Aging and the Liver: An Update

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The issue of whether or not liver function is compromised in the elderly population remains unresolved. Numerous age-related changes in hepatic structure and function have been described, but many of these observations are qualitative, were made under suboptimal experimental conditions, or are simply contradictory. Changes in hepatocellular structural parameters, e.g., increased hepatocyte size, increase in the number of binucleated cells, altered mitochondria, and endoplasmic reticulum, have been reported. However, quantitative morphological analyses have refuted many of these observations. There are few functional data that correlate with structural changes. Serum and biliary cholesterol appear to rise, predisposing elderly people to increased incidences of coronary disease and gallstones, respectively. The rate of liver regeneration declines in old animals, but the regenerative capacity remains unchanged, perhaps reflecting an age-associated reduction in the response to hepatotrophic factors. This senescent change has important clinical implications with regard to surgical intervention for liver disease, e.g., resection or transplantation. Nevertheless, most outcomes studies suggest that age alone should not be a determining factor in such clinical decisions. Geriatric patients exhibit a decline in the hepatic clearance of certain drugs and a marked increase in the frequency of adverse drug reactions, reflecting an increase in polypharmacy regimens and declines in liver volume and blood flow rather than reduced Phase 1 metabolism. Although the livers of elderly subjects are characterized by a decline in adaptive responsiveness and reduced reserve capacity, clinical tests suggest that liver function is well-maintained in this age group.

Aging affects different organs, tissues, and cell types in the same organism in different ways; that is, the extent of age-associated perturbations of structure and function is site-specific. The effects of aging on the mammalian liver have not been clearly resolved. Despite the plethora of age-associated changes in hepatic structure and function that have been described, many of these observations are qualitative in nature, were made under less than optimal experimental conditions, or are simply conflicting [see (1,2) for reviews]. Therefore, the question of whether or not the liver is compromised intrinsically in senescent animals or elderly humans remains unclear. The late pathologist and hepatopathologist Hans Popper stated some years ago that "aging exerts a limited effect on the constitutive functions of the liver and more on its response to extrahepatic factors..." (3). Inasmuch as it has been more than eight years since we last visited this topic, this report is a survey of the current understanding of the effects of aging on liver structure and function.

Liver Morphology

There have been few comprehensive studies on liver morphology during aging, and most of these have been performed in rodents. The few studies that have described the nature and extent of changes in human liver structure have suffered from deficits in experimental design, e.g., a reliance on post mortem samples or on tissues from subjects diagnosed with liver disease. Furthermore, there has been little effort to distinguish changes associated with maturation from those that are clearly a consequence of senescence.

The most frequently cited postmaturational change in human liver is a decline in organ mass, although there has been disagreement concerning even this basic parameter (4-6). One study reported that liver mass declines >40% in humans during the first two to three decades of life, but that it remains virtually stable thereafter (7). Two more recent studies, using more sophisticated and sensitive measurements, concluded that liver volume declines between maturity and senescence in humans (8,9). The implications of reduced liver volume and hepatic blood flow in the elderly are unclear, but may have a critical impact on such parameters as the pharmacokinetic profiles of drugs that undergo mandatory hepatic oxidation.

The liver in elderly humans has been characterized as having fewer, larger hepatocytes with increases in polyploidy and in the binuclear index (3,10-12). Unfortunately, small sample sizes and the qualitative nature of many of these studies preclude any meaningful correlations with functional analyses (13). While nuclear ploidy increases in rodent livers, the data from human tissue are conflicting (14-17). A recent study in humans reported that the rate of hepatocyte polyploidization is slow during the first five decades of life, but that it increases substantially, with subjects between 86 and 92 years of age exhibiting 27% polyploid nuclei (18).

