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Review

Age-related changes in liver structure and function: Implications for disease ?

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Abstract

The geriatric populations of many countries are growing rapidly and they present major problems to healthcare infrastructures from both medical and economic perspectives. The elderly are predisposed to a variety of diseases, which contribute to a marked increase in morbidity in this subpopulation. The incidence of liver disease increases in the elderly, but the cellular and subcellular perturbations that underlie this suspected predisposition to pathology remain unresolved. Several age-related changes have been documented, including (a) a decline in liver volume, (b) an increase in the hepatic dense body compartment (lipofuscin), (c) moderate declines in the Phase I metabolism of certain drugs, (d) shifts in the expression of a variety of proteins and (e) diminished hepatobiliary functions. Other more subtle changes (e.g., muted responses to oxidative stress, reduced expression of growth regulatory genes, diminished rates of DNA repair, telomere shortening) may contribute to reduced hepatic regenerative capacity, shorter post-liver transplant survival and increased susceptibility to certain liver diseases in the elderly.
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Keywords: Aging; Liver function; Liver structure; Liver regeneration; Hepatobiliary function; Liver transplant; Oxidative stress; Drug metabolism

1. Background

Nearly, 13% of the population of the United States is over the age of 65 years; this percentage and the actual number of elderly will increase substantially over the next 50 years. One well-documented effect of aging is a decline in overall health and vitality which contributes to the elderly consuming nearly 40% of all drugs, requiring more frequent and longer hospitalizations in comparison to young cohorts and accounting for 50% of the nation's healthcare budget.

Aging is characterized by normal progressive declines in functions that, cumulatively, diminish a cell's, organ's or organism's capacity to respond to intrinsic or extrinsic stimuli. Although, the aging process does not cause death, the elderly appear to be predisposed to a variety of diseases and, therefore, we assume that aging facilitates the onset and/or progression of many pathologies, including diseases of the liver.

1.1. Mortality due to liver disease

The percentage of deaths attributed to liver disease increases dramatically in humans beyond the age of 45 years. Recent data from California demonstrate a four-fold increase in liver disease-related mortality in both men and women between the ages of 45 and 85 years (Fig. 1(A); Seigel and Kasmin, 1997). The decline in this mortality rate that occurs in the oldest old reflects, in part, the fact that this select sub-population is characterized by traits favoring a longer lifespan, i.e., beyond the 50% survivorship level for the entire population. These observations are corroborated by data collected on a national scale (Fig. 1(B); Regev and Schiff, 2001). Furthermore, statistics from the United States Department of Health and Human Services illustrate that liver diseases cause a substantial loss in potential lifespan prior to 75 years of age. Liver disease reduces lifespan to a greater extent than colorectal and prostatic cancers, to a similar extent as chronic obstructive pulmonary disease and nearly as much as HIV (DHHS 99-1232, 1999).

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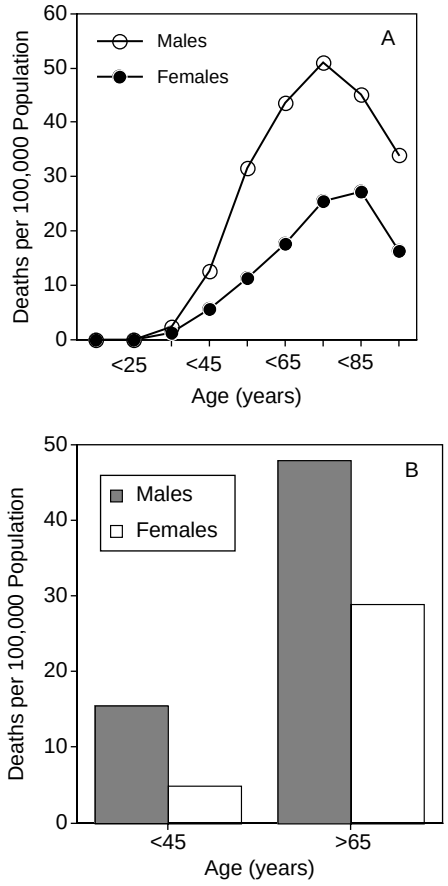

Fig. 1. (A) Deaths per 100,000 California population attributed to chronic liver disease and cirrhosis in males and females as a function of age between 1997 and 2000. (Data obtained from California Center for Health Statistics, Health and Human Services Agency Reports Nos. DS99-06001, DS01-0600 and DS02-09001; Seigel and Kasmin, 1997). (B) Number of deaths per 100,000 population attributed to chronic liver disease in males and females in the United States in 1998. (Data obtained from the National Vital Statistics Report 48, 2000; Regev and Schiff, 2001).

