CHAPTER 1

What is non-alcoholic fatty liver disease (NAFLD), and why is it important?

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Key Points

- Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent form of fatty liver disease caused by over-nutrition; most patients show central obesity.
- NAFLD should be suspected in any overweight person with ultrasound evidence of fatty liver, particularly if metabolic complications such as fasting hyperglycemia, raised serum lipids, and high blood pressure are present.
- Diagnosis of NAFLD requires exclusion of alcoholic liver disease by a lifetime, quantitative history of alcohol intake: the limits of alcohol intake allowable for a diagnosis of NAFLD are 70 g/week (or one standard drink/day) in women and 140 g/week (two standard drinks/day) in men. Lower levels of alcohol intake may actually protect against liver complications of NAFLD.
- NAFLD comprises a pathological spectrum from simple steatosis, which rarely leads to liver fibrosis, through steatohepatitis (or NASH), which can lead to liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).
- NAFLD is associated with a 1.7-fold increase in standardized mortality. Premature deaths are from common cancers and cardiovascular disease, with liver complications being third most common.
- While only liver biopsy reliably indicates NASH versus "not NASH" pathology in NAFLD, there have been recent advances in non-invasive approaches (clinicopathological scores, biomarkers, and transient elastography) to both disease activity and fibrotic severity.
- Lifestyle measures are the first approach to management of patients with NAFLD; weight loss of >7% appears to improve histology but is achieved in less than 50% of patients.
- Tight control of serum lipid abnormalities is vital for reducing cardiovascular risk in patients with NAFLD.

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What is NAFLD?

Fatty liver is stainable fat in hepatocytes (steatosis). Among many causes, obesity and type 2 diabetes (T2D) have never been controversial. Despite this, there is no mention of **non-alcoholic fatty liver disease** (NAFLD) in the current iteration of the International Classification of Disease (ICD-10), developed in 1990. After early Japanese reports [1–3], American authors raised the possibility that obesity and T2D could also be associated with fatty liver disease complicated by liver cell injury and inflammation ("steatohepatitis"), as well as fibrosis or cirrhosis [4–6]. The pathological findings included Mallory hyaline (also termed Mallory–Denk bodies) [5–8], which until the mid-1970s had been regarded as a hallmark of alcoholic hepatitis. In light of this older concept, and to combat the skeptical view that these were likely instances of alcoholic liver disease in persons who had failed to disclose their alcohol dependence, Ludwig in 1980 coined the term "non-alcoholic steatohepatitis (NASH)" [5].

What is non-alcoholic?

While useful in its time, the term NASH has several disadvantages. *First*, it starts with a negative: "not alcohol." This immediately raises the issue about what level of alcohol intake allows one to conceptualize liver disease as alcohol related or not, as discussed elsewhere [9]. A pragmatic definition of NAFLD stipulating no more than one standard drink per day (i.e. 70 g ethanol/week) for women and no more than two standard drinks per day (140 g ethanol/week) for men was proposed in the first edition of this book [10] and has been used by the National Institutes of Health (NIH) NASH clinical research network (CRN) [11]; this definition has been widely adopted for clinical studies, except in France where a slightly more liberal cut-off is favored [12, 13].

The proposed levels of alcohol intake are based on evidence about daily alcohol intake and risk of cirrhosis [9, 14, 15], and the "cut-off" values are set lower than the apparent "threshold levels" so as to avoid the issue of overlap between alcoholic liver disease and obesity, T2D, and metabolic syndrome in progression to cirrhosis. In clinical practice, however, such overlap often exists. Managing safe levels of both alcohol intake and overweight, obesity, or T2D is likely to be critical to obtain optimal outcomes in these cases. Further, patients who may be drinking at safe levels at the time of presentation with liver disease may have a past history of chronic excessive alcohol intake for a prolonged period of time, and may therefore have cirrhosis. Lifetime alcohol intake is therefore important [16] and needs to be incorporated into history taking. However, recent evidence is mounting that levels of alcohol intake between zero (abstinence) and one standard drink per day may be beneficial for both cardiovascular health and the liver, potentially ameliorating or preventing the progression of more banal forms of NAFLD to NASH and fibrosis. These apparently conflicting issues are canvassed more fully by one of us (AMcC) in Chapter 21.

