Recent Perspectives in Occupational Cancer

BY IRVING J SELIKOFF

In recent years, many previously unsuspected carcinogenic agents have been identified and new perspectives established for the evaluation of the increasing numbers of chemical substances introduced into the environment.

Attention is sometimes called to the fact that the first neoplasms for which etiological factors could be established, were occupational cancers. The report 200 years ago by Percivall Pott of cancer of the scrotum in individuals who had been employed as chimney sweeps (1), or that of chemical carcinogenesis in humans first described 80 years ago as "aniline cancer" (2), or that radiation-induced cancer had an occupational starting point among miners in Schneeburg and Joachimstal almost 90 years ago (3), are cited. These claims are true, yet it is equally true that each was an isolated descriptive observation, of muffled impact in its time.

Accelerated development of a connecting mature body of knowledge, the discipline of occupational cancer, has rather been a matter of the past two decades. Although it was related to what went before by the continuing productive studies of the effects of carcinogenic aromatic amines (2), if one event can be said to be the origin of this new phase, it may be the brilliant description in 1955 by Richard Doll of the association between occupational exposure to asbestos and an important risk of death of lung cancer (4). Doll's demonstration of the applicability of chronic disease epidemiology provided an important example for future research. Many of the concepts we now take for granted in the evaluation of occupational carcinogenicity, as, the need for long periods of observation (5), the utility of cohort studies (6), the possibility of coexistence of cancer and other biological toxicity (7), were inherent in his classic report. Similar approaches have guided the best of experimental studies and have increased their relevance to human disease (8).

With this background, a good deal has been learned about occupational cancer in recent years. This has included identification of carcinogenic agents previously unsuspected of such effects and the establishment of a number of perspectives which are now available for the evaluation of other materials used in industry and/or agriculture or which may be introduced in the future (9). The latter achievement is perhaps more important, since the number and complexity of new or recently introduced agents has attracted much attention, and little is known concerning their carcinogenic potential.

LATENT PERIOD

The above term is perhaps inexact since we do not actually know what is happening in tissues between the time of first exposure and initial evidence of clinical disease. Changes may be under way, albeit not detectable with current techniques. Perhaps "period of clinical latency" or "lapsed period" would be more exact (10). In any case, each of these terms describes an important phenomenon—that a considerable time must usually elapse between onset of exposure to an occupational carcinogen and the first evidence of resulting cancer. Generally, this period is 20—35 years, although as little as 10—15 years may suffice, or 35—50 or more years will pass. The time sequence can be affected by a number of variables touched on below, but it is remarkable how their influences operate within relatively narrow constraints.

Understanding this, two conclusions become evident. First, it would have been difficult or impossible to establish the carcinogenicity of substances widely introduced only in the

past 30—50 years, until the last decade or so. Second, we will not be able, with present knowledge, to identify cancer risk in humans of recently introduced agents for another two or even three decades (11), and epidemiology must look to assistance from other disciplines. Parenthetically, a similarly long period must elapse before it can be ascertained whether measures designed to correct an occupational cancer hazard are actually effective. This has been the case, for example, among nickel smelter workers (12).

The importance of the principle of clinical latency has perhaps nowhere been better demonstrated than with lung cancer associated with occupational exposure to asbestos. In our Laboratory, we have been following a cohort of asbestos insulation workers, composed of all 17 800 members of the Union of such workers in the United States and Canada on January 1, 1967 (5). By December 31, 1972, 1356 of these men had died, almost 400 more than had been expected. There were 275 deaths of lung cancer, whereas only 56 had been anticipated. Analysis of the work history of these men indicated that the excess deaths were largely limited to those workers who had achieved more than 20 years from onset of their work (Tables 1 and 2).

The risk of lung cancer with occupational exposure to asbestos could easily be missed, and inaccurate conclusions drawn, if studies are made without the opportunity to observe a sufficient number of individuals 20—30 or more years from onset of work exposure. Similar results have been obtained in studies of uranium miners (13) and workers in nickel refineries (14) and with other agents; indeed, when many lung cancers are seen after significantly shorter periods, as with β-chlormethylether (15), one might justifiably suspect rather intense exposure or particularly virulent agents.

