CANCER OF THE BILE DUCTS AND PANCREAS

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Edited by

Paul E. Preece, MD(Wales), FRCS(Ed.), FRCS(Eng.)

Senior Lecturer and Honorary Consultant Surgeon
Ninewells Hospital and Medical School
Dundee, Scotland

Alfred Cuschieri, MD, ChM, FRCS(Ed.), FRCS(Eng.)

Professor of Surgery
Ninewells Hospital and Medical School
Dundee, Scotland

R. David Rosin, MS, FRCS

Consultant Surgeon
St. Mary's Hospital
London

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Preface

Cancers of the bile ducts are relatively rare, whereas those of the pancreas are more common. Both present with similar symptoms, the alleviation of which depends upon as accurate an assessment of the site of origin and the extent of the lesion as can be achieved. The contributors to this forum, run by the British Association of Surgical Oncology, have had great personal experience in managing these disorders and herein they extend their expertise for others to share.

Contributors

J.V. Anderson, MD, *Department of Medicine, St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE*

Åke Andrén-Sandberg, MD, PhD, *Department of Surgery, Lund University, S-221 85 Lund, Sweden*

P.P. Anthony, MBBS, FRCPath, *Area Department of Pathology, Exeter Health Authority, Church Lane, Heavitree, Exeter, Devon EX2 5DY, UK*

Henri Bismuth, MD, FACS, *Unité de Chirurgie Hepato-Biliare, Hôpital Paul Brousse, 94800 Villejuif, France*

S.R. Bloom, MD, *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS, UK*

K. Bosslet, MD, *Research Laboratories, Behringwerke AG, PO Box 1140, 3550 Marburg, West Germany*

D.C. Carter, MD, *Department of Surgery, Royal Infirmary, Glasgow G4 0SF, Scotland, UK*

Denis Castaing, MD, *Unité de Chirurgie Hepato-Biliare, Hôpital Paul Brousse, 94800 Villejuif, France*

M.J. Cooper, MS, FRCS, *Department of Surgery, Royal Devon and Exeter Hospital (Wonford), Barrack Road, Exeter EX2 5DW, UK*

A. Cuschieri, MD, ChM, FRCS(Ed), FRCS(Eng), *Department of Surgery, Ninewells Hospital and Medical School, University of Dundee, Dundee DD2 1UD, Scotland, UK*

Harold Ellis, DM, MCh, FRCS, *Surgical Unit, Westminster Hospital, London SW1P 2AP*

Ingemar Ihse, MD, PhD, *Department of Surgery, University Hospital, S-581 85 Linköping, Sweden*

H.F. Kern, MD, *Department of Cell Biology and Cell Pathology, Robert-Koch-Strasse 5, D-3550 Marburg/Lahn, West Germany*

Rashad Y. Kirdani, MD, PhD, *Department of Health, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York, NY 14263, USA*

Günter Klöppel, MD, *Department of Pathology, Academic Hospital, Free University of Brussels, Laarbeeklaan 101, B1090 Brussels, Belgium*

Jörgen Larsson, MD, *Department of Surgery, University Hospital, S-581 85 Linköping, Sweden*

M. Lonsdale, FFARCS, *Department of Anaesthesia, Ninewells Hospital, Dundee DD1 9SY, Scotland, UK*

W.A. Macrae, MD, *Department of Anaesthesia, Ninewells Hospital, Dundee DD1 9SY, Scotland, UK*

Christopher Mallinson, MD, *Lewisham Hospital, Lewisham High Street, London SE13 6LH, UK*

A.R. Moossa, MD, *Department of Surgery, University of California San Diego, 225 Dickinson Street, San Diego, California 92103, USA*

Heather B. Nunnerley, MD, *Department of Diagnostic Radiology, King's College Hospital, Denmark Hill, London SE5 9RS, UK*

R.C.G. Russell, MS, FRCS, *The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK*

Avery A. Sandberg, MD, *Department of Health, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York, NY 14263, USA*

H.U. Schorlemmer, MD, *Research Laboratories, Behringwerke AG, PO Box 1140, 3550 Marburg, West Germany*

G. Schulz, MD, *Research Laboratories, Behringwerke AG, PO Box 1140, 3550 Marburg, West Germany*

H.H. Sedlacek, MD, *Research Laboratories, Behringwerke AG, PO Box 1140, 3550 Marburg, West Germany*