Steatosis and NASH

A *second issue* is that NASH is a **pathological diagnosis** (see the "Pathological Definition of NASH" section), not one that can be made clinically or by hepatic imaging (which can show evidence of steatosis; see Chapter 9) or laboratory tests (such as raised serum alanine aminotransferase [ALT]) [17, 18]. Hence, if a person has fatty liver related to over-nutrition, it is not possible to "label" them as having NASH or simple steatosis ("not NASH") without recourse to a liver biopsy. Recent evidence indicates that between 10 and 25% of NAFLD patients have NASH at any one time [9, 19]. In this book, we will use *NAFLD* when referring to the full spectrum of non-alcoholic fatty liver disease or if the pathology is unknown, and *NASH* only when referring to steatohepatitis (which requires pathological definition). Another term that has been used is non-alcoholic fatty liver (NAFL) for the "not NASH" cases of NAFLD, but NAFLD has gained widespread acceptance and will be the preferred nomenclature for ICD-11 (scheduled for release, if approved by the World Health Organization, in 2015).

Pathological definition of NASH

In Chapter 3, Brunt and Kleiner discuss the pathological assessment of fatty liver disease. By an increasing consensus, the diagnosis of NASH requires *recognition by an experienced liver pathologist* [20–27]; the elements are steatosis complicated by liver cell injury (evident as *ballooned hepatocytes*, or Mallory hyaline) with *substantial* lobular (and occasionally portal) [23, 26] inflammation. Inflammation is of mixed cellularity: polymorphonuclear leukocytes, lymphocytes, and macrophages. There is also often a characteristic pattern of pericellular fibrosis with centrilobular accentuation, and an alternative pattern of predominantly portal fibrosis is also recognized (particularly but not exclusively in children) [20, 23]. In the presence of fibrosis, the diagnosis is clearer (referred to as *fibrotic NASH*), and the probability of progression of liver disease to cirrhosis is higher [20–22, 27–30].

Words like "recognition by an experienced liver pathologist" and "substantial" reflect the relative lack of absolute (reproducible) criteria to define NASH pathology. In addition, there is relatively poor interobserver correlation for recognizing ballooning [31], underscoring the problem of pathological definition, even among experts. Special stains can partly overcome this challenge, such as ubiquitin stain, which enhances recognition of Mallory hyaline, and cytokeratin (CK)8/18 immunohistochemistry, which identifies hepatocytes in which this intermediate filament protein has been destroyed [32–34]. These aspects are considered in Chapter 3. In addition, scoring for fibrosis severity is subject to a sampling error [27]. Finally, the relatively high rate (~15%) of improved liver histology (from NASH to not NASH) in placebo arms of clinical randomized controlled trials [RCTs]) [35, 36] suggests either temporal lability or between-sample variability of liver biopsies in NAFLD, factors that "take the gloss off" biopsy as the "gold standard" for NASH diagnosis.

These issues notwithstanding, clinical outcome data (see Chapter 4) do support the dichotomous classification into a NASH versus "not NASH" pathology of NAFLD [22, 27, 37]. Even more reproducibly, they emphasize the critical predictive value of fibrosis [22, 27–30]. Older categorizations, such as the Matteoni *et al*. types 1–4 [28] that were mentioned in the first edition of this book, were very important in advancing our understanding of the particular significance of ballooning and Mallory bodies in NAFLD [32–34], but simpler discriminations (e.g., NASH vs. not NASH, and fibrosis vs. no fibrosis) are now supported by a stronger evidence base for prognostic purposes.