MULTIPLE FACTOR ETIOLOGY

Investigations of occupational exposures for carcinogenicity generally seek to isolate the suspect materials. This is reasonable. Nevertheless, this approach is in a sense artificial, since carcinogenic agents are infrequently used singly, but rather in complex work environments, often with a variety of other substances of unstudied potential, and by individuals whose personal and social environments are equally varied. The possibility of interaction of two or more agents has long been known in the experimental setting; since 1968 it has been shown for occupational cancer in humans as well (16). It was found among asbestos workers, for example, that lung cancer risk was not significantly increased among those men who did not also have a history of cigarette smoking. Those who did, had much more lung cancer than cigarette smokers in general. Asbestos exposure thus markedly increased the lung cancer risk of cigarette smoking; it has been calculated that an asbestos worker who smokes cigarettes has 92 times the risk of death of lung cancer compared with an individual of the same age who neither smokes nor works with asbestos (16). The powerful multiplying effect of the combination of two agents can be appreciated by examining the experience of asbestos insulation workers cited above. When the cohort was established, the smoking habits of the majority of the workers was recorded; 9590 had a history of cigarette smoking, 609 had a history of pipe and/or cigar smoking but no cigarette smoking, and 1457 had never smoked at all. Their mortality experience, with particular reference to lung cancer, is detailed in Table 3. Among those who never smoked, only one lung cancer was seen from January 1, 1967 through December 31, 1972. The pipe and cigar smoking group also had only one lung cancer death. On the other hand, there were 179 lung cancer deaths among those with a history of cigarette smoking, although only 32 such deaths were expected to occur. This, despite the fact that all of these men had worked in the same trade, with equal opportunity for occupational exposure to asbestos.

The significance of the principle of multiple factor interaction has many ramifications. Two are of immediate interest. First, some substances, by themselves, may have no carcinogenic effect; in concert with others, malignancy may occur. Such influence may be additive or multiplicative (theoretically, there could also be a protective effect, as well). As a corollary, substances now deemed innocuous may change their habit in new circumstances; our vigilance must be constant. Too, since there may be many more substances of limited carcinogenic potential than those individually capable of inducing malignancy, and since at least some working environments now tend to become more complex, this may turn out to be of considerable practical importance in the future.

Second, animal studies generally are directed to the investigation of one agent; negative results may therefore be misleading insofar as actual work risk is concerned. (To compensate, one should hasten to add, dosages can be far greater than those which occur in industry, and carcinogenicity enhanced).

SIGNAL CANCERS

Most occupational cancers are identified as occurring as increased numbers of common malignancies. Thus, increased rates (taking age, year and sex into account) of lung cancer occur, for example, with occupational exposure to talc, chromates, arsenic, nickel carbonyl, uranium mining, fluorspar mining, hematite, β-chlormethylether and asbestos; of blad-

Table 1. Expected and observed deaths among 17 800 asbestos insulation workers in the United States and Canada January 1, 1967—December 31, 1972.

	Duration from onset of exposure			
	Less than 20 years		More than 20 years	
	Expected*	Observed	Expected*	Observed
Total deaths—all causes	203.90	249	756.12	1109
Cancer all sites	30.42	64	145.13	511
Lung cancer	8.40	28	47.47	247
Asbestosis	—**	7	**	94
All other causes	173.48	178	610.99	504
Number of persons	12 681		5119	

* Expected rates are based upon age-specific white male death rate data of the US National Office of Vital Statistics. Rates for 1972 were extrapolated from rates from 1967—1971.
** US rates are not available, but these are rare causes of death in the general population.

Table 2. Deaths from lung cancer among 17 800 asbestos insulation workers in the US and Canada, January 1, 1967—December 31, 1972; relation to elapsed period from onset of work exposure.

