OCCUPATIONAL CANCER

Of the Urinary Bladder in Dyestuffs Operatives and of the Lung in Asbestos Textile Workers and Iron-Ore Miners

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The study of occupational cancer has proved to be a valuable method of learning some aspects of the biology of cancer in its wider sense. This form of cancer is an unwitting experiment in man, but until it can be reproduced in animals at will, doubt must always exist as to the exact nature of the carcinogen involved and of its mode of action. The time lag between the observation that cancer occurs in those engaged in certain occupations and the successful induction of the disease in animals may be very long. For example, Percival Pott[1] described cancer of the scrotum in chimney sweeps in 1775, but it was not until 1922 that Passey[2] induced cancer of the skin of mice by means of an ether extract of soot. Similarly, in 1895, Rehn[3] described cancer of the bladder occurring in workers engaged in the manufacture of aniline dyes, but it was not until 1937 that Hueper and his co-workers[4] were able to induce bladder cancer in dogs by means of ingestion of the dye intermediates. So far no attempt has succeeded in reproducing the lung cancers of the Schneeberg and Joachimstal miners (Haurting and Hesse, 1879; Siki, 1930[5]), though this disease has been known for centuries. The induction of a few local sarcomas in rats following injection of cobalt metal (Heath, 1954[6]) might be a stimulus to further experimental work.

We are well advised to be ready to recognize new forms of hazard in any industrial process, but it is even more important to advise industry of the dangers that are likely to be inherent in the manufacture or use of suspected or proved carcinogens. This was certainly done when the new plants for effecting the catalytic cracking of oils were set up (Symposium on a Cancer Control Program, 1951).[7]

As such a variety of occupational cancers is now recognized, this presentation is confined to making a classification of the most important and to discussion of those with which the authors are most familiar (Table 1). It seems hardly necessary to say that, before it can be claimed that any particular form of cancer has an industrial origin, it must be shown that the incidence is significantly higher in exposed workmen than it is in the general population. This is not always easy, as morbidity statistics of cancer in most countries are not available, hospital statistics being quite fallaciously high. Secondly, in sites where there is a high natural incidence, any occupational risk tends to be masked.

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TABLE 1

List of Some Substances Causing Cancer, Industry Concerned, and Site of Cancer

Substance	Industry	Site of Cancer	Proof	
			Industrial	Experimental
Minerals				
Arsenic	Sheepdip manufacture and usage	Skin, lung	Doubtful	0
Chromium (ore)	Electroplating, tanning, dyeing	Respiratory, usually lung	Doubtful	0
Nickel	Chemical manufacturers	Respiratory	Doubtful	0
Silica	Stone blasting	Lung	Doubtful	0
Asbestos	Miners and users	Lung	½	0
Iron (hematite)	Miners	Lung	½	0
Ray, Rium	Fluorescent lamps	Lung, bones	0	1
Unknown				
	Pitchblende miners	Lung	1	0
Oils				
Lubricating	Mule spinners	Skin	1	1
Petroleum	Refiners	Skin	1	1
Tarshes				
Soot	Chimney sweeps	Skin	1	1
Tar	Road workers	Skin	1	1
Rays				
Actinic	Farmers, sailors	Skin, exposed sites	1	1
Roentgen	Scientific personnel	Skin, exposed sites	1	1
Luminous paint (radium)	Dial painters	Skin, exposed sites	1	1
Organic chemicals				
Dye intermediates	Chemical manufacturers, and users	Bladder	1	1

A very significant fact has been observed by many workers and has been emphasized by Kennaway (1950).[8] The "amount" or incidence of cancer in any given population does not vary greatly, as regards either sex or race, but the proportions of the different "forms" or sites of cancer may vary greatly. For example, there is a high rate of carcinoma in organs peculiar to the female, in contrast with the high rates in lung and stomach in the male. Similarly, primary carcinoma of the liver is high in the Javanese in Sumatra, but insignificant in European populations. "There appears to be a general law that when in a given population the incidence of cancer in one particular organ is markedly increased compared with another population, there is then a compensating decrease in the

incidence of cancer in a number of the other organs" (Cramer, 1936).* A constant watch must be kept on "amounts" of cancer if proportions are being altered by industrial forms of the disease.

