Occupational Cancer and Carcinogenesis

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PREFACE

With one or two exceptions, the known human carcinogens have been identified in occupationally exposed workers. The first suspicions have often come from an alert physician. Society has become increasingly concerned with recognizing potential occupational carcinogens as the number of industrial chemicals has grown. Although most neoplasms are initiated by environmental agents, cancer should be considered a preventable disease.

Prevention of cancer depends on identification of the causative factors and on their control, when possible. Occupational carcinogens are among the agents that can be effectively controlled. For this reason, it is critical to examine carefully the factors influencing cancer incidence in the population, with special emphasis on the causative agents in the work environment.

Technological progress in industry increases the necessity for rapid identification and control of carcinogens.

If we are to identify chemical carcinogens prospectively, we must rely on animal experiments and other experimental evidence. The questions then arise of what kind of scientific knowledge can be used to make regulatory decisions, and whether we should lean toward long-term protection of human health or short-term protection of economic enterprise. It will always be possible to find arguments based on the uncertainty of any set of data. Prevention requires that action can be taken on the basis of reasonable evidence that a hazard may exist.

It is sometimes maintained that because of regulatory measures in the workplace, occupational cancer will be of little or no concern in the future. It is certainly true that decreases in the amounts of harmful chemicals will make it more difficult to associate a cancer with a particular cause. However, even though levels of exposures are decreasing, the number of people exposed to a variety of potential carcinogens is increasing. Thus it can be expected that in the future, occupational cancers will be even more important from the point of view of public health. An example of this is the exposure of the public to pesticides or their derivatives. In this case, the only population exposed more than the general public is that of workers manufacturing or handling the pesticides. Cancer risks of such workers signal major public health hazards.

This publication presents a sequential elucidation of the current knowledge of and ideas regarding occupational carcinogenesis. The members of the program committee, as well as the Institute of Occupational Health, the host institute, are deeply gratified by the financial support provided by the Nordic Council of Ministers. Availability of these funds allowed us to organize this International Course on Occupational Cancer.

The preparation of this book has been facilitated by the competent assistance of our secretaries, Ms. Outi Teperi and Ms. Mervi Hirvonen, and by the cooperation of the publisher.

Finally, we wish to extend our appreciation to all the participants who enthusiastically responded to our invitations to join the meeting, for sharing and exchanging their knowledge on this occasion.

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CONTENTS

HISTORICAL PERSPECTIVES OF OCCUPATIONAL CANCER

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Three topics are discussed in this review, which is not intended to give even a short description of the history of occupational cancer. First, the present state and possible future trends of occupational cancer are examined. Such factors as rapid industrialization, increasing amounts of chemical compounds in the environment, and discoveries of new occupational carcinogens such as asbestos and vinyl chloride indicate that occupational cancer is likely to become more frequent in the future. The controversial issue of the proportion of cancers related to occupation is briefly considered. The upward trend of estimates of various authors during a quarter of a century indicates a growing proportion of occupational cancers in the overall incidence of cancer.

Second, some lessons from the past are considered. Careful observations and alertness of physicians and proper documentation of occupational cancer cases are pointed out. Interdisciplinary teamwork and international cooperation have been useful in the past and continue to be desirable. Some details of the studies of skin cancer caused by mineral oil are informative. Individual susceptibility, whether genetically determined or due to pathological conditions, needs further study. As an example of the predictive value of animal experiments, skin cancer related to the oil shale industry in Estonia is discussed.

The third topic—input from experimental cancer research—deals mainly with the problem of modifying factors. Experimental data on such factors could facilitate investigations of life-style effects, using the proposed classification of modifying factors. The problem of nasal cancer in woodworkers may be easier to solve by taking into account some experimental data on tannin-containing material. Some possibilities for future action and suggestions for further research are outlined.