Another semantic issue is what to call "not NASH" NAFLD pathology. It has been referred to in those terms, but others have noted that characterizing a disorder only by two things that it *isn't* [38, 39], rather than a clear statement about what it *is*, increases its vagueness. The problem is considerable given that the majority (75% or more) of NAFLD cases that are biopsied fall into this category [9, 19], and arguably a higher proportion among those not biopsied because of perceived lesser severity. When there is unambiguously no inflammation, no liver cell injury, and no fibrosis, one can use the term *simple steatosis* [28, 31, 37], but many biopsied cases show minor inflammation as well as steatosis (and these are "not NASH" cases), while occasional cases show steatosis with fibrosis but no evidence of NASH at the time of diagnosis [22, 27]. Such cases may have exhibited NASH at some earlier stage, and the presence of residual fibrosis even without NASH (i.e. NAFLD with fibrosis) appears to have similar negative prognostic implications as NASH with fibrosis [22].

NASH without inflammation or fat? The special case of cryptogenic cirrhosis

A final complexity is that cases of cirrhosis may arise from longstanding NASH and no longer exhibit inflammation or even steatosis at the time of histological assessment [40–42]. After excluding known viral, autoimmune, and metabolic storage disorders, as well as alcohol, such cases of "cryptogenic cirrhosis" may now tentatively be regarded as *end-stage NASH* when clear metabolic risk factors such as obesity and T2D or metabolic syndrome are present or were definitely present in preceding decades [9,

40–43]. On pathological grounds, the case is more strongly made when the fibrotic pattern includes pericellular ("chicken wire") fibrosis [24, 25]. Calling a condition *end-stage NASH* when NASH is not present seems counter-intuitive but is no less illogical in the nomenclature of liver disease than primary biliary cirrhosis without cirrhosis (which also applies to the majority of cases). That stated, designing less cryptic or potentially misleading terminology is clearly a desirable future development in this field. Chapter 16 provides an excellent overview of cirrhosis in patients with NAFLD.

Does NAFLD matter?

Another implication of recognizing and defining NAFLD is the broad spectrum of clinical outcomes [9, 22, 27–29, 37, 40–43]. Thus, NAFLD increases age- and gender-standardized mortality ~1.7-fold [27, 44]. Liver outcomes, predicated by the existence of NASH and even more particularly by the presence of fibrosis or cirrhosis, rank third among causes of death [44]. However, cardiovascular disease and common cancers remain more common causes of death, and their relative risk is increased among persons with NAFLD [44–48]. The reasons for this and the clinical implications for overall patient care recur throughout this book. Specific issues, such as the nexus between diabetes (i.e., T2D) and NAFLD (Chapter 6), NAFLD and cardiovascular disease (Chapter 7), and NAFLD, hepatocellular carcinoma (HCC), and other cancers (Chapter 17), will be discussed in detail in this book.

The premature liver and nonliver mortality attached to a diagnosis of NAFLD clearly indicates that fatty liver not due to alcohol (or any other one specific cause) but attributable to over-nutrition has substantive health implications; these include but are not confined to liver disease and cirrhosis. It has been argued that NAFLD is a nondisease [49], and to the extent that it does not have a single cause, one predicable clinical and pathological phenotype, or any specific therapy (other than lifestyle adjustments (Chapters 12 and 22) or bariatric surgery (Chapter 13)), this may be correct [50]. However, the same argument could be applied to high arterial blood pressure, which likewise has undeniable implications for adverse health outcomes, and likewise results from complex environmental–genetic interactions whose pathobiology is only partly understood. NAFLD reflects a perturbation of liver physiology that can have both structural (a phenotype of liver disease) and functional (metabolic or vascular) complications [9, 39, 50, 51].

Do recent advances allow us to suggest a better name than NAFLD?

