Meetings

Carcinogenesis and Carcinogen Testing

Chemical environmental carcinogens constitute the most important known cause of human cancer; viral agents and radiation probably account for only 5 to 7 percent of cancer in man, except in southern areas where ultraviolet radiation increases the incidence of skin cancer. A symposium of 25 papers (*1*) on carcinogenesis and carcinogen testing, organized by Bio-Research Institute of Cambridge, Massachusetts, took place at the Boston Museum of Science on 8 and 9 November 1967.

Epidemiological studies of small population groups exposed to well-defined chemical substances (for example, those in the chemical industry and in certain isolated geographical areas) may constitute the best approach to discovery of new chemical carcinogens. Endogenous substances, perhaps derived from naturally occurring steroids, may be of significance as suggested by a series of potent new carcinogens 11,12-dimethylcyclopenta(*a*)phenanthrene and its 11- or 12-methyl or -methyloxy substituted compounds.

The concept of cocarcinogens (or tumor promoters) is gaining increasing importance. The mechanisms of action of these noncarcinogenic substances, which increase and accelerate the tumor yield of mouse and gerbil skin treated with small doses of known tumor initiators, can now be studied by means of phorbol esters isolated as the active principles of croton oil.

The transformation in tissue cultures of mouse prostate cells in malignant cells, under the influence of polycyclic hydrocarbons, permits studies of mechanisms of the malignant transformation (such as protein binding of carcinogens). Rodent cells and those of primates or of a human diploid cell line possess different degrees of susceptibility to the toxicity of hydrocarbons. Infection with viral agents increased the resistance of the susceptible rodent cells to the toxicity of hydrocarbons.

Infection of mice with herpes simplex or West Nile virus, while methylcholanthrene was being applied to their skins, increased the incidence of tumors, and immunization against these viruses decreased the tumor yield. Treatment with various antimetabolites or antibiotics again raised the rate of tumor production.

Experimentation with animals indicates that heavy metals such as nickel, cobalt, cadmium, lead, and related metal complexes are potential carcinogens. Epidemiological evidence indicates that cadmium oxide is a possible causative factor in certain cancers of the human prostate.

Certain plastics, silica dusts, asbestos, and diatomaceous earths do not conform to the usual dose-response features of drugs and carcinogens, when implanted into the subcutaneous tissue of rats and producing sarcomas. Other modifying factors that must be considered in subcutaneous sarcoma formation are the vehicles used and the presence of derivatives of the carcinogen studied. Dibenzo[*a,i*]pyrene (benzo[*rst*]pentaphene) induced maximum tumor yields when suspended in peanut oil, and successively lower yields with other media, and tumor formation was almost nonexistent with Ringer solution. Related compounds such as 5,8-diacetoxydibenzopyrene and the corresponding diquinone inhibited carcinogenicity. In another test system, mammary carcinogenesis in the rat by polycyclic hydrocarbons administered orally, modifying factors are the potency of the agent, the affinity of the tissue, and the hormonal environment of the host.

Polycyclic hydrocarbons mixed with finely powdered iron oxide produce carcinomas when injected into the tracheobronchial tree of hamsters. By contrast, attempts to cause tracheobronchial carcinomas in rodents by means of tobacco smoke have so far failed. It is possible that the anatomical features of the nasal passages in rodents that breathe only through the nose prevent the delivery to the respiratory tract of noxious substances in smoke.

