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Review Article

Recent Developments in Industrial Carcinogens

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The topic of carcinogens is one about which there is much confusion and also much misunderstanding. This in turn leads to the development of fears and apprehensions. As in clinical medicine, the word cancer in industry immediately seems to lead to despair, whereas our approach should be straight forward and intelligent. I think of cancer in industry just as I do about any other potentially toxic problem in industry. What we need when a problem develops is knowledge—knowledge of the process, knowledge of the chemistry, knowledge of the exposure. The more we know the more likely we are to arrive at satisfactory solutions. In this respect, then, cancer in industry is like any other problem-solving.

First, we have to have some knowledge of the experimental methods used by oncologists to test for carcinogenicity. In the case of the skin, the tests are relatively straightforward. You will note that I say "relatively" because in fact even a skin carcinogenesis test has many elements that may serve to complicate it. Thus we know that mice, hamsters, and rabbits do develop skin cancers in response to chemical agents painted on the skin, while rats and guinea pigs seem to be refractory, and monkeys are resistant, taking long periods to do so. Thus the mouse has generally become the animal species used in this type of experiment. Painting is usually done three times a week. If done more frequently the material applied may so severely damage the skin as to make interpretation of results difficult. If done less frequently the latent period for cancer development may be so long that the animals die before developing cancer. Painting should be done with a minimum of rubbing to avoid damaging the skin. Some workers even use a micropipette so that no rubbing at all is done, just letting the material spread over the shaved skin in an accurately measured dose at each application. The animals should be weighed periodically because if the material being painted is toxic it may interfere with their growth, and we know that this in turn will interfere with tumor development.

Because a skin-painting experiment takes so long—up to two years—people are always looking for shortcuts. They want a chemical test or an accelerated biological test that will give them an answer in a few days or a few weeks. However desirable this may be, so far none of them have held up when examined closely. Thus it was found that some carcinogens would cause atrophy of the sebaceous glands of the skin, and this was once proposed as a "quickie" test. However, in a study of 130 compounds, Bock & Mund[1] found that some carcinogenic compounds did not cause sebaceous gland atrophy, while some non-carcinogenic compounds did. Some chemical tests may have limited application, but because of the wide variety of chemical compounds that have been shown to have carcinogenic activity it would be anticipated that no single chemical test would have universal applicability. Suffice it to say that an expert panel convened to advise the Food & Drug Administration concluded that there were no truly satisfactory short-term tests that had been sufficiently proven that they could substitute for long-term carcinogenesis tests.[2]

Some people have recommended that the material to be tested simply be injected or implanted subcutaneously into rats or mice. This has the advantage of a known dose and minimal handling of the animals.[3] But this method so far has been shown to produce malignant tumors (sarcomas) in response to cellophane, Dacron, polyethylene, polyvinyl chloride, silastic, Pliofilm, Nylon, polymethyl methacrylate, polystyrene, Saran, Ivalon, Kel-F, Teflon, silk,[4] and glass cover slips.[5] In our hands, we found that a complex oil shown to be carcinogenic to the skin when painted caused a local abscess when injected subcutaneously which subsequently sloughed out without tumor formation. Thus this route of testing may have limited application, especially if tumors are produced at a site distant from the site of injection, but if sarcomas at the site of injection are the only tumors formed, interpretation of their significance becomes extremely difficult.

Another suggested test is that of implanting the material in the bladder of mice. This suggestion arose, I believe, from an entire misconception. Thus in the study of bladder tumors occurring in workers in the dye industry, beta-naphthylamine, when administered subcutaneously, was shown to produce bladder tumors in dogs but not in mice. In searching for the reason for this discrepancy it was found that both man and dogs excrete 2-amino-1-naphthol as a metabolite of beta-naphthylamine in their urine, whereas mice do not. Dr. Georgianna Bonser, in England, concluded that maybe beta-naphthylamine was not the carcinogen after all but the metabolite 2-amino-1-naphthol was. To test out this theory she impregnated small wax pellets with 2-amino-1-naphthol and implanted them surgically into the bladders of mice. Sure enough, the mice developed bladder cancer. However, subsequently it has been shown that cholesterol, glass, stearic acid, magnesium stearate, hexadecanol, octadecanol, and naphthalene[6] (the old-fashioned moth ball) all produced bladder tumors and cancers when implanted into the mouse bladder. None of these are suspected of being carcinogenic. Thus this test does not seem to be a very sound one.