Joel. E. Tepper, MD, *Department of Radiation Oncology, University of North Carolina at Chapel Hill, North Carolina 27514, USA*

U. Theiss, MD, *Department of Cell Biology and Cell Pathology, Robert-Koch-Strasse 5, D-3550 Marburg/Lahn, West Germany*

Oscar Traynor, MCh, FRCSI, *Department of Surgery, St. Vincent's Hospital, Elm Park, Dublin 4, Ireland*

C.W. Venables, MS, FRCS, *Department of Surgery, Freeman Hospital, Newcastle-upon-Tyne NE7 7DN, UK*

R.C.N. Williamson, MD, MChir, FRCS, *Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS, UK*

A. Zorr, MD, *Department of Cell Biology and Cell Pathology, Robert-Koch-Strasse 5, D-3550 Marburg/Lahn, West Germany*

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Epidemiology, Aetiology and Pathology of Bile Duct Tumours

P.P. Anthony

INTRODUCTION

The subject of cancer of the biliary tract attracts growing interest, largely due to improvements in surgical techniques and treatment results rather than to a better understanding of the disease. Nevertheless, a number of possible aetiologies and relevant observations have come to light. The situation is in contrast to that in liver cell carcinoma where huge advances have been made following the identification of the hepatitis B virus as the main causative agent, but where prevention rather than treatment is still the only hope. Bile duct carcinoma is also a world-wide disease, whereas liver cell carcinoma is confined mainly to tropical Africa and South-East Asia.

EPIDEMIOLOGY

Knowledge of the world-wide distribution of tumours derives mainly from data which are gathered from cancer registries in many countries. These have been published in successive volumes of the series 'Cancer Incidence in Five Continents' by the International Agency for Research on Cancer, which is based in Lyon, France. The most recent of these books contains information from registries in 37 countries (Waterhouse *et al.*, 1982). These data present a wide range of information, but care is necessary in interpretation as they derive from sources of variable quality. General epidemiological data on cancer can also be found in the series of monographs by Clemmesen (1965, 1969, 1974). The Birmingham Cancer Registry has produced a most useful

handbook on the epidemiology and prognosis of most forms of cancer, based on a population of 5 million people, the characteristics of which make it representative of the UK as a whole and probably of most Western countries as well (Waterhouse, 1974). Trends in cancer morbidity by secular, social, occupational, urban/rural and regional comparisons in England and Wales have been reviewed by Coggon and Acheson (1981). Detailed statistical analyses are published regularly by the Office of Population Censuses and Surveys in the UK and by similar government agencies in other countries. The aims, scope and methods of these surveys have been summarized by Alderson (1982). Finally, specific data on hepatobiliary cancer are to be found in reviews by Aoki (1978), Munoz and Linsell (1982) and Okuda and Beasley (1982). Certainly, much has been achieved and a great deal of information assembled since the first Decennial Supplement on Area Mortality was published by the General Register Office in London in 1864, in which 'cancer' was presented as a single condition! Problems, nevertheless, remain.

Tumours of the liver and biliary tract have been classified under two broad headings in the International Classification of Diseases of the World Health Organisation and all of the above publications have followed the 8th revision produced in 1968. Rubric 155.0 stands for carcinomas of the liver and intrahepatic bile ducts, while rubric 156.0 for those of the gall bladder and extrahepatic biliary tree. Thus, in both rubrics, tumours of bile duct origin are submerged in liver cell and gall bladder tumours, respectively, as well as crossing the boundary between them. Since both liver cell and gall bladder carcinomas are as common or commoner than those of the bile ducts, an accurate epidemiological picture is impossible to obtain. A more detailed coding system for tumours has now been produced, but is not yet in general use. A general pattern of bile duct tumours is nevertheless discernible from series of case reports, autopsy studies and regional or country-wide surveys.