OCCUPATIONAL CANCER IN THE DYESTUFFS INDUSTRY

Why should 1 in 10 or even more of men engaged in the manufacture and usage of certain dye intermediates (aromatic amines) develop tumors of the bladder? These workers are exposed by inhalation, ingestion and absorption of these compounds through the skin and yet the tumors are located in the bladder. This striking observation has fired the imagination of many workers and we think we are justified in stating that we are beginning to understand the reasons. The knowledge thus gained has altered our conception of the range and mode of action of chemical carcinogens in an interesting way.

An extremely good survey of tumors of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry has recently been published by Case and his associates* (Table 2). They have shown that although there is a small spontaneous incidence of bladder tumors in the general population (2½ times greater in males than in females and rare under 55 years of age) the risk is 30 times greater in chemical workers and the age of onset is on an average 15 years earlier. Manufacturers, users and purifiers are affected in descending order of severity, the noxious substances being 2-naphthylamine, benzidine and possibly auramine and magenta. There is no evidence that aniline is incriminated. As the induction period is constant at 15 to 20 years, the age at onset of the disease is dependent upon the age at entry of a man into the industry. This is linked with the fact that it is the length and not the severity of exposure that matters, individual susceptibility being a marked feature. There is no special tendency for industrial tumors to be

TABLE 2

OCCURRENCE OF BLADDER TUMORS IN MANUFACTURERS AND USERS OF DYESTUFF INTERMEDIATES (CASE ET AL.*)

Population at Risk = 4622 Men

Expected deaths in comparable general population	3·5
Actual deaths in industry	197
Actual cases in industry	262
Risk in industry	30 times that of general population
Chemical exposure	Benzidine
	Beta-naphthylamine
	Alpha naphthylamine
Age of onset	15 years earlier than in general population
Induction period	15-20 years
Degree of malignancy	Comparable to tumors of bladder in general population
Survival after diagnosis	20 per cent survived 10 years
Exposure	Length, not severity, affects induction time
Individual susceptibility	A marked feature of unknown cause

more or less malignant than spontaneous ones. This is a killing disease, only 20 per cent of all cases having survived more than 10 years from the first recognition of the disease.

In 1935, certain alterations in plant and technic were made and these have reduced the risk just significantly, but another 243 cases (over and above the 262 traced cases in a population of 4622 men) may be expected among British workers engaged in the manufacture of chemicals during the next few years. In 1945 and 1950, more drastic plant alterations were made and we can expect these to be manifest in about 1965.

Meanwhile, we need to be ever vigilant in recognizing as occupational tumors any that may occur in other industries in which the dyestuff intermediates are in use. Case and Hosker (1954)* have recently demonstrated an occupational bladder-tumor risk in the rubber industry in England and Wales. Attention was drawn to this by the finding of a high incidence of bladder tumors in the hospital records of a County Borough which is an important center of the rubber industry. It is probable that the risk was introduced into the industry in 1928, when a certain antioxidant began to be used. The latter was known to have caused bladder tumors among the men in the chemical industry who manufactured it, and it contained about 2·5 per cent of free naphthylamine, both alpha- and beta-isomers. The treatment of the rubber "mix" containing the antioxidant volatilized quantities of naphthylamines. It needed a most laborious and careful search of records of many kinds to establish this risk on a sound statistical basis and it is satisfactory to report that the manufacturers of the antioxidant immediately ceased its manufacture and the users discontinued its use and destroyed old stocks.

Of great interest to the experimental worker is the search for the reasons for the localization of the tumors in the urinary tract, or perhaps the wider conception of localization along the routes of excretion would be preferable. If 2-naphthylamine is administered by feeding to dogs, all the animals will eventually develop tumors of the bladder, though the number and location will vary in individuals (Hueper and Wolfe, 1937,* Bonser and her co-workers, 1951*). If 2-naphthylamine is fed to mice, hepatomas or benign cholangiomas will occur. If fed to rats or rabbits, occasional benign papillomas of the bladder will be seen. If benzidine is fed to dogs, bladder tumors occur after many years (Spitz, personal communication), but if injected into rats, hepatomas and acoustic gland tumors will be found (Spitz, Maguigan and Dobriner, 1950),* if injected into mice, hepatomas only will occur (Bonser and her associates, unpublished observation) (Table 3). Such localization of tumors suggests that 3 important factors must be at work: (a) species variations in biologic response; (b) excretion of the original chemical or its metabolites along a specific pathway; and (c) concentration of these substances in certain sites.