2. How aging affects the liver

Based on these correlations, it is not unreasonable to suggest that the elderly are predisposed to liver diseases. The next logical step is to determine how aging affects the liver in order to understand why the elderly appear to be more susceptible to liver diseases than are younger cohorts. It should be noted that the extrapolation of data generated in rodents to humans is often fraught with inherent problems. However, the present review incorporates studies performed in both rodents and humans with no effort to segregate the data based on origin.

2.1. Liver volume

One of the most documented age-related changes in the liver is a decline in organ volume. Most studies to date have employed ultrasound to estimate total hepatic volume and have reported declines ranging between 20 and 40% across

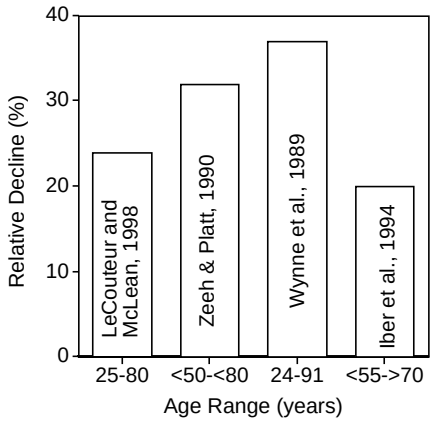

Fig. 2. Age-related decline in liver volume in humans (percentage of original volume) measured by ultrasound. (Data obtained from LeCouteur and McLean, 1998; Zeeh and Platt, 1990; Wynne et al., 1989; Iber et al., 1994).

the lifespan in humans (Fig. 2; Wynne et al., 1989; Iber et al., 1994; Le Couteur and McLean, 1998; Zeeh and Platt, 1990). Marchesini et al. corroborated these findings using galactose elimination rates (Marchesini et al., 1988). Concomitant with the age-related decline in liver volume, hepatic blood flow has also been reported to diminish (Wynne et al., 1987).

Wakabayashi et al. employed liver scintigraphy with radiolabeled galactosyl-albumin to estimate liver functional mass during aging in humans (Wakabayashi et al., 2002). Their data suggest that total hepatic mass in elderly subjects is not diminished, but rather that the mass of functional hepatocytes is decreased. These values are based on (a) the binding of glycosylated protein to asialoglycoprotein receptors on hepatocytes and (b) the assumption that the amount of bound radiolabeled ligand is proportional to the number of functional hepatocytes. However, our laboratory previously reported a marked decline in the number of asialoglycoprotein receptors on rat hepatocytes as a function of increasing age (Daniels et al., 1987). Despite this loss of specific receptors, there was no age-related decline in the biliary secretion of the intact asialoglycoprotein macromolecule (^{125}I-asialoorosomucoid), suggesting that this particular hepatocyte function is not significantly compromised in old rats.

We subsequently performed a quantitative autoradiographic analysis of asialoglycoprotein binding by hepatocytes in young and senescent rats (Daniels et al., 1987). In young adult animals, all of the autoradiographic grains, representing radiolabeled asialoorosomucoid, were localized to Zone 1 hepatocytes, i.e., surrounding the portal tract. However, the ligand binding and uptake patterns in old rats were extended to include hepatocytes throughout the entire liver lobule, including cells in Zones 2 and 3. The loss of hepatocyte asialoglycoprotein receptors in old rats may be compensated, in part, by the recruitment of Zone 2 and 3 cells for ligand uptake. These observations question whether

or not scintigraphy data of this nature represent valid estimates of hepatic functional mass.

Other studies have suggested that the size or volume of the liver lobule increases as a function of increasing age. Vollmar et al. measured the lobular area, as well as the distance between adjacent central veins (terminal hepatic venules) in young and old rats and found that both parameters exhibited a positive correlation with increasing age (Vollmar et al., 2002).

Despite evidence that hepatic blood flow is diminished in the elderly, the sinusoidal perfusion rate in the rat liver remains stable throughout the lifespan (Vollmar et al., 2002). Data from stereological analyses demonstrate that rat liver sinusoidal volume density (relative volume) is unchanged and accounts for 12–15% of total intralobular volume regardless of animal age (Schmucker et al., 1978). Nevertheless, there is evidence of age-related shifts in the hepatic microcirculation attributable to changes in the sinusoidal endothelium. McLean et al. examined sinusoidal endothelial morphology in surgical and post-mortem samples of human liver as a function of donor age (McLean et al., 2003). They reported a 60% thickening of the endothelial lining and an 80% decline in the number of endothelial cell fenestrations (pores) with increasing age. Furthermore, this same group reported similar age-related changes in the baboon liver, i.e., 70% increase in endothelial thickness and 60% fewer fenestrations (Cogger et al., 2003). Changes of this magnitude may impair sinusoidal blood flow and hepatic perfusion, as well as the uptake of macromolecules (e.g., lipoproteins) from the blood.