The age peak of intrahepatic bile duct carcinoma is in the sixth and seventh decades and the tumour is rare under the age of 45. Both sexes are affected equally. There is no association with cirrhosis. A high incidence is seen in South-East Asia. The areas most affected are Hong Kong, the delta of the Pearl river and Canton and the swampy lowlands criss-crossed by canals near Bangkok in southern Thailand (Gibson, 1971; Gibson and Chan, 1972; Kurathong *et al.*, 1985). The high incidence of bile duct carcinoma in these areas is clearly related to a high prevalence of infestation with liver flukes—*Clonorchis sinensis* in Hong Kong and Canton and *Opisthorchis viverrini* and *O. felineus* in Bangkok. Chronic hepatitis B virus infection is also widely prevalent throughout South-East Asia, with a high incidence of liver cell carcinoma everywhere. As a result, although bile duct carcinoma shows the highest incidence rate in the world in these countries, it still only represents a fifth or so of the incidence rate of liver cell carcinoma. In other countries of the region, notably Taiwan, Japan and the Indonesian archipelago, liver fluke infestation is uncommon and intrahepatic bile duct carcinoma rates are much the same as those in Africa, Europe or North America. The aetiology of the disease outside

South-East Asia is, in most cases, unknown although a number of predisposing factors is known.

The exact incidence rate of adenocarcinoma of the extrahepatic biliary tree is unknown in most areas, as published series variably include carcinomas of the gall bladder and of the ampulla of Vater among them (Liguory and Canard, 1983). It is unlikely that there are any significant differences in incidence, which is probably low in most or all parts of the world. Males are affected about as frequently as females and patients are generally in their sixth and seventh decades of life, like those with intrahepatic bile duct carcinoma. Again, there is no association with cirrhosis. On the other hand, carcinoma of the gall bladder is the fourth most common digestive cancer in females of middle and early old age in Europe and North America, the peak being between 55 and 65 years of age; males represent only a third or so of cases. Carcinoma of the gall bladder shows a marked geographical variability, with high incidence rates reported in New Mexico, India and Israel, rising to second or third place in the list of malignancies in women in these areas (Strom *et al.*, 1985). Gall-stones are the major known cause of the disease, together with any factors which predispose to their formation: female sex, age over 55 years, parity, obesity, oestrogen therapy, ileal disease and bypass and abnormalities of bile and lipoprotein metabolism (Bismuth and Malt, 1979). This is in contrast to intrahepatic and extrahepatic bile duct carcinomas which are rarely associated with lithiasis; some aetiologies, notably chronic inflammatory bowel disease, are however common to both.

Table 1-1 summarizes the main features of carcinomas of liver cell, bile duct and gall bladder origin, but only bile duct tumours will be discussed in this review.

AETIOLOGY

The most clearly established predisposing factor to intrahepatic bile duct carcinoma is infestation with liver flukes in parts of South-East Asia. In all other areas, known or suspected aetiologies each account for only a small number of cases. They may be discussed under three main headings: infective and inflammatory causes; congenital anomalies and metabolic disorders; and chemicals and drugs.

Infective and Inflammatory Causes

Infestation with Liver Flukes and Other Parasites

There is a clear correlation between incidence of intrahepatic bile duct carcinoma (cholangiocarcinoma) and prevalence of infestation with *Clonorchis sinensis* in Hong Kong and Canton and with *Opisthorchis viverrini* and possibly *O. felineus* in Bangkok (Gibson, 1971; Gibson and Chan, 1972; Chou and Chan, 1976; Schwartz, 1980; Kurathong *et al.*, 1985).

Table 1-1
Comparison of the Main Features of Liver Cell, Bile Duct and Gall Bladder Carcinomas

	Liver Cell Carcinoma	Bile Duct Carcinoma	Gall Bladder Carcinoma
Distribution	Africa, South-East Asia; uncommon elsewhere	World-wide, with high incidence in South-East Asia	World-wide, with high incidence in Mexico, India, Israel
Age	Young, where common	Old	Middle to old
Sex	Male everywhere	Both	Female
Main aetiology	Hepatitis B virus and aflatoxin	Liver flukes, inflammatory bowel disease, congenital anomalies	Stones
Pre-cancerous changes	Liver cell dysplasia	Adenomatous hyperplasia	Inflammation
Histological type	Liver cell carcinoma	Adenocarcinoma	Adenocarcinoma
Marker	Alpha-fetoprotein	Carcino-embryonic antigen	Carcino-embryonic antigen
Course and death	Liver failure and/or haemorrhage	Obstruction, sepsis, carcinomatosis	Carcinomatosis