A study* of the metabolism of 2-naphthylamine in various species showed that a conversion of the amine to 2-amino-1-naphthol conjugates occurred and that the capacity to form tumors was roughly proportional to the concentration of these substances in the urine. In the dog, the ratio of urinary to serum content of

TABLE 3

RESPONSE OF SPECIES TO ADMINISTRATION OF DYESTUFF INTERMEDIATES

Species	Chemical	Tumor
Man	2-Naphthylamine	Bladder carcinoma
	Benzidine	
Dog	2-Naphthylamine	Bladder carcinoma
	Benzidine	
Cat	2-Naphthylamine	Not known
	Benzidine	
Ferret	2-Naphthylamine	Not known
	Benzidine	
Mouse	2-Naphthylamine	Hepatoma
	Benzidine	
Rat	2-Naphthylamine	Bladder papilloma
	Benzidine	Hepatoma, mammary gland carcinoma, intestinal carcinoma
Rabbit	2-Naphthylamine	Bladder papilloma
	Benzidine	Not known

metabolites was approximately 200:1. In addition, the dog was found to have a high level of urinary sulfatase, which would aid in the liberation of free 2-amino-1-naphthol from the conjugates. A consideration of these factors has led to the hypothesis that aromatic amines and azo-compounds produce their carcinogenic effects at distant sites along the routes of excretion because they undergo metabolic changes in the animal body, which, coupled with certain favorable local factors, determines their site of action (Clayson, 1953).[4]

OCCUPATIONAL CANCER OF THE LUNG

Two aspects only will be considered: its occurrence in (1) asbestos textile workers; and (2) hematite miners. The series of cases presented here are, as yet, unpublished. For published series the reader is referred to Hueper's thorough survey (1952)[5] in which he cites 60 cases of cancer associated with asbestosis, 38 of which were reported in Britain. Hueper also refers to 8 cases with coexistence of siderosis and cancer of the lung.

1. Cancer of the Lung in Asbestos Textile Workers

In 1928, or a little earlier, one of the present authors (MJS) began to collect information and material from the workers in 2 factories, and it will be remembered that he was early in the field in describing the peculiar bodies and the significance of their occurrence, especially in sputum (Stewart, 1928;[6] Stewart and Haddow, 1929;[7] Stewart, Tattersall and Haddow, 1932[8]). Stewart's series consists of postmortem material from 80 persons who had worked in the 2 factories, and were thus likely to inhale asbestos fibers. In 8 persons no pulmonary asbestosis could be demonstrated, though small numbers of bodies were usually present. The effective number for consideration is thus 72, 46 males

TABLE 4

INCIDENCE OF CANCER IN ASBESTOS TEXTILE WORKERS AT POSTMORTEM EXAMINATION

	Uncomplicated Asbestosis	Tuberculosis and Asbestosis	Lung Cancer and Asbestosis	Tuberculosis and Lung Cancer and Asbestosis
	M. F.	M. F.	M. F.	M. F.
Number of cases investigated postmortem (72)	22 18	12* 4	12* 2	1 3
Incidence of lung cancer (per cent)			26.1 8.7	
Average age at death	51 (24) †	47 (12) †	56 (11) †	
Average age at starting work	31 (21) †	28 (12) †	27 (10) †	
Average period of exposure (years)				
Total	23 (21) †	18 (12) †	26 (10) †	
Prior to 1931	11 (19) †	11 (7) †	12 (10) †	
In cases entering after 1931	5 (2) †	7 (5) †		

* One man had asbestosis, tuberculosis and lung cancer.