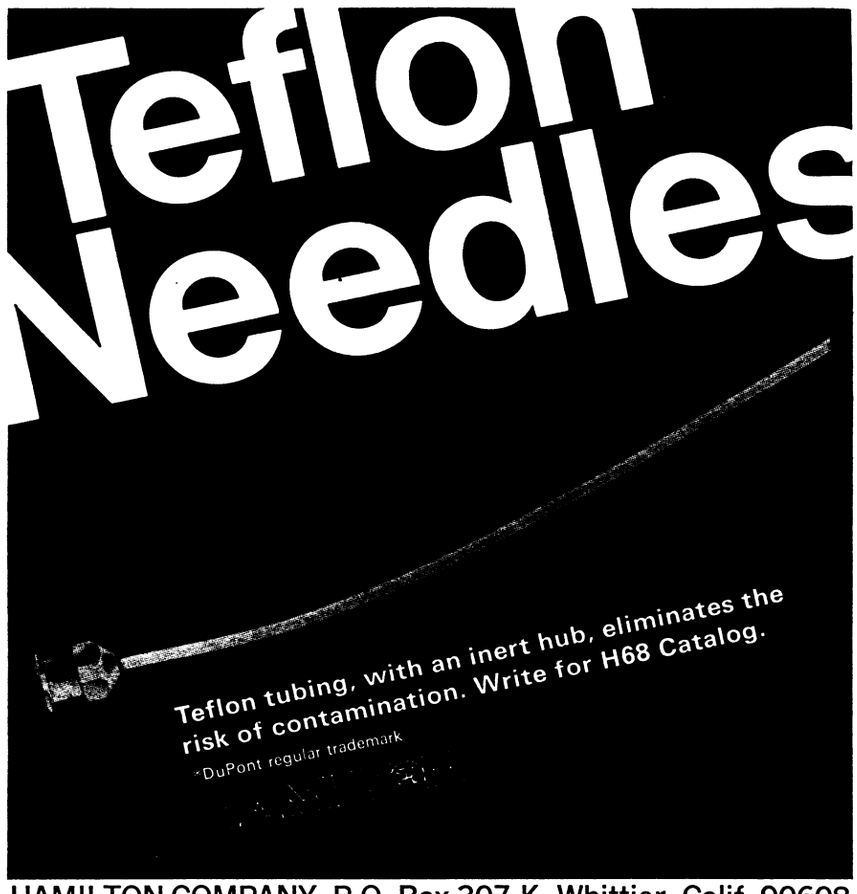
Modifying factors of liver carcinogenesis act upon the activation or detoxification of the carcinogen or upon the growth of the induced tumors. Immunological factors may affect tumor development. Microsome fractions from hepatomas induced with azo dye decreased the tumor yield in rats fed carcinogenic azo dyes. The hepatic carcinogenicity of safrole is also subject to modifying factors such as diet, genetics, and sex.

The essential chemical reaction for the activation of carcinogenic aromatic amines is hydroxylation on the amino nitrogen with esterification of the resulting *N*-hydroxy compounds. Such *N*-acetoxy or *N*-benzoyloxy derivatives are potent carcinogens, react with nucleic acids and proteins, and have mutagenic effects.

A recently discovered potent liver carcinogen is aflatoxin. Experimentally shown to be carcinogenic in trout, ducks, and rats, this widespread contaminant of foodstuffs may have significance for man, and intensive efforts are now under way to relate contamination of food with aflatoxin with endemic prevalence of cancer of the liver, especially in certain tropical regions. Other naturally occurring carcinogens discussed were cycasin, the active principle in cycad meal, and certain pyrollizidine alkaloids.

The methods of carcinogen testing were discussed with reference to animal experiments and the theory and practice of statistics. Infant mice were found to be susceptible to a number of carcinogens. The view was expressed that routine testing should include the use of infant mice together with the more conventionally used young or weanling rats. Accelerated methods of carcinogen testing were reviewed, and a new technique was described by which the latent period of cancer induction can be reduced appreciably. Several carcinogen-injection sites from animals are pooled and transferred into one secondary host, which shows tumors rapidly, often in a few weeks. Because malignant transformation in vivo of subcutaneous fibroblasts occurs extremely quickly in the Syrian hamster, this species deserves additional attention.

The program also included presentations on a nationwide survey on studies of chemical carcinogenesis undertaken by the National Cancer Institute to assist in the planning of programs based on need and scientific promise, measures developed by industry to

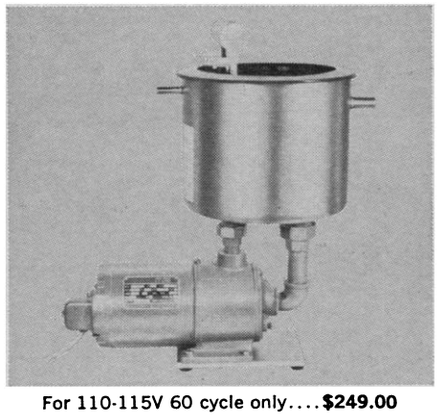


HAMILTON COMPANY, P.O. Box 307-K, Whittier, Calif. 90608

Circle No. 81 on Readers' Service Card

Is The Pressure Getting You Down?

