Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968–1998


Abstract

Background—The age standardised mortality rate per 100 000 population for all causes of liver tumours (International Classification of Disease 9 (ICD-9) 155) has almost doubled in England and Wales during the period 1979–1996. We further analysed the mortality statistics to determine which anatomical subcategories were involved.

Methods—Mortality statistics for liver tumours of ICD-9 155, 156, and subcategories, and for tumours of the pancreas (ICD-9 157), in England and Wales were investigated from the Office for National Statistics, London, from 1968 to 1996 inclusive. Data for 1997 and 1998 were also available on intrahepatic cholangiocarcinomas.

Results—There has been a marked rise in age standardised mortality rates for intrahepatic cholangiocarcinoma. Since 1993, it represents the commonest recorded cause of liver tumour related death in England and Wales. This is evident in age groups older than 45 years. In contrast, mortality trends from other primary liver tumours, including hepatocellular carcinoma, were unremarkable.

Conclusions—The observed increase in mortality from intrahepatic cholangiocarcinoma may represent better case ascertainment and diagnosis due to improved diagnostic imaging, use of image guided biopsies, or increased use of ERCP. However, the trend started before ERCP was introduced nationally, mortality rates have continued to increase steadily thereafter, and there is no clear evidence that diagnostic transfers easily explain the findings. Alternatively, these observations may represent a true increase in intrahepatic bile duct tumours. Epidemiological studies are required to determine whether there is any geographical clustering of cases around the UK.

(Gut 2001;48:816–820)

Keywords: intrahepatic cholangiocarcinoma; age standardised mortality rates; age specific mortality rates

Studies from France, Italy, and the USA suggest that the incidence of hepatocellular carcinoma (HCC) is increasing,1 2 and this may be related to chronic hepatitis C virus (HCV) infection.1 4 Age standardised mortality rates (ASMR) for all causes of malignant liver tumours (International Classification of Disease 9 (ICD-9) 155) have increased from 1979 to 1994 in the UK, but unlike in Southern Europe, the ASMR for HCC has been reported to be relatively static over this time period while the ASMR for intrahepatic cholangiocarcinoma may have been increasing.3

We investigated ASMR and age specific mortality rates (ASpMR) for all liver tumours in England and Wales, starting in 1968, when comparable mortality records began, to determine when the rise in ASMR for intrahepatic cholangiocarcinoma first started and which age groups have primarily been affected.

Methods

Mortality data for 1968–1996 were obtained for the English and Welsh populations from the Office for National Statistics (ONS) in London. Information was requested on:

- ICD-9 155 (all malignant liver tumours)
- ICD-9 155.0 (primary liver tumours, mainly HCC)
- ICD-9 155.1 (intrahepatic cholangiocarcinoma)
- ICD-9 155.2 (histologically unspecified liver tumours)
- ICD-9 156 (all extrahepatic biliary system tumours)
- ICD-9 156.0 (gall bladder tumours)
- ICD-9 156.1 (tumours of the extrahepatic bile ducts)
- ICD-9 157 (pancreatic tumours).

The ICD-9 155.0 code contains information on all primary tumours of the hepatic parenchyma but is overwhelmingly composed of data on HCC. Mortality data, supplied in five year age bands, were considered to be an indicator of incidence because prognosis from liver cancer is poor. Additional mortality data for 1997–1998 were requested, once they had become available, for intrahepatic cholangiocarcinoma, the tumour of primary interest, as initial analysis indicated that the observed trends for this tumour warranted further up to date inspection.

Abbreviations used in this paper: ASMR, age standardised mortality rates; ASpMR, age specific mortality rates; ERCP, endoscopic retrograde cholangiopancreatography; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD-9, International Classification of Disease 9; ONS, Office for National Statistics; OPCS, Office of Population Censuses and Surveys; WHO, World Health Organization.
NUMBER OF DEATHS

The total number of deaths attributed to each ICD category of cancers was analysed by year and sex. No deaths before 1968 are included because coding changes between ICD-7 (1958–1967) and ICD-8 (1968–1978) make it impossible to accurately trace deaths attributed to a particular category earlier than this. Coding changes between ICD-8 and ICD-9 for the tumours under study seemed to be minor, although it is recognised that any change in coding can have an impact on mortality statistics. In our analysis, we mapped the change in code for “unspecified primary or secondary tumours of the liver” across ICD revisions from 197.8 to 155.2.

Two other notable changes to the collection and coding of deaths in England and Wales occurred in 1993 which may affect interpretation of trends in mortality. These include the move back by the Office of Population Censuses and Surveys (OPCS) to the internationally accepted interpretation of World Health Organization (WHO) rule 3, regarding the selection of the underlying cause of death, which was in operation before 1984. In addition, until 1992 it was standard procedure for the OPCS to apply to the person certifying the death for further information regarding the underlying cause of death when the conditions mentioned on the death certificate were vague. The use of such “medical enquiries” to help assign a more definite code to the underlying cause of death was discontinued in 1993.

AGE STANDARDISED MORTALITY RATES

ASMR per 100 000 population were calculated using direct standardisation with the European standard population as a reference population.

AGE SPECIFIC MORTALITY RATES

Initially, ASpMR per 100 000 of the population were analysed by five year age bands but given that tumours are much less common in the younger age groups and that treatment and management may differ between middle and very old age, these were aggregated into more clinically relevant age specific groups. The following age bands were therefore chosen: 20–44, 45–64, 65–74, and 75+.

