ENVIRONMENTAL AND OCCUPATIONAL CANCER

Raymond R. Suskind, M.D.

Much of our knowledge and understanding of carcinogenesis emerges from observation and studies of neoplasms induced by enviromental agents:

chemical

physical

biological

1. Historical

   Lung Diseases - now recognized as cancer-described in Carpathian mountain miners in 16th century. Soot related scrotal cancer described in 1775. Descriptive and mechanism studies of carcinogenesis, related to work, community enviroments, consumer products, life style in the 20th century.

2. There are no safe chemicals-just safe levels of use.

3. Sources and Identification of Enviromental Carcinogens

   a. It is alleged that 50-90% of all cancer from enviromental sources: clinical, physical, biological

   b. Although occupational cancer consists of a modest fraction of all enviromental cancer it is a great significance for a small group of workers in whom incidence may be very high.

   c. Carcinogens produced by industry may contaminate water, air, in food chain and consumer products may contain carcinogens.

   d. Estimate: 500-700 new chemicals introduced annually into enviroment. There is a backlog of 20,000-30,000 chemicals presently used which

should be tested for carcinogenesis.

e. Route: inhalation, ingestion, percutaneous absorption

f. Occupational enviroment:

Raw materials, intermediates, finished products

g. Community environments:

Air, water, soil, food chain, radiation: ionizing and non-ionizing.

Consumer products: foods, drugs, household uses

Life Style: Smoking, nutritional factors, household products

h. Cigarette smoking increases cancer risk from asbestos, uranium, etc.

Epidemiologic information -- cigarette smoking alone associated with high risk for cancer of larynx, esophagus, pancreas, urinary bladder.

Components of cigarette smoke: PNA's,aromatic amines, nitrosamines.

4. Criteria of Proof

Scientific evidence needed to demonstrate carcinogenic risk for man.

a. Identification of clinical problems in occupational exposures.

b. Epidemiologic studies of populations which demonstrate increase in risk for cancer.

c. Assessment of materials, processes, prior to use of carcinogenesis in animals; in vitro models; mutagen/carcinogen relationship, tier examination.

Testing all 20-30,000 by long term animal assessment impossible: a logistics problem. Are short term in vitro tests sufficient?

5. Incidence and Frequency Data

From health statistics, mortality statistics, epidemiological studies focussed on causes of death and morbidity data in relation to exposure: industries, processes, products.

Hamilton County Statistics

6. Mechanism of Carcinogenesis

Biologically, carcinogenesis is regarded as a 2-stage process in which chemicals which are electrophilic reactants combine covalently with nucleophiles in DNA's,RNA's, and proteins. Although the critical cellular target of mutagens is DNA, the cellular targets of carcinogens have not been defined.

In the first stage, the initiator alters DNA of the target cell. In the second stage the promoter activates genes causing the genotype of tumor cell to divide and multiply. There are complex immunological and hormonal restraints which must be overcome as well.

Biotransformation Systems Involved in Carcinogenesis

When an agent is absorbed through the skin, any systemic toxicity that occurs should be the same as that which would occur following exposure to the chemical by any other route, e.g., gastrointestinal tract or by inhalation, unless the skin specifically confers some specific toxic property to the compound. There are basically two considerations which contribute to the rise or fall of concentration of the agent or its metabolite in the bloodstream which is related to the concentration available to the receptors for each chemical agent. These factors are those which affect absorption through the barrier, such as damage to the barrier, hydration, concentration of the area of the skin penetration, etc., and biotransformation.

Let us consider some of the known biotransformation mechanisms in mammalian skin. We know the liver to be an important organ of biotransformation. The skin, however, is able to metabolize only about 2% by unit weight of tissue as compared to the liver. Since the skin is about three times the weight of the liver in man, it is also an important organ of metabolism

of absorbed compounds. When chemicals are absorbed through the skin they may be biotransformed into less toxic or more toxic compounds. The biotransformation systems in the skin include: oxidation, reduction, hydrolytic and conjugative reactions. For example, 17 β-estradiol is converted in the skin to estrone, and hydrocortisone is converted into cortisone.

