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An Epidemiological Evaluation of the Causes of Cancer of the Pancreas[1]

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Summary

Variables that appear to affect the development of cancer of the pancreas include a diet high in fat and/or cholesterol and excessive cigarette smoking. There are a number of variables that appear to play no role in the development of cancer of the pancreas including alcohol, clinically apparent pancreatitis, and weight. In women there exists a positive correlation with diabetes and cholecystectomy.

There are three ways in which tobacco smoke can increase the risk of cancer of the pancreas: containment of tobacco carcinogens in bile which can be refluxed from the bile duct into the pancreatic duct; tobacco carcinogens which can be distributed by the blood stream (such substances could include certain nitrosamines, some of which are known to be organ specific to the pancreas of experimental animals); and, to the extent that cigarette smoking can increase blood lipids and since blood lipids may affect the development of pancreatic cancer, this could be another mechanistic pathway.

How dietary factors can affect the development of cancer of the pancreas is a question that needs answering. The possibility of *in vivo* transformation of cholesterol to a cholesterol epoxide is just one of the possibilities that must be considered. This presentation summarizes the up-to-date epidemiological evidence suggesting the relationship between diet and cigarette smoking to cancer of the pancreas, makes recommendations for future epidemiological and experimental studies that should be undertaken, and proposes preventive steps that should be carried out.

In 1973, we reported on an epidemiological investigation of cancer of the pancreas. This study was based upon retrospective interviews with 142 patients with adenocarcinoma of the pancreas. We also correlated our findings with epidemiological data published up to that time (16). The purpose of this communication is to review our conclusions of our earlier study in the light of the knowledge that has emerged since 1973.

The worldwide distribution of cancer of the pancreas, especially in Japan where diagnostic facilities and vital statistics are as reliable as in the United States, and the increase of pancreas cancer among Japanese immigrants to the United States clearly points to pancreas cancer as being another one of those cancers that are man-made and related to life-style and are consequently also preventable. Some of the smaller differences that exist for different population groups need to be viewed with caution, since cancer of the pancreas is one of the most difficult to diagnose.

In the 1973 study, we determined a number of factors that were related to the etiology of cancer of the pancreas as well as a number of variables for which we found no correlation (Table 1). For the epidemiologist and the experimental oncologist, knowledge of both types of correlations provides useful leads. The fact, for instance, that we found no correlation of alcoholism or of clinically evidenced pancreatitis to pancreatic cancer indicates that these 2 entities are of no etiological significance to the pathogenesis of cancer of the pancreas. On the other hand, our finding that cigarette smoking increases the risk of cancer of the pancreas (Chart 1), a finding supported by several prospective and retrospective studies, and the suggestion that a high-fat diet is associated with cancer of the pancreas (Chart 2) indicate that tobacco smoke and possibly nutrition-related factors play a role in the induction of pancreas cancer.

The finding of an association of long-term diabetes as well as of cholecystectomy to cancer of the pancreas in women but not in men is of etiological interest. These findings being based on relatively few female cases (42 cases), we would like them to be confirmed by additional studies before attempting to involve an etiological analysis.

Differences in sex ratios can provide useful leads to the epidemiologist. The sex ratio of pancreas cancer shows a greater incidence in men (2/1) before age 50 and declines toward although not reaching unity after that age. What is the etiological significance of this finding? Could the effect of the "cigarette factor" be more important in the younger age groups similar to what we observed in, although not necessarily in terms of mechanisms for, myocardial infarction? Or could hormonal factors be more protective for women before menopause simulating what also has been noted for coronary disease? These leads require further study on the basis of both epidemiological and metabolic studies.

The finding that pancreas cancer is relatively rare in Japan, increases among Japanese immigrants to the United States, and occurs somewhat more often among Jewish people in New York City supports the hypothesis that

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environmental factors, most likely to be dietary in nature, increase the risk for pancreas cancer. The somewhat higher incidence of pancreas cancer in American blacks compared to United States Caucasians (recently confirmed by the Third National Cancer Survey) (11), if it is indeed real, requires further elucidation in terms of its etiological explanation (Table 2).