There have been some proposals for a name other than NAFLD or NASH. Given that there are many causes of steatohepatitis (Table 1.1), we asked in 2003: why not call NASH *metabolic steatohepatitis* (MeSH) [10]? Though euphonious, this has not caught on, and it also begs the question as to *which* metabolic factors comprise a *sine qua non* or are most critical for NASH pathogenesis [39, 50]. Likewise, the emerging agreement that NASH is a form of lipotoxicity (see Chapter 5) has led Cusi to suggest the term "liver lipotoxicity" [39]. This may be appropriate (most authorities agree that NASH is caused by lipotoxicity) [50–56]; it does have highly relevant implications for clinical care, and could become accepted. On the other hand, a scientifically precise but clinically meaningful term may need to await better understanding of *which lipid molecules* are involved [50, 53–61], and whether these are the same in all cases. Our understanding would also be greatly improved with better insights into why *some* NAFLD cases are complicated by lipotoxicity (those with NASH), whereas most aren't; are genetic (Chapter 14), developmental (see Chapter 15 on childhood NAFLD), or environmental factors (Chapters 12 and 22) the most important? Finally, more appropriate terminology and classification would flow from information about which treatments that logically follow from the lipotoxicity concept are most effective.

What isn't NAFLD?

In the first edition of this book, the editors recommended that the old term *secondary NASH* be aban-

doned in favor of linking known etiologies to the liver pathology [10]. Thus, conditions like alcoholic steatohepatitis, drug-induced steatohepatitis, and steatohepatitis due to jejuno–ileal bypass have nosological–ontological and classification appeal. These other causes of steatohepatitis are summarized in Table 1.1.

Fatty liver occurring in people with hepatitis C virus (HCV) infection probably isn't NAFLD; most cases do not show evidence of steatohepatitis (though rare cases do), and the virus itself plays a role (see Chapter 23). Nonetheless, overweight and obesity are at least as prevalent in HCV-infected persons as in the general population (i.e., >50% in many geographical regions), and insulin resistance or T2D is more common [62–64], so it can be reasoned that the same metabolic factors that lead to "pure" fatty liver disease (i.e., NAFLD) can lead to steatosis in HCV-infected (or hepatitis B virus–infected) persons. It isn't NAFLD because host–viral interactions have not yet been fully resolved (Chapter 23). The similar challenge of moderate (or clearly excessive) alcohol intake and metabolic risk factor interactions was raised in this chapter; sometimes it gets labeled as NAFLD (particularly when there is active liver disease more than a year after discontinuation of alcohol excess), and sometimes it is still regarded as alcoholic liver disease, but firm guidelines are not yet available (Chapter 21).

Table 1.1 Causes of steatohepatitis*

Alcohol (alcoholic steatohepatitis)
Non-alcoholic steatohepatitis (NASH; see text and Table 1.2)
Drug-induced steatohepatitis (tamoxifen, amiodarone, and methotrexate)
Insulin resistance syndromes (familial and acquired lipodystrophies, and polycystic ovarian syndrome)
Hypernutrition in adults (parenteral nutrition and intravenous glucose)
Jejuno–ileal bypass (historical; discussed in this chapter)
Other causes of rapid profound weight loss (cachexia, bulimia, massive intestinal resection, and starvation)
Jejunal diverticulosis (contaminated bowel syndrome)
A-betalipoproteinemia
Copper toxicity (Wilson's disease and Indian childhood cirrhosis)

*All of these entities (and several other drugs and toxic compounds) may also be associated with fatty liver without steatohepatitis.

A practical (clinical) definition of NAFLD

NAFLD is a spectrum of fatty liver disease (from minor to cirrhosis) caused by over-nutrition as manifest in most cases by central obesity. It likely *contributes* pathogenically to the metabolic complications of overweight, particularly insulin resistance (Chapter 5), glucose intolerance, and atherogenic dyslipidemia (Chapters 7 and 26). There is a close relationship between T2D, the number of components of the metabolic syndrome, and the severity of NAFLD [9, 38, 39, 41, 43, 47, 50, 51, 65, 66]. NAFLD cannot be diagnosed reliably without clear imaging (Chapter 9) or biopsy evidence of hepatic steatosis, and without excluding other causes of fatty liver, particularly excessive alcohol consumption, HCV infection, and medications [41, 67].

