymal nodules. These irregular or rounded opacities are usually noted in the bases of the lungs.

In the Tyler cohort, 53% of the workers have had abnormal pulmonary function studies and approximately one-third have an abnormal chest film. In the group with over 10 years exposure, those with abnormal physiologic studies and those with abnormal chest films tended to merge. Most of the workers with abnormal function studies had a restrictive defect. Only 11% of the workers had an obstructive or mixed defect. Of the total cohort, 139 had x-ray abnormalities considered to be related to asbestos exposure. Our presentation will include an analysis of roentgenographic and physiologic abnormalities related both to age, exposure to asbestos, and smoking history.

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IMEA #3966

Epidemiologic Study of Household Contacts of Asbestos Workers

Henry A. Anderson, M.D.

Asbestosis - parenchymal fibrosis, pleural fibrosis and pleural calcification - has afflicated many occupational groups exposed to asbestiform mineral fibers. The level of asbestos exposure experienced by the general population never employed in asbestos handling trades, however, was not anticipated to pose any health hazard.

That such a hazard might exist was first suggested by Kiviluoto in 1960.[1] He described an abnormally high prevalence of asbestotic pleural calcification (7.9%) among the 6,312 residents of a district of Finland in which an asbestos mine and mill had been operating for many years. In a contiguous district without an asbestos mine, no such instances of calcification were seen in 7,101 films.

The hazards broadened to include a neoplastic risk when Wagner et al.[2] reported mesothelioma occurring in non-occupationally exposed individuals in South Africa, and when Newhouse and Thompson[3] found that 76 cases of mesothelioma at the London Hospital 1910-1964, 11 were the result of neighborhood exposure and 9 of household asbestos contact.

Thus environmental asbestos exposure was established as being potentially hazardous. To the present, nevertheless, the actual incidence of such asbestotic neoplastic risks remains unknown, in the absence of population-bases data.

In 1973, we undertook an investigation to assess the prevalence of asbestos-associated radiographic abnormalities among the household contacts of 1,664 asbestos workers employed for varying periods of time from 1941 to 1954, in a factory producing amosite asbestos products. Many of these had been found to have serious, well-documented asbestos disease.[4]

Radiologic examinations 1973-76, of over 600 household contacts demonstrated that over 35% had chest x-ray changes characteristic of asbestos-induced changes. In some instances the index case (workman) had been employed for less than one month. Pleural fibrosis and calcification were the predominant abnormalities present. The frequency of such changes increased with the duration from onset of first exposure as well as with increasing duration of employment of the index worker. For comparison, a group of 326 individuals stratified by age and sex was selected. All lived in the same highly industrialized community as the study group, but none had known occupational or household asbestos contact. Six cases of pleural fibrosis and no cases of pleural calcification were seen. The prevalence of parenchymal fibrosis,

pleural fibrosis and calcification among the household contacts was statistically significantly different from the prevalence of such changes in the comparison group.

While tracing the family contacts, four cases of pleural mesothelioma have already been discovered. We are establishing a cohort of the family contacts, for evaluation of their mortality experience, 1954-1976.

Environmental contamination from industrial sources may be more widespread than suspected. This study demonstrates that significant household contamination can and does occur and in this instance resulted in characteristic radiologic changes as well as noeplastic disease. As other industrial agents are linked to neoplasms, with 20-30 year periods of clinical latency, the risk of associated household and environemntal exposure must be carefully considered.

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Pulmonary Cytopathology of Asbestos Workers

S. Donald Greenberg, M.D.

In 1929, ferruginous bodies, then called "curious bodies" were first reported in the sputa of individuals occupationally exposed to asbestos dust. Ferruginous bodies in the sputa do not appear to be a marker for severe atypias, rather, their presence correlates best with duration and extent of the industrial exposure to asbestos.

Through November, 1976, approximately 5,000 specimens of 678 former asbestos workers have been examined in the Tyler Asbestos Workers Program and the results constitute the basis of this report. Each former worker visits the Clinic at six month intervals for a complete examination which includes hypertonic saline aerosol inhalation to induce a sputa specimen. After the clinic examination, the worker mails in a home collected spontaneous early morning cough specimen which is a pool of three sequential mornings. This Tyler Asbestor Workers Program is a cancer control project begun in 1974, for a cohort of former workers employed in an amosite asbestos pipe insulation plant for varying periods of time between 1954 and 1972. More than 80% of these men also have a history of cigarette smoking.