	Lung cancer		
Years from onset	Expected deaths*	Observed deaths	Ratio
<10	0.56	0	—
10—14	1.97	5	2.5
15—19	5.87	23	3.9
20—24	9.55	34	3.6
25—29	10.70	56	5.2
30—34	8.20	60	7.3
35—39	4.68	29	6.2
40—44	4.84	27	5.6
45—49	4.51	19	4.2
50+	4.97	22	4.4
Total	55.87	275	4.9

* Expected deaths are based upon age-specific white male death rate data of the US National Office of Vital Statistics. Rates for 1972 were extrapolated from data from 1967—1971.

Table 3. Expected and observed deaths of lung cancer among 17 800 US and Canada asbestos insulation workers, January 1, 1967—December 31, 1972; relation of cigarette smoking.

	No of persons	Deaths from lung cancer		
		Expected*	Observed	Ratio
Smoking habits not known	6144	16.76	94	5.6
History of cigarette smoking	9590	31.60	179	5.7
No history of cigarette smoking	2066	7.51	2	0.3
Never smoked	1457	4.40	1	0.2
History of pipe and/or cigar only	609	3.11	1	0.3

* Expected deaths based upon age-specific US mortality rates for white males disregarding smoking. Lung cancer estimates based upon US rates for cancer of lung, pleura, bronchus and trachea, categories 162 and 163 of the International Classification of Diseases and Causes of Deaths, 7th Revision.

der cancer with β-naphthylamine and benzidine; of leukemia with benzene and radiation. To find the effect of such substances, appropriate population studies are necessary to see if the expected background rates are increased. Sometimes, especially if less common tumors are being considered, as brain or adrenal or kidney or lymphoma, extensive observations are necessary, if not of moderate sized groups over long periods of time (after the 20 year point!), then of very large groups for shorter periods (to achieve an adequate number of "person-years" of observation).

In a number of instances, unusual tumors have been observed in considerable numbers for which the usual expected-observed ratios are almost superfluous. When cancer of the scrotum occurred among Pott's chimney sweeps the absence of biostatistical calculations did not prevent recognition of the unusual situation. Sinus tumors among woodworkers may be looked at in somewhat the same light (17).

Two neoplasms, infrequent in general but common with industrial exposure, have demonstrated that such "signal" tumors can be important factors in identifying occupational carcinogenesis. One, hemangiosarcoma of the liver, has assumed such a role recently and will be discussed below. The second, mesothelioma, has a longer history. First reported in the pleural cavity of an asbestos worker in 1953 (18) and in the peritoneum of another the next year (19), its link to asbestos was firmly established in 1960 (20) when, in a series of 47 cases in one laboratory in South Africa, over a five year period, 45 were shown to have had opportunity for asbestos exposure of one or another type, decades before. The impact of this finding can be gauged by appreciation that, in general, approximately one in a thousand deaths in the general population had been known to be caused by these previously uncommon tumors. With occupational asbestos exposure, these tumors have proven common (21). In some cohorts of asbestos workers, approximately five or six percent of deaths have been due to pleural and peritoneal mesothelioma (5). In others, the percentage is lower; it has been reported, for example, that this neoplasm is less frequent among Quebec chrysotile asbestos miners (22). When found in family contacts, it led to the understanding of the danger of bringing dust from the factory to the home (23), when found amid residents in the neighborhoods about asbestos plants, it bespoke uncontrolled asbestos air pollution in the past. In South Africa's large series of cases, with adequate history, only approximately fifteen percent have been judged not to have had some known asbestos contact (24). Thus, wherever mesothelioma is found, asbestos is sought. In this way, otherwise unsuspected occupational exposures to asbestos have been identified—in shipyards, especially (25).

