Parenchymal liver disease in the elderly

Introduction
Until recently, the subject of parenchymal liver disease presenting in elderly patients had received little specific attention. Many studies have examined changes in morphology and function in the aging liver, initially in rodents and subsequently in humans. In summary, there are no age specific alterations in conventional liver biochemistry (serum bilirubin, serum aminotransferases, hepatic alkaline phosphatase, and other liver blood tests) but a number of dynamic measurements of liver function do decline from early adulthood to senescence.1 Liver size, liver blood flow and liver perfusion decline between the third and tenth decades by 30–40%.2 Most reflections of dynamic liver function—galactose elimination, aminopyrine demethylation, or caffeine clearance—fall pari passu with the reduction in liver volume and blood flow.3–5 Conceivably, some specific liver functions—for example, hepatic nitrogen clearance, are independently impaired, in this case by up to 50% with advancing age.6 It is probably in the area of liver regeneration, however, that reduction in functional capacity of the liver is most apparent and important. A number of studies have suggested increased susceptibility to stress insult in aged experimental animals6–8 but there are no comparable human studies. A clue to the possible mechanism of impaired liver cell proliferation with advanced age has been provided by the demonstration of an age related decline in mitogen activated protein kinase activity in epidermal growth factor stimulated rat hepatocytes.9 The above factors, combined with the influence of lifetime variation in diet, alcohol consumption and smoking, nutritional status, co-existent disease, and genetic influences, form the background for the age related features of parenchymal liver disease described in this article.

Although there are no specific age related diseases of the liver, it is increasingly recognised that consideration of special features and differences between old and young are important in respect of clinical liver disease and its management. The modern paradigm has been in the advance of liver transplantation which is now regularly performed in patients in their eighth and, very exceptionally, ninth decade.10 This review selects a few areas in which understanding of liver disease in old age, its epidemiology, clinical features, and treatment, have altered in recent years.

Viral hepatitis
HEPATITIS A
Although hepatitis A is rare in patients over 65 years of age, even in affluent Western populations, the ratio of deaths to notifications of the disease rises very dramatically with advancing age. In a study from the United Kingdom, the ratio of deaths to notifications rose from 7 per 10 000 persons aged 15 to 24, to more than 400 per 10 000 in those over 65.11 This study also reported that if fulminant hepatic failure developed, then increased age was an adverse prognostic marker. This observation is true regardless of the cause of fulminant hepatic failure as several studies have shown that age is an independent prognostic variable. Since hepatitis A vaccination is readily available, and with increased travel to areas of high endemcity, vaccination of elderly travellers to these regions is strongly advised, although the effectiveness of the vaccine has not been specifically tested in this age group.

HEPATITIS B
Although acute hepatitis B is rare in the elderly population, sporadic cases and very rarely outbreaks may occur. The disease is more cholestatic and one recent report of an outbreak of hepatitis B in an old people's home reported a resultant carrier rate of 59%.12 Hepatitis B vaccination produces a lower antibody response with advancing age, possibly due to a lack of antibody producing B cells.13 None the less, elderly travellers to areas of high endemcity of hepatitis B should be vaccinated. One recent French study of patients over 65 (the vast majority in their 80s) admitted to acute elderly care wards, rehabilitation wards or nursing homes suggested that the prevalence of previous exposure to hepatitis B virus (HBV), as reflected by the presence of anti-HBc, was as high as 16.7% against around 5% for the general adult French population.12 However, in this and in smaller European studies the prevalence of HBsAg positive individuals was extraordinarily low. It seems likely that the very high prevalence of anti-HBc among very elderly individuals found in some communities may represent a cohort effect.

HEPATITIS C
It seems likely that, together with alcoholic liver disease, hepatitis C related liver disease will become numerically the most significant in this age group. Extraordinary differences are emerging as to the prevalence of apparent exposure to hepatitis C virus (HCV) in different parts of the world. In one new southern Italian study 41.7% of people over 60, compared with 10.6% of those under 35 (odds ratio 6.06, 95% confidence interval 3.96–9.26), were anti-HCV positive. In this study no widespread identifiable risk factor (intravenous drug abuse, tattooing, acupuncture, or past surgery) was found to account for this extraordinary high prevalence.11 In Britain and the United States while the prevalence of anti-HCV is higher among the elderly than in younger individuals, it is an order of magnitude lower than in the Italian study.14 15 Increasing understanding of the epidemiology of hepatitis C and of its natural history may now allow us to explain an apparent paradox. Several studies of community acquired hepatitis C, including a high proportion of elderly patients, suggest that it has a rather benign course.15 None the less, in a study of patients admitted to hospital with hepatitis C in Britain, of 25 patients presenting over 65 years of age, 18 of the 20 who underwent liver biopsy had cirrhosis (n=12) or cirrhosis plus hepatocellular carcinoma (HCC) (n=6), and a further four patients developed HCC within two years.17 It seems likely that many elderly individuals remain asymptomatic from HCV even if they may have acquired it 20 or more years before, while a proportion go on to develop cirrhosis but perhaps not as high a proportion as had previously been suggested. Of these, some will present
to hospital with the complications of long standing cirrhosis, including the development of HCC, thus giving the impression to hospital based physicians that hepatitis C is an "aggressive" disease in older people.

Autoimmune liver disease

Autoimmune markers become commoner in old age, indeed one underlying basic mechanism of aging may be the breakdown of immune surveillance. Until recently, however, the relation between advanced age and the features of autoimmune liver disease had been largely ignored.