Results

ALL LIVER TUMOURS

ASMR per 100 000 population for the combined causes of malignant liver tumours increased steadily in the period 1968–1996 from 1.29 to 1.93 in females and from 2.56 to 3.70 in males (fig 1A, B). Total numbers of deaths increased from 967 (396 females; 571 males) in 1968 to 1822 (770 females; 1052 males) in 1996 (table 1).

Primary liver tumours including hepatocellular carcinomas

Data on primary liver tumours revealed fluctuations in ASMR about a stable mean between 1968 and 1978 for both sexes. However, in 1979 there was a noticeable increase in ASMR for both males and females until 1992 (fig 1A, B). In 1993 there was a sharp decline in ASMR to levels more in common with those before 1979.

Intrahepatic cholangiocarcinoma

ASMR per 100 000 population for intrahepatic cholangiocarcinoma increased markedly for both sexes over the period 1968–1996 (fig 1A, B). There was a 15-fold increase in ASpMR per 100 000 population in ages 45 and above (fig 2A, B). The total number of deaths increased from 38 (17 females, 21 males) in 1968 to 736 (387 females, 349 males) in 1996.
This cancer now represents the commonest primary liver tumour in England and Wales, having overtaken hepatocellular carcinoma in 1993 (table 1). Additional data for 1997–1998 showed a further marked increase in mortality rates from the 1996 statistics. ASMR increased from 0.92 and 1.22 in 1996 to 1.12 and 1.37 in 1998 for females and males, respectively, bringing the total number of deaths in that year to 864.

Unspecified tumours of the liver

ASMR for liver tumours in this ICD category showed a small decrease overall, although there was a marked fall in ASMR from 1978 to 1993 in both sexes (fig 1A, B).

TUMOURS OF THE GALL BLADDER AND EXTRAHEPATIC BILIARY TREE

There was a steady decrease in ASMR between 1968 and 1996 (fig 1A, B). Between 1968 and 1978, the total number of deaths for men and women was relatively stable at approximately 700 per year for women and approximately 400 per year for men. Subsequently, the total number of deaths fell from 1043 in 1979 to 585 in 1996 (table 1).

Tumours of the gall bladder

Between 1968 and 1996, both ASMR and total number of deaths attributed to malignant neoplasm of the gall bladder decreased steadily. ASMR fell from 1.21 and 0.84 in 1968 to 0.55 and 0.30 in 1996 for females and males, respectively.

Tumours of the extrahepatic bile ducts

ASMR for malignant tumours of the extrahepatic bile duct fluctuated between 1968 and 1996 (fig 1A, B). Between 1968 and 1978, the total number of deaths for men and women was relatively stable at approximately 700 per year for women and approximately 400 per year for men. Subsequently, the total number of deaths fell from 1043 in 1979 to 585 in 1996 (table 1).

Figure 2 Age specific mortality rates per 100 000 population of England and Wales in (A) females and (B) males for intrahepatic cholangiocarcinoma (ICD-9 155.1).

### Table 1: Numbers of deaths by ICD-9 code in England and Wales 1968–1996

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Table 155, all malignant liver tumours; 1550, primary liver tumours (mainly hepatocellular carcinoma); 1551, intrahepatic cholangiocarcinoma; 1552, unspecified liver tumours; 156, tumours of the extrahepatic biliary tree and gall bladder; 1560, tumours of the gall bladder; 1561, extrahepatic cholangiocarcinomas; 157, pancreatic tumours.

F, female; M, male
Combined intrahepatic and extrahepatic cholangiocarcinoma (ICD-9 code 155.1 and 156.1)

The combined ASMR from all tumours of the biliary tract increased over the time period 1968–1996. The absolute number of deaths also increased from 466 (240 females, 226 males) in 1968 to 912 (493 females, 419 males) in 1996 (table 1).

1. Introduction

Cholangiocarcinoma, arising from the intrahepatic biliary tree, is much less common than HCC on a worldwide basis, but since 1979, after which they began to fall from 0.71 for males and 0.80 for males in 1980 to 0.23 in 1996 for both sexes.

2. Discussion

In England and Wales there has been a steady increase in mortality coded to intrahepatic cholangiocarcinoma. Although ASMR for extrahepatic cholangiocarcinoma have decreased, the increase in intrahepatic tumours outweighs this with a rise in ASMR and in absolute number of deaths for both these two ICD-9 categories combined. Cholangiocarcinoma, arising from the intrahepatic biliary tree, is much less common than HCC on a worldwide basis, but since 1993 this tumour is the commonest recorded cause of malignant liver tumour related death in England and Wales. In South East Asia and China, development of cholangiocarcinoma is mainly associated with liver flukes. In the West the aetiology is largely unknown although the obsolete radiological contrast agent throrotrust has been implicated in causing cholangiocarcinoma. Smoking and alcohol have also been implicated but the evidence is weak. Primary sclerosing cholangitis is the commonest predisposing factor in the UK but it is associated with only a minority of cases.

The steadily increasing ASMR for intrahepatic cholangiocarcinoma may represent an artefactual trend, introduced into the mortality figures by improvement in diagnosis (case ascertainment) resulting from better imaging techniques, by changes in coding practices, or from misclassification of ICD coding (diagnostic transfer). It is also possible that this trend represents a real increase in mortality from this tumour.