ENVIRONMENTAL CANCERS FROM OCCUPATIONAL SOURCES

An important dimension was added to occupational cancer with the discovery that neoplasms might occur with the dissemination of the agent beyond the factory gate, either by its release during the manufacturing process or from resulting waste, or by contamination of households with the offending material being brought home on workers' clothes. Although instances of such disease had been known before (20), the full import of the problem was not appreciated until Newhouse's report in 1965 (23) when she demonstrated that, of 76 confirmed cases of mesothelioma in the files of the London Hospital, of the 45 not known to have had occupational exposure to asbestos, nine had simply lived in the households of asbestos workers ("conjugal disease") and 11 had neither worked with the material nor lived with someone who had been so employed, but had resided, many years before, within one half mile of an asbestos plant in London. This finding was soon confirmed (26), and the principle of carcinogenic risk derived from occupational sources is an important factor in current evaluation of control of environmental cancer, whether it be from radiation-producing power sources, agricultural use of pesticides, air and water pollution from petrochemical industry operations, carcinogenic mineral dust, or other substances or processes (11). These considerations are separate from those involving cancer risk with end-product use, either during further industrial manipulation of materials or in utilization of consumer products.

PETROCHEMICAL INDUSTRY CANCER

There was a curious discrepancy during the first half of this century between continued concern regarding the potential for occupational cancer in the burgeoning petrochemical industry and reliable evidence that this was occurring with any frequency. In considerable part, the contradiction remains. On the one hand, the industry deals with a very large number of chemicals which either have been shown to have carcinogenic potential in laboratory animals, or are related to these chemicals, belonging to such suspect groups as the polycyclic aromatic hydrocarbons or some of the halogenated hydrocarbons; in several instances, as benzpyrene or β-naphthylamine, occupational cancers in humans have been clearly established. On the other hand, the number of chemical agents so incriminated has remained comparatively small and the number of workers involved, limited.

With the recent identification of vinyl chloride induced cancer (27, 28), the situation has changed somewhat. It is still not known whether a good many of the petrochemical industry's materials will turn out to be carcinogenic—in large part, an adequate "latent period" has yet to run its course, to allow for proper evaluation. Still, to find that a key chemical in the giant plastic industry was clearly carcinogenic has been disconcerting. Further, it was sobering to realize that if vinyl chloride's carcinogenicity had been expressed in increased risk of cancer of lung or colon, elevated rates of neoplasms of these sites among the affected workers might not have been identified for some years, at the earliest. The fact that it was an unusual tumor, hemangiosarcoma of the liver, otherwise rare in the general population (perhaps one in 10 000—40 000 deaths), which occurred, attracted attention.

Three cases in one plant, the B F Goodrich Company in Louisville, Kentucky, were sufficent to establish a strong suspicion of the risk (29) and the suspicion became a virtual certainty when the same neoplasm was found in other vinyl-chloride polymerization plants, making vinyl chloride the likely offender, rather than other coexisting chemicals, as special additives or process chemicals, peculiar to the Louisville plant's operation. At the same time, the fact that only a dozen and a half cases came to notice in the first five months after discovery of the condition did little to allay concern, since these cases, when analyzed, had begun work, on the average, approximately 20 years before death, at a time when the vinyl chloride-polyvinyl chloride industry was limited in size and still employed relatively few workers. Of the 19 cases recorded by mid-June, 1974, 15 had begun work 1944—1952, with an overall average of 20.4 years from onset for the group as a whole. Since the great majority of workers in vinyl chloride-polyvinyl chloride plants were first employed during the 1950s and 1960s, it was evident that the full impact of vinyl chloride tumors would not be known for another two decades. Limited data so far available suggests that, at least for polyvinylchloride polymerization workers, the incidence of occupational cancer will be significant. We have examined the mortality experience of a cohort of workers employed at a large polyvinylchloride polymerization facility in the United States. The plant opened in 1946 and from that year to 1963, 257 individuals were employed in the production process for five years or more. While exposures began in 1946, relatively few individuals were employed prior to 1951, when a significant increase in the work force took place. Thus, the majority of the cohort has had a bare 20 years or less from onset of exposure.

An initial report of the experience of these men has been made (30). We have traced each of the 257 individuals to December 31, 1973. Twenty-five were found to have died, of all causes. Three of the deaths, each confirmed at autopsy, were due to hemangiosarcoma of the liver (Table 4). Ages at death were 41, 54, 60. Elapsed time from onset of first exposure to death was 14, 17, 23 years.