2.2. Hepatocyte structure

Although the consensus is that hepatic volume and blood flow decline with increasing age in humans, the effects of aging on hepatocyte structure are less clear. Several qualitative analyses have suggested that aging is accompanied by increases in the volume and/or in the number of dense bodies (secondary lysosomes, residual bodies, lipofuscin) in rodent and human hepatocytes (see Schmucker, 1990; Schmucker and Sachs, 2002 for reviews).

A comprehensive stereologic analysis of the Fischer 344 male rat liver quantitated specific age-related changes in the distribution and/or relative volumes of hepatocyte organelles (Schmucker et al., 1978). The volume of individual hepatocytes increases by 60% during development and maturation, but subsequently declines during senescence yielding hepatocytes of equivalent volumes in senescent and very young animals. These observations are not necessarily in conflict with the reported age-related increase in liver lobular volume since young and old animals contain greater numbers of small hepatocytes in comparison to mature rats, which according to our quantitative data, contain fewer, but larger cells.

The relative volumes of certain hepatocyte constituents also change during aging. The most universal change described is an age-related accumulation of lipofuscin or age pigment which, in turn, reflects a concomitant increase in the volume of the dense body compartment (see Schmucker, 1990; Schmucker and Sachs, 2002 for reviews). Dense bodies in rat hepatocytes also undergo a structural metamorphosis during aging (Fig. 3). Secondary lysosomes in young animals possess a homogeneous electron-dense matrix; those in adult rats exhibit a more heterogeneous matrix with both electron-opaque and lucid areas; and hepatocytes in senescent rats contain larger dense bodies with considerably more electron-lucid lipid-like material in their matrices. The relative volume of the hepatocyte dense body compartment, i.e., volume of dense bodies per volume of liver tissue, increases nearly two-fold with increasing age. The accumulation of dense bodies may be indicative of a decline in the turnover of effete organelles or other cellular constituents (e.g., cholesterol) which, in turn, may contribute to hepatocyte dysfunction by impairing metabolism, secretion or excretion.

The smooth surfaced endoplasmic reticulum (SER) also exhibits a shift in relative abundance during aging. This membranous organelle is the site of a variety of enzymes involved in steroid, xenobiotic, lipid and carbohydrate metabolism. Stereologic analyses have demonstrated a marked age-related decline in SER surface area in rat hepatocytes (Schmucker et al., 1977, 1978; see Schmucker, 1990 for a review). The surface area to volume ratio or concentration of hepatic SER, i.e., μm^2 of membrane surface per μm^3 of liver tissue, is lowest in senescent animals and this decline correlates with diminished hepatic microsomal protein concentrations, as well as with the activities of several constituent SER enzymes, e.g., glucose-6-phosphatase (Schmucker et al., 1980a).

Several qualitative morphological studies have reported age-related changes in the appearances or amounts of other hepatocyte organelles (see Schmucker, 1990; Schmucker and Sachs, 2002 for reviews). However, most of these changes have not been confirmed by quantitative microscopic or stereological studies. In summary, documented age-related changes in the liver include declines in hepatic volume and blood flow; an increase in the volume of the dense body or lipofuscin compartment and a decline in the concentration of SER.

3. Aging, oxidative stress and liver injury

Cells and tissues in old animals and in elderly humans are subject to increased oxidative stress attributable, in part, to a reduced capacity to eliminate metabolically generated superoxide radicals as efficiently as younger cohorts. Numerous studies have attempted to demonstrate a causal relationship between cell injury and age-related increases either in free radicals or in cell sensitivity to these molecules. Zhang et al. used a hyperthermic challenge to increase oxidative stress and associated hepatic injury in young and