When the program began in 1974, specimens were prepared by the "pick and smear" technique; since 1976, the Saccomanno sputum concentration technique has been used.

In most cases ferruginous bodies are easily detected on the routine PAP-stained smears. With the "pick and smear" technique they frequently appear within patches of free alveolar macrophages, while in the Saccomanno smears the ferruginous bodies are scattered among all the cells present. With both techniques, ferruginous bodies have been detected in approximately 33% of former workers.

Previous epidemiologic studies by Selikoff and co-workers has shown that cigarette smoking asbestos workers have a 90 times greater likelihood of developing lung cancer than do non-cigarette smoking, non-asbestos workers. Of the 678 former workers. 325 (48%) have shown squamous metaplasia, 95 (14%) mild to moderate atypia, 34 (5%) severe atypia, 3 (0.4%) suspect cancer and 5 (0.9%) squamous carcinoma.

Of the six patients with squamous cancer cells in their sputa, all were initially x-ray negative. One had localization by blind spur biopsy of the apical-posterior segment of the left upper lobe and left upper lobectomy disclosed squamous cancer-in-situ with microinvasion. One was inoperable at time of thoracotomy with

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metastasis to the pleura. One was inoperable due to poor general condition having had a laryngectomy for carcinoma one year previously. The remaining three have refused bronchoscopy. Two of these latter three with positive sputa cytopathology now reveal an x-ray lesion suggesting carcinoma in the right upper lobe. The remaining patient is still sputum cytopathology positive, x-ray negative. All six of these former asbestos workers with squamous lung cancer were chronic cigarette smokers and worked in the asbestos plant during the first two years (1954-55) of its operation.

Up to this time, approximately 40% of the former workers are less than 40 years old, 50% between 40 and 60 years old and 10% older than 60 years. The peak incidence of lung cancer in cigarette smoking asbestos workers follows 15 to 30 years after exposure. This critical period will not be reached in these workers until 1983, at which time their average age will be 55 years.

Sputum cytopathology is a non-invasive, painless means of early detection of premalignant and malignant pulmonary lesions. No special techniques are necessary for the detection of ferruginour bodies which serve as a marker for the extent of asbestos exposure.

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JMEA #3968

Sandblasters' Silicosis

Morton M. Ziskind, M.D.

About 1930, it was recognized that a rapidly developing form of silicosis occurred in sandblasters, which produced fatal disease after average exposures of ten years. At that time, protection was not well developed and few sandblasters were equipped with respirators and air-supplied hoods. In blasting with sand, the abrasive material is composed of 60% to 95% of free silica. It is expelled from an air hose at a pressure of 60 to 120 pounds per square inch, resulting in the production of a dust cloud composed predominantly of respirable particles of free silica less than 10 microns in diameter. Particles one to three microns form a high percentage of the dust and are most likely to deposit within the alveolar spaces. The development of simple nodular and complicated silicosis depends upon the alveolar deposition of respirable silica, phagocytosis by macrophages, and the death of phagocytic cells leading to phagocytic and fibroblastic proliferation. In severe sandblasters' silicosis occurring in cases with minimal protection carried out within enclosed spaces, the lesions are diffuse and extremely cellular, and associated with early disturbance of pulmonary function. In classical silicosis, symptoms are uncommon in less than 20 years, except for those resulting from prolonged use of cigarettes. In sandblasters' silicosis, distortion of lung structure occurs early and the symptoms of shortness of breath, cough, expectoration, weight loss, and even fever, have occurred after exposures of the order of two to three years. The diagnosis of accelerated silicosis as seen in sandblasters depends upon the history of the exposure and the roentgenographic patterns of disease. Nodulation occurs early with almost annual progression. Diffuse disease approaching pneumonic proportions may appear within a few years leading to reduction of lung volumes, and diminution of air flow rates; pulmonary diffusing capacity falls and the arterial oxygen tensions are reduced and drops further during exercise. Infectious complications of the disease are common and are usually produced by mycobacteria. In a recent series of 85 silicotic sandblasters, one-half of the mycobacterial infections were atypical; five of the individuals developed systemic mycotic complicating infections. An important complication of rapidly developing silicosis is the development of autoimmune reactions. Forty-five percent of a large series of silicosis sandblasters developed antinuclear antibodies. In 10% of the patients, frank collagen disease appeared, the most common varieties noted being rheumatoid arthritis, and localized and diffuse scleroderma. There is no specific treatment for silicosis. Mycobacteriosis can be controlled with chemotherapy but progressive structural changes are accelerated. Autoimmune phenomena may be responsive to adrenal corticoid drugs. Only preventive measures can eliminate this form of silicosis which is the consequence of an important