Better ascertainment from improved diagnostic imaging, use of image guided biopsies, and from the national availability of techniques such as endoscopic retrograde cholangiopancreatography (ERCP) could account for these observations. ERCP was first available in the UK in the late 1970s after the rise in ASMR started, and became available in most UK hospitals in the mid 1980s. The increased mortality rates have continued after the initial endoscopic learning curve and the general availability of the technique should have led to an expected plateau in these values. It is therefore unlikely that our observations on intrahepatic cholangiocarcinoma are solely caused by an improvement in diagnosis from ERCP. Furthermore, it is the distally located extrahepatic bile duct tumours, total numbers of deaths from which have actually decreased, that are more easily visualised with ERCP, rather than the intrahepatic tumours which often involve much smaller bile ducts. The definitive diagnosis of intrahepatic bile duct tumours is histological, and in a large proportion of cases this is made from tissue obtained at surgery or at post mortem. However, this is dependent on the experience of the local pathologist and therefore there may be interobserver differences in interpretation. This factor in itself would not account for the year-on-year rise in intrahepatic cholangiocarcinoma that we have reported.

There have been a few changes to the collection and coding of mortality data from 1968 to 1998 which could potentially render our findings artefactual. However, no discernible “steps” in mortality trends for intrahepatic cholangiocarcinoma have been introduced by changes in coding practices. This is in stark contrast with the mortality trends for primary liver tumours which changed from ICD-9 to ICD-10 and for unspecified liver tumours, which provide clear illustrations of the impact of coding changes. In 1979 when ICD-9 was first introduced, subtle changes in the number and type of diseases which fed into both these categories of tumours led to an increase in primary liver tumours and a simultaneous decline in unspecified liver tumours. In 1993, both the rule 3 coding change and the death certificate changes introduced further artefact, with the latter having the dominant effect on these tumour types. Prior to 1993, it was routine practice for OPCS to obtain follow up information from the certifying doctor about the cause of death, approximately six weeks after the initial death certification. In many instances, information that became available with post mortem confirmed or changed the cause of death and this was rectified with this process. With the absence of follow up medical enquiries on death certificates from 1993, there was an increase in the number of deaths assigned to categories of less specific causes. The sudden change in mortality statistics between 1979 and 1993 for primary and unspecified liver tumours are thus artefactual and any examination of time trends for these tumours is limited to cautious comparisons of data from before 1979 and after 1993.

Diagnostic transfer from tumours of the gall bladder and extrahepatic biliary tree to intrahepatic cholangiocarcinomas is an alternative explanation for our findings but the increase in ASMR and absolute number of deaths from intrahepatic tumours outweighed the decrease in the other malignancies. Simple diagnostic transfer is therefore unlikely. Diagnostic transfer may also occur between intrahepatic cholangiocarcinoma and undifferentiated metastatic adenocarcinoma in the liver but it is probable that histologically ill defined tumours...
tend to be reported in the unspecified category than reported specifically as intrahepatic cholangiocarcinoma. Diagnostic transfer from pancreas to intrahepatic cholangiocarcinoma could account for the small decrease in ASMR for pancreatic tumours and the marked increase in ASMR for intrahepatic bile duct tumours but this is unlikely because it is unusual to confuse the two diagnoses from an anatomical standpoint.

Another explanation for the steady rise in ASMR for intrahepatic cholangiocarcinoma between 1968 and 1998 is a true increase in incidence of this tumour. The reason intrahepatic cholangiocarcinomas have increased in place of tumours of the rest of the biliary tract may be because of the larger surface area of the intrahepatic biliary tree compared with that of the gall bladder and extrahepatic biliary tree, allowing greater exposure to potential carcinogens, which may have been more prevalent over the past 30 years. Furthermore, intrahepatic bile ducts contain the majority of actively dividing cholangiocytes, which would make malignancies of this part of the biliary tree more likely. If improved imaging and the availability of ERCP has led to better case ascertainment, intrahepatic tumours may be detected at an earlier stage, before invasion of the extrahepatic biliary tree has occurred. However, the absolute rise in both ASMR and total number of deaths from the combined ICD-9 categories for intra- and extrahepatic bile duct tumours is also further evidence that the observed trend may, in part, be real rather than apparent.

The oral contraceptive pill has also been implicated in the development of cholangiocarcinoma, although case control studies have failed to substantiate an increased risk. The time period when oral contraceptives became widely available in England and Wales and the age groups involved with increased mortality from intrahepatic cholangiocarcinoma do not entirely match. Furthermore, this trend in mortality statistics is also seen in men, making the “pill” an unlikely candidate as the sole cause of this phenomenon, although there are many chemicals which could potentially have entered the food chain which have oestrogenic properties. We have shown a dramatic increase in ASMR and ASpMR for intrahepatic cholangiocarcinoma from 1968 to 1998 in England and Wales. Epidemiological studies are required to determine whether there is any geographical clustering of cases around the UK and whether any clusters can be related to occupational exposure. Further studies are needed to compare the observed trend in mortality statistics with that for other countries. Given that current treatment outcomes for cholangiocarcinoma are poor, such studies may lead to a better understanding of the aetiology of these tumours and institution of appropriate preventative measures.

Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968–1998

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Pancreas and biliary tract (1949)

Notes
LETTERS TO THE EDITOR

Ulcerative colitis is more strongly linked to chromosome 12 than Crohn's disease

Editor,—Lesage and colleagues reported failure to detect linkage to the IBD2 locus on chromosome 12 in a panel of 95 families containing more than two cases of inflammatory bowel disease, and mixed families (including Crohn's disease (CD), ulcerative colitis (UC) and mixed families) with a locus (called IBD2) located on chromosome 12. In a recently published study in the journal, we failed to demonstrate a positive linkage to chromosome 12 using an independent panel of 95 CD multiplex families (Gut 2000;47:787–91). This result was different from the previous report and we proposed several explanations for the observed discrepancy.

