

Occupational Diseases and Industrial Medicine

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Chapter 15

Occupational Cancer

There are many diverse forms of neoplastic growths constituting a group of disorders rather than a specific disease entity. Ewing, years ago, defined a neoplasm as an autonomous new growth of tissue. Cowdry offers this definition of cancer: "Cancer is a condition manifested by a wide variety of cells of the body from before birth to the point of death in more or less remote response to the action of hundreds of influences. . . ." The over-all incidence of cancer has been increasing steadily for more than a century. Despite tremendous amounts of study and research, the etiology of cancer remains a mystery. Such diverse agents as the various forms of ionizing radiations, ultraviolet light and a few chemicals ranging from complex organic structures to metallic salts can initiate the development of cancer in man.

Exposures to cancer-producing agents occur in many occupations and are not limited to manufacturing industries. The farmer, sailor and outdoor worker suffer a high incidence of skin cancer from exposure to the ultraviolet portion of sunlight. Within industry, there is exposure to chemical cancer-producing agents and to some types of ionizing radiations. Cancer-producing agents are called carcinogens. Most occupational cancers occur in the skin and the respiratory system, since they are directly exposed to the various carcinogenic agents (oils, waxes, coal tar, pitch, soot and asphalt). Inhalation of chromium dust, nickel dust and nickel carbonyl, coal tar fume, "isopropyl oil" vapors, and radioactive dusts and gases may cause cancer of the respiratory tract. In addition, inhalation and absorption of β -naphthylamine or benzidine dust or vapors cause cancers of the urinary bladder, the tissues affected being those undergoing the greatest intensity of exposure to the carcinogenic material.

Cancer does not appear at once upon exposure to a carcinogen nor among all individuals exposed. In general, it is believed that the greater the intensity of

the exposure. Apparently, discontinuation of jobs, have no signs of some time been demonstrated.

As with ordinarily, it is impossible to determine the characteristics of the prevalence in an employment occupation.

In vocational cancer is not as common. In 1954, occupational cancer exposure cancers, and skin cancer.

History

Although among the earliest of cancer, it has emphasized assembly dates, respectively.

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the exposure and the more potent the carcinogen, the sooner cancer will develop. Apparently, once sufficient exposure has been incurred in a susceptible individual, discontinuing the exposure does not prevent the development of cancer. Workers who have been exposed a few or a number of years to a carcinogen and then changed jobs, have been known to develop cancer many years later. In the intervening years, no signs or symptoms appeared. Perhaps a microscopic cancer *in situ* existed for some time prior to the development of overt cancer, but such lesions never have been demonstrated in connection with an occupational exposure to a carcinogen.

As with all occupational diseases, occupational cancer is poorly reported. Ordinarily, the establishment of a specific case of cancer as occupational in origin is impossible until a carcinogenic substance has been identified in the work environment. Moreover, the occupational cancer has no specific identifying characteristics. The problem of skin cancer is particularly difficult because of its prevalence in the general population. Scrotal cancer and bladder cancer, developing in an employee who has been exposed to a carcinogen, readily are recorded as occupational because of the low incidence of these cancers in the general population.

In view of the inherent difficulties in establishing a diagnosis of an occupational cancer and the paucity of materials established as carcinogenic to men, it is not astonishing that the total recorded cases of occupational cancers is small. In 1954, Hueper collected all such cases. He has recorded 750 cases of occupational cancer in the United States. About half of these are bladder cancers from exposure to specific aromatic amines. Coal tar and pitch accounted for 110 skin cancers, chromates for 75 lung cancers and a few heavier petroleum oils for 70 skin cancers.

History

Although in 1531 Paracelsus noted the prevalence of a deadly lung disease among the Schneeberg miners, it is unlikely that he recognized it as cancer. Sir Percival Port, in 1775, identified and described the first recorded occupational cancer. His description of scrotal cancer from soot among chimney sweeps emphasized both severe prolonged exposure and the latent period. Eckardt (1939) has assembled the historical data on a world-wide basis in an interesting table including dates, reported agent, site and number of cases reported (Table 13.1).

Eckardt properly points out that the actual number of cases is undoubtedly much larger due to inadequate reporting and lack of recognition. Particularly in skin cancers is this true. We have not accepted arsenic, saltpeter, and asbestos as adequately proved carcinogens and believe that they probably act only as co-carcinogens.

