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Summary of the Informal Discussion of Alcoholism and Nutritional Imbalance[1]

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Dr. Wynder, the first discussant, felt that the association between alcohol and head and neck cancer was an important epidemiological lead that the scientific community had not fully exploited. It has been estimated that, without alcohol, the rate of incidence of cancer of the mouth, larynx, and esophagus in the United States and Western Europe would fall about 50%.

Dr. Wynder noted that, with the exception of beer, the increased risk of head and neck cancer seems to be related to total alcohol consumption rather than to the type of beverage used. This would reduce the likelihood that the association between alcohol and cancer is caused by carcinogens in the alcoholic beverages.

Several participants, however, felt that carcinogens in alcoholic beverages played an important role in the etiology of head and neck cancer.

Dr. Day cited data from France that indicated that the source of alcohol was an important determinant in the carcinogenic potential of a beverage.

Dr. Martinez pointed out the great differences in the presence and amount of chemical contaminants in alcoholic beverages consumed by different populations. For example, fusel oil, a by-product of distillation and possibly carcinogenic, is found in varying quantities in different liquors. In Puerto Rico where there is a high rate of head and neck cancer, there is also frequent consumption of "moonshine" rum, which contains far more fusel oil than the commercial rum produced under government control.

Dr. Weisburger added that Gibel in Professor Graffi's institute in Berlin reported about 4 or 5 years ago that fusel oil was carcinogenic to animals. However, no one has replicated this finding and it might be worthwhile to look again at whether fusel oils are actually carcinogenic.

Dr. Weinhouse questioned whether the process of aging whiskey in charcoal-lined barrels, probably reeking with various polycyclic hydrocarbons for which alcohol is an excellent solvent, might produce carcinogens in these beverages.

Dr. Wynder stated that, although alcohol is a very important cofactor in the origin of head and neck cancers in the United States and Western Europe, epidemiological data clearly indicated that alcohol consumption by itself does not increase risk to these cancers. Increased risk of cancer occurs only if the heavy drinker is also a smoker. Yet in Sweden, cancers of the oral cavity and esophagus are associated with the Plummer-Vinson syndrome even in the absence of smoking, suggesting that nutritional imbalance can be a sufficient causal factor.

Dr. Wynder speculated that the Plummer-Vinson patient may be born deficient in nutritional status whereas the alcoholic individual develops nutritional deficiencies later in life. If such a difference did exist, it might account for the lack of association between smoking and head and neck cancer in Swedish women.

After World War II, the Swedish Government by law added iron and other vitamins to flour throughout the Northern part of Sweden. The subsequent decline in the frequency of the Plummer-Vinson syndrome probably accounted for the decreasing incidence of cancer of the pharynx and hypopharynx in Swedish women that has occurred since that time.

The circumstances in Sweden illustrate that effective preventive measures against head and neck cancer can be achieved even though the precise mechanisms of the disease are not clearly understood.

As to experimental research on the relationships of alcohol, nutrition, and cancer, some studies have shown that riboflavin deficiency in animals leads to atrophy, hyperkeratosis, and hyperplasia of the skin in mice, a condition marked by increased susceptibility to tumorigenic agents. Other experimental studies have indicated that 1 possible mechanism of alcohol carcinogenesis is through absorption of tobacco carcinogens.

A question arose whether it might be feasible to study experimentally possible carcinogenic effects of alcohol on the mitochondria in epithelial cells.

Dr. Hoberman responded indicating that in the search for alcohol effects the metabolic consequences of a product of alcohol metabolism, namely acetaldehyde, a highly reactive molecule, had received too little emphasis. The metabolic effects of alcohol on epithelial cells depend upon the presence of enzymes necessary to oxidize alcohol and produce acetaldehyde. Current knowledge suggests that the alcohol-metabolizing system and the distribution of alcohol dehydrogenase does not extend to epithelial cells. However, Lieber in a recent article in the *New England Journal of Medicine* has demonstrated that, in chronic alcoholism, for reasons not clearly understood, the concentration of acetal-

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dehyde appearing in the blood is remarkably high.

Whether this acetaldehyde can produce changes upon reaching the epithelium that may ultimately lead to carcinogenesis is not known. Data from Ruben's laboratory at Mount Sinai Hospital in New York City indicate that acetaldehyde does cause certain changes in mitochondrial metabolism.

Although data are not currently available on the role that acetaldehyde might play as a toxic compound on epithelial cells, it was felt that productive experiments in this area could be performed.