The first explanation may be lack of statistical power in our replication study. We investigated a similar number of affected pairs (n=157, all CD pairs) compared with the first linkage analysis (n=186, 81 CD pairs, 64 UC pairs, and 43 mixed pairs). Because linkage tests may exhibit large fluctuations when applied to family sets of similar size for complex genetic disorders, we tested if a gene with a lod score of 2 was compatible with our observation and we were able to reject the hypothesis. We thus concluded that genetic heterogeneity may occur in Caucasian family panels for IBD susceptibility.

Parkes et al have recently demonstrated that this genetic heterogeneity may be related to sporadic susceptibility model. UC is more tightly linked to IBD2 than CD. This study confirms our conclusion that there is genetic heterogeneity in familial IBD. As expected, this heterogeneity may be in part reduced by an adequate genetic classification scheme from a methodological point of view, Parkes' report demonstrates that working on homogeneous genetic groups may be preferable to pooling several phenotypes for linkage studies. Considering CD and UC families as separate subgroups, Parkes et al suggested that the IBD2 locus has only a marginal role in CD susceptibility. This conclusion is in complete accordance with our demonstration that the relative risk attributable to IBD2 in CD multiplex families is low.

In practice, it is difficult to know what is the weight of this IBD2 locus in both CD and UC. A line of evidence, including the above mentioned reports, and a large collaborative work performed on more than 600 multiplex IBD families clearly suggests that the role of the IBD2 locus is weak in CD families. In contrast, its role in UC is difficult to estimate to date. In their recent work, Parkes et al pooled previously investigated families from UK and US panels. Because these families were a priori known to be positively linked to IBD2, this study provides a biased estimate of the risk attributable to IBD2. Other works using unselected family panels are required to answer this question.

Interestingly, the IBD1 locus has been postulated to play a major role in CD and to be less important in UC families. In this context, it would be postulated that IBD1 is a CD susceptibility locus and IBD2 is a UC gene. Some truth may reside in this assertion. However, a line of evidence including analysis of mixed families suggests that CD and UC have common familial risk factors and does not allow a simple dichotomous classification of UC and CD genes. Many additional steps, including gene identification, are now required before we can understand the underlying genetic model for IBD which will certainly be confirmed as a complex genetic disorder.

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Reply

Editor,—In 1996, Satsangi et al reported a positive linkage between inflammatory bowel disease (IBD) multiplex families (including Crohn's disease (CD), ulcerative colitis (UC) and mixed families) with a locus (called IBD2) located on chromosome 12. The attributable risk of sibling recombination (s) of this IBD2 locus was calculated to be 2. In a recently published study in the journal, we failed to demonstrate a positive linkage on chromosome 12 using an independent panel of 95 CD multiplex families (Gut 2000;47:787–91). This result was different from the previous report and we proposed several explanations for the observed discrepancy.

The first explanation may be lack of statistical power in our replication study. We investigated a similar number of affected relatives (n=157, all CD pairs) compared with the first linkage analysis (n=186, 81 CD pairs, 64 UC pairs, and 43 mixed pairs). Because linkage tests may exhibit large fluctuations when applied to family sets of similar size for complex genetic disorders, we tested if a gene with a lod score of 2 was compatible with our observation and we were able to reject the hypothesis. We thus concluded that genetic heterogeneity may occur in Caucasian family panels for IBD susceptibility.

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Intestinal permeability: the cellobiosemannitol test

Editor,—I should like to bring to your attention a conceptual error in the paper by Daniele et al (Gut 2001;48:28–33) regarding the cellobiosemannitol test. The authors suggest that improvement in the cellobiose/mananitol ratio reflects improvement in permeability from the use of oral glutamine. However, only mannitol excretion improved significantly with glutamine; cellobiose excretion remained unchanged. As the authors explain in their methods section, it is the increased cellobiose excretion that reflects increased permeability, not the decrement in mannitol excretion. Therefore, modifications in sugar transport induced by 5-fluorouracil (5-FU) reflected only an absorptive, not a permeability, defect. The decrement in mannitol excretion parallels the decrement in α-xylose excretion, probably reflecting decreased transcellular passage of the test sugars induced by 5-FU and improved with glutamine.

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Reply
Editor,—I thank Dr Craig for raising this issue but I do not see any conceptual error. The apparent inconsistency that he points out in our paper (Gut 2001;48:28–33) is due to the controversy surrounding transcellular permeation of mannitol, as well as of other monosaccharides. While transcellular permeation of mannitol is well known, its use for osmotic shrinkage of membrane vesicles and as an extracellular fluid marker suggests that, at least in part, mannitol diffuses through the intercellular tight junctions. Thus it seems justified talking of permeability for mannitol. One of the reasons for its use in combination with cellobiose is the different molecular sizes of the two probes: the smaller size of mannitol allows its passage through the small tight junctions of the villi while the larger cellobiose passes through the larger tight junctions of the crypts.

Finally, we did find an increase in cellobiose excretion after fluorouracil (5-FU) that was in part prevented by oral glutamine. Although this difference did not reach statistical significance, overall the data indicate increased intestinal permeability after 5-FU, partially prevented by oral glutamine.

