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Industrial Carcinogens

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NEW YORK AND LONDON

to the crude saltpeter. At best it can probably be said at this time that this occupation requires further intensive study.

In 1929, Martland reported on bone sarcomas among radium watch-dial painters. These cases have received so much publicity and attention, that it suffices here only to mention them in their historical perspective.

In 1932, Grenfell reported the occurrence of lung and sinus cancer cases among workers in the Mond nickel works. It is believed by most people today that these cases resulted from long continued exposures to low concentrations of nickel carbonyl, a highly toxic gas in higher concentrations; but this is not definitely established as yet.

In 1935, Lynch and Smith reported lung cancers among asbestos workers who had developed asbestosis. Although there are still those who do not agree thoroughly that asbestos was the cause in these cases, most authorities believe that the incidence of lung cancer among asbestosis cases is higher than would be anticipated.

Finally in 1952, Weil et al. reported nasal sinus cancers among workers in isopropyl alcohol manufacture. Although a waste product called isopropyl oil is suspect as the specific agent, considerable doubt exists as to the exact etiologic agent.

In reviewing the historical aspects of occupational cancer, it is essential to realize that cancer of the scrotum occupies a unique position. This is so because cancer of the scrotum is such a rare disease that it is easy to associate it with a given occupation if more than one or two cases are observed. Only about 15 cases of scrotal cancer occur per 100,000,000 males per year. Thus, whenever cancer of the scrotum is observed, it should be considered occupational in origin until it is proven otherwise. Even in cases reported as having occurred among occupations not usually associated with exposure to carcinogens * (such as commercial, finance and insurance occupations) a complete and careful occupational history from childhood to the development of the disease seems warranted. Such a history, if carefully taken, may disclose earlier occupational contacts which really were responsible for the development of the disease. Thus, many individuals who enter more sedentary occupations as an adult, may have engaged in strenuous and dirty occupations in adolescence. Thus, a few years ago, a prominent New York newspaper featured a picture of the son of the Governor of the State of New York engaged in a summer occupation of road-building. He was pictured working, bare-

* See page 37 of Reference 3.

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responsible for the cancers observed in the nickel refining industry in England—and if so—in what amounts.*

Asbestos and Asbestosis

Clinical Features—The lung cancers seen in cases of asbestosis are generally squamous cell carcinomas arising from the bronchial epithelium. In addition to the cancers observed, squamous metaplasia of the epithelium in various adjacent and distant regions of the bronchial epithelium is observed. The most complete analysis of a large series of these cases is contained in the Annual Report of the Chief Inspector of Factories of England for the year 1954.[3] In this report, a total of 344 asbestosis deaths was analyzed, of which 205 were men and 139 women. Cancer of the lung was observed in 55, or 16%. Among the men, 41 lung cancers, or 20%, were observed while 14 were seen in women, or 10.1%. This makes the male:female ratio for lung cancer approximately 2:1, which compares with a male:female ratio in the general population of 5:1 or greater. The mean age at death of men with lung cancer and asbestosis was 55 years, while the mean age in women with lung cancer and asbestosis was 45.6 years. This compares with a mean age of 53.7 years for men with asbestosis without lung cancer and 42.8 for women with asbestosis without lung cancer. The mean age at death for asbestosis complicated by tuberculosis was 45.2 years in men and 35.1 years in women. These data suggest that asbestosis, uncomplicated by lung cancer poses a greater threat to longevity than when lung cancer is present. Thus, the control of asbestosis should eliminate this occupational cancer.

No case of lung cancer developed in an individual, male or female, who had less than 2 years exposure, although 7 cases, all in women, of asbestosis without lung cancer or tuberculosis, and 5 cases, again all in women, of asbestosis with tuberculosis developed with exposures of less than 2 years duration. The first cases of lung cancer in women developed when they were between 30–39 years of age, whereas in men the first cases appeared in the 40–49 year age group.