Tobacco

The findings of both pro- and retrospective studies that the risk for pancreas cancer increases only in cigarette smokers but not in cigar or pipe smokers suggest that tobacco smoke must be inhaled to exert its effect. Primarily, 2 ways are envisioned in which tobacco components, or their metabolically activated forms, can reach the pancreas, namely, either via refluxion from the bile duct into the pancreatic duct or through the blood stream. The pathological finding by Berg (W. D. Berg, personal communication) that patients with cancer of the pancreas often have concomitant carcinoma *in situ* in the main pancreatic duct, the knowledge that cancer of the pancreas arises most commonly in the head of the pancreas, and the findings by Hansson (3) that bile reflux can occur in primates makes the bile reflux hypothesis attractive. On the other hand, it is known that certain carcinogens such as nitrosamines are peculiarly organ specific and have been shown to produce pancreatic lesions in hamsters similar to those existing in men. Recently, Pour *et al.* (12) reported significant carcinogenic activity of di(2-hydroxypropyl)nitrosamine in the pancreas of hamsters. The authors noted that the histology of these lesions as well as their site of origin is similar to that occurring in man. This particular nitrosamine has not been identified in tobacco smoke. There are a variety of other nitrosamines which in minimal concentration have been identified in cigarette smoke (5, 6). Furthermore, it appears not unlikely that tobacco smoke contains also traces of nitrosamines that can be metabolically activated to carcinogens that are structurally comparable with the active form(s) of diisopropanolnitrosamine. Tobacco smoke contains also a great diversity of other carcinogens active in animal models (Chart 3) (5, 6, 14).

Since chemists and, on the basis of a small number of cases, workers exposed to β-naphthylamine have been reported to have an increased risk for pancreas cancer, it would underscore the view that chemical exposure, be it in relation to agents inhaled or absorbed through the skin, can be carcinogenic to the pancreas (8, 9). Certain arylamines sometimes induce pancreas cancer in animals, but not reproducibly, perhaps paralleling the human situation. A 3rd mechanism that would account for the greater risk for smokers to develop pancreas cancer is related not to tobacco carcinogens but to the apparent correlation of cigarette smoking and elevated serum cholesterol levels, particularly in heavy and in younger cigarette smokers (4). The mechanisms involved here may relate indirectly through the greater release of catecholamines subsequent to the inhalation of nicotine (7). Thus, if blood lipids in some way relate to the induction of cancer of the pancreas and if cigarette smoking increases serum lipids, this is another

Table 1

Variables studied with regard to pancreatic cancer

Positive association	No association
Male	Alcohol intake
Cigarette smoking	Clinical pancreatitis
High fat and/or cholesterol diet	Diabetes in men
Cholecystectomy in women	Weight
Diabetes in women	
Selected occupations	
Jewish	

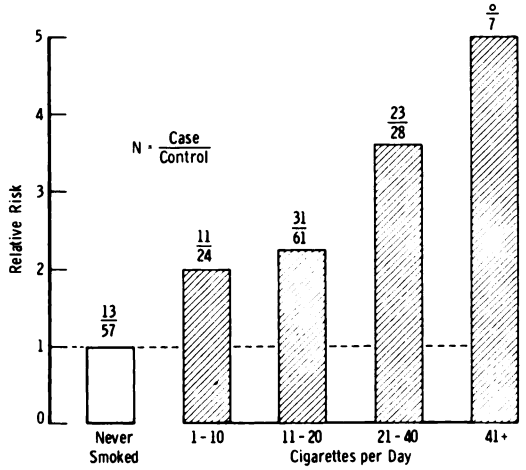

Chart 1. Relative risk of pancreatic cancer by number of cigarettes smoked (male).

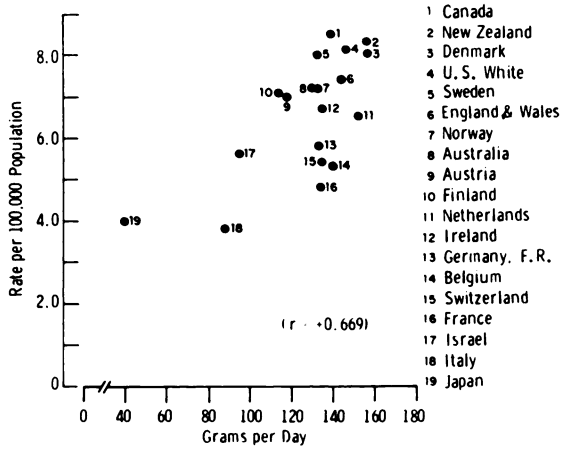

Chart 2. Correlation between male pancreatic cancer death rates, 1964 to 1965 (Segi *et al.*, Cancer Mortality for Selected Sites in 24 Countries (1964-1965). Sendai, Japan: Tohoku University School of Medicine, 1969) and total fat intake in selected countries., 1963 to 1965 (Food and Agriculture Organization. Food Balance Sheets. New York: United Nations, 1969).

