Carcinoma of the pancreas is a disease in which surgery can offer little more than palliation and in which other forms of therapy are equally unsatisfactory. In America, for example, Elmer-Dewitt (1992), using figures obtained from the National Cancer Institute, has shown that only 3.1% of patients diagnosed as having cancer of the pancreas between 1981 and 1987 were alive 5 years from the time of the diagnosis. Moreover, this dreadful disease is becoming more common.

Increasing Incidence

In 1958, Rodney Smith wrote: “Malignant tumours of the pancreas are relatively uncommon. Carcinoma is the only one encountered with any frequency and even this accounts for only 1%–2% of all carcinoma.” By 1973, however, cancer of the pancreas had become the fourth commonest cause of death from cancer in the United States (Levin and Connelly 1973), its incidence having trebled since 1930, while in England and Wales its incidence had approximately doubled during a similar period (Adelstein 1977). Now, in most Western countries, there is an annual incidence of between 9 and 10 cases per 100 000 of the whole population. The number of cases reported to the Mersey Regional Cancer Registry are probably typical: in 1971 there were 12.9 male cases and 9.2 female cases per 100 000; in 1972 the corresponding figures were 13.6 males and 8.2 females; and in 1973 the numbers were 10.4 males and 9.0 females. The accuracy of this has been confirmed more recently by Dr Ruth Hussey, who found an annual incidence of between 10.6 and 12.7 per 100 000 between 1983 and 1987 (personal communication).

The Mersey Cancer Registry receives registrations, not only from the industrial areas of Merseyside, but also from the mainly rural areas of Clwyd, Gwynedd and the Isle of Man. In people over 75 years of age the incidence is said to rise towards 100 per 100 000 of this population (Levison 1979). The increase affects both sexes (Adelstein 1977) and is probably world-wide. Japan is not, of course, representative of the other Eastern countries, for there the diagnostic facilities and vital statistics are as reliable as in the United States (Wynder 1975), but in Japan there has been a fourfold increase in the incidence during the past 25 years (Segi et al. 1969). Figures collected by the World Health Organization were quoted in an anonymous note in the *Lancet* (1978) that drew attention to an alarming increase in the incidence in the northern European countries, for example Scotland, or Sweden where, in 1972, the incidence was 16.6 per 100 000.

A more recent study of the epidemiology of pancreatic cancer is that of Fontham and Correa (1989), where it is pointed out that, although death rates for pancreatic cancer in the USA have risen steadily since about 1930, there has been a recent levelling off. In Britain it has been estimated that over 6000 are killed by the disease every year, but, at least in England and Wales, the graphs for cancer deaths published by Davis et al. (1990) show a levelling off in the number of deaths from pancreatic cancer in both sexes in recent years.
Statistics such as those that have just been quoted include all cases registered as pancreatic cancer and take no account of the microscopic structure of the cancers. Only a proportion of the registered cases have had the diagnosis confirmed by microscopic examination, but carcinoma that has originated from epithelium of the pancreatic ducts is so overwhelmingly preponderant among the microscopic types that the statistics almost certainly reflect the incidence of this type of carcinoma rather than that of the rarer types. The statistics also depend entirely upon the diagnosis, often unconfirmed by an autopsy, of the cause of death (Höpker 1987). It is well known that certified causes of death, particularly without an autopsy, are very unreliable (Cochrane and Moore 1981; Kircher et al. 1985).

Aetiology

Geographical, Racial and Social Factors

The results of attempts to find associations between such factors and the incidence of cancer of the pancreas have been reviewed by Levison (1979). No clear pattern could be recognised amongst the inhabitants of the various parts of the USA when the age-adjusted death rates for cancer of the pancreas were correlated by sex and race with demographic and industrial information, except that the rates were higher in urban areas, especially in males (Blot et al. 1978). The study just mentioned did not indicate any association with socioeconomic or industrial conditions, although an earlier study (Krain 1971) had suggested that there was an inverse relationship between socioeconomic class and pancreatic cancer, while Fraumeni, in 1975, had found that the rising frequency within the USA was in males and in blacks, the increased incidence in the blacks having become recognisable only after 1950. Although there are marked differences between the incidence in various racial groups both in the USA and internationally, no satisfactory explanation has been offered. The possible effect of migration, however, may be significant, for people who move from areas where the incidence of pancreatic cancer is low to areas where it is high seem to be particularly at risk (Haenszel and Kurihara 1968; Mancuso and Sterling 1974); thus change of environment, possibly because of an associated change in dietary habits, seems to be important.

In general, comparisons of the incidence of the disease in different parts of the world point to its being a disease of the industrialised western countries, in which the diet tends to have a high content of fat or cholesterol, or both fat and cholesterol (Wynder 1975). Many epidemiological findings about the incidence of carcinoma of the pancreas, however, remain unexplained, while some, for example the observation by Williams and Horm (1977) that there is a positive association between college attendance (but not income) and cancer of the pancreas in American males, seems inexplicable.

Smoking and Environmental Influences

As long ago as 1796 Erasmus Darwin wrote: "The unwise custom of chewing and smoking tobacco for many hours in a day not only injures the salivary glands, producing dryness in the mouth when this drug is not used, but I suspect that it also produces schirrhus of the pancreas." Darwin's idea received some support from the anonymous author of a letter to the Lancet published in 1829, but it was not until the 1970s that the results of investigations into the aetiology of cancer of the pancreas began to suggest that there might be an important association between cigarette smoking and pancreatic carcinoma.

In several epidemiological studies, for example those of Krain (1970), Wynder et al. (1973) and Williams and Horm (1977), the association could be demonstrated, and Wynder (1975) has suggested ways in which cigarette-derived carcinogens may reach the pancreas, or how changes in the blood lipids induced by smoking may affect the development of pancreatic cancer. In 1989, after a comprehensive review of the epidemiological publications on possible risk factors in the development of pancreatic cancer, Fontham and Correa came to the conclusion that cigarette smoking was the best established risk factor in the aetiology of the disease.

Experimental work by Longnecker and Curphey (1975) and by Pour et al. (1975) has shown that carcinogens injected into rats and hamsters induce exocrine pancreatic hyperplasia, adenomas and carcinomas while the alimentary administration of N-methyl-N-nitrosourea to inbred guinea pigs by Reddy and Rao (1975) induced pancreatic adenocarcinoma. Thus the entry of carcinogens, whether through the lungs from cigarette smoke, or from atmospheric pollution, followed by distribution through the bloodstream to act eventually upon the pancreas, may be aetiologically important, while entry of remotely acting carcinogen by the alimentary route has also been shown experimentally to be