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Interoffice Communication

To D. A. Kuhn

From J. J. Hall

Date March 9, 1978

Subject Highlights of Symposium on Carcinogenesis, March 1-3, 1978

Epidemiological Studies - Joseph F. Fraumeni, NCI

The speaker discussed some recent developments in epidemiology. No new "revelations" were presented. Some points of interest are listed below:

. Variation in cancer rates over time:

- lung - increasing (tobacco?)
- stomach - decreasing
- other sites - relatively unchanged
- 200% increase in myeloma (1948-1971)
- blacks: 46% increase - male
  15% increase - female

. NCI geographic studies - mortality studies of US by counties highlight high-risk environments

- high incidence counties:

  lung, bladder, liver - associated with chemical industries
  lung, nasal, skin - associated with petroleum industries

- skin cancers high in southern U.S. - probably a result of high U.V light exposures
- counties with artificially fluoridated water supplies showed no significant excess
- high rates of oral cancers for women in rural southern counties, possibly a result of snuff dipping

. 40% of male cancers and 90% of lung cancers have a tobacco etiology. Alcohol potentiates the effects of tobacco smoke.

. Ionizing radiation accounts for approximately 2-3% of all cancers. Even low doses are apparently dangerous for susceptable individuals based on data from occupational and atomic bomb exposures

- dose/response curves are reasonably linear for survivors of atomic bomb exposures
- latent period - 15 to 40 years

. Industrial Exposures

- Should animals be tested at the maximum tolerable dose (e.g., 20% of diet)?
  - dose should be high for safety factor
  - route of administration should be the same as the potential human exposure
  - at least two species, preferably three, should be tested
  - at least three dose levels should be administered so that a dose/response curve can be generated
- At this point a single universal model system cannot be recommended or relied upon.
- Animal testing has utility and limitations. They are subject to over-interpretation and political pressures.

Carcinogenesis Studies on Organ Cultures of Animal and Human Respiratory Tissues - Umberto Saffiotti, NCI

This speaker has developed an approach to carcinogen testing which attempts to avoid some of the pitfalls inherant in extrapolating the results of animal studies to predict human carcinogenic risk. The experimental technique involves exposing (in vitro) human epithelial tissue from the primary target organ to a potential carcinogen while using epithelial tissues from the appropriate animal target organ as a control.

Initial studies are underway of respiratory tract carcinogenesis using benzo [a] pyrene. Other studies are being developed.

In Vitro Chemical Carcinogenesis - Charles Heidelberger, USC

This was a technical discussion of the biochemical effects of polycyclic aromatic hydrocarbons upon mouse prostate and mouse embryo fibroblasts in vitro.

The Mutagenic Properties of Chemical Carcinogens and the Relationship of This Property to Possible Mechanisms of Neoplastic Induction - David J. Brusick, Litton Bionetics, Inc.

Dr. Brusick discussed the close correlation between the results of short-term screening test for mutagenicity and rodent model assay systems for carcinogenicity. Implied in this correlation is a similarity between the steps of cellular alteration involved in mutagenesis and carcinogenesis.

He noted that there is evidence to support the "single-hit" theory. However, because DNA has the capacity to repair itself, perhaps multiple hits are required on a particular cell before the final "single hit" pushes the cell over the line into the abnormal state. He further hypothesized that there is a normal level of cell mutation and cell transformation within the body which is negated by the DNA repair system. It is only when a chemical mutagen or carcinogen induces an abnormally high rate of cell neoplastic activity that the DNA repair system become "saturated" and cancer results.

Molecular Probes for Genetically Toxic Chemicals: Exploitable Features of DNA Damage - R. R. Hewitt, UT Cancer Center

This speaker noted that mutagenic, carcinogenic and/or teratogenic effects of chemicals may be cause by their reactivity with the DNA molecule. Often discussing several types of DNA lesions including single--and double-standard breaks, intrastrand cross links, base damage, etc., Dr. Hewitt noted that several analytical methods are being developed which can identify and classify DNA lesions. His proposal was that these techniques could be utilized as low-cost, sensitive, screening device to identify potentially hazardous chemicals.