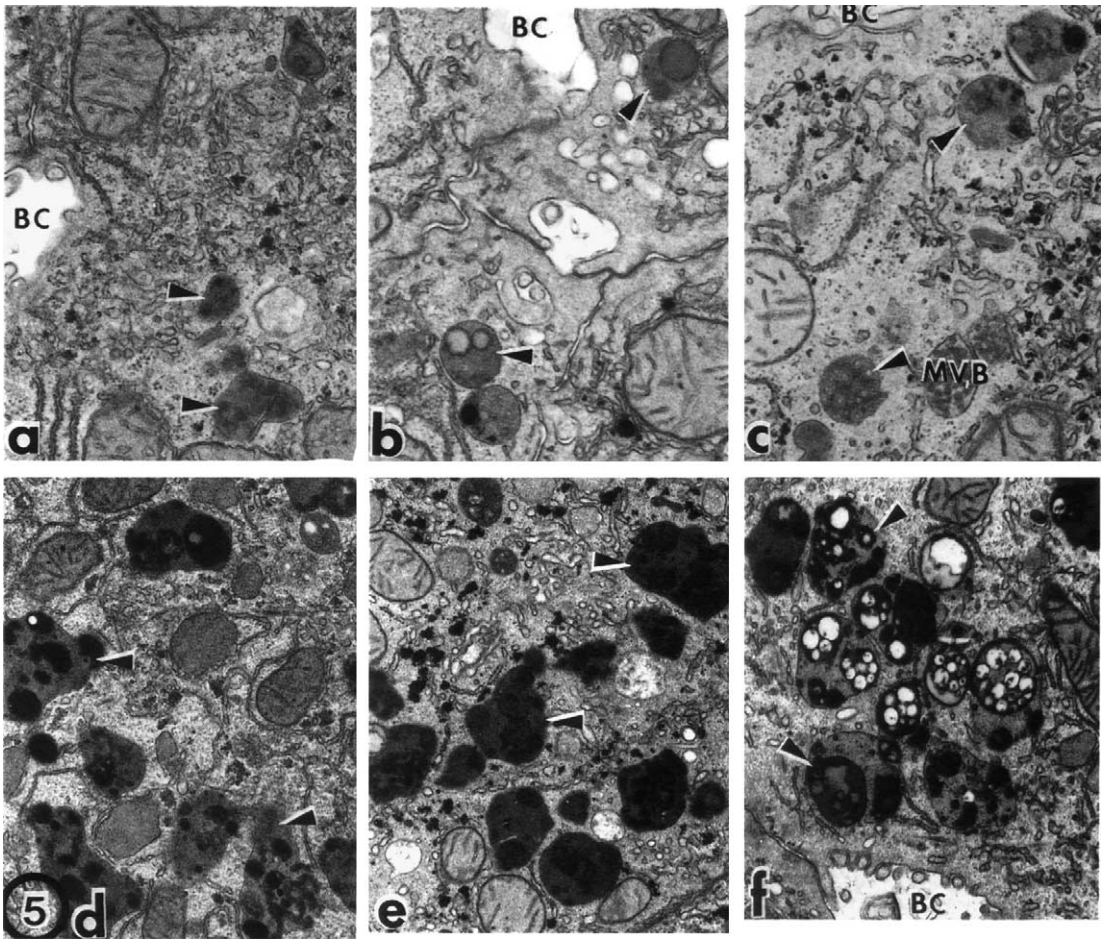

Fig. 3. Electron microscopic images of typical dense bodies (secondary lysosomes, residual bodies) in Zone 3 hepatocytes in 1 month (a), 6 months (b), 16 months (c), 20 months (d), 25 months (e) and 30 months (f) old Fischer 344 rats.

old rats (Zhang et al., 2003). A small, transient increase in oxidative damage was observed in young animals, whereas old rats exhibited extensive hepatocyte injury within 24 h of the heat challenge. These investigators concluded that old rats had less effective protection against oxidative injury in comparison to the young animals.

Such morphological changes are often preceded by shifts in biochemical predictors of oxidative injury, e.g., increases in lipid peroxides and hepatic DNA oxidative damage. Intano et al. recently reported a 50% age-related decline in DNA base excision repair in mouse hepatocytes (Intano et al., 2003). These data suggest that DNA damaged by free radicals or other insults is repaired more slowly in old in comparison to young animals and, therefore, presents a greater opportunity for cell dysfunction. Hamilton et al. reported significant increases in the level of oxidatively damaged DNA in the livers of senescent mice and rats in comparison to young animals (Hamilton et al., 2001). However, these increases were not attributable to a diminished capacity for DNA repair, but rather to an age-related increase in DNA or cell sensitivity to oxidative stress.

The mechanism(s) responsible for increased cell sensitivity to oxidative stress has not been resolved, although several studies have noted marked age-related increases in the expression and activity of stress-induced transcription factors, i.e., NF-κB. Helenius et al reported a significant age-related increase in NFκB binding activity (activation), but no concomitant changes in the expression of its mRNA or in those of its primary inhibitors (IκBα, IκBβ Helenius et al., 2001). These authors concluded that while the expression of NFκB was not affected by age, its enhanced binding activity may influence the expression of certain target genes. One of these target genes is the hepatic antioxidant enzyme, heme oxygenase. Lavrovsky et al. demonstrated concomitant age-related increases in the steady state level of inducible hepatic heme oxygenase mRNA and in the activation of NFκB, suggesting that increased oxidative stress in old animals is accompanied by enhanced induction of an antioxidant enzyme via the transcription factor NFκB (Lavrovsky et al., 2000). A recent study has implicated the oxidative stress-induced upregulation of pre-apoptotic genes in enhancing the sensitivity of hepatocytes in old rats to oxidative injury (Ikeyama et al., 2003). These researchers demonstrated elevated basal H_2O_2 and EGF-induced gadd 153 gene expression in the livers of old rats in comparison to young animals.