INTRODUCTION

Occupational cancer is one of the most important fields in cancer research not only because of past developments and future aspects, but mainly because of the numerous practical and theoretical implications; the involvement of many medical, technical, economic, and social features; and the possibilities for developing efficient measures of prevention.

In considering the historical perspectives of occupational cancer, one could proceed in different ways. It is not my intention to give even a short review of the history of occupational cancer, which started more than 200 yr ago. I am confident that most of us have had the opportunity to read such excellent handbooks and articles as those by Hueper (1942, 1966) and Hunter (1957) and many other review articles on occupational cancer published in various journals. I would like to draw your attention to the most useful and widely known series published by the International Agency for Research on Cancer (IARC), the orange "Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man" (Tomatis, 1976; Tomatis et al., 1978), of which 21 volumes have been published and 3 or 4 more are in press and preparation. These monographs contain in a condensed from the most relevant and thoroughly evaluated information on occupational carcinogens, including data on occurrence, production, and utilization as well as experimental and human data. The principal value of these monographs is that they are prepared using the expertise of specialists working in relevant fields all over the world.

I restrict myself to three main topics that may be of interest in view of our future goals and the problems likely to be faced. I hope and I am sure that other contributors will correct or clarify some of my views, so that objective opinions will be reached by all participants. The topics I will discuss are the following:

1. Present state and possible future trends of occupational cancer.
2. Some lessons from the past.
3. Potential input from experimental research.

PRESENT STATE AND POSSIBLE FUTURE TRENDS OF OCCUPATIONAL CANCER

The rapid worldwide industrialization that started about a century ago and is accelerating during the era of technical revolution is familiar to everybody. Present-day industrial production is characterized by innumerable technologies, occupations, and professions that are spreading from highly industrialized to developing countries, involving a rapidly growing number of workers. Such expansion of industry means that some old problems and unresolved questions may reappear in other geographic areas.

In industrialized countries the number of workers involved in some older industries is decreasing as technology becomes more sophisticated. As a result, the population exposed to occupational carcinogens may diminish in some branches of industry. In addition, some decrease in the incidence of occupational cancer should result from preventive measures already applied.

However, new industrial processes and technologies producing new chemicals are rapidly developing. Various figures reflect this process. According to Maugh (1978), the computer registry of the Chemical Abstracts Service contained 4,039,907 chemical compounds in November 1977 and on the average 6000 compounds are added every week. About 63,000 compounds are in common use. Gronow (1978) refers to estimates that some 5000 new chemicals are being introduced annually in the form of new commercial products, chemicals, foods, and drugs.

Whichever figures are correct, there is no doubt that the number of chemicals to which humans are exposed increases continuously. For example, the output of the plastic industry was 0.1 million tons in 1930 and 30 million tons in 1970 (Selikoff, 1976). Human exposure to chemicals takes place not only in factories but also, in their neighborhood (vinyl chloride) and in the homes of workers (asbestos). Moreover, the amounts of various household chemicals (solvents, sprays, cleaners, cosmetics, etc.), whose chemical compositions are not always known to users, are also rapidly increasing, and we are not sure that the product is always safe.

During the last few decades new occupational carcinogens have been discovered, mainly because their production was recently begun or was rapidly increasing. The most important ones are asbestos and vinyl chloride, whose histories are generally known and will be discussed in other presentations. Cadmium (Lemen et al., 1976), beryllium (Wagoner et al., 1978) and *o*-toluidine (Rubino et al., 1978) have been considered as human carcinogens; however, at this stage the data seem to be insufficient.

An ad hoc working group, convened by the Unit of Chemical Carcinogenesis of the IARC on January 15–17, 1979, discussed evidence for the human carcinogenicity of 54 chemical compounds and industrial processes. As far as I know this was the first representative discussion by the most qualified epidemiologists and experimentalists, who tried to agree on decisions and, I believe, reached a remarkable consensus. Their conclusion was that only 18 of the 54 compounds or processes met the criteria for human carcinogens; among them were soot, tars, and oils, which are somewhat obscure entities containing perhaps hundreds of individual compounds in various concentrations, carcinogens, solvents, modifiers, and others. Beryllium was not considered a sufficiently proved human carcinogen and *o*-toluidine was not discussed. For Cd the decision "limited evidence" was reached. Undoubtedly, such international working groups will have to be convened from time to time to revise and reevaluate the evidence in the light of new information.