It has been demonstrated that chemical carcinogens bind to skin constituents. For example β-propiolactone when applied to mouse skin binds covalently to skin DNA and the degree of binding to skin DNA varies directly with the susceptibility of the mouse species to tumor formation. The enzyme system for the generation of reactive metabolites involved in binding of PAH to DNA is the mixed function oxidase system. Aryl hydrocarbon hydroxylase (AHH) is a class of enzymes involved in liver and skin metabolism of PAH carcinogens. It is a mixed function oxidase requiring NADPH and O_2 for optimum catalytic activity. It is found in the microsomal fraction of the endoplasmic reticulum.

It is now believed that the three enzymes: AHH, epoxide hydrase (a microsomal enzyme that cleaves arene oxides into dihydrodiols which are metabolized by AHH into diol-epoxides) and glutathione-s-epoxide transferase, a cytosolic enzyme, are all essential for the metabolism of polycyclic aromatic hydrocarbon carcinogens. Tumor susceptibility of a particular species is probably dependent on the relative activities of these enzymes in the target organ.

There is now additional evidence of the role of cutaneous metabolism in tumor promotion. When TPA or 12-o-tetra-decanoylphorbol-13-acetate is used as a promoting agent for skin tumor development with 7,12-DMBA (dimethylbenz(a)anthracene), the promotion is uniformly associated with the increase in activity of ornithine decarboxylase (ODC) with the resulting increase in skin putrescine. Non-promoting hyperplastic agents do not raise

the ODC level. When ultraviolet light (UVB) is added to that system, there is a dramatic increase in epidermal ODC and s-adenosyl-L-methionine decarboxylase (AMD) activities of hairless mice before an increase in epidermal DNA synthesis occurs. The induced ODC activity and rise in putrescine level can be supressed with vitamin A (13-cis retinoic acid), and other retinoids. Whether promoting agents other than TPA are accompanied by the same increase in ODC and putrescine has not been determined. Unfortunately, there is a limited amount of information about the rates of absorption or flux of either PAH's or other known carcinogens in human skin. There is better information regarding penetration of nitrosoamines, hydrazine, plastic monomers, chromium compounds, aromatic amines, and some of the regulated industrial carcinogens.

7. Major Target Organs and Principal Agents:

Skin, Resniratory Tract, Bladder, Liver, Brain, Hematopoetic systems, Connective Tissue, Multiple Organ Systems

Skin Cancer

The most ubiquitous carcinogenic stimulus for the skin is UVR. The critical factors are:

Wavelength 290-320 nm

The intensity of radiation

Duration and number of exposures

And a most important genetic factor--pigment

Ionizing radiation: accidental, occupational, therapeutic and military uses of ionizing radiation and their consequences are well known.

Trauma and burns are among the other physical agents. In the recorded history of enviromental cancer of the skin, material containing polynuclear aromatic hydrocarbons--of which benzo(a)pyrene is the most easily identified,

were among the first to be indicted as an occupational cause of skin cancer. (First really by George Bauer - Agricola in 16th century - lung cancer among Bohemian miners.)

When our forefathers in Colonial America were revolting against George III in 1775, Percival Potts, a surgeon at St. Bartholomew's Hospital in London, broke a leg and during his convalescence found the time to write the first paper about cancer scroti in chimney sweeps and related the cancer to the soot. Since then, many observations have been made about the cause-effect relationship between the components of fossil fuels after burning or refining, and this includes coal shale, and skin cancer. There's a marked increase in cancer of the skin of workmen in coal tar industries, gas plants, oil and shale refineries, and in machine operators using lubricating oils in the textile industry, as well as machine shops. These occurrences have been traced to the polycyclic aromatic hydrocarbons which fossil fueul and their derivaties contain.

The skin is an excellent model system in which to detect carcinogenic carcinogenic potency and study carcinogenic mechanisms. For example, automobile soot from the tail pipe when applied repeatedly to mouse skin will induce cancer. Examination of the soot compounds reveals several B(a) Ps.

Arsenic and Cancer

Arsenic causes skin and lung cancer: Observed in mining and refineries, from sheep dip (arsenic trioxide) and the insecticide lead arsenate. In all of these exposures, cancer of the skin is the result of inhalation or ingestion of the dust as well as percutaneous absorption. Keratoses and skin cancer can be induced by the therapeutic use of Fowlers Solution, which is potassium arsenite.