However, the importance of changes in gene expression to the role of oxidative stress in the aging process remains unresolved. Thomas et al. examined gene expression patterns in the livers of very young and old rats and humans using gene array analysis (Thomas et al., 2002). These investigators noted three-fold or greater changes in the expression of 582 genes in aged rat livers and in 192 genes in livers from elderly humans. However, a few patterns of expression were similar in both species, especially in the antioxidant and cytochrome P450 families, suggesting a link between aging and the hepatic capacity to detoxify compounds and to protect against superoxide radicals.

3.1. Hepatic Phase I drug metabolism

The age-related loss of SER provides an appropriate transition to the next topic, hepatic Phase I drug metabolism, since many of the enzymes responsible for this major drug biotransformation pathway are localized to this organelle. As noted above, the elderly constitute the largest group of drug consumers; i.e., 65% of this population is medicated and many are on polypharmacy regimens. A major consequence of geriatric polypharmacy is a marked increase in the incidence of adverse drug reactions (ADR's) i.e., males and females exhibit three and four-fold increases in ADR's, respectively, between 20 and 60 years of age (Fig. 4).

Most studies on aging and liver drug metabolism have been performed using inbred male rats and demonstrated strong negative correlations between age and hepatic microsomal Phase I drug-metabolizing activity (Schmucker and Wang, 1980b, 1981, 1983, 1984). However, similar studies in non-human primates found no such correlations (Maloney et al., 1986; Schmucker and Wang, 1987). We subsequently measured several indices of Phase I drug metabolism in human liver microsomes as a function of donor age and gender, including the microsomal content of cytochrome P450 and the activity of NADPH cytochrome P-450 reductase (Fig. 5; Schmucker et al., 1990). Interindividual variability, particularly among older subjects, precluded any statistically significant age or gender-related differences. Nevertheless, this issue remains controversial (Zeeh and Platt, 2002). Sontaniemi et al. measured several indices of antipyrine metabolism in humans as a function of age and demonstrated good correlations between subject age, hepatic cytochrome P450 content, antipyrine clearance and antipyrine $t_{1/2}$ (Fig. 6; Sontaniemi et al., 1997). These data suggest that the disposition of this particular Phase I metabolized compound is compromised in the elderly. Of particular note is a recent comprehensive review of the influence of age and gender on the efficacy of hepatic CYP3A-dependent metabolism of xenobiotic and endogenous substrates (Cotreau et al., 2005).

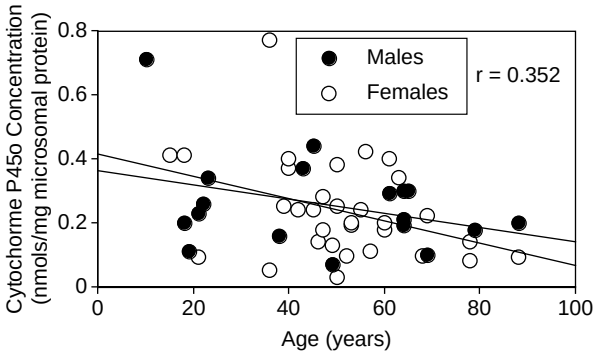

Fig. 5. Liver microsomal concentrations of total cytochromes P-450 in men and women as a function of age. (Data from Schmucker et al., 1990).

3.2. Hepatobiliary functions

If aging compromises hepatic functions and predisposes elderly patients to liver diseases, basic liver function tests may prove predictive. Unfortunately, few studies have compared age and clinical liver function values. Tietz et al. conducted a large retrospective analysis in which they

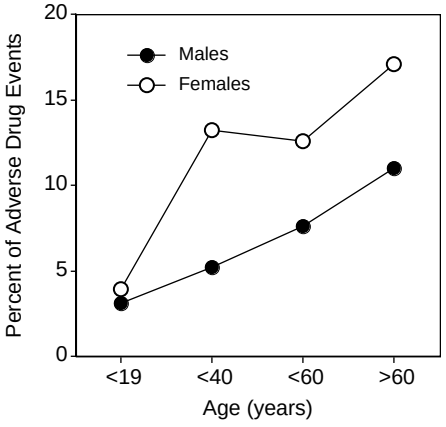

Fig. 4. Correlation of age and the percentages of male and female patients experiencing post-marketing adverse drug reactions. (Data from the FDA Annual Postmarket Adverse Drug Experience Report).