The frequency of hepatocytes with enlarged nuclei in humans reportedly increases by 20% between the first and eighth decades of life (10). Several studies reported no change or an increase in the binuclear hepatocyte index during aging in rodents and humans (19-20). However, our own studies in inbred Fischer 344 rats did not demonstrate a significant age-associated change in the number of binuclear hepatocytes (21). DePriester et al. (22) suggested that an age-associated increase in the hepatocyte binuclear
index, coupled with no change in hepatocyte volume, results in an increase in the nucleocytoplasmic ratio. In agreement with this and other studies, our own analyses demonstrated that age-associated changes in the hepatocyte nucleocytoplasmic ratio reflected concomitant shifts in cell and nuclear volumes (21,23,24; see Figure 1). Although aging appears to be accompanied by an increase in hepatocyte nuclear ploidy, changes in cell and/or nuclear volumes are less apparent in part, to an age-associated increase in interindividual variability.

The results of most fine structural analyses have not yielded evidence of marked or consistent age-associated alterations in rodent hepatocytes (Figure 2). Although there are conflicting data, several investigators have reported that aging in rodents and humans is associated with (a) an increase in individual mitochondrial volume and (b) a decline in the number of mitochondria in the liver (19,25,26). Recently, Sastre et al. (27) reported that hepatic mitochondria isolated from old rats were larger than those obtained from young adult animals. However, it should be noted that these data were derived from mitochondrial suspensions using flow cytometry, not from intact tissue using electron microscopy and stereological analysis. The impact of such structural changes on mitochondrial function has not been elucidated, although two studies have demonstrated age-associated deficits in liver mitochondrial respiratory rates (28,29).

Perhaps the only definitive evidence of an age-associated structural change in the liver is an increase in the volume of the dense body compartment, i.e., secondary lysosomes and residual bodies, and the concomitant accumulation of lipofuscin (see ref. 1 for a review). Four separate stereological analyses reported two- to eightfold increases in the relative volume of the dense body subcellular compartment as a function of increasing age (21–23,30). However, other studies have shown that constituent lysosomal acid hydrolases exhibit variable activities and heterogeneous distribution patterns in rodent livers during aging, and that lysosomal function does not necessarily correlate with an increase in the volume of this organelle compartment (31–35).

Most hepatocyte subcellular compartments undergo few or no changes in volume or distribution during aging. A few organelles or cytoplasmic inclusions exhibit age-associated alterations in appearance or density. For example, two stereological studies reported that the volume of rat hepatocyte cytoplasmic lipid droplets undergoes a biphasic response during aging, i.e., a gradual postmaturational increase followed by a decline during senescence (21,36; see ref. 1 for a review). Quantitative structural and functional data from several laboratories have suggested that the relative amount of rough-surfaced endoplasmic reticulum reflects concomi-

![Figure 1](https://example.com/figure1.png)

**Figure 1.** The effect of aging on the hepatocyte nucleocytoplasmic ratio in male Fischer 344 rats. The data were derived from nuclear and cytoplasmic volumes obtained by light and electron microscopic stereological analyses of perfusion-fixed tissue (21). Each point represents the mean value for six animals ± SD.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Electron micrographs of liver tissue from 1 month (A) and 30 months (B) male Fischer 344 rats depicting typical hepatocyte fine structure in these two age groups. There are no marked differences in hepatocyte architecture with the exception of an age-associated increase in the number of lysosomal-derived dense bodies (arrowheads). Asterisks (*), bile canaliculi; arrows, rough surfaced endoplasmic reticulum; S, sinusoidal surface or space of Disse. 7,000–9,500X.
tant shifts in the protein synthesizing capacity of the rat liver during aging (21,37-41). Information concerning the effects of aging on other hepatocellular membrane compartments, e.g., the smooth-surfaced endoplasmic reticulum (SER), is conflicting. Our own stereological analyses demonstrated a significant loss of SER from rat hepatocytes in lobular zones 1 and 3 between maturity and senescence (21,41). This observation correlates well with a concomitant decline in the yield of liver microsomal protein from similarly aged rats of the same strain (42). The only other study to measure SER surface area in rat hepatocytes during aging reported an initial loss of membrane followed by an increase during maturation and senescence, such that the oldest animals examined contained similar or greater amounts of this organelle than young rats (24). The fact that the liver contains a heterogenous population of hepatocytes (a) whose individual ages do not correlate directly with host age and (b) that exhibit structural differences according to their sublobular location may obscure age-associated changes in cell structure.