The diagnosis of occupational cancer in asbestos workers is considerably simplified in comparison with other occupational cancers because

* In a recent private communication from Dr. J. Gwynne Morgan, Chief Medical Officer of the Clydach works of the Mond Nickel Company, Ltd., calcined dust, rather than nickel carbonyl was proposed as the etiologic agent. Dr. Morgan has prepared a complete manuscript of his observations which is now in press.

of the requirement of the pre-existence of asbestosis. This chronic fibrosing disease of the lung could hardly be missed at the autopsy table. Another factor which supports the occupational origin of this type of cancer is the presence of asbestos bodies. These bodies have been well described by Lynch,[17] but a review of their characteristics may be helpful. They vary from 10 to more than 100 microns in length, and from about 1 to 12 microns in thickness. They have a central translucent fiber, presumably asbestos, surrounded by a shiny, golden or brownish substance. They may have knobs at one or both ends. The shaft may frequently be beaded. Spherical forms of various sizes may also be seen, although these may be the longer-knobbed-end structures seen on end under the microscope, or broken off from the shaft. Characteristically, they give a Prussian Blue reaction for iron. In cases of asbestosis, they are seen usually in the bronchial tract, the adjacent alveoli and the peribronchial connective tissues and lymph nodes. In the alveoli, they may be enclosed by mono- or multi-nuclear phagocytes or foreign body giant cells. In the connective tissue they may cause some surrounding fibrosis. They may be found in the sputum, but their presence there is not essential, since they are not found in the sputum of some advanced cases of asbestosis. It would seem that a case of lung cancer in an asbestos worker should not be diagnosed as occupational in origin unless asbestosis and/or asbestos bodies have been found. It should be remembered, however, that asbestos bodies may be absent from advanced cases of asbestosis or present in individuals with no evidence of asbestosis. Their presence is only an indication of exposure to asbestos. Their absence has no significance.

Lung cancer in asbestosis cases seems not to vary from lung cancer in general. The prognosis and treatment are identical, although the embarrassment of pulmonary reserve by the fibrosis in the lungs may limit the cases in which pneumonectomy can be performed.

Etiologic Agent—It is not clear at present whether these cancers result from the asbestos per se, or whether they arise as a result of some other mineral impurities contained in certain forms of asbestos. Although this may seem academic, it is of importance for two reasons. First, it may help us understand carcinogenic mechanisms, and second, if some forms of asbestos do not lead to lung cancer formation, this may be extremely important from a practical and medico-legal standpoint. A recent study by Braun and Truan [5] denies the existence of a lung cancer hazard in the Canadian asbestos industry, even though asbestosis may be observed.

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This suggests that the causative agent of asbestosis may be different from that for lung cancer. This lends some support to the concept of impurities present in some asbestos but not in others. Finally, since squamous metaplasia is also observed in practically all cases, it may be that asbestos only serves to produce the squamous metaplasia, which serves simply as a suitable field for some other carcinogen to produce the malignant changes. Cancer, then, would only develop where this carcinogen was present. From a medico-legal standpoint, of course, this may be unimportant, since whether lung cancer is produced or only promoted by asbestos would have little significance.

Isopropyl Alcohol Manufacture

In 1952, Weil, Smyth and Nale [26] reported 4 cases of sinus cancer, one case of lung cancer, one carcinoma of the vocal cord and one papilloma of the vocal cord among a group of men involved in the manufacture of isopropyl alcohol. This experience has been confirmed by another manufacturer of isopropyl alcohol, where three sinus cancers and two cancers of the intrinsic larynx were found. From the combined experience of these two plants, it seems possible to conclude that the sinus and intrinsic larynx cases were related to occupation. The single lung cancer case observed can hardly be said to have any relation to occupation, since it has no statistical significance. Its presence, however, should serve to alert the profession to continue careful review of future developments in lung cancer incidence in this operation.

Etiologic Agent—Despite extensive animal testing, it is not clear today what the causative agent in these cases was. In each of the plants involved, evidence was developed that no cancers appeared if employees began their work in the plant after a particular date. This observation suggests that whatever the causative agent may have been, it was removed by alterations of the manufacturing process subsequent to that date. The most significant change in the process, which occurred at about this time was a reduction of the strength of the sulfuric acid used. In brief, the process consists of bubbling propylene through sulfuric acid to form isopropyl sulfates. This is subsequently hydrolysed by water to form isopropyl alcohol and weak sulfuric acid. The isopropyl alcohol is distilled off the weak sulfuric acid, and the acid reconcentrated for re-use. When the concentration of the sulfuric acid used was high, a small amount of impurities was formed which is called isopropyl oil. This is a complex, variable mixture of isopropyl ethers, isopropyl

due to changes in operations or failure of control measures and would permit the early introduction of additional personal or unit control measures or maintenance.