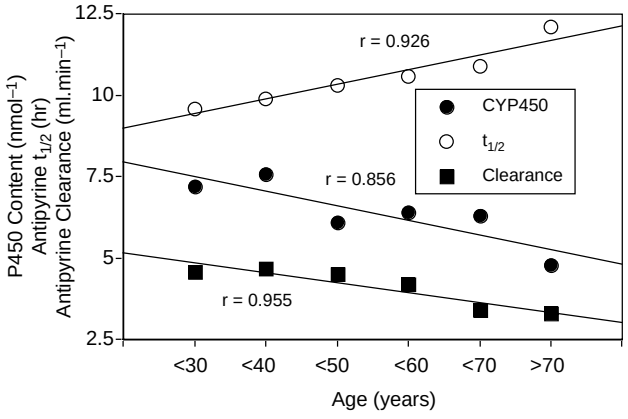

Fig. 6. Liver microsomal concentrations of cytochromes P-450, antipyrine plasma $t_{1/2}$'s and antipyrine clearance rates in men and women versus subject age. (Data from Sontaniemi et al., 1997).

concluded that the only indices to exhibit a correlation with age were the serum bilirubin values, indicative of a hepatobiliary deficit (Tietz et al., 1992). We measured bile flow and bile acid secretion as a function of age in inbred male rats (Schmucker et al., 1985). Our data demonstrated that both the basal and taurocholate-stimulated rates exhibited marked age-related declines, suggesting that hepatobiliary function is compromised in senescent rats. Einarsson et al. reported that the biliary secretion of both cholesterol and phospholipids increased with age in rodents, with the former contributing to cholesterol saturated bile (Einarsson et al., 1985).

One possible cause for the age-related decline in bile salt secretion, coupled with the increase in cholesterol secretion, is a concomitant decline in bile salt synthesis. There have been few studies on the critical rate-limiting enzyme in this hepatic pathway, 7α-hydroxylase. However, Bertolotti et al., recently measured the production of 7α-hydroxylated cholesterol in humans as a function of age and observed a weak negative correlation (Bertolotti et al., 1993). A decline in the amount of hydroxylated cholesterol may reflect diminished 7α-hydroxylase activity, perhaps resulting from post-translational modifications such as occur in a number of rat liver enzymes (see Schmucker, 2001 for a review).

Despite cholesterol-saturated bile, the hepatic clearance of high density lipoprotein (HDL) cholesterol declines with increasing age in humans. Bravo et al. showed that the clearance rate of radiolabeled HDL cholesterol in elderly subjects lags behind that measured in young adult subjects (Bravo et al., 1994). Whether or not this contributes to a diminished hepatocyte cholesterol pool and, therefore, to a decline in bile acid production, is unknown. Nevertheless, certain changes described above, coupled with reduced gallbladder contractility, may contribute to the documented age-related increase in the incidence of gallstone disease (Wang, 2002).

3.3. Liver adaptive responsiveness and regeneration

A major characteristic of the aging process is a decline in the cellular capacity to respond to stimuli or to changes in the milieu, i.e., diminished adaptive responsiveness. Hepatocytes respond to a variety of growth factors. For example, Sawada et al. demonstrated a marked age-related decline in the proliferative response of rat hepatocytes to growth factors following partial hepatectomy (Sawada and Ishikawa, 1988; Sawada, 1989). Despite the fact that the rate of hepatic regeneration is slower in old rats, these livers eventually achieve their original volume. One factor that may contribute to diminished survival of transplanted livers in the elderly is the hepatic capacity to regenerate following transplantation.

The mechanism responsible for the age-related decline in the post-hepatectomy hepatocyte proliferative response has not been identified. However, a recent study has implicated an age-related shift in the liver specific cyclin-dependent kinase proliferation inhibition pathway in the diminished hepatic regenerative capacity in old rodents (Iakova et al., 2003). The authors suggest that specific gene repression in old animals blocks the induction of c-myc and subsequent cell proliferation following partial hepatectomy.

Another possible reason for the age-related decline in the hepatic regenerative response is diminished expression of a gene coding for a critical Forkhead Box transcription factor, i.e., Fox M1B. Studies have shown that reduced expression of Fox M1B correlates with reduced proliferation of regenerating hepatocytes and fibroblasts from old mice and elderly humans, respectively (Ly et al., 2000). More recently, Costa and co-workers showed that regenerating livers in old mice exhibited diminished expression of Fox M1B, but that subsequent transfection of these animals with the Fox M1B gene restored this expression and enhanced other indices of hepatocyte proliferation (Wang et al., 2002). Their data clearly showed that the onset of cell proliferation in old transfected mice preceded that observed in normal young mice. An age-related decline in DNA repair may also contribute to reduced hepatic responsiveness. Intano et al. recently reported a 50% age-related decline in DNA base excision repair in mouse hepatocytes (Intano et al., 2003). These data suggest that DNA damaged by free radicals or other insults is repaired more slowly in old in comparison to young animals and, therefore, presents greater opportunity for cell dysfunction in the former age group.