The habit of eating raw or undercooked fish is clearly responsible. Dogs, cats, pigs and rats are also affected in these areas. The life cycle of flukes is similar to that of other parasites, notably schistosomes, and requires conditions of poor environmental hygiene with faeces discharged into water, snails as intermediate hosts, liberation of free-swimming cercariae and their ingestion by certain species of fresh water fish and, finally, ingestion by man and mammals. The cercariae hatch in the duodenum and the juvenile flukes migrate through the ampulla of Vater into the common bile duct to reach second-order intrahepatic ducts, where they mature and lay eggs. These, in turn, are excreted in bile to leave the body on defaecation and so the cycle is endlessly repeated. Infestation is acquired early in life and is common. In Hong Kong, for example, flukes are found at autopsy in about 25 percent of cases over 2 years of age (Gibson, 1971). The frequency rises abruptly and is high in adult life; over 70% are infested by the age of 60 in parts of Thailand (Kurathong *et al.*, 1985). Morbidity does not necessarily relate to intensity of parasite load as judged by egg counts in stools. This, however, may not be accurate. Patients may present with cholangitis, liver abscess or carcinoma of the intrahepatic bile ducts. Stone formation is rare, but pancreatitis has been recorded. Both sexes are affected and those with bile duct carcinoma are older than those with liver cell carcinoma who are also much more commonly males. The two types of tumour have now been clearly separated and there is no aetiological relationship between them: liver cell carcinoma is clearly associated with chronic hepatitis B virus infection and not with flukes.

It seems therefore that the carcinogenic effect of flukes is slow and requires several decades at least. Changes seen prior to the appearance of malignancy are hyperplasia of the bile duct epithelium, adenomatous proliferation of glands and an increase of mucus-secreting goblet cells (Fig. 1-1) The mucins produced in human and animal clonorchiasis are those that are normally found in the biliary tree (Chou and Gibson, 1970). An inflammatory reaction is absent or mild, ulceration uncommon and squamous metaplasia rare (Gibson and Sun, 1970). Duration of the infestation rather than its intensity seems more clearly related to the structural changes seen. The presence of flukes may not, in itself, be enough. In experimental animals, the concomitant administration of dimethylnitrosamine or N-nitrosodimethylamine and of cercariae of *Opisthorchis viverrini* was necessary to produce tumours (Thamavit *et al.*, 1978; Flavell and Lucas, 1982). Since the diet of Thais is rich in fermented fish products that contain substances transformable to nitrosamines, similar mechanisms may operate in man.

There are many other parasites that settle in the liver and bile ducts, notably *Schistosoma mansoni* and *S. japonicum* and *Fasciola hepatica*, but these are not related to neoplasia (Nakashima *et al.*, 1975).

Primary recurrent (pyogenic or Oriental) cholangitis is associated with intrahepatic bile duct carcinoma in China, Korea and Thailand, but this is probably due to the high prevalence of liver fluke infestation in these patients as discussed above.

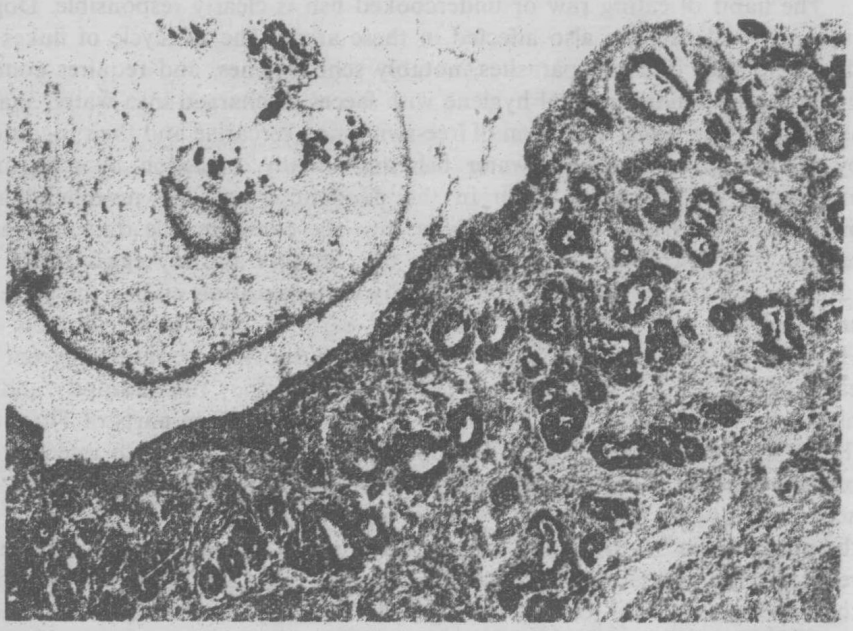

Fig. 1-1. A female *Clonorchis sinensis* fluke, containing eggs, lies free in the lumen of a bile duct (top left). The epithelial lining of the duct shows adenomatous hyperplasia (H & E, × 125).