Eliminate the Hazard of Inadequate or Fluctuating Water Pressure which can mean the Loss of Valuable Time and Material!



GET A BUCHLER DUAL ASPIRATOR PUMP

For 110-115V 60 cycle only....**$249.00**

• Raises and holds pressure at 40 psi. • Provides 2 independent and powerful aspirators. • Noiseless operation—continuous duty—minimum maintenance. • Can be installed without plumbing or building alterations.

Request Buchler Bulletin No. S-2-9000

BUCHLER INSTRUMENTS

LABORATORY APPARATUS • PRECISION INSTRUMENTS

BUCHLER INSTRUMENTS, INC.

1327 18TH STREET, FORT LEE, NEW JERSEY 07024

render the human environment safe, and governmental efforts in this direction.

This symposium demonstrated the noticeable progress in understanding mechanisms of chemical carcinogenesis through application of modern methods of molecular biology and pathology, genetics, and pharmacology. Advances of practical significance for carcinogen testing and prevention of disease through elimination of hazards will undoubtedly result from the progress of research in this field. The proceedings of the symposium will be published as volume 11 of *Progress in Experimental Tumor Research* (S. Karger AG, Basel, Switzerland).

F. HOMBURGER

Bio-Research Institute,
Cambridge, Massachusetts 02141

Note

1. The following authors participated in the symposium: I. Berenblum, Rehovoth, Israel; F. Bischoff, Santa Barbara, Calif.; E. Boyland, London; G. Bryson, Santa Barbara; W. J. Burdette, Houston; A. Cantarow, Bethesda; M. M. Coombs and C. J. Croft, London; T. L. Dao, Buffalo; C. Deckers, Louvain, Belguim; G. Della Porta, Milan; L. Diamond, Philadelphia; R. E. Eckardt, Linden, N.J.; A. Furst, San Francisco; C. Heidelberger, Madison, Wis.; D. Hoffmann, New York; F. Homburger, Cambridge, Mass.; N. Mantel, Bethesda; E. C. Miller and J. A. Miller, Madison, Wis.; E. L. Richardson, Boston; U. Saffiotti, Chicago; M. Shimkin, Philadelphia; C. M. Southam, New York; B. L. Van Duuren, New York; J. H. Weisburger, Bethesda; G. Wogan, Cambridge, Mass.; E. Wynder, New York.

Calendar of Events

National Meetings

August

1–3. Conference on **Dermatology**, Aspen, Colo. (W. C. Eisele, Univ. of Colorado Medical Center, 4200 E. 9th Ave., Denver 80220)

3–9. National **Poultry** Science Assoc., Fort Collins, Colo. (R. E. Moreng, Animal Science Bldg., Colorado State University, Fort Collins 80521)

11–15. National **Medical** Assoc., Houston, Tex. (S. C. Smith, 520 W St. NW, Washington, D.C. 20001)

12–14. American Inst. of **Aeronautics and Astronautics**, Pasadena, Calif. (W. J. Brunke, Meetings Manager, 1290 Sixth Ave., New York 10019)

12–16. American **Crystallographic** Assoc., Buffalo, N.Y. (W. L. Kehl, Gulf Research & Development Co., P.O. Box 2038, Pittsburgh, Pa. 15230)

15–16. American Inst. of **Aeronautics and Astronautics**, Pasadena, Calif. (W. J. Brunke, Meetings Manager, 1290 Sixth Ave., New York 10019)

18–21. **Botanical** Soc. of America, Davis, Calif. (Botany Dept., Indiana Univ., Bloomington)

Circle No. 85 on Readers' Service Card