Nickel Refining

If nickel carbonyl is responsible for the sinus and lung cancer cases seen in the nickel refining industry, exposure in this case would be to a gas. Control of this cancer would be facilitated by more precise knowledge of the causative agent. Until such knowledge has been developed, control measures must be general in nature, designed to contain within the process by engineering methods, any inhalable materials, gaseous or particulate. Housekeeping should be of the best, and wherever gaseous or particulate materials cannot be contained or ventilated, use of respirators should be insisted upon. Since nickel carbonyl decomposes on contact with water, advantage of this principle might be taken in designing respirators, and other protective or control equipment.

The establishment of a medical program in this industry should be designed for the detection of early nose and lung cancers. A thorough and careful examination of the nose and nasopharynx, performed prior to entry into this work and repeated at periodic intervals, should be done. This should be done by someone thoroughly familiar with the pathology of the nose and nasopharynx, and preferably the periodic repetition of the examination should be done by the same individual in order that changes will be evident. X-rays of the sinuses and chest should be done at the time of this examination and interpreted by someone thoroughly familiar with the problem. Any changes observed should be followed up rigorously until a definitive diagnosis has been made. It would probably be desirable to attempt to correlate urine or blood nickel levels with exposure patterns and atmospheric nickel concentrations in an effort to provide an additional check of exposures. Wherever exposures cannot be controlled by other means, the men should be provided with adequate respirators and instructed adequately in the importance of their use. Re-education of the men in the importance of all protective measures can be done at the time of the periodic re-examinations.

Asbestos Handling

The solution of the problem of lung cancer resulting from asbestos lies in the control of the problem of asbestosis. The disease is the result

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of the prolonged inhalation of asbestos dust, so that its control lies in the control of the dustiness of the operation. Enclosure of equipment with the provision of exhaust ventilation should eliminate much of the dustiness. Use of wet processes wherever possible, and the establishment of good housekeeping routines to clean up accumulated dust will help. Elimination of all unnecessary ledges, nooks and areas where asbestos dust may settle will also help control this operation. Wherever dustiness cannot be controlled by any of these means, adequate dust respirators should be provided. The use of double lockers, one for street clothes and one for work clothes, seems warranted in this industry, but no special washing or showering facilities seem necessary. Periodic dust measurements in the working environments should be undertaken and if levels are increasing, the reasons for this should be sought.

Individuals selected for this work should have a careful pre-placement examination. This should be designed specifically to detect any pulmonary abnormalities, or any encroachment on the pulmonary reserve. A pre-placement chest X-ray should be included as a part of this examination. Any pulmonary abnormalities found should be carefully evaluated before the individual is permitted to work in this occupation. These examinations should be repeated at yearly intervals, at which time sputum examinations for asbestos bodies should be done. The absence of such bodies from the sputum has no special significance, but their presence in the sputum should serve to alert the physician to the possibility of excessive exposures. The technique of examining the sputum for asbestos bodies includes digestion of the sputum by warm sodium hydroxide, followed by centrifugation and decanting. The decanted residues are spread over several slides, mounted in Canada balsam and examined. The electron microscope can also be used for examining these bodies more carefully, but great care must be exercised or they may fracture.

It should be remembered that asbestos is widely used in a large variety of other occupations and industries. Whenever it is used in such a way that dust can be produced, and the work is of such a nature as to permit prolonged, repeated inhalation of the dust, a potential asbestosis hazard exists. Each such use must be carefully evaluated in terms of the potential hazard. There seems to be a considerable individual variation in the susceptibility to asbestosis, some people developing it rapidly, while others may have comparable exposures with no signs of the disease, even after considerable periods of exposure.