At this point I would like to bring up the problem of *N*-nitroso compounds (NC). No firm data are available on the role of these powerful animal carcinogens in the etiology of human cancer. The discovery by Magee and Barnes (1956) that *N*-nitrosodiethylamine is a hepatocarcinogen for rats opened a new era in cancer research. About 120 NC have been tested since then, 80% of which have induced cancer in various species and organs.

NC have been found in various environmental media. Ten years ago the IARC initiated activities to develop reliable and comparable analytical methods for NC. I had the opportunity to participate in this work. International meetings of chemists and biologists on the analysis and formation of NC began in 1969 and are being held every 2 yr; the proceedings of these meetings (4 volumes) and their recommendations as well as analytical collaborative studies have considerably contributed to our knowledge about the presence of NC in environmental media.

NC are used and produced in various branches of industry and volatile NC have been found in the air of some chemical plants (Fine et al., 1976). Nitrosodiethanolamine was found in some synthetic cutting fluids in concentrations up to 3% and in some cosmetic products (Fan et al., 1977a, 1977b). An important feature is the possibility of formation of NC in the organism from various amines and nitrite, the latter being either of environmental orgin or reduced in the gastrointestinal tract from nitrate. Nitrous gases (NO_x) occurring in various fumes and regularly generated during the combustion of nitrogen-containing material reacting with water also yield nitrite and can nitrosate amines and amides.

At the 5th meeting on the analysis and formation of environmental NC, held in Durham, N.H., in 1977, it was recommended that epidemiologic studies be carried out in situations where NC have been found in the environment, primarily the working environment, and also that environments where there are excess incidences of some cancers be analyzed.

It has been observed that besides the main cancer site associated with an occupational carcinogen, cancers at other sites can appear more frequently. In the case of As, lung and skin are affected; asbestos induces not only lung cancer and pleural or peritoneal mesothelioma, but also cancer of the gastrointestinal tract; mineral oils produce skin cancer and lung cancer.

Langård and Norseth (1978) observed that gastrointestinal cancer occurs more often than expected in chromate pigment workers, who are known to have an elevated risk of lung and nasal cavity cancer. McMichael et al. (1976) found among rubber workers during a 10-yr period (1964–1973) a marked excess of death from some specific cancers including the stomach, colon, prostate, lymphatic, and hematopoietic systems and identified hazardous occupations. It seems that a diversification of cancer sites in populations of workers exposed to recognized human carcinogens is taking place.

Another development appears to be the steadily increasing number of occupations and professions exhibiting a higher than expected incidence of cancers at various sites.

Tola et al. (1978) reported investigations that substantiated earlier findings on increased mortality from lung cancer in iron foundry workers in Finland. It was shown that asbestos, Ni, and hexavalent Cr could not be incriminated, and that exposure to polycyclic aromatic hydrocarbons (PAH), using benzo[*a*]pyrene (B[*a*]P) as an indicator, was more common in cancer cases than in controls.

Englund et al. (1978) investigated mortality and cancer incidence among painters, plumbers, and insulators in the Swedish house building trades and found that total mortality and number of cancers deviated little from expected figures. As to specific cancer sites, painters had a twofold increase of esophageal and liver cancer and plumbers a twofold increase of lung cancer, more than twofold increase of laryngeal cancer, and a 70% increase of stomach cancer. Specific carcinogens were not identified in this study.