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American industry, the maintenance of steel structures used in shipbuilding and the oil industry. To protect the workers who must carry out this work, the most practical measure appears to be the substitution of materials which contain little or no free silica. Coal ash, steel grit and other substitutes are being used for this purpose. Modern protective devices can reduce the hazard, if they are kept in optimum working order. During the painting interval which follows sandblasting for most of these workers, hoods are removed and the blaster is exposed to residual suspended dusts. During this period, paint masks which supply inadequate protection are worn. Until the risk of this dangerous interval is reduced, the use of sand as an abrasive in ship and steel yard operations and maintenance of steel structures will continue to be unacceptable.

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JMEA # 3969

Pulmonary Changes of Amorphous Silica Exposure

R. Keith Wilson, M.D.

Free silica is present in nature as three distinct forms; polymorphic crystalline, cryptocrystalline (small crystals - 400 Å), and amorphous forms. The polymorphic crystalline forms are quartz, tridymite, and cristobalite. Quartz is converted to tridymite at a temperature of about 1000° C, tridymite converts to cristobalite at a temperature of about 1400° C, and cristobalite melts at about 1700° C.. The cryptocrystalline forms are flint, opal, chert, and chalcedony, and these are converted to tridymite and cristobalite under the same temperature conditions as quartz. Silica is present in amorphous form in nature as diatomite or diatomaceous earth, and is produced industrially in amorphous form by precipitation at high temperatures of sodium or calcium silicates. Amorphous silica is widely used in industry as an extender for diverse products such as paint and cake mixes. Amorphous silica is also converted to tridymite and cristobalite under the same temperature conditions as quartz.

The occurrence of pulmonary fibrosis due to exposure to crystalline silica is well known, while the fibrogenic potential of amorphous silica is uncertain. Cooper and Cralley found definite radiographic evidence of pneumoconiosis in 25-50% of diatomaceous earth workers depending on their exposure history. Oechsli et al., found 17-23% of diatomite workers had radiographic changes consistent with penumoconiosis, but the changes seemed to be present only in workers exposed to calcined diatomite. Calcination is a purification process which subjects diatomite to high temperatures, thereby producing cristobalite in varying quantities. Cralley et al., found no new pneumoconiosis in diatomite workers in one plant 16 years after careful dust control of the calcined product was instituted. An additional risk occurs with the widespread industrial utilization of calcined diatomite, although no studies of these workers exist.

The commercially prepared amorphous silica products have no crystalline silica content. Surveys by Plunkett and DeWitt and Volk of commercial amorphous silica workers revealed no evidence of pneumoconiosis with 8-12 years of exposure. Thus, pure amorphous silica does not appear to be fibrogenic. In any industrial process, including calcination of diatomite, amorphous silica exposed to appropriate temperatures is converted to crystalline silica which has definite fibrogenic potential.

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JMEA
#3970

Immunological Mechanisms Involved in Industrial Pneumoconiosis

Mark Schuyler, M.D.

Alterations of both humoral (B cell) and cell mediated (T cell-macrophage) immunity are important consequences of industrial dust exposure which may relate to the pathogenesis and/or complications of the resultant pneumoconiosis.

The lung has a full complement of immunocompetent cells (macrophages, T and B lymphocytes). The macrophage is not only important in phagocytosis, but is the effector cell of cell mediated immunity, and processes antigens prior to lymphocyte recognition. B cells can evolve into immunoglobulin secreting plasma cells and T cells can be effector or regulatory cells in either humoral or cell mediated immunity. Thus, dust inhalation can alter local and systemic immune function through interaction with cells present locally within the lung.

The following is evidence of immunologic abnormalities in pneumoconioses. Patients with both silicosis and asbestosis have a high incidence of anti-DNA autoantibodies. In silicosis and probably coal worker's pneumoconiosis (CWP) there is an increased incidence of connective tissue diseases, particularly scleroderma. Lung autoantibodies have been reported in CWP. Silicosis is well known to be associated with increased susceptibility to infections with intracellular organisms, especially mycobacterial. In addition, there is evidence of altered cell mediated immunity in silicosis, CWP, and asbestosis.