Hepatic Function

Although there is evidence that aging affects certain hepatic functions, the field of geriatric hepatology remains conflicting and uncertain (see refs. 43-45 for reviews). This uncertainty is attributable, in part, to the marked increase in interindividual variability in many physiological parameters that characterizes elderly people.

Liver function tests.—The results of liver function tests in elderly subjects are conflicting or inconclusive. Numerous tests have failed to identify significant age-associated deficits in hepatic functions (46). In early studies, bromsulphthalein retention was the only index that changed as a function of age in a comprehensive battery of liver function tests (47). More recently, Tietz et al. (48) evaluated 15,000 laboratory values in more than 200 subjects across a substantial age spectrum and concluded that many liver functions were well maintained in the elderly subjects based on parameters such as hepatic enzyme profiles, and serum albumin and HDL cholesterol values (see Figure 3). Bilirubin values decline with increasing age, perhaps reflecting reduced muscle mass and hemoglobin concentration. Fabbrì et al. (49) reported a 30% decline in functional hepatic nitrogen clearance (p < .01), i.e., the rate of conversion of α-amino nitrogen into urea nitrogen, in subjects over 70 years in comparison to those under 55 years of age. Bohnen et al. (50) measured a battery of liver functions in subjects across an age span of 60 years and concluded that significant and clinically relevant changes in serum lipid and enzyme levels occurred in the elderly subjects.

Biliary function and cholesterol metabolism.—Studies in several laboratories, including our own, demonstrated age-associated deficits in a variety of biliary functions, including bile flow and bile acid secretion. For example, both basal and taurocholate-stimulated bile flow and bile acid secretion rates are diminished (p < .05) in old rats in comparison to young adult animals (51; see Figure 4). Bile acid synthesis declines in geriatric subjects, although the hepatic
secretion of cholesterol increases with age (52). Reduced bile acid synthesis in elders may reflect a significant diminution in the rate of cholesterol 7α-hydroxylation (53). An age-associated decline in the hepatic metabolism of LDL cholesterol further exacerbates elevated serum cholesterol levels (54–56). Collectively, these events probably contribute to increases in the cholesterol saturation of bile, in the frequency of gallstones, and in the incidence of coronary heart disease in elderly people.

Drug clearance.—Drug clearance in general, and the clearance of drugs that undergo mandatory Phase I hepatic metabolism in particular, appear to be compromised in elders (see refs. 57,58 for reviews). Reduced drug clearance predisposes elders to an increased incidence of adverse drug reactions (ADRs), especially because many geriatric patients are subject to polypharmacy regimens. The FDA has reported that the percentage of polypharmacy, i.e., five or more drugs taken simultaneously, in individuals over 60 years of age is equal to that measured in all younger age groups combined. Prescribing potentially inappropriate drugs may affect up to 25% of community-dwelling elders and contribute to the well-documented increase in the incidence of ADRs in this age group (59–61).

For many years, data derived from experiments using inbred male rats, and from less than critical clinical pharmacokinetic studies, substantiated the belief that the age-associated decline in hepatic drug clearance was due to reduced Phase I metabolism. Declines in the amounts and activities of specific liver microsomal monooxygenases, as well as in the amount of the intracellular site of these enzymes, the SER, contributed to this perception. Contrary to the data in inbred male rats, there is little evidence that reduced drug clearance in elderly humans reflects deficiencies in the cytochrome P-450-dependent metabolism of these xenobiotics. Unlike the rat cytochromes P-450, the human liver isoforms do not appear to exhibit many age-dependent shifts in their relative concentrations or activities (62–64). A recent correlated in vivo and in vitro study in humans suggested that a 30% decline in hepatic drug metabolism after 70 years of age reflected similar reductions in the liver cytochromes P-450 content and antipyrine clearance rate (65). However, two 1988 studies have shown that liver volume and hepatic blood flow in healthy, ambulatory elders declines appreciably in comparison to young subjects (8,9). The losses of liver mass and hepatic blood flow, rather than intrinsic alterations to constituents of the microsomal monooxygenase system, contribute to reduced drug clearance in the elderly subjects.