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Occupational Carcinogens

There are three categories of carcinogenic materials to consider. First, the established occupational carcinogens that have been proved beyond doubt as causing occupational cancer. Second, materials that are suspected of causing occupational cancer but not proved. Third, materials in use in industry that have been established as carcinogens for some types of animal in the laboratory but which have not been implicated as producing occupational cancer in man. Agents falling into the first two categories are presented in Tables 15.2 and 15.3. Table 15.2 presents the generally accepted and established carcinogens and the sites characteristically affected.

Table 15.2. Established Occupational Cancer Producing Agents, with Sites*

AGENT	TISSUE
4-Aminodiphenyl (xenylamine)	Bladder
Anthracene, crude	Skin
Asphalt	Skin
Benzidine and derivatives	Bladder, ureter, kidney
Chromates	Respiratory system
Creosote	Skin
	Lip
Ionizing radiation (all types)	Skin
	Lungs
	Blood forming organs
	Bone
	Eye
Isopropyl oil	Larynx and sinuses
Mineral oil, crude	Skin
Naphthylamine-beta	Bladder, ureter, kidney
Nickel and nickel carbonyl	Respiratory tract
Paraffin, crude	Skin
Pitch	Skin
Shale oil	Skin
Soot	Skin
Spindle oils, aromatic	Skin
Tar, coal	Lip
	Skin
Ultraviolet rays	Skin
	Eye
Wax, crude from coal	Skin

* Modified from Occupational Cancer, a Challenge to the Physician, New York State Occupational Cancer Committee.

Table 15.3. Suspected Occupational Cancer Producing Agents, with Sites*

AGENT	TISSUE
Aromatic organic chemicals	Liver
Arsenic	Skin
	Liver
	Respiratory system
Asbestos	Lung
Benzol	Blood forming organs
Beryllium	Lung
Carbon black	Skin
Chlorinated hydrocarbons	Liver
Estrogens	Breast (male)
Isopropyl oil	Lung
Mineral oil, crude	Respiratory system
	Lip
Naphthylamine-alpha	Bladder, ureter, kidney
Pitch	Lip
	Bladder
Radiant heat	Skin
Sodium nitrate, crude	Skin
Tar, coal	Respiratory system
	Bladder
	Blood forming organs

* Modified from Occupational Cancer, a Challenge to the Physician. New York State Occupational Cancer Committee.

Table 15.3 presents those materials that have been suspected of producing occupational cancer but are in dispute or have not been proved as a specific carcinogen.

Several points should be noted concerning Tables 15.2 and 15.3. In Table 15.2, the potency of the established carcinogens is not indicated. Particularly among the oils is this important. For example, shale oil is a much more potent carcinogen than crude mineral oil. Also, despite the high incidence of mule-spinner's cancer of the scrotum in the textile industry in Great Britain, none has occurred in the United States. The difference in the carcinogenic property of the oil in use is the best explanation. In the United States, particularly since the studies of Braun and Truan, there is considerable conviction that asbestosis does not predispose to the development of lung cancer. Until further evidence is forthcoming, we have arbitrarily placed asbestos in the unproved or doubtful group and arsenic in the suspected group. Finally, some substances appear on both lists. This comes about because a substance may be a proved carcinogen for one site, skin for example, but not be established as a carcinogen for another site, such as the lung. Aniline does not appear on either list since it now has been established that it is non-carcinogenic

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despite reports to the contrary in the older literature. Some entries in Table 15.3 are probably only cocarcinogens.

Numerous materials have been established in the laboratory as carcinogens. Even potent ones in the laboratory, although appearing in some occupational environments have not been incriminated as causing occupational cancer in man; 3, 4-benzpyrene is one example. It is known to be present in the exhaust vapors of motor vehicles, yet no increased incidence of cancer among garage workers or other exposed groups has been demonstrated.

The U.S. Public Health Service has compiled and published a survey of materials tested for carcinogenic activity. The second edition appeared in 1951, P.H.S. Publication 149. The student desiring to look up any specific material is referred to this voluminous publication.