Miners with rheumatoid arthritis and CWP have a different course than those without rheumatoid arthritis (Caplan's syndrome), perhaps related to anti-DNA antibodies. One of the causes of progressive massive fibrosis (PMF) may be vasculitis associated with autoantibodies.

Although the causal relationship between dust exposure and pneumoconiosis is clear, there are additional factors which can alter the response of an individual to the dust. The same exposure can lead to varying severity of disease in the same group of workers. There is poor correlation between the amount of silica in a lung and the severity of silicosis, and between pulmonary asbestos fiber content and severe asbestosis. Progression of disease can occur in pneumoconioses after cessation of exposure. Lymphocytes, plasma cells, and immunoglobulins are prominent in silicotic nodules and asbestosis, and to a lesser extent in the macules of CWP. Thus, immunologic mechanisms may be important in the pathogenesis of pneumoconiosis.

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In vitro, silica and some forms of asbestos are potent and selective macrophage toxins. In animal experiments silica exhibits the same macrophage toxicity and also alters T and B cell function, perhaps as secondary phenomena. The initial cellular exudate evoked by animal exposure to either silica or asbestos may be mediated by activation of the alternative pathway of complement.

The above cellular effects of dusts may be related to both the fibrosis and the increased susceptibility to malignancy characteristic of some of the pneumoconioses. Fibrosis may be secondary to a factor released by dusted macrophages or could be caused by antigen-antibody complexes. Depressed immune surveillance may be part of the reason for the increased incidence of malignancies in asbestos exposed people. Alternatively, one of the abnormal antibodies produced might damage the mechanisms for recognition and/or control of malignant cells.

Thus, immunologic abnormalities can be sequelae to dust exposure, alter the response of that exposure, and be importnat in the pathogenesis and complications of pneumoconiosis.

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JMEA #3971

The Cytology of Cancer of the Lung and Its Relationship to Squamous Cell Metaplasia

Geno Saccomanno, Ph.D., M.D.

It is generally accepted that many of the tumors of the lung originate from malignant transformation of squamous cell metaplasia. The causes of squamous cell metaplastic formation may be carcinogenic effect, but may be due to Vitamin A deficiency, inflammatory, acute and chronic, or may be related to secondary effect of chronic irritation from healed inflammatory disease. The methodology of these transformations from normal epithelium may be much more complex than hereto thought and, in many ways, may vary in its genesis at various sites of the tracheobronchial tree. These various related matters will be presented and discussed in cytological and histological materials.

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AMEA #3972

Changes in the Tracheobronchial Tree in Relationship to Cigarette Smoking and Lung Cancer - Human and Experimental Studies

Oscar Auerbach, M.D.

Hypothesis:

A. In individuals who die of lung cancer, are there changes in the walls of the tracheobronchial tree which may be considered as preliminary stages of the development of lung cancer?

B. In individuals who die of causes other than lung cancer, are these same changes present in the tracheobronchial tree and are they proportional to the amount of cigarettes which they smoked?

C. If the carcinogenic agent is removed (cessation of smoking) before the point of no return, will regression of the changes occur?

D. Can these same changes be reproduced in a large animal by inhalation of cigarette smoke into the tracheobronchial tree?

Three separate studies of the tracheobronchial trees of human beings were done. The following changes were observed in all three studies:

1. Basal cell hyperplasia
2. Stratification
3. Squamous metaplasia
4. Atypical basal cells
5. Carcinoma in Situ
6. Early invasion

In all three studies these changes increased with the severity of cigarette smoking, namely; the least number of such findings were present in non-smokers with a progressive increase as the smoking habits increased. The greatest number of changes were present in the individuals who died of lung cancer, all of whom were smokers.

The results of this study leads us to the conclusion that these hypotheses are answered in the affirmative and also to the conclusion that cigarette smoking today is the single most important factor in the development of lung cancer.

In another study multiple factors were considered; namely, cigar and pipe smokers, urban and rural smokers and those who gave up

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the smoking habit. Cigar and pipe smokers showed findings that fell in between non-smokers and cigarette smokers, but closer to the non-smoker. Living in the rural areas is no different from urban areas if one is a cigarette smoker.