Somewhat similar results were obtained by Williams et al. (1977) on the basis of the third National Cancer Survey in the United States. Lung cancer was found more often than expected in the trucking, air transport, wholesale painting, building construction, and building maintenance industries and in those involved in the manufacture of furniture, transportation equipment, and food products. Controlling for cigarette smoking did not change these associations. Goldsmith (1978a, 1978b) analyzing these data, concluded that population studies are a useful guide to undetected cancer hazards and smoking rarely causes false positive results.

The role of smoking in occupational carcinogenesis has been the subject of much discussion and controversy. Hueper (1966) emphasized that the available evidence indicates clearly that occupational and industry-related factors are distinctly more important than is conceded by proponents of the cigarette theory. Epidemiologic studies have demonstrated the synergistic effect of smoking with asbestos (Hammond and Selikoff, 1973) and with uranium dust (Archer et al., 1976). However, for many other occupational cancers such an effect has not been established.

I would like to consider briefly the controversial issue of the proportion of cancers related to occupation in the overall cancer incidence. Estimates published in the United States (Bridpord et al., 1978) conclude that occupation-related cancers may account for 20% or more of total cancer mortality in forthcoming decades. These estimates have been strongly criticized (Editorial, 1978). I do not intend to judge whether this figure is correct or not. The estimates may not equally be applicable to all countries. It is, however, interesting to follow the evolution of such estimates during a quarter of a century (Table 1).

The estimates have a distinct upward trend, which is consistent with industrial development during the last three or four decades. I will not forecast any precise figures, but there is little doubt that similar estimates by the year 2000 will show even higher

TABLE 1. Estimates of Proportion of Occupational Cancers

Year	Author	Proportion (%)
1954	H. Druckrey	1
1967	D. B. Clayson	1
1976	J. Higginson and C. S. Muir	1–3
1977	E. L. Wynder and G. B. Gori	1–10
1977	S. S. Epstein	5–15[a]
1977	P. Cole	10–15
1979	J. Higginson	1–5
1979	J. Higginson and C. S. Muir	2–6[b]

[a]For males.
[b]For the Birmingham area.

proportions. These considerations show that a thoughtful approach is needed to the strategy of cancer prevention. To my mind emphasizing only the necessity for changing personal habits underrates the importance of preventive measures in industry and is as wrong as the opposite approach—disregarding the conclusive evidence of the carcinogenic action of tobacco smoke. Both avenues must be followed in a balanced way.

Summarizing our consideration of the present state and possible future trends of occupational cancer, we can see that occupational cancer does not belong to the past. On the contrary, there are numerous indications that the proportion of occupational cancers in the overall cancer incidence will increase. New carcinogens will be introduced and new associations between known carcinogenic hazards and certain sites are being and will be discovered as latent periods are exceeded.

SOME LESSONS FROM THE PAST

The history of occupational cancer, like any other history, can teach us many lessons. I would like to recall some of them, especially some helpful details.

The beginning of the history of occupational cancer, the description of scrotal cancers in chimney sweeps by Percival Pott, is a brilliant example of the thoughtfulness and ability to generalize of an experienced physician. The same attitude in the recent past has resulted in important discoveries, such as the carcinogenicity of diethylstilbestrol and vinyl chloride. Selikoff (1976) has given some examples of discoveries made by alert and inquisitive physicians.

At present it is still of primary importance to observe and carefully evaluate the observations. It requires a background of knowledge. Unfortunately, there still are general practitioners who do not inquire about the occupational history of cancer patients and have little if any knowledge of the technological processes or substances to which the patient was exposed.

Insufficient knowledge was apparently the main reason for an episode described by Kipling (1974). In 1954 Dr. Robert Murray found that of 130 cases of skin epithelioma treated in one Manchester hospital in 1 yr, 81 were probably of occupational origin and yet only 3 were notified.