Chief Sites

As indicated earlier, the site of action of an occupational carcinogen is the tissue it reaches in greatest concentration for the longest period of time. In other words, it is the tissue suffering the greatest exposure. Thus it is not astonishing that, of the four major sites of occupational cancer, two—the skin and respiratory tract—are tissues of primary contact by carcinogens. The third site, the urinary tract, particularly the urinary bladder, is the body tissue most exposed when a carcinogenic material rapidly is removed from the blood by action of the kidneys. The fourth and last chief site, the hematopoietic system, is the site of origin of leukemia which is caused by various forms of ionizing radiations and benzol.

Skin. Eckardt states that over 75 per cent of occupational cancers are of the skin, with coal tar and shale oil being the chief carcinogens. Fortunately, skin cancer lesions are readily apparent and therefore cures are more easily effected. Skin cancer of occupational origin is particularly poorly reported. It is believed that cases occurring among farmers and outdoor workers due to ultraviolet radiation are treated by busy practitioners but seldom reported. Occupational skin cancers are predominantly squamous cell carcinomas, having no distinguishing characteristics from non-occupational skin cancers. As might be expected, the exposed portions of the body—the head, neck, hands and arms—incur most such cancers. This results from direct contact with the carcinogenic materials or deposition of such vapors directly upon exposed skin surfaces.

Pigmentary changes in the skin have been reported from exposure to carcinogenic oils but are not believed to be a precancerous skin response. However, areas of skin hypertrophy and atrophy occurring on skin exposed to carcinogenic oils are associated with skin cancers. Skin cancers developing under such conditions are considered occupational. Unexposed portions of the body also are subject to skin cancer, particularly if the clothing becomes saturated with the carcinogenic material. Thus, oil soaked trousers convey the oil to the scrotum

provoking mule-spinner's type scrotal cancer. Generally the latent period in skin cancer is long, 20-40 years or longer, thus years of exposure ordinarily are requisite for the development of such cancers. In this connection, regular cleansing of the skin certainly must play a part in delaying or preventing the occurrence of skin cancer.

Several materials produce skin cancer and there are probably others that have not been identified. The presently accepted skin cancer agents include ultraviolet light; ionizing radiations, alpha, beta and gamma; coal tar, soot, pitch, creosote, crude anthracene, and crude waxes; shale oils and crude shale paraffin oils; petroleum products, lubricating oils, crude paraffin oils, fuel oils, tars, asphalt, pitch, and carbon black. The chief groups exposed to these agents are:

ULTRAVIOLET LIGHT. Farmers, ranchers, construction workers and especially outdoor workers are exposed, with greater risk in the south and at high elevations where the intensity of light is greater.

IONIZING RADIATIONS. These agents affect radiologists, dentists, veterinarians, chiropractors, x-ray technicians, and scientists and technicians in various nuclear energy industries.

COAL PRODUCTS. Work groups exposed to coal tar, pitch, soot, creosote or crude anthracene include workers engaged in handling these materials in:^{*}

Gas works	Briquette works
Coke ovens	Road building and repairing
Blast furnaces	Coal-tar-pitch pipe making
Tar distilleries	Battery making
Patent fuel manufactories	Cord making
Lens industry during polishing	Paint making
Building and allied trades	Electrical equipment works, making
Roofing felt preparation and handling	cables, carbon brushes, carbon electrodes and insulation
Flooring materials	Work of seamen and fishermen
Weatherproofing materials	Creosote or tar preservation of wood
Sweeping roads	Working with impermeable paper and cardboard
Making of felt	Caulking of ships

SHALE PRODUCTS. Work groups engaged in the production of shale oils and shale paraffin oils, European mule-spinners, machinists and others who worked continuously with shale oils. Little or no shale oil presently is being produced in this country and it appears that little is being used in American industry.

PETROLEUM PRODUCTS. Those exposed to these agents are workers engaged in the primary production and refining of petroleum products, as well as

^{*} Table modified from Coal Tar and Cutaneous Carcinogenesis in Industry, F. C. Combes, Charles C Thomas, 1954.

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mule-spinners, gunsmiths, paraffin pressmen, and a large number of varied metal and tool industrial workers.