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Evaluation of the role of CFTR in alcohol related pancreatic disease

Editor,—In up to 30% of patients with idiopathic pancreatitis (IP) a mutation of at least one or both alleles of the cystic fibrosis transmembrane conductance regulator (CFTR) gene can be identified. The study by Malats et al (Gut 2001;48:70–4) addressed the question of whether CFTR mutations, possibly together with environmental factors such as alcohol, may be associated with chronic pancreatitis or pancreatic cancer. The vast majority of the pancreatic patients (86.4%) investigated by Malats et al were diagnosed as having alcoholic pancreatitis (AP), and 75.4% of the cancer patients were daily drinkers. The authors found no statistically significant difference in the prevalence of delta-F508 (0%, 2.4%) and the 5T allele (10.5% 5.5%) in the AP or cancer groups compared with the expected prevalence in the general population. The lack of a positive association of both delta-F508 and the 5T allele with AP is neither surprising nor argues against involvement of CFTR variations in the development of AP, considering the following.

In cystic fibrosis (CF), the degree of correlation between CFTR genotype and CF phenotype varies between clinical components but is highest for pancreatic involvement. CFTR mutations can simplify be divided into “severe” and “mild” mutations. The degree to which mutations impair CFTR function. Approximately 85% of CF patients suffer from pancreatic insufficiency (PI) while ~15% are pancreatic sufficient (PS). Generally patients with two “severe” mutations are associated with at least one “mild” mutation (fig 1). In CF, pancreatic insufficiency is seen rather frequently in PS patients but not in PI patients. Today, more than 850 CF mutations have been reported to the CF Consortium (http://www.genet.sickkids.on.ca/cftr). The deletion delta-F508, accounting for about 70% of mutant CF alleles worldwide and approximately 53% in Spain, studied by Malats et al, is responsible for severe functional loss of CFTR function. Three additional studies on the prevalence of an abnormal CFTR allele in AP have been published as full papers. Pooling these four studies, one or two mutant CFTR alleles were detected in 9/217 (4.1%) patients with AP. But the detection rate varies between 0% and 8.5% depending on the sensitivity of the screening method to detect an abnormal CF allele in the corresponding population (53–94%). None of the studies revealed a positive association of the 5T allele with IP or AP. Compared with the general population, delta-F508 was significantly more frequent in patients with an abnormal CFTR allele, who are more permeable to alcohol, and as an extracellular fluid volume marker the cellobiose/mannitol test. The authors suggest that, at least in part, mannitol ratio reflects improvement in permeability for mannitol. One of the reasons for its use in combination with cellobiose is the different molecular sizes of the two probes: the smaller size of mannitol allows its passage through the small tight junctions of the villi while the larger cellobiose passes through the larger tight junctions of the crypts.

Finally, we did find an increase in cellobiose excretion after fluorouracil (5-FU) that was in part prevented by oral glutamine. Although this difference did not reach statistical significance, overall the data indicate increased intestinal permeability after 5-FU, partially prevented by oral glutamine.

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Figure 1 Disease manifestation according to residual cystic fibrosis transmembrane conductance regulator (CFTR) function as a result of the combination of severe or mild CFTR genotype. CF; cystic fibrosis; PS; pancreatic sufficiency; PI; pancreatic insufficiency; CBAVD, congenital absence of the vas deferens.

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British and US Caucasian, but not in Australian or Spanish AP patients.

Up to now no environmental or genetic cofactor was identified in patients with mutant CFTR alleles associated IP, suggesting that impairment of CFTR function alone may be enough to induce pancreatitis. On the other hand it may be speculated that patients with an abnormal CFTR allele, who develop pancreatitis in conjunction with alcohol abuse, may be characterised by a higher residual CFTR function, which by itself is not capable of inducing pancreatitis.

Therefore, to delineate the genetic background of pancreatic disease in AP it seems to be more appropriate to investigate the prevalence of uncommon mild variants (“atypical mutations”) in large cohorts of AP patients than to test for the more common (“severe, typical”) mutations of the CFTR gene in small patient groups. It has to be considered that the test kits for CFTR mutations often used in routine screening are usually designed to detect the more severe CF mutations. This would result in missing a substantial number of patients with these mutations, as suggested by preliminary data on more comprehensive genetic testing in patients with ICP.*

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Reply
Editor.—We agree with the view of Ockenga et al that from an ideal research perspective a complete analysis of the cystic fibrosis transmembrane conductance regulator (CFTR) gene should be performed for cases of pancreatitis before a definitive statement on
the role of this gene in chronic pancreatitis can be made. Moreover, it is well known that 18–30% of patients with CFTR related disorders (congenital bilateral absence of the vas deferens and bronchiectasis) have only one CFTR mutated allele. Thus, despite our study being based on only the two most common CFTR mutations (F508del and 5T), these two alterations should suffice to rule out or confirm a potential role of CFTR in patients with chronic pancreatic diseases. Furthermore, complete analysis of CFTR in the general population has led to the identification of amino acid variants of yet unknown functional significance in about 10% of subjects. It is highly likely that complete analysis of CFTR would render a large number of amino acid changes of uncertain clinical and functional consequences, as it has been shown for patients with asthma. As we proposed in our paper (Gut 2001;48:70–4), only the design of large studies specifically addressing these issues in target and adequate control populations and a comprehensive molecular analysis of CFTR will answer the question on the role of this gene in chronic pancreatic disease.