† Figures in parentheses represent the number of cases for which the information was available.

and 26 females. In Table 4 the data in regard to the association of asbestosis and cancer are given. Cancer arising primarily in pleurae, lungs or bronchi was present in 26.1 per cent of males and 8.7 per cent of females. This significantly higher incidence in males may be accounted for by the fact that 7 women died before the cancer age, 4 following parturition or abortion and 3 from tuberculosis. There was no significant difference in average age at death, average period of exposure or average age of starting work between males with uncomplicated asbestosis and those with the complication of lung cancer. This is interesting, as in the dyestuff industry death was accelerated by the supervention of bladder cancer. It was noted that the degree of fibrosis was rather less in the lungs with cancer than in those without. Tuberculosis significantly lowered the age at death.

A fair assessment of the period of exposure is difficult in such a series of cases. Taking into account the known fact that after a carcinogen has ceased to be applied to a tissue a latent period is required before the development of the malignant change, it was decided to use the period from the first entry into the factory until death as the period of exposure. This disregards absences from the factory for any reason. It also presupposes that once the fibers have gained access to the lung the carcinogenic process is set in motion, becoming fully developed at the end of the latent period.

Two interesting features deserve mention. The morbid anatomy and histology of the 13 lung cancers of which full notes were available was unusually varied. Four were large tumors situated near the lung hilum, disseminating in characteristic fashion and of adenocarcinomatous or oat-cell type. Seven were situated in the periphery of the lung, usually near the base, 3 disseminating by blood and lymph streams and the other 4 remaining confined to the lung substance. Six of these were adenocarcinomatous or of oat-cell type, 1 being spindle cell and possibly a rhabdomyosarcoma. Small peripheral cancers were described by Bonham and Spencer (1953)[9] as the likely precursors of the large hilar masses

usually seen at postmortem examination. The peripheral cancers in this series may, therefore, represent a stage prior to hilar involvement. Two tumors were pleural in distribution, 1 disseminating and 1 not. Both were adenocarcinomas, the former having spindle-cell areas.

Attention must also be drawn to the 4 peritoneal cancers, 1 in a male and 3 in females. This is a very high number in such a small series of cases. All these tumors were anaplastic carcinomas, the primary site not being found in any organ. The possibility of an origin from the sequestrated bronchial epithelium present in the diaphragmatic areas of hyalinosis is suggested, but without any clear proof.

No adequate comparable postmortem material from persons working under factory conditions and not exposed to asbestos dust is available with which to compare the incidence of lung cancer in asbestos workers. The incidence here cited is very high and by comparison with the incidence in iron-ore miners must be highly significant. The occurrence of occupational lung cancer in the exposed female is noteworthy.

In connection with this particular form of industrial hazard, it must be emphasized that since the introduction of regulations for the control of asbestos dust in 1931, the amount of exposure of the workers to dust has been enormously reduced and we shall therefore expect to see a disappearance of those severe degrees of pulmonary fibrosis that have been described heretofore and possibly a disappearance of associated cancer. All the present cases that had asbestosis and cancer had been exposed prior to 1931.

2. *Cancer of the Lung in Iron-Ore Miners*

One of the authors (JSF) has had a unique opportunity to study this disease (Stewart and Faulds, 1934).[9] He has personally conducted postmortem examinations on 192 Cumberland hematite miners during the last 20 years and in addition has performed postmortem examinations on 2378 Cumberland males above the age of 20 years, unselected in regard to cancer or lung disease. The difference in incidence of lung cancer in these 2 groups is statistically significant (Table 5). The age of onset is not significantly delayed, most of the miners having entered the mines under the age of 30 years. All the miners' lungs contained free silica and iron at death, but there was no significant difference in the content of either mineral in the lungs with and without cancer. There was, however, an interesting difference in the degree of fibrosis (Table 6) and this has great significance when a similar occurrence in relation to asbestosis is remembered. All the tumors were classified as oat-cell or squamous cancers.