Telomere length has been identified as a critical factor in cellular aging (Wright and Shay, 1992; Lundblad and Blackburn, 1993). The sequential shortening of telomeres is a normal process that occurs during cell replication. Once telomeres reach a minimal length, no more cell divisions occur. A basic assumption is that somatic cells in old animals and humans possess shorter telomeres than do those in young cohorts. (Aikata et al., 2000; Cherif et al., 2003). However, most of the telomere shortening occurs during the first 40 years of life with no significant change thereafter. Takubo and Kaminishi measured the rates of telomere shortening in several human cell types over the entire lifespan (Takubo and Kaminishi, 2001). The fastest shortening rates were observed in the cell types with high turnover rates, such as intestinal enterocytes and esophageal epithelial cells. Interestingly, hepatocytes exhibited the next fastest rate of shortening despite being relatively long-lived cells. This may have implications with respect to the age of liver donors since shorter telomere length equates with a diminished capacity to undergo cell division.

These observations raise the question of whether or not there are correlations between age, hepatocyte telomere length and the incidence of liver disease. Aikata and others have addressed this very issue in normal and diseased human livers in hybridization studies (Aikata et al., 2000; Takubo et al., 2000). The mean telomere length in healthy livers is approximately 10 kilobase pairs at 80 years of age and these hepatocytes retain their proliferative capacity.

However, the mean telomere length in diseased livers of elderly subjects was approximately 5 kb pairs, which is considered to be the Hayflick limit of proliferation (5–6 kb pairs). Therefore, short telomere length may compromise hepatic regeneration and contribute to a poor prognosis in liver disease or as a donor liver.

3.4. Liver transplantation

The age of liver transplant donors and/or recipients has been subject to considerable discussion. Fourteen years ago, Fortner and Lincer assessed the effect of age on liver recipient post-transplant mortality and reported that the rate increased with patient age, i.e., approximately 13% between 50 and 75 years of age (Fig. 7(A); Fortner and Lincer, 1990). More recent studies have confirmed this correlation with respect to post-transplantation survivorship. However, data from two other studies showed only small differences in the percent survivorship at 3, 5 and 10 years post-transplantation (Fig. 7(B); Collins et al., 2000; Garcia et al., 2001).

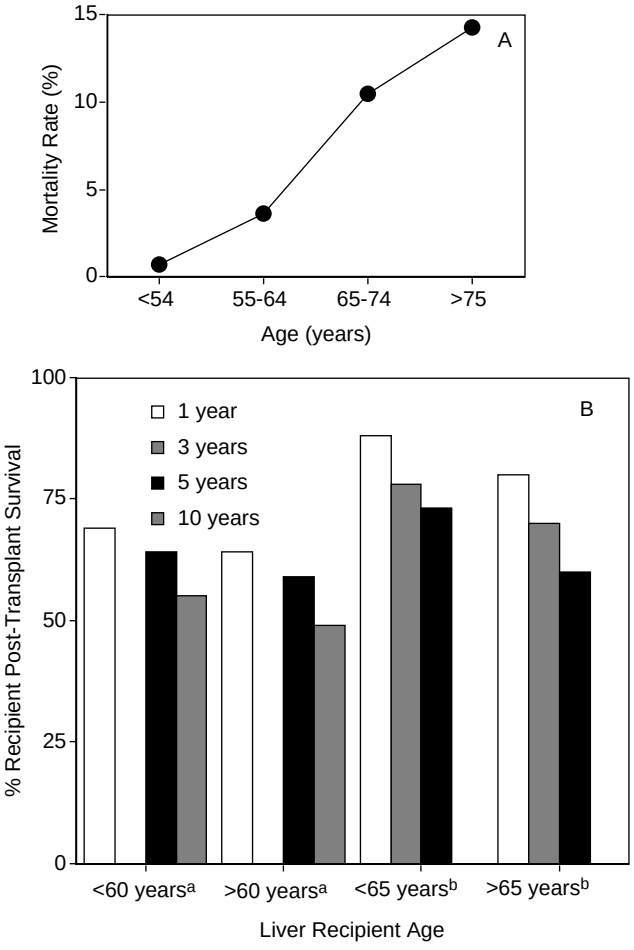

Fig. 7. (A) Post-transplant mortality as a function of liver recipient age. (Data from Fortner and Lincer, 1990). (B) Liver transplant recipient survival at post-transplant intervals in patients under 60 and over 65 years of age. (Data from Collins et al., 2000; Garcia et al., 2001).

The effect of donor age on the susceptibility of transplanted livers to reperfusion injury has also been the subject of recent study. Unfortunately, the data are conflicting. On the one hand, Le Couteur et al. examined the extent of hypoxia-re-oxygenation injury in the perfused livers of young and old rats (Le Couteur et al., 1994). These investigators found no age-related differences in several indices, including lactic dehydrogenase (LDH) release and bile flow, suggesting that aging does not increase hepatic susceptibility to reperfusion injury. On the other hand, Gasbarrini et al., studied the effect of aging on the sensitivity of isolated hepatocytes to re-oxygenation injury, i.e., 2 h of anoxia followed by 1 h of re-oxygenation (Gasbarrini et al., 1998). These data showed (a) significantly greater LDH release and (b) more extensive cellular injury in hepatocytes isolated from old rats in comparison to cells from young animals.