Arsenic workers and lung cancer; lympatic cancer; Pb arsenite and Ca arsenite 1947-73 - Decendents. Ratio of observed to expected deaths from respiratory cancer 3.45:1. Lymphatic and hematopoetic 3.85:1. (Dow)

Respiratory System Cancer

The lung, like the skin is a vulnerable organ since carcinogens in dusts, fumes or vapors in the air we breathe have ready access to it. If dusts like uranium happen to contain sources of ionizing radiation, cancer of the lung will result. Uranium miners have an unusual increase in lung cancer.

In the 1930's, cases of lung cancer were reported in coal gas plants both in Japan and the British Isles and, more recently, Lloyd found that the lung cancer death rate in coke oven workers was 2.5 times higher than expected. Most of the lung cancers in coke oven operations occur in men who work on top of coke ovens, and those employed five or more years at full-time topside jobs show a tenfold excess risk of lung cancer. When one looks at the overall problem of lung cancer in communities, however, it becomes obvious that the major etiologic factor appears to be cigarette smoking.

Death from lung cancer is about eight times more frequent among men who smoke than among non-smokers (87/100,000 as compared with 11/100,000), and death from lung cancer is 60 times more frequent among men who smoke two packs of cigarettes per day than non-smokers.

The Urban Factor

Smoking, however, does not completely account for the increased incidence of this disease. Many studies indicate that urban dwellers have approximately twice as high an incidence of lung cancer as those living in rural communities. Within urban communities the incidence is greater where more general industrial pollution is present. For example, in a study done by Haenszel, the age adjusted lung and bronchus cancer rates in an urban population were 20.9 per 100,000, while in rural areas it was 7.5 per 100,000 persons. These were from metropolitan counties. In non-metropolitan counties the urban rate was 15.1 and the rural rate 7.5 per 100,000. If one considers

cancer of lung among white cigarette smokers, the urban factor is evident.

In the concentrations in which polycyclic aromatic hydrocarbons or POM are found in urban or non-urban air, they appear to have little or no effect on human skin.

While urban concentrations of B(a)P vary makedly among the cities, a rough estimate of the city-dweller exposure is about 8-10 ug/1000 m^3. While it is difficult to construct dose response curves for lung cancer as related to exposure to B(a)P, there is little doubt that the concentration to which gas workers or coke oven topside workers are exposed is several thousand times greater than the concentration in cigarette smoke. Nevertheless, it would appear that the consistent exposure to cigarette smoke is a more significant factor in lung cancer production than are some of the industrial exposures.

The problem is complicated and would indicate that multiple enviromental factors, synergism and genetic factors prevail. There is much experimental evidence which indicates that in lung cancer enhancing factors include phenolics which are found in cigarette tar as well as in fossil fuel combustion emmissions. More recently, it has been shown that SO_2 enhances the carcinogenic potential of polycyclic aromatic hydrocarbons like B(a)P in animals. Other tumor promoting agents are polyphenols and paraffin hydrocarbons like dodecane, epoxides, hydroperoxides, peroxides and lactones. The critical experiments carried out by Laskin, Kushner, and Drew exposed rats and hamsters in inhalation chambers to a combination of SO_2 and B(a)P aerosol, which separately produced no lung tumors. In these experiments the animals were exposed to 10 PPM of SO_2 for six hours per day for five days a week, plus a combination of 10mg/m^3 of B(a)P and 3.5 PPM of SO_2 for one hour per day five days a week. No significant alterations were found in the hamster.

In rats, however, squamous cell maligancies of the lungs were induced in two of 21 receiving the combination for one hour per day, whereas five of the 21 rats receiving the same mixture for six hours per day plus 10 PPM of SO_2 developed lung tumors.

Nickel. There are specific chemical agents which are known to produce a substantial increase in lung cancer in industry. These include nickel and nickelcarbonyl, $NI(CO)_4$' as seen in nickel refinery workers. In these populations, in addition to cancer of the lung, cancer of the nasal cavity and nasal sinuses were also observed.

Chromates. The lung cancer death rate among chromate workers was reported in one study to be 18 times expected. In the plant producing bichromate from chromite the cancer rate was increased. There were no lung cancer deaths in plants processing bichromates to produce chromic acid and basic chromic sulfate (Machle and Gregorius).