Table 2

Age-adjusted incidence rates (per 100,000) for cancer of the pancreas by race and sex[a]

Incidence rate for	Race	
	Black	White
Men	17.2	12.2
Women	9.8	7.3

[a] For source, see Ref. 11.

pathway through which cigarette smoking could effect the development of pancreatic cancer.

Nutrition

The migrant pattern of pancreatic cancer, the relatively high level of this disease in American Jews, although their cigarette consumption is relatively low as is well reflected in their lower rate of lung cancer, and the association of pancreatic cancer to fat consumption in various countries suggest that diet, especially in terms of fat and/or cholesterol intake, affects the development of pancreatic cancer. The relationship exists not for obesity but rather for the make-up of the diet. These epidemiological leads could not be followed up by obtaining dietary information on patients with pancreatic cancer. We consider such information to be too unreliable to be meaningful. Furthermore, the general dietary pattern of most Americans is too similar. How such a diet could effect pancreatic carcinogenesis remains an open question. Data on pancreatic cancer are part of a general finding that "overnutrition" relates to a variety of cancers, including cancer of the colon and kidney, as well as endocrine-related cancers such as breast, ovary, endometrium, and prostate (Chart 4). The specific mechanism whereby diet leads to these various cancers may obviously differ from cancer to cancer. One may wonder whether the *in vivo* conversion of cholesterol to a cholesterol epoxide may be of etiological significance. Black and Douglas (1) have shown that such a conversion can occur in the skin, and Wilk (M. Wilk, personal communication) has suggested that the *in vivo* formation of cholesterol epoxide is possible elsewhere in our bodies. Serum cholesterol epoxide has been shown to be relatively high in individuals with a high serum cholesterol level (2). The carcinogenicity of such epoxides for epithelial tissues still has to be established. Such studies are currently in progress in our own laboratory. Also we have recently shown that 2 bile acids, lithocholic acid and taurodeoxycholic acid, applied intrarectally, act as tumor promotors in the colon of rats previously initiated with methylnitrosoguanidine (10).

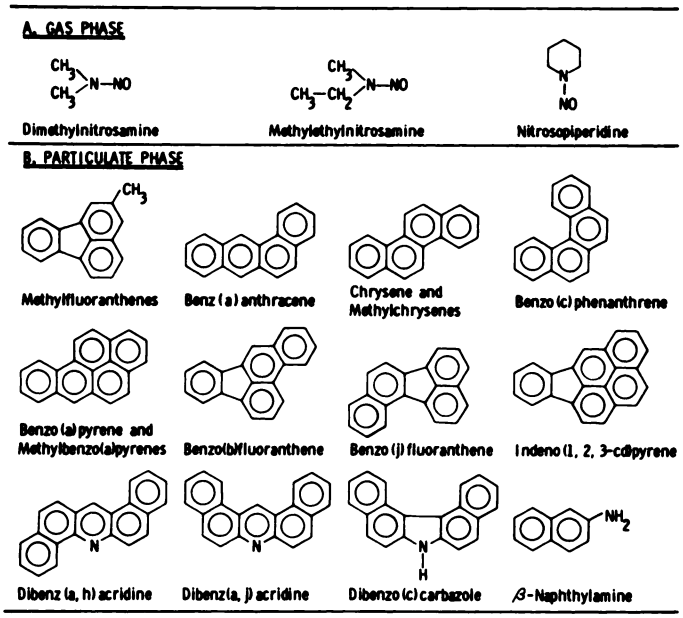

Chart 3. Identified carcinogens in tobacco smoke.

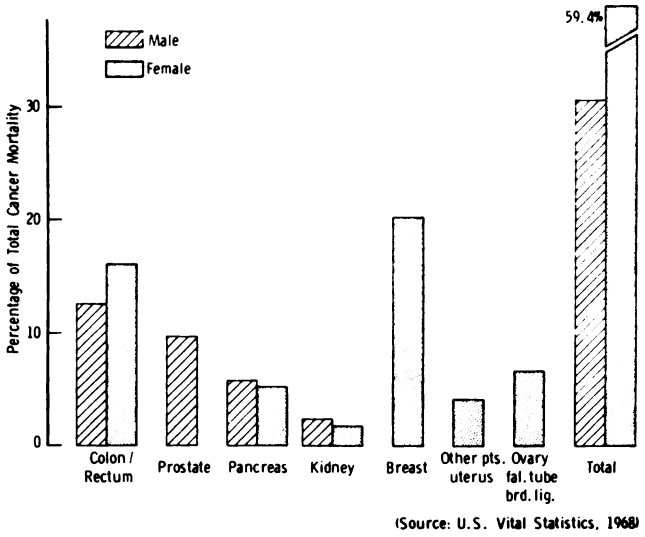

Chart 4. "Overnutrition"—related cancer deaths by sex, U. S., 1968. *pts.*, parts; *fal.*, fallopian; *brd. lig.*, broad ligaments.