We first described the strong correlation between obesity and serum TNF-α in 1998. Adipose tissue synthesises a number of proinflammatory cytokines. The negative correlation found in the Adelaide study is surprising given the findings in larger studies of non-NASH subjects, and may be due to the small study numbers and not correcting for modest alcohol intake. Alcohol consumption is considered a risk factor for the development and progression of liver disease in patients with fatty livers. We previously showed a strong negative correlation between any alcohol consumption and serum TNF-α levels in a general population sample. Moderate consumption is known to suppress TNF-α production by monocytes, probably by suppressing post-transcriptional TNF-α production. Furthermore, alcohol also has effects on TNF-α function mediated via high density lipoprotein (HDL). Alcohol enhances HDL levels by stimulating lipoprotein lipase activity in adipose tissue. HDL not only inhibits TNF-α release from macrophages but also protects certain cells against TNF-α induced damage.

If TNF-α is important, then modest alcohol intake should be protective via suppression of TNF-α. This raises the possibility that TNF-α is not important in early steatohepatitis. In defining patients with NASH, alcohol consumption must be rigorously excluded. In the Adelaide study, 10 of 22 patients drank up to 20 g of alcohol per day; however, even modest amounts of alcohol have effects on TNF-α levels and function.

The known interaction between alcohol and obesity in the pathogenesis of fatty liver and steatohepatitis suggests that investigators must look to factors other than TNF-α in studying the early pathogenesis of this condition. In the same way that altered cytokine homeostasis has been implicated in alcoholic liver disease, NASH is probably caused by changes to more than one proinflammatory cytokine. Interleukin 6 (IL-6) is a proinflammatory cytokine, a hepatocyte stimulator, and inhibitor of hepatic apoptosis. It has been suggested that hepatic steatosis is due to the rate of hepatocyte apoptosis becoming insufficient to match the rate of hepatocyte proliferation. IL-6 induced liver regeneration may render the liver more susceptible to the effects of other insults. Unlike TNF-α, serum IL-6 exhibits a positive correlation with both obesity and alcohol intake (fig 1). So far IL-6 has not been studied in the aetiology of NASH.

Future studies examining the link between TNF-α and NASH will need to rigorously control for alcohol consumption and assess many other aspects of the inflammatory cytokine network.

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Reply

Editor,—Our recent paper found increased small bowel bacterial overgrowth (50% versus 22%) and twofold increased systemic levels of tumour necrosis factor α (TNF-α) in patients with non-alcoholic steatohepatitis (NASH) compared with control age and sex matched subjects (Gut 2001;48:206–11). Poullis and Mendall question the finding of elevated TNF-α levels in blood in NASH subjects and quote their own work of elevated TNF-α levels in obese control subjects.1 There was no correlation between TNF-α levels and obesity in our study whereas their study showed a correlation with obesity. How can this be explained? The question comes down to whether TNF-α is being produced predominantly in adipose tissue or in the liver, and which of these contributes to elevated systemic levels. At the moment this cannot be resolved. TNF-α will need to be investigated in liver biopsies and TNF-α levels sampled from the hepatic vein (not entirely impossible). The same should be done in animal models of obesity. In the meantime, it would be important to ascertain what proportion of obese patients have unrecognised NASH and whether this could explain the elevated TNF-α levels in obesity. Several lines of evidence suggest TNF-α is upregulated in the liver in alcoholic liver disease and presumably this is reflected in serum levels. We doubt therefore whether a low (<20 g/day) consumption of alcohol reduces systemic TNF-α levels but this could be formally studied. We have re-examined our data and found that there is no difference in mean TNF-α levels between those who...
reported no alcohol consumption and those who drank alcohol. Finally, we would also comment from our recent work that shows that the C\textsuperscript{13}D-xylene/H\textsubscript{2}-CH\textsubscript{4} breath test is only positive in 60–69% of cases of small bowel bacterial overgrowth, mostly because it depends on bacterial overgrowth being present on the day of testing. Thus small bowel overgrowth may have contributed even more to NAS\textsubscript{H} than indicated in our paper.

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This book is basically divided into three parts: in the first 14 chapters the relevant anatomy and physiology of nausea and vomiting, various research methodologies, therapeutics, relevant neuropptides, and the economic impact of nausea and vomiting are covered. Next there are 13 chapters on “hands on” advice for diagnosing and treating the patient with nausea and vomiting. Finally, the last chapter in an excellent and extensive essay on nausea/vomiting as an evolutionary response of the ancient reptilian brain. The reptilian brain appears to respond to an increasing number of nauseating precipitants created by our modern lifestyles, technologies, and therapeutic, as well as specific diseases/disorders. Why is this?

The authors raise many provocative issues. They reject the simplistic notion that nausea and vomiting are regulated solely as a response to a putative ingestion of toxic substances. This time honoured concept simply does not reflect the many situations where nausea and vomiting occur in the absence of toxic ingestants. Ofactory system stimuli are discussed in detail with regards to nausea and vomiting during pregnancy. The authors review an interesting concept that relates nausea and vomiting and gravity, as gravitational forces affect the basic organisation of brain function. Refreshing ideas and perspectives on nausea and vomiting are offered that encompass philosophy and psychological viewpoints, as well as physiology and pharmacology.

Nausea is more debilitating than vomiting. The authors stress that nausea should be clearly separated from vomiting when studying pathophysiological mechanisms and developing therapies. Indeed, vomiting is the cure for nausea (at least temporarily)! Nausea is an “early warning system” evoked as the organism attempts to maintain homeostasis in response to the stimulus. Nausea/Vomiting is described as an “accident” of cascading stimuli that ultimately overwhelm homeostasis and the inhibitory circuits that prevent the uncontrollable and potentially injurious vomiting reflex.

