MODERN MONOGRAPHS IN INDUSTRIAL MEDICINE • 4

Industrial Carcinogens

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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.

backed, with a shovel. The likelihood of his occupation in later years being listed as "day laborer in a road-building crew" seems highly remote. The sole purpose of this discussion is to point out that the recorded occupation of an individual is most likely to be his most recent or present occupation, whereas, the occupation of significance in terms of a disease such as occupational cancer, may have been engaged in so long ago that it may have been forgotten by the individual unless he is reminded of it by careful questioning by the examiner.

Although it is relatively easy to associate a rare disease like cancer of the scrotum with occupation, the difficulties are vastly increased with cancers of other sites. Thus, cancer of the skin occurs "normally" with an incidence of about 30 per 100,000 per year. This is about a 2,000 times greater incidence than cancer of the scrotum. Thus, where one case of cancer of the scrotum may constitute sufficient evidence to establish the occupational origin of the cancer, it may take 50 or 100 cases of cancer of the skin, or cancer of other sites, to establish the relationship between the occupation and the disease. In fact, it is scientifically unsound to attribute a given type of cancer to an occupation unless it can be established with statistical significance that the incidence of this type of cancer among employees is higher than in the general population, or in an employee group comparable in all other characteristics except the occupation. To do so requires knowledge, not only of the number of cancers, but also of the population at risk. Chance alone may account for the occurrence of cancer in a given individual. Certainly the student of occupational cancer must not overlook the opportunity to conduct meaningful epidemiological studies when his "index of suspicion" has been raised by observations on single cases. Nonetheless, he must be cautioned not to make premature or prejudiced decisions until his evidence has a high statistical validity. Unfortunately many historians in the field of occupational cancer have apparently been unaware of this admonition and hence the literature contains many case reports of occupational cancers that cannot be accepted because of inadequate statistical evidence for their occupational origin.

The history of occupational cancer is summarized in Table 1.

Examination of this table reveals some interesting facts which are important to point out in order that the subject of occupational cancers can be kept in proper perspective.

First, over 75% of the occupational cancers have been of the skin. Of these, about 60%, or about 45% of all occupational cancers, have

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The lung cancer cases presumably arise from the bronchial epithelium and are squamous cell carcinomas in the majority of cases. However, little complete descriptive information on these cancers is available. Ninety of the 93 lung cancer cases had died by the end of 1950. Early detection followed by pneumonectomy undoubtedly will be the most important therapeutic route.

Improvements in the plant and the provision of dust respirators may have been effective in partially controlling these cases. Thus, the Chief Inspector of Factories reports that no nose cancers, and only 2 lung cancers, have occurred in workers whose employment started after 1924, when such improvements were first instituted. In addition, no cases have been reported from similar operations carried out both in Canada and the United States.

Etiologic Agent—The causative agent in these cases has not yet been positively identified. Many investigators suggest that it is nickel carbonyl, $Ni(CO)_4$. Because of the extremely toxic nature of this compound, which is a gas at ordinary temperatures, it is difficult to devise experiments which permit continued low level exposure of animals without producing some acute deaths. Hueper [15] has injected finely divided nickel, obtained by decomposing $Ni(CO)_4$, into animals with the production of a few sarcomas. Since nickel carbonyl rapidly decomposes on contact with water to finely divided nickel and carbon monoxide, it has always been presumed that in the moist body cavities, such as the lung and sinuses, the tissues are actually exposed to finely divided nickel. Although Hueper's experiments lend some support to the theory that nickel carbonyl is the responsible agent, they can hardly be accepted as conclusive evidence of this fact, since mucosal structures were not involved. In view of the increasing use of nickel as a catalyst in various commercial chemical operations (e. g., hydrogenation of cotton-seed oil to make edible solid fats, oxo-alcohol process to make higher alcohols from hydrocarbons), it seems highly desirable to have definite answers about nickel carbonyl. This is because nickel carbonyl is readily formed from nickel and carbon monoxide under appropriate conditions of temperature and pressure. So-called "inert gas" which may be used to flush out units prior to repair, may contain as much as 1.5–2.0% of carbon monoxide. Several accidental acute poisonings from nickel carbonyl have occurred as a result of flushing out, with "inert gas," units in which nickel was the catalyst. Such episodes merely confirm that nickel carbonyl may be formed, and emphasize the desirability of knowing if nickel carbonyl is

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.