After Dinner Speech: Present and Future Perspectives in Environmental Carcinogenesis--John Higginson, Director of the International Agency for Research on Cancer.

Dr. Higginson delivered an entertaining talk spiced with anecdotes which contained a number of noteworthy thoughts:

- Workplace cancer accounts for 2-5% of all cancers. A slide was presented showing standard mortality ratios (SMR) for various occupations. Comments:
  - Esophogeal cancers high for Armed Services personnel. A result of the availability of duty-free liquor and tobacco?
  - SMR's vary greatly by occupation but when standardized by social class, all occupations have similar SMR's. Therefore, not only occupation but also life style is a etiological factor.
  - A slide showing SMR's of women categorized by the occupation of their husband showed approximately the same pattern as the workers' SMR's. Suggests that life style has a lot to do with what have been called job-associated hazards.
  - A slide showing smoking habits as a function of occupation showed lower cancer rates in occupations where smoking is less prevalent.

- Rates in northern Iran are extremely high for esophogeal cancer where alcohol and tobacco should not be a factor. Liver cancer is high in Europe. Without the technology to identify chemicals, epidemiologic data are difficult to interpret and can easily lead to a false hypothesis.

- Absence of fiber in the diet is not a carcinogen but is definitely a carcinogenic risk. Diet is extremely important, not only as it relates to carcinogens in the diet.

- Cancer is preventable without understanding its mechanism. A slide was shown which listed steps (albiet infeasable) which could reduce cancer:

Step	Cancer Reduction
Stop All Smoking	40% (male)
Stop All Drinking	5-10%
Prostatectomy	20-30%
Nipplectomy	40%
Hysterectomy	10%
Arab dress	-
Celibacy	-
Etc.	

- There is little evidence that industrialization, per se, results in higher cancer rates.

- The rate of stomach cancer incidence is falling. Possibly antioxidant food additive (e.g. BHT) prevent oxidation in gastric juices.

- "We are trying to prove what we want to believe". (1975 cancer scare) Without lung cancer, U.S. rates are declining.

- Inability to extrapolate from animal test data is a major problem since we are forced to rely heavily on animal tests.

- Epidemiologically it is difficult to prove a negative result.

- Research is needed on the concept of "safety". A slide showing risks of death for various activities was shown.

1½	cigarettes	equivalent risk
50	miles by car	
250	miles by airplane	
6	minutes in a canoe	
20	minutes at age 60	

Inihibition of Chemical Carcinogenesis - L. W. Wallenberg, University of Minnesota

An increasing number of compounds have been uncovered which have the capacity to inhibit chemical carcinogenesis when administered prior to or simultaneously with a carcinogen. Many of these inhibitors are synthetic compounds, others are naturally occurring constituents of, for example, vegetables.

Several phenol antioxidants such as the food additives BHT and BHA have been shown to inhibit a wide range of carcinogens. (This phenomenon opens speculation as to the cause of the reduction in the rate of stomach cancers).

One interesting point is that disulfuran tends to inhibit carcinogenesis from dimethylhydrazine (DMH). Disulfuran is apparently metabolized to carbon disulfide which inhibits cancer of the large bowel caused by DMH.

Very little information on the mechanism of inhibition. Inhibitors indentified thus far exhibit a great diversity in chemical structure. What impact inhibition of carcinogenesis will have on solving the human cancer problem is, as of yet, unknown.

Kinetics of Tumor Formation and Low Risk Assessment - E. Scherer, Netherlands Cancer Institute

This most interesting presentation attempted to present a mathematical stochastic model relating dose to risk of incidence. The speaker implied that classical dose/response curves do not apply to carcinogens in light of the multiple hit theory of cancer causation. Unfortuantely the speaker was not supplied with the proper teaching aids and his presentation suffered.

In summary, it is apparent that there is significant data to indicate that the disease of cancer is unique in its biochemical mechanism and perhaps carcinogens cannot be considered to have the same toxicological characteristics. (Vis a vis a "safe" threshold level) as other substances. However, it does seem obvious that lower doses are associated with lower risks even if the risk does not reach zero. Perhaps the rational solution to the current dilemma will result from further research into the etiology of the disease and better understanding of low-level risks of cancer compared with other risks which are routinely accepted.

DJH/vm