Dr. Weisburger, in commenting on Dr. Wattenberg's demonstration that antioxidants and other naturally occurring food contaminants, such as some flavones, inhibit cancer production by a variety of carcinogens, cited contrasting experiments. Dr. Raineri with the Naylor Dana Institute has shown that cancer of the esophagus induced by dinitrosopiperazine is enhanced by certain enzyme inducers rather than reduced. Also, Dr. Fiala at the same institute found that dimethylhydrazine-induced colon cancer increased with inducers like phenobarbitol in contrast to Dr. Wattenberg's experiments with disulfiram where a pronounced reduction was found.

Thus, when considering the relation of environmental factors including nutrition to carcinogenesis, one should take into account the carcinogens, the target organ, and the species. This applies to the entire problem under discussion at this conference and in particular to Dr. Day's report on esophageal cancer.

Dr. Hoffman and his colleagues at the Naylor Dana Institute reported that a nitrosamine, nitrosonornicotine, which occurs in burned and unburned tobacco, does induce cancer of the esophagus in animals.

Other animal studies have shown that nitrosamines can be formed in the stomach by the reaction of nitrite with certain precursors. While not all animal data can be transferred to the human situation, this may be 1 area that should be investigated in the human setting.

Dr. Weisburger in commenting on the papers presented by Dr. Bull and Dr. Vitale thought it unlikely that immune competence had any effect in primary tumor formation by chemical carcinogens. Experiments at the Naylor Dana Institute with rats heavily immunosuppressed by injection of a gamma fraction of lymphocytic serum resulted in severe lymphopenia. However, cancer formation in the liver with one carcinogen and cancer formation in the large bowel with another carcinogen were unaffected, even though these animals were severely immunosuppressed. Skin heterografts held for a long time and yet the carcinogenic process was not affected. From these studies it can be concluded that immune status does not have a primary effect in chemical carcinogenesis in most epithelial tissues.

However, in terms of metastatic lesions there may very well be an effect, because in the same type of experiment with transplantable tumors, tumor allografts grew very easily in immunosuppressed animals whereas no growth occurred without immunosuppression.

Perhaps judgment on this subject should be held in abeyance. This area is discussed in 2 excellent reviews, one by Krips and Borsos and the other by Stuttman.

Dr. Fraumeni summarized several current studies at the National Cancer Institute relating to immune status and carcinogenesis in humans. In 1 study in which a series of patients with primary immune deficiency syndromes were observed, a clear excess of lymphocytic and reticular tumors was found. With the apparent exception of stomach cancer, there was no excessive occurrence of other tumors such as carcinomas among the immunodeficient patients.

In a 2nd study, a group of over 10,000 kidney transplant recipients receiving heavy doses of immunosuppressant drugs to prevent rejection experienced a 25-fold increase of non-Hodgkin's lymphomas. There was only a 2-fold excess of other cancers but this increase was limited to selective sites. For example, there was an excess of certain neoplasms of the skin including melanomas, which is consistent with other findings on blocking antibodies in melanoma. There was an excess of adenocarcinomas of the lungs, which is interesting in terms of some experimental reports that lung adenomas are increased selectively in immunodeficient animals. There was also an increase in bladder tumors among the transplant recipients and an increase in leukemias among a small segment of patients who received heavy doses of radiation to prevent rejection.

Finally, in a 3rd study, a number of cancer-prone families and their normal relatives were examined for evidence of subclinical immune defects. These defects were found only in families that were predisposed to lymphocytic and reticular tumors and stomach cancer.

Therefore, if nutritional imbalance influences the development or growth of cancer via the immune system, then these effects are limited to only certain tumors such as lymphomas or perhaps stomach cancer and some other less common tumors.

The question was posed whether the transplant and immunodeficiency disease patients were younger than the general population and whether their shorter life expectation might influence the type of cancers that occurred.

Dr. Fraumeni replied that there was a sufficient number of individuals who survived to adult age ranges in both the transplant and immunodeficiency syndrome groups to evaluate adequately the risk of adult cancers in these groups.

It seemed to be the consensus of the participants that observational studies on the association of alcohol and cancer had provided some valuable clues to the etiology of cancers of the head and neck. However, more experimental work is required to develop these clues into formal models of the possible mechanisms of alcohol effects in the development of cancer. Such an effort will require the skills of nutritionists, biochemists, immunologists, pathologists, and others. If such multidisciplinary research efforts did result from this conference, one of its major purposes will have been fulfilled.

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