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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.

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

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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

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.

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Direct skin contact with mined asbestos may lead to the production of skin lesions. These consist of painful wart-like structures in the palms of the hands. They presumably are formed from the penetration of the asbestos needles through the skin where they set up reactions. The presence of such skin lesions may alert the physician to occupations involving asbestos exposures.

Isopropyl Alcohol Manufacture

Although the exact etiologic agent involved is still unknown, it is probable that these cancers developed as the result of the inhalation of a gas, mist or vapor. Control measures, therefore, should be designed to contain within the unit all mists, gases or vapors. Modern plants for the manufacture of isopropyl alcohol have been engineered to accomplish this. They are almost completely a closed system requiring very little work. In one such plant it was almost impossible to detect any odoriferous materials. This contrasts with the older lead still type plant which was extremely malodorous. It is likely that reduction of the strength of the acid used in this process, plus the improved design of the plant, has eliminated this problem.

However, since the exact causative agent is unknown, one cannot be certain that it has been eliminated from the environment. For this reason a medical program designed to detect upper respiratory cancers should be put in operation for workers in this process. Since statistical studies show that men engaged in the operation less than nine years are not subject to the hazard, the program need be instituted only for those employees who have worked more than a minimum time within the plant. In one plant this minimum time interval was set at five years, and all employees with a cumulative time within the plant in excess of five years, were brought into a special medical supervision program. This program included a careful examination at yearly intervals of the nose, nasopharynx and upper respiratory tract by a competent ear, nose and throat specialist who had been familiarized with the problem. Chest X-rays on an annual basis, and sinus X-rays at any indication were included in the program. Papanicolaou smears were taken, also, but were not found to be particularly helpful since several false negatives were found. The frequency of chronic sinus infections also makes the nasopharyngeal findings and the Papanicolaou smears very difficult to interpret.

RADIATION PROTECTION

The increasing use of radiations and radioisotopes may make a few words about radiation protection helpful here. It has been found extremely useful in industries engaging in radiation work to establish a radiation protection committee of some type. Represented on this committee should be management, the safety department, the medical department and radiation protection officers. It should be the function of this committee to review all contemplated radiation usages in order to determine that the individual using the radiation is technically competent, that the protective and monitoring devices he intends to use are adequate, and that his inventory and disposal methods are sound. In the use of high activity sources, many of the control measures can be engineered directly into the building housing the source. Thus, special rooms or buildings with three-foot thick concrete walls, lead lined walls, maze entrances, special thickness leaded glass and remote control manipulators may be necessary. Personnel monitoring devices such as film badges and exposure meters can be purchased and should be required of all personnel working with radiations or radiation sources. Responsibility for radioisotopes use should be provided through some form of authorization sheet, requiring approval of the committee, and periodic inventories which account for any losses should be required to be submitted to the committee. Area monitoring devices to measure background radiation levels should be used. Designated radiation protection officers, who have received some formalized special training in radiation physics and the biologic effects of radiations should be appointed by the committee and should have the primary responsibility for radiation safety. Through membership on the committee they can bring to the committee's attention any untoward incidents, and receive sufficient authority to institute the necessary corrective or remedial measures.

The creation of such committees within industry has been found to be a highly useful device. It serves to alert all employees who deal with radiations to the hazards involved. The committee can prepare operating manuals and review acceptable exposure levels as they are changed by official agencies, incorporating any necessary changes in their own program. Through membership of the medical department on the committee, proper medical supervision of employees can be accomplished since any accidents which occur will be brought immediately to the medical depart-

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