CHRONIC PANCREATITIS AND PANCREATIC CANCER

PANCREATIC cancer is the 5th leading cause of death from cancer and the 11th most common cancer in the United States[1]; each year 24,000 people die of pancreatic cancer in this country. The incidence of pancreatic cancer increased dramatically several decades ago, but it has remained fairly stable over the past 15 years (9.1 per 100,000). Although the five-year survival rate has improved only slightly in recent years (from 3 percent in 1970 through 1973 to 5.4 percent in 1981 through 1987 among whites and from 2 percent to 4.3 percent during the same periods among blacks), nearly all patients with the disease die of it, and most die within one year of diagnosis.[1]

Relatively few risk factors are known for cancer of the pancreas.[2] The incidence is higher among men than women, and blacks have a noticeably higher rate than whites.[1] The relative risk associated with cigarette smoking has ranged from 1.6 to 3.1 in prospective epidemiologic studies and from 1.9 to 5.5 in case–control studies. A dose–response relation with the number of cigarettes smoked or the duration of smoking has not, however, been demonstrated consistently.[2] Several studies have reported a significant protective effect associated with the consumption of fruits and vegetables,[3-5] and some have shown an increased risk associated with meat consumption.[2] Most epidemiologic studies have observed little or no association of pancreatic cancer with alcohol consumption.[2] The results regarding the association of coffee consumption with the risk of pancreatic cancer have been inconsistent, but most prospective studies show no association.[2] Finally, there are relatively few positive associations of pancreatic cancer with occupation,[2] although a recent study reported a fourfold to fivefold increased risk associated with exposure to DDT and its derivatives during their manufacture.[6]

The relation of chronic pancreatitis to pancreatic cancer has been addressed but has not been clarified by epidemiologic studies. Most studies of pancreatic cancer have had a case–control design, and single studies have usually had too few patients with chronic pancreatitis to provide meaningful results. Lowenfels and colleagues address this important issue in this issue of the *Journal*,[7] reporting the results of a large cohort study. They are to be commended for this ambitious undertaking. They report a large, significantly increased risk of pancreatic cancer in a cohort of patients with chronic pancreatitis, diagnosed in seven clinical centers in five European countries and the United States. Their multivariate statistical model included the potential confounding variables of age, sex, clinical center, smoking status, and drinking status (as recorded in medical records) and produced a standardized incidence ratio of 16.5 for patients with two or more years of follow-up.

These findings must be viewed in the light of potential methodologic problems. Although the possibilities of misclassification and detection bias are briefly discussed by the authors, the potential for these errors is great and must be thoroughly considered. The recruitment of patients began in 1946, when it was virtually impossible to diagnose chronic pancreatitis and distinguish it from pancreatic cancer with certainty. Only about one quarter of the patients underwent endoscopic retrograde cholangiopancreatography, and less than 20 percent had a computed tomographic scan — two tests that most clinicians now consider essential in diagnosing chronic pancreatitis. Theoretically, by excluding any patients given a diagnosis of pancreatic cancer within the first two years of follow-up, the authors eliminated patients whose initial diagnosis was chronic pancreatitis but who may truly have had pancreatic cancer. This exclusion policy undoubtedly helped minimize the misclassification problem but could not eliminate it totally.

Cancer was histologically confirmed in 83 percent of the patients in whom it was diagnosed after two years. Many of the remaining patients may have had another, slower-growing cancer, such as a cystadenocarcinoma or an islet-cell tumor, and such patients might well not have been eliminated by the two-year exclusion policy. Nearly half the patients with pancreatic cancer were eliminated from the study when patients with less than two years of follow-up were excluded, suggesting that a large fraction had been misclassified as having chronic pancreatitis when they actually had pancreatic cancer and supporting our concern about the accuracy of the original diagnosis of chronic pancreatitis. An additional observation illustrating the possible influence of a misclassification error is that the risk of pancreatic cancer was markedly lower when data for the first two years of observation were excluded: the standardized incidence ratio was 26.3 for all patients, 16.5 for patients with two or more years of follow-up, and 14.4 for patients with five or more years of follow-up.

The possibility of detection bias also deserves consideration. Since all the subjects in this study had been given a diagnosis of chronic pancreatitis, pancreatic cancer may have been more likely to be detected in them than in the general population with whom the subjects were compared. The magnitude of this potential bias cannot be estimated, but the authors state that if the background incidence was in fact twice as high as the reported rates, the standardized incidence ratio would be 8.2. However, if both misclassification and detection bias were influencing the results, a lower standardized incidence ratio would be likely.