Future Studies

Future epidemiological investigations should try to explore further possible reasons for the higher reported incidence of cancer of the pancreas in blacks. Additional studies should be carried out in women to verify our previous data linking diabetes and gallbladder diseases to pancreatic cancer as well as providing an explanation for the current sex ratio. Epidemiological studies should be carried out in some Indian tribes known to have a high rate of gallstones (13).

Efforts should be expanded on the pathogenesis of the disease in order to determine more specifically the site of cellular origin of pancreatic cancer. Epidemiologists should recognize the limits of their art and should broaden their base to include metabolic studies using humans and primates as experimental tools. We ought to test the bile reflux concept. We should examine the bile for the presence of tobacco-derived and other carcinogens. We should evaluate serum lipids and the makeup of adipose tissue in patients with cancer of the pancreas. Experimentally, we should not limit research to small laboratory animals that have an anatomic relationship of the bile duct to the pancreatic duct quite dissimilar to the system in man but rather work with animals with an anatomic structure similar to the biliary-pancreatic system existing in man.

When properly designing and interpreting experimental findings, it is important that it be done by a "task force" made up of members with broad experience in etiology. If such a group is formed as an integral part of a broader task force for pancreatic cancers, it is likely that etiology will take a distinct priority over efforts towards early diagnosis and treatment. It is also important that the makeup of the

etiology task force be properly balanced so that it represents all branches of etiology ranging from epidemiology to molecular biology.

Preventive Measures

It is apparent from the anatomic location of the pancreas that early diagnosis and consequent effective therapy, at least within the framework of our present knowledge, is unlikely to improve significantly. It behooves us, therefore, to introduce appropriate preventive measures although we may not now know the precise mechanism whereby specific factors affect the pathogenesis of cancer of the pancreas. The history of preventive medicine has, of course, amply shown that knowledge of mechanism is not required in order to prevent an illness. Since cigarette smoking contributes to about one-third of the incidence of cancer of the pancreas in males, if we were able to convince all males to stop smoking or if we were able to develop a completely harmless cigarette, we could reduce the incidence of pancreatic cancer in males by this percentage. In terms of securing less harmful cigarettes, we must of course determine which components in cigarette smoke are the culprits, the polycyclic aromatic hydrocarbons, the nitrosamines, or nicotine, by affecting catecholamines and thus blood lipids. While tar and nicotine levels of American cigarettes have been reduced and while the tar from such cigarettes has been shown to be decreasingly carcinogenic to mouse skin, it remains to be established in on-going epidemiological studies whether the smoking of low-tar, low-nicotine cigarettes is associated with the reduction of pancreatic cancer. We have demonstrated this with such cigarettes for cancer of the lung and more recently for cancer of the larynx (Ref. 15; E. L. Wynder, L. Covey, and K. Mabuchi. Cancer of the Larynx, in preparation). Concurrently with programs in the area fostering the development of less harmful cigarettes, we need to extend our programs on antismoking education to the public at large and also to extend the utilization of effective smoking cessation programs. Some success along these lines was achieved, particularly among educated male adults. The Smoking Cessation Clinic at the American Health Foundation currently has a 25% success rate for quitting for 1 year among individuals who smoked an average of 30 cigarettes a day (L. Shewchuk, R. Clark, A. Jaffin, D. Burton, M. Foreman, and R. Dubren. An Intervention Model for Heavy Smokers. Techniques and Preliminary Results, unpublished data). Since smoking cessation effects the reduction of a whole variety of other diseases, such programs should be increasingly encouraged.

As far as diet is concerned, even though we are not yet fully certain of the precise role of fat and cholesterol, we should join our colleagues working towards the prevention of cardiovascular diseases in recommending "the prudent diet" (Chart 5). This calls for the reduction in total calories, a reduction in fat intake from a level of 42 to 44% of calories as it exists among American people today to 35% or less, and modification of the polyunsaturated fatty acid/saturated fatty acid (P/S) ratio of 0.3 to 1.0 and a reduction in the intake of cholesterol from an average of 500 to 800 mg/day to less than 300 mg/day. We believe that such a