NASH is a pathological form of NAFLD characterized by histological evidence of steatosis with hepatocellular injury, substantial liver inflammation, and often pericellular fibrosis (Chapter 3). The metabolic factors discussed here are virtually always present in cases of NASH (e.g., insulin resistance >95% and metabolic syndrome ~85%) [68, 69], and cirrhosis may be established or develop during 10-year follow-up (Chapter 4) [28–30, 44, 70]. As inferred by being a subset of NAFLD, the exclusion of other causes of liver disease is a rigorous requirement to diagnose NASH.

Need for consensus of definitions

Journal reviewers and editors have *de facto* introduced guidelines for accepting the diagnosis of NAFLD, but to date there is not international consensus on a definition of NAFLD or NASH other

than that based primarily on the histological diagnosis. Given that 20–40% of surveyed populations have hepatic triglyceride levels that exceed 5.5%, or steatosis by hepatic imaging [66, 71], it is not practical to restrict diagnosis to the small proportion of patients who submit to liver biopsy. A primary care perspective of indications for liver biopsy is presented in Chapter 8.

An Asia-Pacific Consensus on NAFLD published in 2007 also recommended histology as the gold standard for diagnosis, but recognized the impracticality of this in many cases [67]. They therefore proposed two complementary *operational definitions*. These are based largely on detection of steatosis by ultrasonography, for which rigorous criteria are stipulated as "at least two of increased echogenicity, with liver echogenicity greater than kidney or spleen, vascular blurring and deep attenuation of the ultrasound signal" [67] (see Chapter 9 for a detailed discussion of imaging findings in NAFLD).

First operational definition: Fatty liver can be defined by the presence of at least two of (the above) three findings on abdominal ultrasonography; NAFLD is highly likely provided that other causes of liver disease have been rigorously excluded, particularly significant alcohol intake (the levels stated in this chapter) and medication use.

Second operational definition: For patients with unexplained ALT elevation, NAFLD is highly likely to be the cause if hepatic imaging results are compatible with fatty liver, and metabolic risk factors are present.

It would be relatively simple to integrate these two definitions into one, and it is hoped that regional liver societies may soon meet to derive an International Consensus on NAFLD terminology and classification.

Is NAFLD an epidemic, and how common is NASH?

The epidemiology of NAFLD is covered in Chapter 2 and clinical outcomes are charted in Chapter 4, particularly in relation to histological severity (see Chapter 3). Few in the field are now so xenophobic as to regard NASH as a "Western disease"; it is common and likely increasing in most societies other than where there is famine or traditional (active and self-sustaining) lifestyles or economies. In this book, we have deliberately chosen authors from five continents (Africa and Antarctica have been neglected) and tasked colleagues to give overviews on NAFLD in South America and Hispanic peoples (Chapter 20), Chinese and South Asian populations (Chapter 18), and Japan (Chapter 19). The reason Japan was included is because studies there antedated those from the rest of the world on several perspectives. In particular, serial community-based studies conducted over 25 years give us insights into what is clearly an epidemic, the factors that predicate the incidence, or, conversely, the resolution of NAFLD, and the lifestyle changes in an ethnically uniform country that are implicated in the closely linked NAFLD and T2D epidemics.