4. Non-hepatocytes

4.1. Kupffer cells

While most studies on aging and the liver have focused on hepatocyte structure and function, there are a few data pertaining to other liver cell subpopulations, including Kupffer and stellate cells. Aging appears to affect the hepatic clearance of certain drugs and cholesterol. However, the Kupffer cells constitute another critical clearance mechanism in the hepatic sinusoids that removes particulates (e.g., antigen/antibody complexes, effete cells). Few studies have examined this particular liver function as a consequence of aging.

Although Kupffer cell morphology remains virtually unchanged during aging in rodents, their phagocytic capacity in animals and humans has been reported to decline with age (see Brouwer et al., 1983 for a review). A subsequent study in rodents reported a positive correlation between declines in the contents of the cytoskeletal components actin, myosin and vimentin (68–76%) and a decline in Kupffer cell phagocytosis of polystyrene beads (Sun et al., 1998). Similarly, Videla et al. reported a 35% decrease in the clearance of colloidal carbon by perfused livers isolated from old rats in comparison to that measured in organs from young animals (Videla et al., 2001). Vollmar et al. infused young and old rats with latex spheres and measured particle retention by Kupffer cells (Vollmar et al., 2002). Their data showed, quite unequivocally, that (a) age does not affect this Kupffer cell function and (b) the lobular uptake gradient does not shift toward Zone 3 as it does for hepatocyte asialoglycoprotein binding.

4.2. Sinusoidal endothelial cells

There have been few studies on the effects of aging on the structure and function of hepatic sinusoidal endothelial cells. Few changes have been reported, i.e., an accumulation

of ferritin and declines in glucose-6-phosphatase and Mg-ATPase activities (see De Leeuw et al., 1990 for a review). As noted above, several studies have reported a thickening of the endothelial cells and a concomitant loss of fenestrae with increasing age (Cogger et al., 2003; McLean et al., 2003). These investigators examined the effect of acute oxidative stress on the perfused rat liver treated with H_2O_2 as a model of aging (Cogger et al., 2001). Interestingly, their ultrastructural analysis revealed that the sinusoidal endothelial cells became swollen and more porous; whereas their later study reported a loss of porosity in these lining cells with increasing age in humans and primates (Cogger et al., 2003; McLean et al., 2003). These conflicting data suggest that acute oxidative injury in the perfused rat liver either (a) does not mimic age-related changes to these cells in vivo or (b) the reported age-related changes are not examples of oxidative stress injury.

4.3. Stellate cells

The stellate or vitamin A-storing cells have been implicated in the etiology of hepatic fibrosis (see Friedman, 1999 for a review). Although there have been few studies on the effects of aging on this cell population, Vollmar et al. demonstrated an age-related increase in the size of individual vitamin A fluorescent foci coupled with a decline in their number in rats (Vollmar et al., 2002). These data suggest that the livers of senescent rats may contain fewer, larger stellate cells in comparison to young cohorts. These same investigators also measured the amounts of retinyl esters, the storage form of vitamin A, in the rat liver as a function of age. The hepatic content of the major retinyl esters increased with increasing age, which correlates with the larger fluorescent foci in old animals. Whether or not this shift in hepatic vitamin A content affects liver function or contributes to the onset or progression of fibrosis is unknown. Lastly, van der Loo et al., (2004) reported that the hepatic content of vitamin A increased ($p < .0001$) in the livers of old rats, whereas the plasma levels of this antioxidant decreased ($p < .0001$) in these same animals. These observations raise questions pertaining to the availability of vitamin A stored in the liver in response to oxidative stress in old animals.

5. Summary

The multitude of functions assigned to the mammalian liver and its central role in human physiology suggest that it may be particularly susceptible to the insults of aging. One consequence of aging appears to be an increase in the incidence of liver pathologies, which may compromise hepatic function in the elderly. Despite the growing geriatric population and the magnitude of healthcare problems associated with this group, the effect of aging on the liver has not be subjected to comprehensive study. Aging is accompanied by a few documented structural changes in liver morphology and cell structure, i.e., diminished volume, increased lipofuscin content and, perhaps, a loss of smooth surfaced endoplasmic reticulum. However, the functional ramifications of these changes, if any, have not been clearly elucidated. With the exception of diminished bile acid secretion and increased biliary cholesterol, liver function tests have failed to identify significant age-related deficits. However, the rate of liver regeneration, i.e., hepatocyte proliferation following injury, is decreased in old animals and humans and this may enhance the progress of hepatic diseases and compromise liver transplantation in the elderly.

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