In a study of 216 cases which included 72 cigarette smokers, 72 ex-cigarette smokers, (namely individuals who had smoked for at least 10 years and had given up the habit for at least five years) and 72 non-smokers, the important findings were that individuals who had given up smoking showed a great decrease in the number of atypical cells in the bronchial epithelium and also a great drop in the incidence of carcinoma in situ.

A study on changes in the tracheobronchial tree of the epithelium of smoking dogs showed changes similar to those of smoking human beings. There was a chronologic development of atypism, squamous metaplasia and carcinoma in situ as smoking progressed.

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JMEA #3973

Immunological Mechanisms in the Pathogenesis of Lung Cancer

R. Russell Martin, M.D.

Epidemiological studies have consistently indicated an association between cigarette smoking and lung cancer, and the risk of carcinoma following certain industrial exposures (especially asbestosis) is increased in cigarette smokers. Studies of immunocompetent cells within the lung are of considerable interest in defining functional alterations which may be relevant to initiation and proliferation of pulmonary neoplasms. The broncho-alveolar spaces contain abundant macrophages, lymphocytes, immunoglobulins and other proteins; the lung is capable of acting as a significant immunological organ.

Changes in pulmonary alveolar macrophages (PAMs) with cigarette smoking are striking. In addition to consistent morphological alterations, PAMs from cigarette smokers are functionally changed: they are less responsive to the lymphokine migration inhibitory factor (MIF), they become agglutinable by the plant lection concanavalin-A, they are more metabolically active and migrate more rapidly in vitro, but phagocytosis is reduced. The content of immunoglobulins (particularly IgA and IgG) and the number of T lymphocytes in the bronchial lumen are increased with cigarette smoking. The ability of PAMs to mediate in vitro macrophage-dependent lymphoproliferative responses (including lymphocyte proliferation to soluble microbial antigens and to lymphocyte alloantigens) is impaired by cigarette smoking. In addition, there is a marked increase in the aryl hydrocarbon hydroxylase (AHH) microsomal enzyme system in PAMs of smokers. This enzyme detoxifies the polycyclic aromatic hydrocarbons (such as benzanthracene and benzpyrene) which are inhaled as part of cigarette smoke.

Most lung cancer patients have been or are presently cigarette smokers. Studies of immunologic reactivity in lung cancer patients must take into account the alterations induced by cigarette smoking. Studies with PAMs from lung cancer patients indicate additional abnormalities of function, including reduced phagocytic capacity, an even more impaired ability to mediate lymphocyte proliferation in vitro and abnormal induction of the AHH enzyme system.

Cell mediated immunity (involving interactions by lymphocytes and macrophages) plays a role in the eradication of neoplastic foci, or in the containment of tumors once they become established. Documentation that immunoreactive cells are present in the lung raises the possibility that they might engage in the defense against malignancy. If bronchial epithelial cells undergo transformation into malignant cells, failure of lymphocytes and/or macrophages to recognize this transformation and to move with proper aggression might be a factor in allowing a bronchogenic carcinoma to become established. Once formed, the progression of a pulmonary neoplasm may be more rapid and the response to therapy may be less satisfactory in the presence of macrophage or lymphocyte impairment.

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JMEA #3974

Chemoprevention of Lung Cancer Using Retinoids

Michael B. Sporn, M.D.

The development of epithelial cancer, such as carcinoma of the lung, mammary gland, bladder, uterus, and colon, is a disease process that takes many years to reach its final, invasive stage in humans. This disease process has the potential to be controlled by physiological or pharmacological means during its preneoplastic stages. Mechanisms whereby the progression of preneoplastic lesions can be stabilized, arrested, or reversed will be discussed. Pharmacological enhancement of such mechanisms by vitamin A and its synthetic analogs (retinoids) offers a possibel means for prevention of invasive epithelial cancer. We have called this non-cytotoxic approach to control of cancer, "chemoprevention," in contrast to the cytotoxic approach of conventional chemotherapy.

Retinoids are potent agents for control of cell differentiation in many epithelial tissues. Direct effects of retinoids on normal and prenoeplastic cell differentiation can be measured in organ culture. In experimental animals, deficiency of dietary retinoids enhances susceptibility to chemical carcinogenesis. Natural retinoids, fed at high dietary levels, have some ability to prevent chemical carcinogenesis in epithelial tissues of bronchi, trachea, stomach, uterus, and skin of experimental animals. However, natural retinoids have limited usefulness for chemoprevention of cancer because of inadequate tissue distribution and excessive toxicity. Synthetic retinoids have,therefore, been made and shown to be more potent and less toxic than natural retinoids for prevention of cancer of the lung, mammary gland, and bladder in animals.