Adequate registration of cancer cases is of utmost importance for epidemiologic studies, proper functioning of health services, and prevention. Shortcomings in primary medical documentation are not at all infrequent. Lee (1976) published another example. Of 50 men who died with scrotal cancer, only 19 had scrotal cancer noted as the cause of death. Six death certificates mentioned other malignancies without mentioning carcinoma of the scrotum (three listed carcinoma of the prostate; two, carcinoma of the bronchus; and one, advanced carcinoma). Evidently, a mortality study based on death certificates would pick up only about 40% of the cases.

An important landmark in the history of occupational cancer was the identification and isolation of the powerful carcinogen B[*a*]P in 1930–1933 by a team under the distinguished leadership of Sir Ernest Kennaway (1955), whose extensive contribution to cancer research and especially to occupational cancer is well known. The discovery of B[*a*]P was achieved by a unique collaboration of experts in various disciplines—biochemistry, chemistry, and physics. The cooperation of industry was also most valuable. The work had an international aspect as the German chemist Erich Clar provided PAH (1,2,5,6-dibenzanthracene and other compounds) synthesized in his laboratory to Kennaway's team in London as reference compounds. At this time international cooperation was a matter of personal contacts, which are still fruitful in scientific endeavours. Nowadays, multidisciplinary teams and task forces are widely engaged and international cooperation occurs to a much greater extent and has a solid organizational framework in many fields. In occupational cancer, however, more international collaboration is desirable, especially in investigations concerning infrequent cancer sites. Pooled data obtained by using coordinated methodologies would be more valuable and result in speedier decisions.

The story of skin cancer caused by oil is instructive in some of its details. Classical studies by Leitch (1924), Scott (1922), and Henry (1946) proved the causal relationship between shale oil or mineral oil and skin cancer. Numerous cases of epitheliomatous ulceration were recorded in the United Kingdom and regularly published in the annual reports of the Chief Inspector of Factories. In recent years numerous although declining numbers of new cases have been reported (Table 2).

Special epidemiologic investigations confirmed the etiology of these occupational cancers. One of the most interesting recent studies was published by Waterhouse (1975), who used the data of cancer registries and showed that in the Birmingham area the incidence of scrotal cancer increased during the last decade.

Measures to prevent skin cancer in the British cotton spinning industry have been taken repeatedly. A special committee recommended in 1948 that technical white oils (treated with sulfuric acid) be used to oil mule spindles (Ministry of Labour and National Service, 1952). In 1953 the Mule Spinning (Health) Special Regulations, in force from 1954 on, required that spindles of self-acting mules be oiled only with oils of animal or vegetable origin (Ministry of Labour and National Service, 1953).

As cases of skin cancer continued to appear in the engineering industry, especially in the Birmingham area, a special study was undertaken by the Medical Research Council (1968), which did not discover any known carcinogens in petroleum-derived mineral oils. Kipling

TABLE 2. Notified Epitheliomatous Ulcerations due to Pitch, Tar, or Mineral Oil in Britain[a]

Year	Due to pitch and tar	Due to mineral oil	Total
1950	167	28	195
1951	159	19	178
1952	124	33	157
1953	196	60	256
1954	143	30	173
1955	–	–	–
1956	–	–	–
1957	–	–	–
1958	–	–	–
1959	190	36	226
1960	154	19	173
1961	–	–	–
1962	159	24	183
1963	–	–	–
1964	–	–	–
1965	–	–	–
1966	–	–	–
1967	61	20	81
1968	64	19	83

[a]From annual reports of the Chief Inspector of Factories.

(1971) discussed the problem of skin cancer in the engineering industry, comparing the condition in Birmingham with that described by Thony and Thony (1970) in Cluse (Savoy Alps) and concluded that the causative agents are unknown.