Liver regeneration.—Although the liver’s regenerative potential appears to remain intact in aging rats, the rate of regeneration declines with increasing age (66). This conclusion is based on the observation that it takes considerably longer for partially resected livers in old animals to regain their original volume in comparison to young animals. However, the regulation of hepatic regeneration is poorly understood regardless of animal age. The effects of aging on the circulating levels of hepatotrophic factors, e.g., epidermal growth factor (EGF), transforming growth factor-α (TGF-α), and the hepatic responses to these factors are important issues in any consideration of liver regeneration. For example, circulating EGF levels decrease markedly in elderly humans, and the response of hepatocytes to this trophic factor is diminished in old rats (67–69). The basis for reduced hepatic responsiveness to EGF in senescent rats has not been entirely resolved. Studies initiated in our laboratory demonstrated a significant age-associated loss of EGF receptors (>50%) from rat hepatocytes, whereas Sawada did not detect any differences in EGF binding kinetics between young and old rats (69–71). Sawada’s data suggest that deficits in events distal to receptor binding may contribute to the age-associated declines in hepatic responsiveness to EGF and, ultimately, in the rate of liver regeneration.

Despite the fact that diminished hepatic regeneration following surgery is a critical clinical issue in decisions of whether or not to perform liver resection in elderly patients, there is a paucity of data concerning this function in elders. Retrospective analyses have shown that mortality rates associated with liver resection were somewhat higher in subjects over 60 years of age (72–74). On the one hand, Fortner and Lincer (72) demonstrated strong correlations among patient age, increased operative mortality, extent of resection, and hepatic insufficiency (Figure 5). On the other hand, several studies have reported that major hepatic resection in elderly patients is not associated with increased postoperative morbidity or mortality (75–79). Age is also a major consideration in decisions concerning liver transplantation, for both the donor and the recipient. However, the issue of age as a limiting factor in determining the suitability of a liver donor has been somewhat assuaged in recent years with livers from donors up to 65 years of age being considered viable for transplant. Nevertheless, the age of

Figure 5. Effect of aging on the postoperative mortality rates in patients undergoing hepatic resection. Although the rate increases with patient age, the number of patients undergoing this procedure diminishes markedly with increasing age. The numbers above each respective bar represent the number of deaths per number of procedures. Data from Fortner and Lincer (72).
potential recipients has both clinical and ethical implications, including whether or not elderly patients can tolerate the physiological stress associated with liver transplant.

Another index of the age-associated decline in liver function is reduced hepatic responsiveness to a variety of extrinsic stimuli. The classic studies of Kato and Adelman demonstrated significant labs in the induction of certain liver enzymes, microsomal mixed function oxidases and glucokinase to phenobarbital and glucose, respectively, in old rats in comparison to young animals (80; see ref. 81 for a review). A more recent example is the marked age-associated decline in the induction of heat-shock or stress proteins following injury (82,83). Increased expression of these proteins is considered to be a protective response, and there is evidence that they are important for liver repair. Some researchers have postulated a correlation between reduced expression of stress proteins and an increase in the incidence and severity of liver diseases in elders.

Summary

There are few age-associated changes in liver structure that correlate with perturbations in hepatic function. With the exceptions of (a) a loss of organ volume and (b) an increase in the relative volume of dense bodies, the evidence for other suspected age-associated changes in hepatic structure is either conflicting or suspect. Aging is not a uniform process, as organ-specific aging and interindividual variability in the elderly are well documented. Physiological and morphological studies suggest that, compared with other organs, the liver seems to age fairly well. Perhaps the most compelling evidence for the maintenance of hepatic function into advanced age comes from clinical practice, wherein livers from elderly subjects, including one donor other organs, the liver seems to age fairly well. Perhaps the form process, as organ-specific aging and interindividual incidence for other suspected age-associated changes in hepatic the exceptions of (a) a loss of organ volume and (b) an
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