The current status of basic research in the fields of cell biology of retinoids and prevention of carcinogenesis in experimental animals with retinoids now warrants consideration of the use of these agents to prevent epithelial cancer in man. For this purpose, it would be necessary to administer retinoids chronically during preneoplastic stages of the disease. Possible use of retinoids in human populations at high risk for development of cancer will be discussed.

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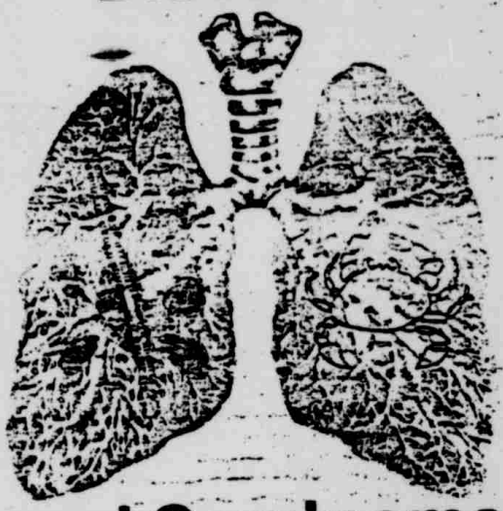
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The Office of Continuing Education
Baylor College of Medicine
Houston, Texas

announces a symposium on

Occupational Pulmonary Diseases



and Carcinoma of the Lung



Friday and Saturday
February 25-26, 1977

presented by the
Department of Pathology
Baylor College of Medicine
in cooperation with
American Thoracic Society
Texas Chest Foundation
Texas Thoracic Society
University of Texas School of Public Health
at
Jesse H. Jones Library Building Auditorium
Texas Medical Center

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Program

Occupational Pulmonary Diseases and Carcinoma of the Lung

Friday, February 25, 1977
Jesse H. Jones Library Building Auditorium—Houston

8:00 Registration

Asbestosis Session

John S. Chapman, M.D., Moderator

8:45 Introductory Remarks
Jack L. Titus, M.D., Ph.D.
Fred M. Taylor, M.D.

9:00 Welcome
John S. Chapman, M.D.

9:15 An Overview of Occupational Pulmonary Diseases
Daniel E. Jenkins, M.D.

10:00 Diffuse Pulmonary Parenchymal Changes in New Orleans Asbestos-Cement Workers
Hans Weill, M.D.

10:30 Coffee

11:00 The Tyler Asbestos Workers Program
George A. Hurst, M.D.

11:30 Panel Discussion
Moderator: John S. Chapman, M.D.
Panelists: George A. Hurst, M.D.; Daniel E. Jenkins, M.D.; Hans Weill, M.D.

12:15 Lunch—Doctors' Club

1:30 Crystallography and Mineralogy of Occupational Pulmonary Diseases
Arthur Langer, Ph.D.

2:00 Physiologic and Radiographic Abnormalities in Asbestos Workers
Charles G. Spivey, M.D.

2:30 Coffee

3:00 Epidemiology of Household Contacts of Asbestos
Henry A. Anderson, M.D.

3:30 Pulmonary Cytopathology of Asbestos Workers
S. Donald Greenberg, M.D.

4:00 Panel Discussion
Moderator: John S. Chapman, M.D.
Panelists: Henry A. Anderson, M.D.; S. Donald Greenberg, M.D.; Arthur Langer, Ph.D.; Charles G. Spivey, M.D.

4:45 Adjourn

6:30 Meet the Faculty Social Hour
8:00 Doctors' Club (cash bar, with chips and dips)

Saturday, February 26, 1977
Jesse H. Jones Library Building Auditorium—Houston

Silicosis, Uranium Mining, and Carcinoma of Lung Session

Marcus M. Key, M.D., Moderator

8:45 Welcome
Marcus M. Key, M.D.

9:00 Sandblaster's Silicosis
Mortin M. Ziskind, M.D.

9:20 Pulmonary Changes of Amorphous Silica Exposure
W. Keith Wilson, M.D.

9:40 Immunological Mechanisms Involved in Industrial Pneumoconioses
Mark R. Schuyler, M.D.