Finally, it must be noted that diseases of bile ducts, including carcinomas, which are associated with liver fluke infestation can no longer be considered a purely Oriental problem. Schwartz (1986) reported a case of intrahepatic bile duct carcinoma (cholangiocarcinoma) in a Chinese immigrant whose liver was heavily infested with *Clonorchis sinensis*. He noted that over 500 000 South-East Asian refugees have been admitted to the USA since 1975 and estimated that at least a quarter of these are fluke carriers.

Chronic Inflammatory Bowel Disease

Biliary tract carcinoma is a rare complication of chronic inflammatory bowel disease and is associated almost exclusively with ulcerative colitis (Ritchie *et al.*, 1974; Wee *et al.*, 1985). A common preceding condition is peri-cholangitis of small, intrahepatic or sclerosing cholangitis of large, intrahepatic and extrahepatic bile ducts. These are now considered to be small and large duct variants of a single disease, primary sclerosing cholangitis (Wee and Ludwig, 1985). The tumours are more often extrahepatic than intrahepatic and carcinoma of the gall bladder also occurs. The risk in ulcerative colitis increases with duration of the disease, which is at least 10–15 years, and extent of colonic involvement, which is usually total. The overall risk has been

estimated to be 9–21 times of that of the rest of the population. Tumours may develop after total proctocolectomy: approximately one-third of patients developed cancer up to 8 years after surgery. Diagnosis of carcinoma may be difficult because the symptoms are similar to those of cholangitis.

Typhoid Carrier State

A six-fold increase of hepatobiliary cancer, not otherwise specified, was reported among 471 typhoid carriers over a matched control population of 942 non-carriers in New York City by Welton, Marr and Friedman (1979). It was suggested that this was due either to reflux of bile, altered and rendered carcinogenic by *Salmonella typhi*, from the gall bladder into the intrahepatic biliary tree or to the possible presence of the organisms in the liver.

Congenital Anomalies and Metabolic Disorders

It seems that almost any form of congenital anomaly of the biliary tree is associated with an increased risk of bile duct carcinoma. These include secondary biliary cirrhosis due to extrahepatic biliary atresia (Kulkarni and Beatty, 1977), long-standing choledochal cyst presenting in the second decade of life or later (Voyles *et al.*, 1983), congenital hepatic fibrosis (Daroca, Tuthill and Reed, 1975) with or without small bile duct hamartomas known as von Meyenburg complexes (Homer, White and Read, 1968) and solitary or multiple cysts (Bloustein and Silverberg, 1976; Imamura *et al.*, 1984). The most frequently reported congenital anomaly is congenital cystic dilatation of the bile ducts or Caroli's disease (Fig. 1-2) which can be considered to be a premalignant condition (Chaudhuri *et al.*, 1982; Dayton, Longmire and Tompkins, 1983). In some cases, the anatomical abnormality had resulted in stone formation and/or sepsis (Koga *et al.*, 1985) and some of the tumours which appeared subsequently were partly or wholly squamous.

Intrahepatic stone formation, however, is not always related to congenital bile duct anomalies or cysts and may rarely occur in primary Oriental and other forms of chronic cholangitis, with or without flukes, and be complicated by carcinoma (Chen *et al.*, 1984; Nakanuma *et al.*, 1985).

An interesting suggestion has been repeatedly made from Japan, most recently by Kimura *et al.* (1985), that many gall bladder carcinomas and, by inference, bile duct carcinomas arise in patients with an anomalous pancreaticobiliary ductal union which results in reflux of pancreatic juice up the biliary tree.

Bile duct carcinoma may rarely complicate an inborn error of metabolism such as familial cholestatic cirrhosis or Byler's disease, an enzyme deficiency i.e. of alpha-1-antitrypsin, or a genetic abnormality such as mucoviscidosis. The vast literature on the subject of congenital anomalies and metabolic disorders and tumours associated with them has been summarized recently by