Incidentally, these studies of the metabolism of beta-naphthylamine have led to extensive metabolic studies and brisk scientific arguments about what truly is the carcinogenic agent. One school supports the 2-amino-1-naphthol metabolite

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as the carcinogen, whereas another believes that hydroxylation of the nitrogen atom of the amino group (so-called N hydroxylation) is the carcinogen, while yet others believe different metabolites are the true carcinogen. These studies have been fascinating from a biochemical standpoint and have served to keep many cancer biochemists hard at work in the laboratory but probably do not have much practical implication for industrial cancer prevention.

However, the studies of the implantation of cholesterol, glass, stearic acid, and other materials into the bladder, previously mentioned, may have serious practical considerations for other studies. Thus diethylene glycol and other materials are claimed by some to be a carcinogen on the basis that they have produced bladder cancers in mice. However, such tumors and cancers never developed unless first a bladder stone was produced. The question then arises—is the chemical a carcinogen, or is the stone the carcinogen? It is interesting to note that the first experiments with cyclamates were undertaken with such bladder implantation techniques and had to be discounted until feeding experiments were completed. Even now the cyclamate picture is not clear because there is some question that the experimental animals may have been infected with bladder parasites. It is well known that Bilharzia, a bladder infestation of humans by Schistosoma hematobium, is associated with bladder cancer. In Egypt, where Bilharzia is endemic, bladder cancer incidence is quite high. The Schistosomes enter the body through the skin from water in which the Egyptians are walking in caring for their fields. From there they enter the bloodstream and ultimately end up in the bladder. Incidentally, the secondary reservoir for the Schistosoma hematobium is the snail, and much work is going on trying to find an agent that will kill the snail without producing other undesirable ecological effects. The approach is like killing the mosquito to eliminate malaria.

Another approach that has been recommended to try to shorten the necessary test period for carcinogens is the use of newborn or very young (suckling) mice.[7] It was suggested that an increased incidence and earlier appearance of malignancies could be obtained from a single injection of potent carcinogens. However, newborn rats did not respond in the same way as newborn mice.[8] Rather, they responded like adult mice. Further, more complete studies have shown that this test method probably has few true advantages.[9] It may be that the use of newborn or very young mice was predicated on the absence of detoxifying enzymes in the newborn which subsequently appear as the animal ages. It is known that a benzpyrene hydroxylase exists in the gastrointestinal tract,[10] and it is further known that newborns are frequently lacking enzyme systems that are present in adults. Even today, however, there are those who strongly urge the newborn as a test animal system.

Turning to experimental lung carcinogenesis, it is now beginning to appear that multiple factors are probably necessary to produce lung cancers in experimental animals. Thus in rats a combination of repeated influenza virus infections plus ozonized gasoline[11] or sulfur dioxide and benzo(a) pyrene[12] or 7,12-dimethyl-benz(a) anthracene plus india ink[13] or, in hamsters, hematite plus benzo(a) pyrene[14] all have led to lung cancer production. The evidence indicates that pure polyaromatic compounds like benzo(a) pyrene are rapidly removed from the lungs. However, when introduced with particles or with SO_2 which may impair the ciliary removal mechanisms, residence time within the lung may be much prolonged, and it is this increased residence time which the experimentalists believe leads to the production of lung cancer. This experimental work on lung cancer is in its very early stages, and it is too soon yet to draw definitive conclusions on it.