DOSE-DISEASE RESPONSE RELATIONSHIPS

Discussion of this thorny question, with social, ethical and economic implications co-mingled with scientific perspectives, was stimulated and made much more acute in the evaluation of regulatory measures necessary for the control of vinyl chloride cancer. While it has been generally agreed that the risk of malignancy increases with intensity and duration of exposure, there has been much less concordance in the evalu-

Table 4. Causes of death among 25 workers exposed to vinyl chloride for 5 or more years.

Cancers of all sites	9
Hemangiosarcoma of liver	3
Neoplasms of lymphatic and hematopoietic tissues	2
Brain (Glioblastoma)	1
Pancreas	1
Colon	1
Bone	1
Cirrhosis (with esophageal varices)	1
Post-operative bleeding (Cholelithiasis	1
Cardiovascular diseases, other	14

ation of whether a lower threshold existed below which cancer would not occur. There have been few data bearing directly on this aspect of the question and, in the nature of things, it might be that such data are unlikely to appear. "Negative" experiments, to be convincing, would have to involve very large numbers of animals and, more important, observation of very large numbers of vinyl chloride workers exposed for prolonged periods of time at measured low levels of exposure to the monomer. Even if these data should be obtained, they would always be only an approximation, since further study conceivably could show exceptions. Theoretical considerations would seem to indicate that there is no identifiable lower threshold limit for carcinogenic agents (31). The proposed regulations for the control of occupational exposure to vinyl chloride in the United States seem to approach the problem from this point of view; a level of one part per million has been proposed (32) which, interpreted in practical terms, might be considered a "no threshold" level but one which allows for inevitable mistakes and accidents which might occur in the industrial environment, as well as recognition of practical problems concerned with instrumental monitoring of the work environment.

PRETESTING OF NEW MATERIALS

Recognition of the long period of clinical latency between onset of exposure to materials in the occupational environment and their carcinogenic effect, if this is to occur, has recently raised the corollary question whether we might anticipate such evaluation and shorten, or eliminate, this period of uncertainty. Much attention is now being paid to this possibility. Until recently, however, expectation and desire exceeded promise. Although structural similarity to known carcinogens might occasion a high level of suspicion, cancer potential does not necessarily follow structural resemblance; many exceptions are known. Further, while suspicion could be directed to agents with biological activity other than cancer, many are known with toxic effects on kidney, liver, lung, central nervous system, without concomitant recognized cancer potential.

Experiences with vinyl chloride and β-chlormethylether suggests, however, that laboratory screening might be feasible, for at least some agents. In each instance, laboratory studies were able to establish the carcinogenicity of a chemical substance which was later shown to be carcinogenic in man (28, 33). It is not known whether such experimental screening approaches will be equally productive with other agents, nor whether other laboratory techniques, including mutagenic studies, will extend their utility (34). Certainly, this is to be hoped for and much work is being initiated to provide information on the question. Guidelines that would point priorities for selection of agents to be tested are also being discussed, and include such considerations as chemical structure, evidence of other biological activity, number of workers likely to be exposed. For substances already in use, similar considerations could apply, with the added dimension that epidemiological studies should be suggested when there are available groups of workers whose exposures began 10—15 or more years ago.

References and Notes:

1. P Pott, *Cancer of the Scrotum, Chirurgical Observations* (Hawes Clark and Collings, London, 1775) pp 63—68.
2. J C Arcos and M F Argus. *Chemical induction of Cancer* (Academic Press. New York, 1974) Vol IIB pp 3 — 4.
3. A Pirchan and H Sikl, *American Journal of Cancer* **16**, 681 (1932).
4. R Doll, *British Journal of Industrial Medicine* **12**, 81 (1955).
5. I J Selikoff, E C Hammond and H Seidman, in *Biological Effects of Asbestos,* P Bogovski, J C Gilson, V Timbrell and J C Wagner, Eds (International Agency Research on Cancer, Lyon, 1973) pp 209—216.
6. T F Mancuso and E J Coulter, *Archives of Environmental Health* **6** (2), 210 (1963).
7. I J Selikoff, J Churg and E C Hammond, *Journal of the American Medical Association* **188**, 22 (1964).
8. J C Wagner, G Berry, J W Skidmore and V Timbrell, *British Journal of Cancer* **29**, 252 (1974).
9. E C Hammond and I J Selikoff, in *Analytic and Experimental Epidemiology of Cancer,* W Nakahara, T Hirayama, K Nishioka and H Sugano, Eds (University of Tokyo Press, Japan, 1973) pp 41—49.
10. I J Selikoff and E C Hammond, *Environmental Research* **4** (2) ii—iii (1971).
11. I J Selikoff and E C Hammond, *Proceedings of the 7th National Cancer Conference*, Los Angeles, 687 (1973).
12. R Doll, L G Morgan and F E Speizer, *British Journal of Cancer* **XXIV** (4), 623 (1970).
13. F E Lundin, Jr, J W Lloyd, E M Smith, V E Archer and D A Holaday, *Health Physics* **16**, 571 (1969).
14. E Pedersen, A Hogetveit and A Andersen, *International Journal of Cancer* **12**, 32 (1973).
15. W G Figueroa, R Raskowski and W Weiss, *New England Journal of Medicine* **288** (21), 1096 (1973).
16. I J Selikoff, E C Hammond and J Churg, *Journal of the American Medical Association* **204** (2), 106 (1968).
17. E D Acheson, R H Cowdell and E Rang, *British Journal of Industrial Medicine* **29**, 21 (1972).
18. A Weiss, *Medizinische* **3**, 83 (1954).
19. F Leicher, *Archiv für Gewerpathologie und Gewerbehygiene* **13**, 382 (1954).
20. J C Wagner, C A Sleggs and P Marchand, *British Journal of Industrial Medicine* **17**, 260 (1960).
21. J B Enticknap and W J Smither, *ibid* **21**, 20 (1964).
22. J C McDonald, A McDonald, G W Gibbs, J Siemiatycki and C E Rossiter, *Archives of Environmental Health* **22**, 677 (1971)
23. M L Newhouse and H Thompson, *British Journal of Industrial Medicine* **22**, 261 (1965).
24. I Webster, *South African Medical Journal* **47** (5), 165 (1973).
25. P G Harries, *Annals of Occupational Hygiene* **11**, 135 (1968).
26. J Lieben and H Pistawka, *Archives of Environmental Health* **14**, 559 (1967).
27. PL Viola, A Bigotti and A Caputo, *Cancer Research* **31**, 516 (1971).
28. C Maltoni and G Lefemine, *Environmental Research* **7**, 381 (1974).
29. J L Creech and M N Johnson, *Journal of Occupational Medicine* **16**, 150 (1974).
30. W J Nicholson, H Seidman, E C Hammond and I J Selikoff, *Annals of New York Academy of Sciences,* in press.
31. *Evaluation of environmental carcinogens,* Report to the Surgeon General, USPHS, April 22, 1970, Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens.
32. *US Department of Labor Occupational Safety and Health Administration, Exposure to vinyl chloride: occupational safety and health standards* (Federal Register 39:35890—35898, October 4, 1974).
33. B L Van Duuren, B M Goldschmidt, C Katz, L Langseth, C Mercado and A Sivak, *Archives of Environmental Health* **16**, 472 (1968).
34. U Rannug, A Johansson, C Ramel, C A Wachtmeister *Ambio* 3, 194 (1974).

35. Research supported by grant ES 00928 of the National Institute of Environmental Health Sciences and by the Environmental Cancer Research Project of the American Cancer Society R-53 B.

Dr Selikoff serves as Professor of Community Medicine at the Mount Sinai School of Medicine of the City University of New York; and as Director of its Environmental Health Sciences Center. A past President of the New York Academy of Sciences, his interests now emphasize problems of environmental cancer, particularly those associated with materials in industry. However, his research has in the past also included other diseases; and for many, his achievements in environmental disease research are matched by his contributions in the introduction of isoniazid for the chemotherapy of tuberculosis, for which he was honored by the Lasker Award of the American Public Health Association in 1955. His address: Mount Sinai School of Medicine, Fifth Ave and 100 Street, New York, N Y 10029, USA.