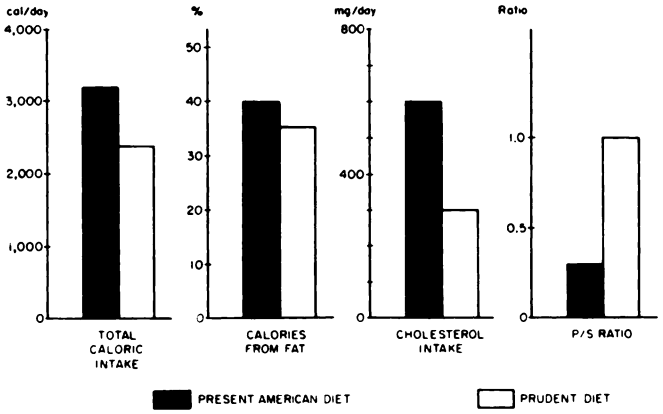

Chart 5. Prudent diet and present American diet.

prudent diet as part of a "prudent life-style" will decrease our risk for a number of diseases, which may well include cancer of the pancreas.

In addition to individual life-style modification, we are recommending the further reduction of tar and nicotine levels of cigarettes to tobacco manufacturers. Also, we are urging the food and agriculture industries to work towards a reduction in the cholesterol content of eggs, a reduction of fat content of milk, and a reduction of the fat in beef which can be accomplished through greater use of range feeding. We feel particularly strong about the value and promise of these managerial changes because history has taught us that modification of widely used environmental factors by society itself has generally been more successful than behavioral changes of each individual.

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Informal Discussion following the Paper by Wynder

Dr. Pledger: Dr. Wynder, you have referenced the Jewish population of New York City as having a higher frequency of pancreatic cancer. Is this conclusion in relation to the environs of the city, or do you have data from other Jewish populations residing outside of the city?

Dr. Wynder: We are about the only group in the country that does this kind of epidemiological research. From that point of view we are fortunate to be in New York, for here there are more Jews than in Israel. But to answer your original question, those data are not available for the Jewish population in other cities at present.

A very fruitful area for more research would be Israel, where Michael Davies' studies do not yet contain sufficient cases. He has shown for colon and breast cancers that the Jew from Europe has a high rate of these diseases, as well as coronary disease. On the other hand, the Jews that came from Asia and Africa have the lower rates of the populations from which they came. From this it appears that it is not genetic but environmental.

Dr. Scarpelli: I would like to ask whether the P/S ratios shown in one of your tables refers to the amount of polyunsaturated *versus* saturated fatty acids in blood?

Dr. Wynder: Yes, the P/S ratio comes from our colleagues in the coronary artery disease field where they are further advanced in the area of nutrition. It has only been in recent years that nutrition has begun to be considered important in the cancer field. In fact, the American Cancer Society and the National Cancer Institute are sponsoring an international workshop on nutrition and cancer that I have the privilege of chairing with Dr. James Peters of the National Cancer Institute and Dr. Steven Vivona of the American Cancer Society.

Dr. Flamm: To what extent do the factors identified in your talk explain the rather marked increase in pancreatic cancer rates occurring in the last decade in your general population?

Dr. Wynder: First of all, when we talk about increase of any disease, we have to make sure it is real. Clinicians know how difficult it is to diagnose cancer of the pancreas and, particularly, the population that is not properly posted. Years ago there were quite a number of people posted; we now post fewer people. Part of the increase in pancreatic cancer may well be due to better diagnosis, particularly in our cancer centers, but clearly the rise in cigarette smoking may also contribute to the increase.

In addition, there has not only been an increase in fat consumption by the general population, but that increase has coincided with the fact that the population is becoming more sedentary. It has been shown in several studies that, if you take population groups and induce them to exercise properly, elevated blood lipid levels can be reduced. To conclude, we have at least 3 or 4 factors that could account for the increase in pancreatic cancer: better diagnosis, more cigarette smoking, more fat intake, and a more sedentary way of living.

Dr. Alarif: I was wondering if in your studies you could find any common correlation between, say, preserved meat, particularly food which has nitrate in it, and cancer of the pancreas? Simply from an experimental point of view, you all know that nitrosamines and nitrosamides have been the more efficient agents for inducing pancreatic cancer. I was wondering, particularly, if people who eat corned beef sandwiches, for example, might have any significance in this respect.

Dr. Wynder: This is, of course, one area to be considered. My colleague, John Weisburger, holds a similar concept which we discuss frequently. In terms of a classical epidemiological study, however, the kind of detailed dietary history that would be necessary to include is almost impossible to obtain.

In terms of diet, the only thing we can do is to look at special population groups within our own country. The Seventh Day Adventists are a good example. Sometimes one thinks one has to go to Africa or to Outer Mongolia to do a good epidemiological study, but we can do it right here in our own country. The Seventh Day Adventists, as you know, don't smoke or drink, eat very little meat, and have a