One very interesting lung cancer experiment in rats was that conducted by Laskin *et al.*[15] These workers exposed rats to 0.1 ppm of bis(chloromethyl) ether six hours per day, five days per week for a total of 101 exposures. Nineteen out of 30 rats so exposed developed squamous cell cancers of the lung or cancers of the nasal epithelium. Of interest in this connection is that subsequently in a chemical plant in California where bis(chloromethyl) ether was produced several cases of lung cancer were reported. I have only seen newspaper-type reports of these cancers in these chemical workers, so I am not able to comment intelligently further on them. If in fact this is so, it may represent the first time the detection of a carcinogen by laboratory tests has subsequently been followed by the appearance of cancers in humans. Usually epidemiological studies have shown the presence of cancers in humans, and this in turn has led to an intensive search in the laboratory for the carcinogen. It is of interest that these workers have also been able to produce lung cancers in experimental animals with 2,3-dichloro-p-dioxane, ethyl bromoacetate, and epichlorhydrin,[16] although these are weak carcinogens. The demonstration of weak pulmonary carcinogenesis in animals with these compounds should alert everyone to minimize human exposures to them and to follow workers exposed to them with extra vigilance.

For completeness it should be mentioned that pulmonary carcinogenesis in animals has been demonstrated for beryllium,[17] nickel carbonyl,[18] and radioactive materials.[19] Interestingly enough, inhalation pulmonary carcinogenesis has not yet been demonstrated in experimental animals for chromates[20] or asbestos,[21] although the former has produced malignancies when injected intramuscularly or intrapleurally,[22] and the latter has produced pulmonary fibrosis (asbestosis) when administered by inhalation[21] and malignancy when given intrapleurally[23] in animals. Finally, various epoxides, lactones, and peroxy compounds have been shown to have a carcinogenic potential.[24]

With this far-from-complete review of experimental carcinogenesis which has been given only to emphasize the complexity of the problem, I should now like to turn to some interesting recent epidemiological work. I shall not try to cover skin cancers in coal tar workers, mule spinners, cutting oil users, wax pressmen, and the like, lung cancers in chromate workers, nickel refining, or asbestos workers (other than insulators), bladder cancers in the dye industry, nasal cancers in nickel refining and isopropyl alcohol manufacture, or bone sarcomas in radium dial painters because these have been covered in my book[25] or other works. Presumably we are discussing recent developments.

Much publicity has been given recently to asbestos as a pulmonary carcinogen and producer of pleural or peritoneal mesothelioma. Actually pulmonary cancer in asbestos workers has been recognized for 25 to 30 years.[26] The condition was catapulted into prominence by the observations of Wagner[27] in South Africa among miners and processors of asbestos and especially by Selikoff and his coworkers[28] among insulation workers. What has made Selikoff and his associates' work

unusual has been their use of union records to study this condition. Because insulators usually don't work for one single employer, but rather move from job to job wherever work is available and thus work for multiple employers, it was very difficult to obtain any kind of picture of what their health experience had been except through union records. When these were examined it was found that of 632 workers who entered the trade before 1943 and were traced through 1962, 45 had died of cancer of the lung or pleura. Only 6 to 7 men would have been expected to die of lung or pleural cancer if the normal incidence had prevailed. Another interesting observation has been that the incidence of lung cancer among asbestos insulation workers who smoke cigarettes is far greater than for those who do not smoke.[29] It is to be hoped that the industrial hygiene measures introduced among these workers will soon have this situation under control.[30] There is still some dispute among workers in this field of whether the asbestos is a direct carcinogen or whether its carcinogenicity is due to certain oils that may be present in the asbestos naturally or through contamination.[31] [32] Of perhaps more concern has been the observation that asbestos bodies can be found in the lungs of a very high percentage of people who come to autopsy and have never been exposed to asbestos in their work.[33] Although this is of concern to many people, no one is yet prepared to say what its significance is. It is important not to jump to as-yet-unwarranted conclusions on this observation, as I have often heard Dr. Selikoff say in talks on the subject.

As many people suspected, lung cancer incidence among uranium miners has been shown to be increased.[34] Again, the risk seems to be much higher among smoking miners than among nonsmoking miners. There have been 62 lung cancer deaths among 3,414 white miners and two among 761 nonwhite miners. There seems to have been established a dose-response relationship which may hopefully permit the elimination of this disease in the future.

