Carcinoma of the exocrine pancreas continues to have one of the poorest outlooks of any cancer. Although worthwhile gains in survival may be achieved by early diagnosis and referral to a specialist surgeon, further improvements are unlikely without reliable screening techniques and improved adjuvant therapy.

THE EXTENT OF THE PROBLEM
Carcinoma of the exocrine pancreas continues to represent one of the greatest oncological challenges that faces surgeons and physicians today. It accounts for over 90% of pancreatic tumors and despite improvements in surgical technique, peri-operative care, and adjuvant therapy, the outcome of the disease has scarcely improved since the middle of the century. Increasingly common, pancreatic cancer is now the fourth and fifth leading cause of cancer death for men and women in the United States, respectively. Its incidence has increased threefold since the 1930s, and now stands at approximately 9.5/100,000/year. Excluding small tumors confined to the pancreatic head, pancreatic cancer is virtually incurable; any intentionally curative surgery requires a difficult and hazardous operation. 1

The incidence of pancreatic cancer varies with sex, age, and race, and males are affected twice as often as females. The disease is uncommon in those under 45 years of age, and over 80% of cases occur in the 60- to 80-year age group. Racial groups at a higher risk include New Zealand Maoris, Native Hawaiians, and black Americans (14.4/100,000). It is unclear whether these differences represent a purely genetic influence, although an environmental input is suggested because native Africans have a lesser chance of developing the disease. Finally, pancreatic cancer is more common in urban regions; however, it does not show any relationship to social class.

Risk Factors. The etiology of pancreatic cancer remains obscure. Smoking and dietary fat have been implicated by epidemiological studies, and recent investigations have tested the hypothesis that DNA damage derived from carcinogen exposure and diet is involved in pancreatic carcinogenesis. 2
significantly higher level of DNA adducts were detected in pancreatic cancer patients compared with controls. In addition, smoking and body mass index were positively correlated with the number of adducts within pancreatic tumors and normal adjacent tissue, supporting the hypothesis of DNA damage. There are several anecdotal reports about pancreatic cancer within multiple family members from the same generation, but in any disease with more than 100,000 new cases internationally each year, chance aggregations are likely.

Diabetes mellitus is difficult to evaluate as a risk factor because glucose intolerance may also be a consequence of pancreatic cancer. This phenomenon is probably a result of profound insulin resistance, rather than islet cell destruction, because resection may improve the endocrine function of the remaining gland. An unidentified soluble factor, which may account for the insulin resistance, has recently been described. When patients with diabetes with a duration of more than 1 year are taken into consideration, however, diabetics have a relative risk of developing pancreatic cancer of 2.1 compared with nondiabetics, suggesting that pancreatic cancer occurs with increased frequency among people with long-standing diabetes.

Although chronic pancreatitis and pancreatic cancer often coexist, chronic pancreatitis may actually predispose sufferers to subsequent malignancy, and associated ductal hyperplasia increases this risk further. K-ras mutations at codon 12 and 13 have been identified in up to 95% of pancreatic cancers, and similar mutations have been identified in patients with chronic pancreatitis exhibiting ductal hyperplasia, thereby providing a genetic basis for the potential progression of chronic pancreatitis to pancreatic cancer. Inactivation of p53, p16, and DPC 4 genes are also thought to play a crucial role in pancreatic carcinogenesis.

**Presentation.** As with most cancers, the size and stage of the tumor at presentation profoundly influence outcome. Worldwide reports have shown resectability rates of only 10% to 20%. Tumors that are less than 2 cm in size have a reported 5-year survival of 37%; however, identification at this stage is exceptional. Unfortunately, the first symptoms of the tumor are nonspecific and include malaise, anorexia, weight loss, change in bowel habit, and epigastric discomfort. The timing of obstructive jaundice reflects the precise site of the tumor in the head of the pancreas, but once present, it progresses relentlessly with time. Courvoisier’s law states that a palpable gallbladder in obstructive jaundice is seldom the result of gallstones, but this is a relatively late sign in pancreatic cancer and of limited diagnostic value.

A recent onset of diabetes should be regarded with suspicion, as should a sudden increase in the insulin requirement of a diabetic. Occult bleeding is present in as many as 90% of patients and results in anemia in approximately 50% of patients at the time of presentation. As many as 5% of patients with pancreatic cancer will present with either acute or chronic pancreatitis. Since Trousseau’s original description, it is acknowledged that thromboembolic complications are more common in patients with malignant disease; indeed, migratory thrombophlebitis may be the presenting feature of this particular cancer. It is interesting that patients with pancreatic cancer have higher levels of tissue factor, which is the primary initiator of coagulation in humans. Moreover, tissue-factor expression correlates strongly with the degree of histologic differentiation in specimens of ductal adenocarcinoma, and is greater in poorly differentiated tumors. Therefore, in addition to its procoagulant function, tissue factor may have a role in tumor progression. With this possibility in mind, an ongoing international multicenter trial is investigating the effect of low molecular weight heparin on the outcome of patients with advanced malignant disease.

**Investigation.** Increasingly, improvements in diagnostic radiology are enhancing the ability to diagnose pancreatic cancer and select appropriate treatment for affected patients. Ultrasound scanning is often carried out as the first-line investigation and is particularly effective at demonstrating duct dilatation and the level of obstruction. Tumors appear as hypoechoic areas, and portal venous blood flow can be assessed by the use of pulsed Doppler scanning.

Contrast-enhanced spiral computed tomography (CT) scanning is now regarded as the premier modality for pancreatic imaging. It is excellent at identifying tumors of more than 2 cm in size (sensitivity > 90%) and in assessing the major vessels for the presence of local tumor invasion. However, it is of limited value in assessing smaller primary tumors and detecting the presence of liver metastases less than 1 cm in size or peritoneal seedlings. Gadolinium-enhanced magnetic resonance imaging (MRI) may be particularly effective at identifying subtle changes in pancreatic contours and the overall vascularity of the gland to further increase staging reliability.

Malignant tumors have an increased glucose metabolism, and Friess' investigated this property in pancreatic cancer with the use of positron emis-