At that time, in 1971, when I was working with the IARC, I had the opportunity to discuss the occupational skin cancer problem with Kipling. I told him about a recent publication of Kolyadich et al. (1971) concerning the appearance of high concentrations of B[*a*]P in cooling mineral oils during uses that involved high temperatures (pyrolysis). Before use, the oils contained B[*a*]P only near the detection limit. We also discussed the paper of Bingham and Falk (1969) describing a 1000-fold increase of carcinogenic activity in mouse skin tests of solutions of B[*a*]P and benz[*a*]anthracene when 50% of the neutral solvent was replaced by *n*-dodecane, a long-chain aliphatic hydrocarbon. Kipling agreed that these facts might have a relation to the skin cancer cases and in his next paper (Kipling, 1974) he mentioned these data as possible explanations. During my work in Lyon I also met Thony and Thony from Cluse, who described the work of the "decolleteurs," among whom they found more than 60 cases of skin cancer. It appeared that these workers bought from industrial enterprises cheap used mineral oil, which they regenerated by sedimentation before reusing it as cutting oil.

Kipling and Waldron (1978) also discussed the problem of oil aerosols in workplaces in connection with a statistically significant excess of second primary tumors of the bronchus in men with a first primary tumor of the scrotum.

A general conclusion from the mineral oil story is the suggestion that during use or technological treatment, changes of chemical composition of various materials can occur and previously unsuspected associations may come to light.

Studies of occupational cancer have revealed many facts about the individual susceptibility of workers exposed to the same carcinogenic hazard. Data of Williams (1958) quoted by Saffiotti (1973) on dye workers exposed a 2-naphthylamine and benzidine are a good example. Similar data on skin tumors (malignant and benign) in a group of tar workers were reported by Fisher (1953). Table 3 shows a clear dose-response relationship but at the same time reveals marked individual differences.

Smith (1952) reported on skin cancer prevention measures in the Scottish oil shale industry. One practice was to prescreen potential employees and pick men with swarthy skin, as they do not appear as susceptible to oil irritation. Men with auburn hair and men who freckle readily or have preexisting skin disease, especially psoriasis, are not hired as paraffin pressmen.

Studies of xeroderma pigmentosum have disclosed molecular mechanisms associated with skin cancer in homozygotes. Marx (1978), reviewing the data on this and other genetic disorders of DNA repair, pointed to the possibility of related defects in heterozygotes, who are much more numerous. It would be most interesting to learn whether the association between irregularities in skin and hair pigmentation and elevated susceptibility to skin cancer would also be explained by defects in DNA repair mechanisms.

Other genetic factors, perhaps of a complicated biochemical nature and not reflected by easily recognizable external features, may be associated with other cancer sites such as lung or bladder. Research in this direction may give some clues to aid in the selection of workers who are less prone to develop cancer during their lifetime.

Individual susceptibility may, however, be not only genetically determined. Certain pathological processes, which may in turn have some genetic or congential background, can increase the disposition to develop cancer. Hueper (1957) gives a complete list of pathological conditions that must be regarded as contraindications for employment in various occupations.

Medical, administrative, and legislative practices indicate that the results of animal

TABLE 3. Incidence of Skin Tumors in Coal-Tar Distillery Workers in Relation to Exposure Time[a]

Exposure years	Total no. of workers	No. with tumors	Percent with tumors
0–4	98	5	5
5–9	30	5	17
10–14	28	9	32
15–19	19	9	47
20–24	28	14	50
25–29	10	5	50
30–34	18	11	61
35–39	5	3	60
40–44	3	3	100
45	2	2	100
Total	241	66	27.38 (average)

[a]From Fisher (1953).

experiments are often not regarded as sufficient evidence on which to base preventive action. It is certainly true that most occupational carcinogens have been discovered by clinical observations and epidemiological studies and subsequent animal experiments have confirmed causal relationships. However, the few instances when the opposite process has taken place—experimental demonstration of carcinogenicity preceding the discovery of occupational cancer cases in workers, as with vinyl chloride and bis(chloromethyl) ether—should be considered as highly significant and proving the predictive value of animal experimental data. There is little doubt that if preventive measures had been applied on the basis of experimental evidence, many occupational cancer cases would not have occurred.