Asbestos. First suggestion of association of cancer of lung and asbestos was made in 1935 by Lynch and Smith who describes sq cell cancer in a South Carolina textile worker with asbestosis. In 1947, a study in England demonstrated that 32 cases of lung cancer occurred in 235 persons known to have died with asbestosis between 1924-1946. This constituted a 13.2 incidence as compared with a 1.32 incidence in persons having silicosis in the same time period. There are now many studies which show a clear association between an occupational exposure to asbestos and a higher-than-expected incidence of bronchiogenic cancer of the lung. Some studies show different degrees of risk among different occupationally exposed groups, probably related to dose as well as other factors. Primary malignancies of pleura and peritoneum are also seen in asbestos workers and those who live near mills, mines or have had household contacts. The outstanding feature is the long period, commonly over 30 years, between the first ex-

posure to asbestos and appearance of a tumor.

Important aspects of pathogenicity are type of asbestos, fiber size and co-factors like cigarette smoking.

Work of Selikoff strongly suggests a synergism of cigarette smoking and asbestos exposure in the increased risk of lung cancer in insulation workers.

Chloromethyl methyl ether and ethyleleimine have been found to be carcinogenic in a sufficient number of animal experiments to warrant their inclusion among the industrial carcinogens for which new standards have been set for workplaces (January 29, 1974).

Carcinoma of the lung has been found in CME industrial exposures in which bis(chloro)methyl ether is found as a contaminant.

Inhalation exposure of rats and hamsters to chloromethyl methyl ether will induce tumors of low incidence. However, exposure to bis(chloro)methyl ether will result in a high incidence of tumors of the olfactory epithelium and squamous cell carcinoma of the lung.

Bladder Cancer

Workers exposed to benzidine and beta-naphthylamine have a high incidence of bladder cancer. The carcinogenic agent is believed to be a metabolite 2-amino, 1-naphthol.

Benzidine related substances which will induce tumors in animals are:

α-naphthylamine
β-naphthylamine
benzidine
dichlorobenzidine
4-aminobiphenyl
4-nitrobiphenyl

These are also on the DOL list of carcinogens. The removal of cyclamates from food and drink was the result of experiments in which rats were fed a

cyclamate - saccharine mixture. Unexplained bladder tumors were induced. Rats convert cyclamate to cyclohexylamine, which is carcinogenic for the bladder.

Liver

Populations ingesting moldy food infected with aspergillus flavus which grow on wet peanuts and corn have an increased incidence of cancer of the liver. The inducing agent is a lactone type of compound called aflatoxin. Others causing hepatomas are N. nitrosodimethyl amine and ethyleneimine.

Angiosarcoma

Vinyl Chloride and Thorotrast

Multiple Tumors

8. Regulated Carcinogens

Asbestos

β-Naphthylamine

a-Naphthylamine

4-Aminobiphenyl

4-nitrobiphenyl

Benzidine

3,3-dichlorobenzidine

bis-chloromethyl ether

ethyleneimine

β-propiolactone

methyl chloromethylether

4,4-Methylenebis (2-chloroaniline)

2-acetylaminofluorene

4-dimenthylaminoazobenzene

N-nitrosodimethylamine

vinyl chloride

coke oven emissions

9. Prevention and Control of Enviromental Carcinogens

Prior to use safety assessment

National Toxicology Program Report of NTP Panel on Clinical Carcinogenesis Testing and Evaluation

References

1. Occupational Carcinogenesis, Eds. Saffioti, U. and Wagoner, J.K., Annals of N.Y. Academy of Sciences, Volume 271, 1976.

2. Ames, B.H. et al, Carcinogens are Mutagens. A Simple test System combining Liver Homogenates for Activation and Bacteria for Detection. Proc. Nat. Acad. Sci. 70:2281-2285, 1973.

3. Federal Register, October 4, 1977, DOL, Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk.

4. Federal Register, January 29, 1974, DOL, Carcinogens, Occupational Health and Safety Standards.

5. Ott, M.G. et al, Respiratory Cancer and Occupational Exposure to Arsenicals. Arch Environ. Health, Vol. 29, Nov. 1974.