Gastroenterologists are not the only medical providers dealing with the problems of nausea and vomiting. “Nausea is in the air; nausea is everywhere” is a phrase I often use when lecturing about the multidisciplinary problem of nausea and vomiting. The second major portion of the book incorporates 18 chapters in which a practical approach to the diagnosis and treatment of nausea and vomiting is described for many medical and surgical specialties. From allergy and immunology to gastroenterology, oncology, surgery, and sports and space medicine these chapters are an introduction to the treatment of nausea and vomiting by various specialists. These chapters are a bit uneven in their thoroughness and somewhat redundant in that each specialty ultimately uses similar drugs and comfort techniques for their patients. The tremendous lack of progress in the therapy for nausea and vomiting makes this area an open field for drug and non-drug development.

The final chapter is an extensive essay on nausea and vomiting that encompasses stimulating paragraphs that are well worth reading for any student of nausea and/or vomiting. Topics range from the adaptive purpose of nausea as a warning sign of ongoing problems in the internal/external environment, as marshalling social support for the sufferer, and as a powerful stimulus for problem solving to redirect these symptoms in the future.

I highly recommend this book as thoughtful and thought provoking reading for anyone interested in the common and sometimes debilitating symptoms of nausea and vomiting. The authors provide excellent reviews and new insights that are now necessary to consider in the fight against nausea and vomiting.

K KOCH

www.gutjnl.com

Would I feel tempted to buy this book? At £12.00 it is a give away price and an excellent buy. It provides an up to date and easily read guide to our present understanding of the cause, diagnosis, and management of Crohn’s disease and ulcerative colitis. It certainly provides an authoritative handbook for specialist registrars or even concerned patients. Its one weakness lies in the absence of references— but within 100 pages could one realistically expect to achieve this? Its role as a handbook for a consultant is less clear. Most of the information it contains should be already known to him or her, but it certainly could refresh that knowledge.

Inflammatory bowel disease is laid out in an attractive format with clear subtitles, useful summary tables, and a good range of illustrations. The impact of inflammatory bowel disease on aspects of life such as fertility, sexual relations, education, employment, and the consequences of the disease in childhood are dealt with in a limited way. The growing role of the specialist nurse in counselling and support is not considered in this book, although it could provide useful background reading for anyone working in such a role.

I was particularly impressed by the inclusion of such esoteric treatments as arsenic suppositories in the text although this was omitted from the index. Remicade was also absent from the index but dealt with in the text. In future editions the index could be strengthened by a more uniform inclusion of key terms. Another useful innovation could be the listing of reliable web sites.

With the growth of expensive, lengthy, but definitive textbooks that are almost by definition out of date at the time of publication, there is a clear need for cheap authoritative works that will have a relatively short shelf life and can be quickly revised or replaced. The philosophy behind the Health Press gives hope that they may be able to fill this important niche in the medical book market. Critical to this approach is the need for low cost.

J F MAYBERRY


We are in the throes of a revolution in the printing world, the ramifications of which cannot be accurately foreseen but are certainly as likely to have as dramatic effect on global culture as did Johann Gutenberg’s invention of printing in the 15th century. We should all be pleased to see that the medium of a textbook just cannot be the way of the future for this sort of book. As much of the neologisms in the IT language, multimedia is a fairly ghastly word, nevertheless one just feels there ought to be a CD or DVD to go with the book.

Whether anybody will be publishing books like this in five years time is anyone’s guess—but I wouldn’t bet on it. Doubtless trees will be happier but in any case the present publishers proudly in a preface that their policy is “to use paper manufactured from sustainable forests”. Jolly good of them too!

I FORGACS

CORRECTIONS

An error occurred in the Science @Sert article by Playford RJ (Gut 2001;48:594–5). The text and reference 1 should refer to the author “Kinzler” and not “Kinzlker”. Professor Playford apologises for the incorrect spelling. The authors of Gut 2001;48:816–20 have notified the journal of a computational error they made in figure 2. The correct figure is printed here. The one line of text that describes the figure, under the heading “intrahepatic cholangiocarcinoma” on p817, should now read, “There was, on average, a 12-fold increase in AspMR per 100 000 population in ages 45 and above, with larger increases at older ages and in women (fig 2A, B)”. The authors apologise for this error, and wish to point out that all the rest of the data are correct, and this does not change the findings reported upon in the paper or the interpretation.

NOTES

Sir Francis Avery Jones British Society of Gastroenterology Research Award 2002

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2002 Award. Applications (TWENTY COPIES) should include:

• A manuscript (2 A4 pages ONLY) describing the work conducted
• A bibliography of relevant personal publications
• An outline of the proposed content of the lecture, including title
• A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 2001 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Birmingham in

Figure 2 Age specific mortality rates per 100 000 population in England and Wales in (A) females and (B) males for intraduodenal cholangiocarcinoma.
March 2002. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2001.

Hoppkins Endscopy Prize 2002
Applications are invited by the Endoscopy Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2002 Award. Applications (TEN COPIES) should include:
- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

An applicant need not be a member of the Society. The recipient will be required to deliver a 20 minute lecture at the Annual meeting of the Society in Glasgow in March 2002. Applications (TEN COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2001.

Falk Symposium No 123: VI International Symposium on Inflammatory Bowel Diseases
This Falk Symposium will be held on 3–5 September 2001 in Istanbul, Turkey. Further information: Falk Foundation e.V. - Congress Division, Leinenweberstr. 5, PO Box 6529, D-79041 Freiburg, Germany. Tel: +49 761 15 14 0; fax: +49 761 15 14 359; email: symposia@falkfoundation.de

Falk Symposium No 124: Medical Imaging in Gastroenterology and Hepatology
This Falk Symposium will be held on 28–29 September 2001 in Hannover, Germany. Further information: see Falk Symposium No 123 above.