Recently an outbreak of bladder cancers occurred among workers in the electric cable industry.[35] This apparently resulted from the former use of beta-naphthylamine as an antioxidant in the rubber sheathing used on the cables. Since this material has not been used by the rubber industry as an antioxidant since about 1945, it is anticipated that these tumors will soon disappear. However, it does point out the long latent period that can occur, and that in searching for etiologic agents in occupational cancer it may be important historically to go far back into the processes to find the responsible agent.

Among 8,047 workers in a metal smelter works, 147 respiratory cancer deaths among 1,877 total deaths were reported.[36] The causative agent in this case was believed to be arsenic trioxide exposures by inhalation, although some relationship to SO_2 exposures was also demonstrated. This recalls the association between sulfur dioxide and benzo(a)pyrene in animals demonstrated by the NYU group and previously discussed.[12]

A real surprise has been the demonstration in England[37] of an increased risk of nasal cancer occurring in woodworkers in the furniture industry. This seems to be associated with the use of hard woods. To date, no one has come forward with a good guess as to what the causative agent might be in this situation. Undoubtedly, this observation will lead to extensive laboratory studies, both chemical and biological, in an attempt to uncover the causative agent.

The accumulation in the literature of cases of leukemia following benzene exposures[38-41] leads to the inevitable conclusion that benzene is a leukemogenic agent, particularly in cases that have previously displayed a panmyelopathy.[44] Although this had long been suspected, the data reported in the literature was not sufficiently convincing to establish the leukemogenic nature of benzene. However, the more recent observations seem to establish this association beyond a doubt. More recent observations of chromosome changes in workers exposed to benzene[45] [46] lend further weight to the leukemogenic nature of benzene. In any event, in our own operations we are proceeding as if benzene was a leukemogenic agent, eliminating exposures wherever possible and reducing them to the lowest possible level where complete elimination cannot be accomplished.

It has been reported[47] [48] that lung cancer incidence in fluorspar miners is 29 times the expected rate. It was found in this situation that radon and radon daughter exposures are in excess of the maximum permissible concentrations and it is believed that this is the cause. In this respect, these lung cancers are similar to those seen in uranium miners and in the old Joachimsthal-Schneeburg mines.

A study of lung cancer among coke oven workers in the steel industry[49] showed that they suffered a 2-1/2 times increased incidence of that disease. This increased to five times among men who worked topside on the ovens, and to ten times if they worked five or more years fulltime topside. It is likely that exposure to very high levels of benzo-a-pyrene and similar polycyclic aromatic compounds occurred, although it is quite possible, due to the complex chemical nature of coal tar, that other promoting or co-carcinogenic, such as phenols or nitrogenous, compounds have contributed to the increased incidence. Undoubtedly, intensive chemical and biological studies of this situation will be undertaken which will in time elucidate the causative agents and their comparative significance.

I have tried to develop for you tonight some of the more recent developments in experimental carcinogenesis as applied to industrial problems, and some recent epidemiological studies of industrial cancers. I believe our approaches to occupationally induced cancer should not differ from the approaches we use in any potential occupational toxicity problem. We should study and become intimately acquainted with the processes involved, not simply by studying engineering or flow diagrams, but by actually getting out into the work place and observing just what is done. This will give us some idea of the personal hygiene of the workers involved as well as possible industrial hygiene measures that may be applicable. We should conduct appropriately designed toxicological tests, in this case carcinogenic tests, understanding fully the limitations and pitfalls of any such tests we conduct. We should carefully examine the workers involved to detect early signs of exposure or early pre-cancerous changes. Thus appropriate urine or blood analyses for nickel or chromium, or for phenols in the case of benzene exposures should be made. In some cases early biopsy or Papanicolaou smears of appropriate secretions should be undertaken. At every opportunity, we should stress the avoidance of unnecessary exposure. I can think of no area where the cooperative efforts of industrial hygienists, industrial nurses and industrial physicians can have a more salutary effect than in the control of industrial carcinogens and thus in the control of occupational cancers.

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