Primary biliary cirrhosis

Although the mean age of presentation of primary biliary cirrhosis (PBC) is 50–55 in most large case series, studies based upon epidemiology and case finding suggest that the mean age at detection is around 60 years. In our own epidemiological study of PBC in north east England, of 111 new incident cases diagnosed over age 65 with a mean follow up of five years, 26% had died of liver related causes. In this study the point prevalence of PBC in women over 65 was 1:1000 in 1994 and over one third prevalent PBC patients were over 65. Once typical symptoms and complications of liver disease have developed, then all series have shown that age is an independent adverse prognostic indicator even when deaths from liver disease alone are considered. None the less, among initially asymptomatic antimitochondrial antibody (AMA) positive patients, it is one’s impression that a number of older individuals, often picked up during screening for other autoantibodies, may show a particularly slow and indolent course. Indeed, it has recently been suggested that this group may represent a discrete entity within PBC as a whole. It is at present my view that in a person over 65 years old with asymptomatic liver disease but with suspected PBC (AMA positive, abnormal liver biochemistry and compatible histology) no treatment is indicated as overall prognosis in this group as a whole only deviates from the normal elderly population after 10 or more years. At the other end of the spectrum, several studies have now shown that in very carefully selected elderly patients with PBC, liver transplantation may be a successful treatment option.

Autoimmune hepatitis

Although this has been thought to be largely a disease of younger individuals, recently Newton et al found that about 20% of all patients diagnosed with autoimmune hepatitis were over 65 at presentation. While there were no notable clinical or prognostic differences between the elderly and younger groups, the elderly had a more severe initial histological grade. Diagnostic score was slightly lower at presentation in the elderly group. As with PBC it is one’s impression that there may be some polarity in the clinical features of autoimmune hepatitis in this age group. Newton et al showed that some elderly patients, even with quite severe histological change, who were none the less not treated with steroids had an excellent prognosis, whereas there are a few elderly patients with autoimmune hepatitis presenting with clinically very aggressive disease (overlap jaundice, ascites and encephalopathy) whose prognosis is very poor indeed. Diagnostic criteria for autoimmune hepatitis remain the same regardless of age.

Alcoholic liver disease

Recent studies have shown that there are important pharmacokinetic differences in ethanol metabolism between older and younger subjects. Among men, the area under the curve was significantly greater in older subjects in both the intravenous fed and oral fasted states, but interestingly not in the oral fed state. In women there was a highly significant difference in the oral fasted state only. These age related differences seen most clearly in the fasted state imply decline in one or more mechanisms responsible for rapid ethanol metabolism within the first hour after ingestion. Although conventional hospital practice suggests that most patients present with severe alcoholic liver disease in their fifth or sixth decade, one study from the United States suggested that the peak incidence of presentation with alcoholic cirrhosis was the seventh decade. In a British series 28% of patients with alcoholic liver disease presented over age 60 and in France a large retrospective study suggested that as many as 20% of patients with alcoholic cirrhosis were over age 70. Recent sophisticated age-period-cohort analysis of European trends in liver cirrhosis mortality has suggested that liver cirrhosis mortality attributable to alcohol is likely to decline in western and southern European countries. However, conceivably as a result of changes in risk of exposure to hepatitis B and C and of changed dietary habits, the combination with ethanol may lead to a cohort of increased mortality from “mixed” cirrhosis (at least in part attributable to alcohol) in populations over age 60 or 70 in northern and eastern European countries.

Among those who do present to hospital with alcoholic liver disease over 60 years of age, symptoms are more severe with a higher frequency of presentation with complications of portal hypertension, and prognosis is directly related to age. In one United Kingdom study mortality in those presenting under age 60 was 5% at one year and 24% at three years; in those over age 60 it was 34% at one year and 54% at three years, whereas of those presenting over age 70, 75% were dead at one year. Among the oldest patients over half developed HCC.

Primary hepatocellular carcinoma

At least in Western countries HCC may be considered a disease associated with aging. Interestingly, it has been demonstrated recently that in an experimental model there was a twofold increase in the number of DNA bases damaged by oxidative stress in advanced age. This type of damage, seen in experimental HCC, may be induced by known carcinogens. In our own series of 110 cases of HCC in the United Kingdom about half presented at age 65 or over, 80% of whom had cirrhosis. Survival in the over 65s was 10.5 weeks compared with 18.5 weeks in younger patients, and the older patients had a worse Okuda stage at presentation. Several studies have suggested that the principal cause associated with HCC in older patients is HCV whereas in countries of high endemicity in younger patients it is HBV. In an excellent Korean study the ratio of HBsAg positive compared with anti-HCV positive patients with HCC was 29.7 for patients under 50 but was 0.9 for those over 60. Similar figures have been found in European studies. Presumably, this reflects the fact that HBV is acquired in the first years of life whereas acquisition of HCV, although partly cohort related, seems to occur largely in adulthood. In view of the epidemiology of HCV discussed earlier we can anticipate an increase in HCV related HCCs in many countries in the next 10 or 20 years.

Liver transplantation

In the past few years attention has increasingly focused both on the age of liver transplant recipients and of donor livers. As in other areas of very expensive high technology medical treatment, demand from over 60 and even over 70 year olds for liver transplantation, particularly in affluent countries, is growing. This is partly fuelled by the increasing understanding that long term cirrhosis, almost regardless of cause, in an older person carries a cumulative risk of
HCC. In patients in whom meticulous preoperative assessment shows optimal cardiac and respiratory function and no evidence of renal impairment or other significant intercurrent illness aside from underlying chronic liver disease, then one year patient and graft survival is similar in over 65 year olds to the majority of transplant patients. This is not the case in older patients with fulminant liver failure. It year old stothemajority of transplant patients. This is not thenoneyearpatient and graft survival is similar in over 65 current illness aside from underlying chronic liver disease, no evidence of renal impairment or othersignificantinter-
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