9th Asian Conference on Diarrheal Diseases and Nutrition
This meeting will be held on 28–30 September 2001 in New Delhi, India. The organisers hope the meeting will promote meaningful and effective collaboration among individuals/institutions towards control of the major health problems in Asia, particularly those affecting women and children. Further information: Professor M K Bhan, Coordinator, Centre for Diarrheal Disease and Nutrition Research, All India Institute of Medical Sciences, New Delhi. Tel: +91 11 6963822; fax: +91 11 6862662; email: ascodd2001@rediffmail.com

VI Congress of the International Xenotransplantation Association
This congress will be held on 29 September to 3 October 2001 in Chicago, USA. Further information: Felicissimo & Associates Inc., 205 Viger Avenue West, Suite 201, Montreal, Quebec, Canada H2Z 1G2. Tel: +1 514 874 1998; fax: +1 514 874 1580; email: info@ixa2001chicago.com; website: www.ixa2001chicago.com

Falk Symposium No 125: Cytokines in Liver Injury and Repair
This Falk Symposium will be held on 30 September to 1 October 2001 in Hannover, Germany. Further information: see Falk Symposium No 123 above.

Falk Symposium No 126: Hepatocyte Transplantation
This Falk Symposium will be held on 2–3 October 2001 in Hannover, Germany. Further information: see Falk Symposium No 123 above.

EASL Single Topic Conference
The EASL Single Topic Conference “Liver fibrosis: from basic science to clinical targets” will be held on 12–13 October 2001 in Florence, Italy. Organisers: Massimo Pinzani (University of Florence) and Detlef Schuppan (University of Erlangen-Nuernberg). The aim of the conference is to provide the latest information on this key area of hepatology and to translate the current knowledge into clinical terms. It is directed at both the expert in the field and the general hepatologist. Further information: Massimo Pinzani, Dipartimento di Medicina Interna, Università degli Studi di Firenze, Viale GB Morgagni, 85, I-50134 Firenze, Italy. Tel: +39 055 4277845; fax: +39 39 055 417123; email: m.pinzani@dcf.unifi.it

Lecture Course in Coloproctology
This course will be held on 15–17 October 2001 in Harrow, UK. Professor Russell Stitz from Australia will be the Sir Alan Parks Visiting Professor and, for the first time, there will be a Sir Francis Avery Jones Visiting Professor, which will be Professor Paul Rutgeerts from Belgium. Further information: The Administrator, St Mark’s Academic Institute, St Mark’s Hospital, Northwick Park, Harrow, Middx, HA1 3UJ, UK. Tel: +44 (0)20 8235 4046; fax: +44 (0)20 8235 4039; email: stmarks@ic.ac.uk; website: www.stmarkshospital.org.uk

International Symposium on Hyperammonemia, Liver Failure and Hepatic Encephalopathy
This symposium will be held on 20–22 October 2001 in Valencia, Spain. Further information: Cátedra Santiago Grisolía, Fundación Museu de les Ciències Príncep Felipe, Ciutat de les Arts i les Ciències, Avda. Institut Obrero, s/n, 46013 Valencia, Spain. Tel: +34 96 197 44 66; fax: +34 96 197 44 70; email: catedrasc@cac.es

ICGH-2: The Second Iranian Congress of Gastroenterology and Hepatology
The main Iranian meeting of gastroenterologists and researchers in this field will be held on 27 October to 1 November 2001 in Tehran, Iran. Further information: Dr Shahin Merat, Digestive Diseases Research Center, Shariati Hospital, N. Kargar Street, Tehran 14114, Iran. Tel: +98 911 717 3966; fax: +98 21 225 3653; email: merat@ams.ac.ir; website: www.ams.ac.ir/igch.

Falk Symposium No 127: Autoimmune Diseases in Pediatric Gastroenterology
This Falk Symposium will be held on 8–9 November 2001 in Basel, Switzerland. Further information: see Falk Symposium No 123 above.

42nd Annual Conference of the Indian Society of Gastroenterology
This conference will be held on 23–29 November 2001 in Lucknow, India. The programme includes two pre-conference symposia (on gastrointestinal motility and scientific communication, on 23 November), a one day postgraduate course or CME (24 November), and an endoscopy workshop (28–29 November). Further information: Dr S R Naik, Department of Gastroenterology, SGPGI, Lucknow 226014, India. Tel: +91 522 440700 or 440800, ext 2400; fax: +91 522 440078 or 44007; website: www.sgpgi.ac.in/conf/igsg2001.html

41st St Andrew's Day Festival Symposium on Therapeutics
This will be held on 6–7 December 2001 in Edinburgh, UK. Further information: Ms Eileen Strawn, Symposium Co-ordinator. Tel: +44 (0)131 225 7324; fax: +44 (0)131 220 4393; email: e.strawn@rcpe.ac.uk; website: www.rcpe.ac.uk

14th Intensive European Course of Digestive Endoscopy
This course will be held on 17–18 December 2001 in Strasbourg, France. Further information: Michele Centonze Conseil, 6 bis rue des Cendriers, 75020 Paris, France. Tel: +33 1 44 62 68 80; fax: +33 1 43 49 68 88; email: mail@m-centonze-conseil.com