THE CARCINOGENIC FACTORS. The precise mode of action of ultraviolet light in the production of cutaneous cancer is unknown. The same is true of ionizing radiation. However, in both instances, intensity and duration of exposure are important. Also, absorption of these forms of energy by the basal proliferating layer of the skin cells appears to be necessary. In coal products, carcinogenic properties are found chiefly in the heavy oils and anthracene oil. Pure anthracene itself is not carcinogenic but 1, 2-benzanthracene and 3, 4-benzpyrene are among several identified carcinogens in coal-tar and coal heavy oils. Coal products are the richest sources of carcinogenic agents yet discovered.

The carcinogens in petroleum products are closely related carcinogens to the benzanthracene and benzpyrene found in coal products, the benzenoid hydrocarbons. Petroleum oils vary greatly in their carcinogenic ability depending upon the source, with shale oils being the more potent. Arranged in order of carcinogenic potency, depending upon their source are oils from: Venezuela, Borneo, Rumania, Persia, California, Mexico, Mid-continent, Texas, Pennsylvania and Russia. Refined oils are the least carcinogenic and the sulfonated oils used as detergents are harmless. Pure mineral oil and vegetable oils are innocuous. In the United States, carcinogens are not found in the mineral oil fraction of lubricating or cutting oils. The chlorinated hydrocarbon present in lubricating and cutting oils can cause a folliculitis but never produces cancer.

SUSPECTED SKIN CARCINOGENS. These include arsenic, sodium nitrate (saltpeter), radiant heat, chemical and physical trauma.

Among those exposed to arsenic are workers engaged in mining and refining ores containing arsenic and workers engaged in the production of and working with arsenic alloys. Nursery and agriculture workers using arsenical insecticides also are exposed.

Arsenical skin cancers are exceedingly rare, if they exist. Such a diagnosis would depend upon:

1. History of prolonged exposure.
2. Characteristic arsenical skin manifestations.
3. Demonstration of arsenic in the skin, hair and urine.

It is the firm belief of those who have studied the evidence carefully that arsenic acts essentially as a cocarcinogen but is not in itself carcinogenic.

An excessive rate of skin cancer has been reported among the sodium nitrate or saltpeter workers in Chile. However, it is believed by many that this high rate likely is due to some factor other than the sodium nitrate, possibly ultraviolet radiation. Radiation heat, chemical and physical traumas are not carcinogens, at the most they act only as cocarcinogens.

Respiratory Tract Cancers. Soluble gases and particulate matter from inhaled air are deposited in the thin film of fluid covering the respiratory tract. With continuous respiration, these materials accumulate on the walls of the re-

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NICKEL. First from Great Britain, and more recently from Norway, have come reports and convincing studies implicating nickel as a respiratory tract carcinogen. The evidence for its being the agent responsible for cancer of the nasal sinuses is overwhelming. Also, the evidence indicates with certainty that it is a lung cancer carcinogen. Study of the work population in a Mond process plant has shown that the groups suffering the greatest exposure are those engaged in calcining the ore and those engaged in the extraction process using sulfuric acid upon the calcined material. In years past, much dust was produced and good dust suppressive measures were not used. However, the gas nickel carbonyl produced in the Mond process of refining nickel originally was believed to be the only carcinogenic agent. Recently five cases of lung cancer have been reported from a small Norwegian nickel refinery utilizing an electrolytic process, not the Mond process, and so not producing nickel carbonyl. Thus the risk of cancer is not confined to nickel carbonyl but is probably inherent in both solid and gaseous forms of nickel. Prolonged inhalation experiments with animals have produced adenomatoid changes in the lungs of rats and guinea pigs but no carcinomas.

"ISOPROPYL OIL." In the manufacture of isopropyl alcohol using concentrated sulfuric acid, small amounts of impurities called "isopropyl oil" are formed. As this process was used originally, four cases of cancer of the sinuses, one cancer of the larynx and one cancer of the lung occurred in the work group. With a change in process, "isopropyl oil" is not formed and no further cases of cancer have occurred. Experimentally, "isopropyl oil" has produced skin cancers and there is no doubt that it produces sinus and larynx cancer. Perhaps it is capable of producing lung cancer but this remains to be established. Among the chief constituents of "isopropyl oil" are isopropyl sulfates, isopropyl ethers, and some polypropylenes. Precise chemical identification of the carcinogen has not been accomplished.