10:00 Sputum Cytopathology of Uranium Miners with Progressive Atypia as an Index of Cardinogenesis
Geno Saccomanno, Ph.D., M.D.

10:30 Coffee

11:00 Cause and Effect Relationships Between Cigarette Smoking and Lung Cancer
Oscar Auerbach, M.D.

11:30 Panel Discussion
Moderator: Marcus M. Key, M.D.
Panelists: Oscar Auerbach, M.D.; Geno Saccomanno, Ph.D., M.D.; Mark R. Schuyler, M.D.; R. Keith Wilson, M.D.; Mortin M. Ziskind, M.D.

12:15 Lunch—Doctors' Club

1:30 Immunological Mechanisms in the Pathogenesis of Lung Cancer
R. Russell Martin, M.D.

2:00 Chemoprevention of Lung Cancer Utilizing Retinoids
Michael B. Sporn, M.D.

2:30 Coffee

3:00 Panel Discussion
Moderator: Marcus M. Key, M.D.
Panelists: R. Russell Martin, M.D.; Michael B. Sporn, M.D.

3:45 Role of the Federal Government in Occupational Lung Diseases
James A. Merchant, M.D., Dr. P.H.

4:15 Critique and Summary of the Symposium
Kaye H. Kilburn, M.D.

5:00 Adjourn

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Professor of Medicine and Chief, Pulmonary Disease Division, Tulane University School of Medicine, New Orleans, Louisiana

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New York, New York

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Senior Medical Investigator, ... Hospital, East Orange, ... Professor of Pathology, College of Medicine and Dentistry of New Jersey, Newark, New ...

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Professor of Medicine, Southwestern Medical School, University of Texas, Dallas, Texas

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Principal Investigator, Tyler Asbestos Workers' Program, and Superintendent, East Texas Chest Hospital, Tyler, Texas

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James A. Merchant, M.D., Dr. P.H.
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Mark R. Schuyler, M.D.
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Charles G. Spivey, Jr., M.D.
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Michael B. Sporn, M.D.
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Professor of Medicine, Tulane University School of Medicine, New Orleans, Louisiana

Morton M. Ziskind, M.D.
Professor of Medicine and Chief, Pulmonary Disease Division, Tulane University School of Medicine, New Orleans, Louisiana

Registration:

Registration fee is $150.00 which includes luncheons (February 25-26, 1977); fee for related health personnel (Therapist, Technologist, Nurses, etc.) is $50.00.

Written notification of cancellation must be received prior to February 10 to obtain partial refund of fee (a $15.00 administrative fee is retained); thereafter no refunds will be made.

Continuing Education Symposium
Occupational Pulmonary Diseases and Carcinoma of the Lung
Jesse H. Jones Library Auditorium, Houston
February 25-26, 1977

Please make check payable to:
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Return registration form and check to:
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Baylor College of Medicine
Texas Medical Center
Houston, Texas 77030

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Office of Continuing Education
Baylor College of Medicine
Texas Medical Center
Houston, Texas 77030

Occupational Pulmonary Diseases and Carcinoma of the Lung

February 25-26, 1977
Jesse H. Jones Library Building Auditorium
Houston

This two-day program will be presented with emphasis on the scientific background, clinical diagnosis, and prevention of occupational pulmonary diseases, highlighting illnesses which are characterized by altered host-immunologic responses and complicated by pulmonary fibrosis and carcinoma of the lung.

Program Director:
Dr. S. Donald Greenberg
Professor of Pathology, Otorhinolaryngology and Medicine
Baylor College of Medicine

Program Co-Director:
Dr. Daniel E. Jenkins
Professor of Medicine and Community Medicine
Baylor College of Medicine

Accreditation:
This Continuing Medical Education offering meets the criteria for 12 hours of credit in Category 1 for the Physician's Recognition Award of the American Medical Association; and is acceptable for 12 Prescribed hours by the American Academy of Family Physicians.

Hotel:
Guest rooms have been reserved at

Marriott Motor Hotel
2100 S. Braeswood Blvd. at Greenbriar
Houston, Texas 77030
Telephone:
(713) 797-9000 (Houston area)
(800) 492-6993 (Toll Free)

Accommodations should be arranged directly with Marriott Motor Hotel prior to February 10, 1977; reservations made after that date are subject to availability. Please indicate that you are a registrant for the course Occupational Pulmonary Diseases and Carcinoma of the Lung.

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