TABLE 5

CANCER OF THE LUNG IN IRON-ORE MINERS

	Number	Lung Cancers	Percentage Incidence
Iron ore miners	192	17	8.85 ± 2.04
Cumberland males over 20 years	2378	44	1.85 ± 0.27

TABLE 6

MINERAL CONTENT, DURATION OF OCCUPATION AND PULMONARY FIBROSIS IN IRON ORE MINERS

	Number in Group	Average Age at Death	Average Duration of Occupation (Years)	Average Per Cent Mineral Content by Dry Lung		Degree of Fibrosis
				Silica	Iron	
Bronchial carcinoma	15	61	32 (11)	1.11	5.3	
Silicosis alone	50	60	34 (50)	1.49	6.3	1 1 1
Silicosis and tuberculosis	75	57	28 (68)	1.11	5.1	1 1
No silicosis and no tuberculosis	20	62	26 (19)	0.59	1.01	0

Figures in parentheses represent the number of cases in which the information was available

The common factor in these 2 types of occupational lung cancer is silica, and it is suggested that this may be the carcinogenic agent. The presence of silica (as silicic acid) causes pulmonary fibrosis, which precedes the initiation of the malignant process. The fibrosis is usually of lesser degree, however, in those lungs in which cancer supervenes. On published evidence the case for an etiologic relationship between nodular silicosis *per se* and lung cancer is much less strong than in silicosis associated with siderosis and in asbestosis. Hueper (1942) examined the literature very thoroughly and came to the conclusion that "the available evidence supporting a causal relation between silicosis and cancer of the lung is unimpressive." It seems possible, therefore, that the fibrous nature of the reaction of the presence of hematite dust may exert a modifying effect on the chemical action of the silica or on the fibrotic process itself. Further study of the nature of the carcinogenic process in pneumoconioses is thus obviously needed.

SUMMARY

The value to the cancer problem as a whole of the study of occupational cancer in the field and by experiment, together with the time lag between these aspects, is discussed. A short consideration of the total amount of cancer in the population follows, and a classification of the types of recognized occupational cancer.

A more detailed consideration of industrial bladder and lung cancer follows. With regard to the former, the extent of the hazard, the nature of the chemicals involved and their metabolism in various species are discussed. In regard to the latter, the occurrence of lung cancer in a group of 72 male and female asbestos textile workers and in 192 hematite miners in Cumberland, England, is described.

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CLINICAL PATHOLOGY OF YELLOW FEVER

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Yellow fever, whether transmitted in its urban epidemic form by the *Aedes aegypti* mosquito, or by forest mosquitoes in its sylvan (jungle) form, exhibits clinical pathologic features conforming precisely with its significant anatomic pathology. Caused by a virus essentially hepatotropic in its natural state for man and other primates, its classical anatomic lesion is a morphologically specific and typical hepatitis. Associated with this hepatitis are profound prothrombin deficiency and a hemorrhagic diathesis. In severe cases a lower nephron (tubulo-glomerular) nephrosis develops with oliguria and retention of urea, and often coma, followed by uremic coma and death.

Extensive clinical pathologic studies were made during the recent involvement of Panama and Costa Rica by a wave of the disease in its sylvan form, which originated from eastern Panama late in 1948, entered Costa Rica in 1951 and terminated in Costa Rica about March, 1953. Nicaragua was invaded in 1952, and at the present time the wave is active in northern Honduras and is approaching southern Guatemala and Yucatan, maintaining an over all velocity of 13 miles per month between epidemic centers. The history of the origin and progress of this wave has already been described in current literature.[1-6]

Although 11 persons dying of the disease were autopsied in Panama from November, 1948, to February, 1952, very little clinical pathologic data were acquired, because of the short duration of their period of hospitalization and the severity of clinical cases in which recovery occurred. Nevertheless, the material obtained was adequate to establish for the first time that the kidney lesion of yellow fever is a typical lower nephron (tubuloglomerular) nephrosis.[7, 8, 9]

A major reason for the scarcity of clinical data in Panama was the predominance of West Indian Negroes among the burning population in the vicinity of the Panama Canal, and the well-known natural tolerance of the Negro race to yellow fever. This phenomenon had long been recognized when Negro women who had had the nursing during past epidemics in the southern United States remained well, as pointed out by Matas.[10] All the Panamanians who died and the few patients with clinical disease who were hospitalized were Cholos of native Indian and Spanish ancestry.

Another reason for the scarcity of clinical data was the intensive vaccination program conducted in Panama and the Canal Zone at the time, which prevented major epidemics, except in inaccessible localities. After the minor epidemic in

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