COAL TAR. Lung cancer arising from industrial contact with coal tar has occurred with certainty only among coal gas workers. Generally, only workers employed in the retort house, having extensive prolonged exposure to the vapors and fume, have developed lung cancer. These cases have occurred when workers suffered direct exposure to the fume while working over or about the old style horizontal retorts. Operation of the modern type retorts may or may not be attended with some risk of lung cancer. It will take time and detailed investigations to settle this problem.

SUSPECTED RESPIRATORY TRACT CARCINOGENS. As with skin, arsenic must be listed as a possible carcinogen. However, from the evidence, this is true only when the individual has been grossly overexposed to inorganic arsenic for a long period of time and exhibits gross chronic arsenicism. Probably such an exposure could occur only when working with inorganic arsenical materials with little or no effort to control the arsenical dust in the work atmosphere.

Three cases of lung cancer associated with pulmonary berylliosis have been reported. Also, Vorwald has produced carcinomas in rats following the inhalation

of beryllium. Although beryllium may be a carcinogen, evidence that it is the agent producing lung cancer in man is lacking. As a precautionary measure beryllium dust should be carefully removed from the work atmosphere.

Urinary Bladder Cancer. As previously pointed out, beta-naphthylamine and benzidine produce cancer of the bladder. Alpha-naphthylamine is suspected of this, but it has not been proved. Aniline definitely does not produce bladder tumors and should be cleared of this implication. Beta-naphthylamine is metabolized in the body to 2-amino-1-naphthol and has been indicted as the carcinogen. Less clear is the carcinogenicity of the metabolite of benzidine, but perhaps 4, 4-diamino-3-diphenyl hydrogen sulphate is the culprit. The uncertainty arises because benzidine is a much less potent cancer producing agent, and the carcinogenic metabolite probably produced in much smaller quantity. One other compound, xenylamine, or 4-aminodiphenyl, has proved to be a potent agent in producing bladder cancer. Studies of its metabolite excreted in the urine indicates the presence of 4-aminodiphenyl and 4-amino-3-diphenyl hydrogen sulphate, which later increases in quantity and hydrolyzes to 3-hydroxy-4-aminodiphenyl. Thus the orthohydroxy amine conjugates have been isolated in high concentrations as urinary metabolites from bladder cancer agents beta-naphthylamine and 4-aminodiphenyl. A much weaker bladder cancer agent, the orthohydroxy metabolite of benzidine, is present in the urine in a lower concentration.

WORK GROUPS EXPOSED. In places where the primary aromatic amines beta-naphthylamine, benzidine, xenylamine, and perhaps alpha-naphthylamine are used, workers run the risk of developing bladder tumors. The men actually engaged in handling these materials are most exposed when scraping or cleaning filters, or when materials being worked produce dusts, or vapors. In modern plants with built-in protection, perhaps the maintenance men constitute the most exposed group.

Workers employed in the manufacture of basic dyes, the manufacture of some rubber anti-oxidants where alpha-naphthylamine or xenylamine are used in the process, and where benzidine is used to harden rubber, may be exposed to bladder cancer agents. Adequate protection should be provided for textile workers and employees in the printing industry where alpha-naphthylamine and benzidine are used. Beta-naphthylamine also has been demonstrated in small amounts in coal tar from gas works, and so workers in this industry should be adequately protected.

PREVENTION. Good engineering control of dusts and vapors, the use of closed systems, and observance of meticulous personal hygiene are required. Estimations of the amount of free amine in the urine have been reported as useful in checking the adequacy of protective measures.

The Hematopoietic System. Ionizing radiations, particularly gamma or x-rays and benzol, are the agents most incriminated in the production of occupational leukemias. Whether these agents are true carcinogens or merely act as co-carcinogens is unknown.

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IONIZING RADIATION. The action of various forms of ionizing radiation is discussed in Chapter 20. It is sufficient to state here that occupational exposure to gamma and x-rays occurs in the nuclear energy industry, hospitals, medical clinics, physicians' offices, research laboratories, and in some industries where x-ray is used to detect flaws in metal castings or to examine a variety of other materials. All workers with these agents should observe adequate precautions and not be careless or indifferent concerning personal exposure. In many industries, the equipment is installed in such a manner that when in operation a worker cannot be exposed.