These reservations aside, the findings of this study should be put into perspective. There are few data in the literature on the frequency of chronic pancreatitis in the population, but at least two studies have reported an incidence of 3.5 to 4 per 100,000.[8,9] If the standardized incidence ratio is assumed to be 16, the attributable risk for the proportion of pancreatic cancer that is explained by chronic pancreatitis may

be only approximately 0.1 percent annually (or perhaps 24 cases annually in the United States), as compared with an attributable risk of approximately 30 percent for cigarette smoking. Thus, although the paper by Lowenfels and colleagues is interesting and provocative, even if their assumptions are entirely correct, chronic pancreatitis accounts for only a small fraction of the cases of pancreatic cancer seen each year in this country. Given its grim prognosis, we need to direct our efforts toward identifying improved techniques for the early detection and treatment of pancreatic cancer. We must also elucidate other risk factors if effective methods of prevention are to be developed.

University of California
Davis, CA 95616 ELLEN B. GOLD, PH.D.

Johns Hopkins Medical Institutions
Baltimore, MD 21205 JOHN L. CAMERON, M.D.

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TRETINOIN (RETINOIC ACID) REVISITED

ALTHOUGH it is easy to dismiss problems such as postinflammatory hyperpigmentation under the rubric of "cosmetic concerns," pigmentary disorders are a frequent cause of distress because of our society's excessive focus on appearance. Postinflammatory hyperpigmentation is a common cause of visits to the dermatologist, and the number of agents available for its treatment is limited. The report by Bulengo-Ransby and colleagues on the efficacy of tretinoin (retinoic acid) as a single agent in black persons with postinflammatory skin hyperpigmentation in this issue of the *Journal*[1] adds to our knowledge about both tretinoin and the hyperpigmentation itself.

The use of tretinoin in patients with hyperpigmentation is not new. Various formulations combining hydroquinone, tretinoin, and a topical steroid have been advocated for use by patients with chloasma, postinflammatory hyperpigmentation, and freckling since the mid-1970s.[2-4] The initial report on the use of this combination stressed the need for all three components to produce the desired effect,[2] but tretinoin alone had some beneficial effect in several of the early studies. This new study of a large group of patients demonstrated a greater effect of tretinoin on pigmentation than previously described.[1] The mechanism of action of tretinoin on postinflammatory hyperpigmentation remains speculative, but in cultured melanoma cells this agent can inhibit inducible melanogenesis.[5]

The mainstay of treatment for postinflammatory hyperpigmentation has been hydroquinone. It is available in over-the-counter preparations containing 1 to 2 percent hydroquinone (such as Porcelana and Esoterica); a preparation with a slightly higher concentration (3 to 4 percent) is available by prescription. Although the cutaneous pigmentation caused by this drug is a source of concern, it has not been a major problem in the United States. In South Africa, where hydroquinone has been used in concentrations of 5 percent or more, the incidence of this type of pigmentation appears to be higher.[6] The greater drawback of hydroquinone as a single agent is that its effect on hyperpigmentation is slight.[7] A comparison of tretinoin with hydroquinone or a combination of the two is needed to determine the relative usefulness of these treatments.

Postinflammatory hyperpigmentation may develop in susceptible persons for a variety of reasons, some of which are quite minor. The common causes, such as acne, eczema, and irritation from shaving, are likely to recur. Thus, the development of new lesions in half the patients studied by Bulengo-Ransby et al. within six months after treatment was discontinued is not surprising. Although the number of patients who were followed after treatment was small, these findings emphasize that unless the underlying cause of the postinflammatory change is addressed, an unending cycle of inflammation followed by pigmentation followed by intervention is likely to occur. A greater understanding of the mechanisms underlying postinflammatory changes will be needed in the long run to determine optimal treatment.

Many physicians have been hesitant to prescribe tretinoin for acne or other disorders in black patients because side effects such as burning or stinging of the skin, erythema, scaling, and pigmentary changes were thought to be more common among them than among other patients.[8,9] In the current study,[1] the patients' tolerance of tretinoin was very similar to that reported previously in white patients.[1] Although patients participating in a clinical study often receive more information on the use and side effects of medication and on adjustments of dosage than do pa-