The strictness and efficiency of preventive measures may vary, mostly depending on economic and technological aspects. It appears that preventive measures based on experimental evidence and developed in accordance with technological innovations have to a certain degree diminished the cancer risk in the Estonian oil shale industry. More than 25 yr ago we started animal experiments to determine the carcinogenicity of various primary thermal processing and commercial products of Estonian oil shales. The experience of the Scottish oil shale industry—although its raw material, technology, and products differed considerably—served as a general example. Products derived from high-temperature processing of oil shale appeared to be potent carcinogens.

Various technological changes aimed at diminishing exposure of workers to carcinogenic oil shale products, such as hermetization and automation, as well as personal hygiene measures were applied. According to our proposal (Bogovski et al., 1963), the technology of coking of high-temperature chamber-oven tar was introduced at the oil shale processing plant in Kohtla-Järve. This coincided with economic interests. The number of workers exposed to the tar was thus considerably reduced and the coke was much less carcinogenic than the initial tar. Some carcinogenic risk, however, remained in the oil shale industry, as demonstrated by recent epidemiologic studies of Etlin (1978) showing a statistically significant (men, $p < 0.05$; women, $p < 0.01$) excess skin cancer incidence in a cohort of oil shale processing plant workers (2003 persons), who had been working 10 yr or more, compared with urban populations of the oil shale region and of the whole Estonian S.S.R. (Fig. 1). The incidences of cancers at other sites (lung and stomach) were lower than in control populations. Increased skin cancer rates may be associated with expsoures before technological changes were introduced. On the other hand, it is possible that without these changes the skin cancer incidence may have been higher. This and other similar situations demonstrate that animal experiments, if properly conducted and convincing, can have a predictive and also, to a certain extent, a preventive value.

The principal lesson to be learned from the somewhat controversial issue of the relationship between experimental and epidemiologic evidence of carcinogenicity seems to me to be that experimental data should be accepted as sufficient to warrant beginning preventive measures. Unfortunately, experimental data are often not considered justification for action.

Moreover, there is sometimes an unexplainable resistance to action even when sufficient human evidence is available (Wagoner, 1976; Epstein, 1976, 1977). This is illustrated by a comparison of legislative actions in various countries in relation to environmental carcinogens. An inquiry demonstrating marked differences between countries in this regard was carried out by the IARC (1974). Montesano and Tomatis (1977) presented convincing documentation. The difficulties of international coordination and standardization are well known; however, it is surprising that scientific facts are so differently understood and used as basis for legislative action.

An important lesson from the past is that occupational cancers have a multifactorial etiology. Even in point source exposures the concept of one effect-one cause is false. Well-known examples are asbestos and uranium mining combined with smoking. It is probable that other combinations will be found. Perhaps the observation that Ni refining or auramine production is more strongly associated with occupational cancer than Ni or