The incidence of leukemia among radiologists has been reported as high and there is experimental evidence to support such reports. Leukemia has been produced in mice by x-rays, with small repeated doses being more effective than larger exposures over a shorter period.

The use of radioactive isotopes emitting gamma rays in industry (particularly Cobalt⁶⁰, Iridium¹⁹², Cerium¹³⁷, and Thulium¹⁷⁰) has been increasing. In some places, gamma radiography is replacing x-rays as a means of examining castings, forgings, etc., and no doubt will find increased uses in industry. Such materials are well guarded and shielded and so far no cases of leukemia associated with the industrial uses of radioactive isotopes have been reported. Although radium and thorium have considerable use in industry, cases of leukemia in those working with these substances have not been reported. As yet, these materials have not been indicted as the causative agents of occupational leukemia.

BENZOL (BENZENE). The many industrial uses of benzol as a solvent are discussed in Chapter 11. There its depressant effects upon the hematopoietic system are presented, but not its production of leukemia. The gradual transformation of the bone marrow from aplasia to hyperplasia has been reported. Also, leukocytosis has been reported as a transitory finding in the early stages of benzol intoxication. The varied peripheral blood findings in benzene workers have been referred to as the "leukemoid condition." This reaction is only one of many bone marrow reactions to benzol intoxication. Among such reactions are complete aplasia, aplasia with leukemoid reaction, acute leukosis without peripheral leukocytosis, and finally acute leukemia. All forms of acute and chronic leukemia have been observed among workers suffering from benzol intoxication. However, the acute or subacute myeloid types of leukemia appear to dominate. Vigliani has suggested that perhaps many cases of aplastic anemia actually were aleukemic leukemias.

As stated in Chapter 11, we are not inclined to give credence to the reports of long delayed cases of benzol intoxication developing even years after the exposure to benzol has ceased. However, it seems possible that leukemia might develop at some time after a prolonged exposure to benzol had ceased.

SUMMARY

Thousands of chemicals have been examined as to their carcinogenic powers and this information is contained in the previously mentioned Public Health

Service publication. Numerous materials established as, or suspected of being, carcinogenic agents are used in industry, yet today it is astonishing how seldom we see a true occupational cancer. This can be attributed to the institution of strict controls, chiefly engineering, through closed systems, ventilation, personal protective devices, and others, which serve to prevent exposure. As more workers in the older age groups continue to work in industry, more cases of so-called "naturally" occurring cancer will be found among these older employees.

At this time it is believed that we have established as carcinogens only the more potent of these agents. Moreover, it is known that marked variation exists between individuals as to cancer susceptibility. Theoretically, the weaker carcinogens should be able to produce cancer only in the more susceptible individuals. Awareness of all these facts makes it clear that detecting the weak carcinogens is next to impossible solely upon a clinical basis. Studies to establish a weak carcinogen of necessity must be of the epidemiological-statistical type embracing large groups of people who have been exposed for long periods of time. Although these studies are arduous, they are needed to clarify the status of doubtful or disputed cancer-causing agents, and to uncover presently unknown environmental carcinogens.

We should recognize the woefully weak and inadequate status of our present knowledge of cancer etiology and the means by which carcinogens produce cancer. It appears certain that some or many materials we now accept as carcinogens are in reality only cocarcinogens. However, this makes little difference. If, as a result of its presence in the work environment, workers develop cancer, such a material must be entirely eliminated from the work environment. If it is continued in use, it must be so completely controlled that no worker may be expected to develop cancer.

The possibility of a non-carcinogenic material being metabolized in the body and a carcinogenic metabolite being produced always must be recognized. Also, the long latent period is characteristic of weak carcinogens. Particularly in cancer of the internal organs are these factors of importance. Every physician should be alert to the possibility of occupational cancer arising from new materials not now suspected of being carcinogenic.

Finally, we would be remiss in closing this chapter without making a plea for the keeping of full medical records on all employees, not only as to diseases diagnosed within the industrial clinic, but on all cases diagnosed and treated outside, thus making complete medical records available for all employees. Such records are indispensable when work groups are under study for an occupational disease, particularly cancer.

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