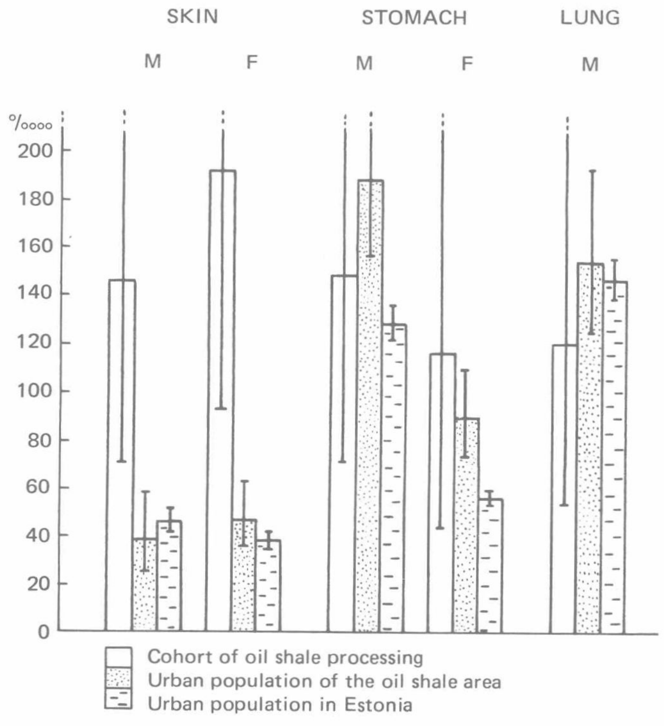

FIGURE 1. Truncated incidence rates (ages 35–75) of cancer (three sites) in oil shale processing plant workers compared with the urban population in the oil shale area and in Estonia.

auramine per se will be explained in terms of some multifactorial effect. The same may be relevant to the action of As.

INPUT FROM EXPERIMENTAL CANCER RESEARCH

In the preceding section experimental research was repeatedly mentioned. Experimental data on carcinogenicity having predictive value should be always taken into account. There are, however, other experimental data related to mechanisms of carcinogenesis that may considerably diversify our way of thinking and approaches to the occupational cancer problem.

A most important but not yet well-defined field of cancer research is represented by a vast amount of experimental studies of factors that modify the action of carcinogens. The modifying effect of solvents and hydrophilic-lipophilic substances on the carcinogenic response in skin painting experiments has been thoroughly investigated in this country (Setälä, 1954; Setälä et al., 1959). In our experiments with high-temperature shale oil we found that petrolatum (medicinal vaseline) considerably increased the carcinogenic effect of solutions of this tar (Bogovski, 1961).

Bingham and Falk (1969) reported a 1000-fold increase of the carcinogenic potency of B[*a*]P and benz[*a*]anthracene due to *n*-dodecane. Many other examples of the modifying effect of various substances could be given (e.g., Bogovski, 1969). Recent papers of Falk (1976), Newberne (1976), and Bingham et al. (1976) deal with various aspects of modifying factors, and many data have been published on the modifying action of diet (McLean, 1973; Vitale, 1975; Alcantra and Speckmann, 1976; Gori, 1977). An important practical aspect of modifying factors is the possibility that a carcinogen may act at a dose or concentration that is considered insignificant or is at or below the detection limit.

In the last couple of years much has been said and written about life-style in connection with epidemiologic studies of environmental cancer. Wynder and Gori (1977) included in life-style excessive smoking, alcohol consumption, overnutrition, and industrial exposures.

First, I believe that industrial exposure or working conditions, as far as recognized human carcinogens are concerned, should not be included in life-style. In fact, Higginson and Muir (1979), in their figures 1 and 2 indicating the estimated proportions of cancer due to selected environmental factors, depict occupational cancers separately.

It seems to me that at our present state of knowledge it would be very helpful, on the basis of experimental evidence concerning various modifying factors, to try to build up a coherent approach to life-style studies. To facilitate a systematic analytical approach, I would like to propose a classification of modifying factors, which certainly will be neither complete nor final, but nevertheless could be helpful in systematizing existing data and carrying out research to resolve questions and accumulate new facts.

All modifying factors (MF) can be divided into cocarcinogenic and anticarcinogenic. Another subdivision expresses the relationship to the host—environmental MF or host-dependent MF (hereditary, congenital, or acquired during lifetime). In the proposed classification, MF are segregated according to the sequence of events of carcinogenesis, which are continuously becoming less obscure (Burnet, 1977; Weinstein, 1978; Miller, 1978). It would be useful to include among the steps of tumor development the formation of carcinogens or their precursors in the organism, taking into account established factors concerning nitroso compounds. Promoters must be considered as MF acting during relevant events of carcinogenesis. The general outline of the classification could be presented in the form of a table (Table 4).

Obviously, it would be impossible to compose a common classification of MF fitting all cancers and carcinogens. Classifications should be worked out separately for each cancer site