In Japan, the community prevalence of steatosis detected by routine health checks was about 13% before 1990, 30% by 1998, and ~32% in men and 17% in women in 2008 [72]. In 2011, Wong and colleagues reported that the point prevalence of steatosis in Hong Kong Chinese (by proton magnetic resonance spectrometry (MRS)) was 27% [66], which is broadly comparable with similarly obtained data from the Dallas region reported in 2004 (20% in African Americans, 24–30% in White Americans depending on gender, and >40% in Hispanic Americans) [71]. Similar data from ultrasound screening of overtly well, middle-aged outpatients attending a US Army Healthcare Facility in 2010 found that steatosis (NAFLD) prevalence was 46%, with highest prevalence in Hispanics followed by White Americans and then African Americans [19].

There is general acceptance that overweight and obesity are epidemics. Furthermore, the proportion of overweight individuals who have metabolic complications (30–40%) is sufficient to account for the parallel pandemic of T2D. The same logic applies for NAFLD. Rates of obesity now surpass 30% in several states in North America (and in Mexico), and continue to rise in many countries, notably populous ones like China, India, Indonesia, and Brazil, all of which have high rates of NAFLD. The prevalence of NAFLD may therefore increase further through the 2010s, although the change,

incrementally, may be less dramatic than during the 2000s.

As far as the rate of liver complications is concerned, the duration of NASH may be just as salient as the current prevalence of NAFLD. If patients are now developing a fatty liver at a younger age and NAFLD continues for longer, this will likely affect the severity of liver disease in middle and later life. In all studies, age correlates with disease severity, and if this is a surrogate marker of disease duration rather than a pathobiological effect of aging, the rate of liver complications through the 2010s could increase disproportionately to changes in the prevalence of NAFLD.

Until recently, estimates of the prevalence of NASH were made on relatively small data sets, such as autopsy studies after sudden death or liver biopsies at the time of bariatric surgery [9, 10]. When the epidemiology of NASH was reviewed a decade ago for the first edition of this book, it was estimated that 3–10% of NAFLD cases had NASH [73]. More recent data indicate the proportion could be higher; the aforementioned study on overtly well outpatients at a US Army Healthcare Facility found that 25% of overweight persons with steatosis on ultrasonography had NASH on liver biopsy. A Hong Kong community study reported in 2012 found that ~4% of those with steatosis by MRS had significant liver fibrosis by transient elastography. The development of reliable biomarkers of NASH "activity" (the amount of liver cell apoptosis and necrosis, and the extent of inflammation) [74–76] and fibrosis stage [77, 78] may ultimately be informative as to what proportion of people with NAFLD actually have NASH; the current status and future prospects for non-invasive assessment of NAFLD and NASH, including biomarkers and transient elastography [79], are discussed in Chapter 10.

Risk factors

Who gets NAFLD?

NAFLD is quite unusual in lean individuals, <3% in one recent large survey [80], other diagnoses, such as liver involvement with celiac disease, rarer disorders, or established cirrhosis with catabolism, should be considered [80]. It has been reported that lean cases of NAFLD are not so uncommon in Asian countries, but it remains unclear whether persons who are apparently lean (i.e. their waist circumference, Body Mass Index (BMI), and other anthropometric indices fall with ethnic-specific normal ranges) are truly lean in the metabolic sense. It is quite common for Asian men to gain weight but not to "expand" body measurements outside a broad normal range; they tend to develop insulin resistance and eventually its complications of T2D and metabolic syndrome. The term *lean but metabolically obese* has been coined for this phenomenon. Compartmental studies have characterized skeletal muscle as the initial site of insulin resistance in lean young men at risk of T2D (and likely NAFLD) [81]. The later development of hepatic insulin resistance in NAFLD has been attributed to accumulation of diacylglycerol (DAG) with resultant activation of protein kinase C-epsilon (PKC-ε) [82]. Recent observations indicate that postprandial abnormalities of insulin secretion are a universal finding in NAFLD [83, 84]. This finding is consistent with the proposal that aberrant nutrient handling is pivotal to NAFLD pathogenesis, irrespective of body weight. The extent to which this is genetically determined (as seems likely) requires further study. These issues are discussed in Chapters 5, 14, and 22.

The vast majority of patients with NAFLD have central obesity (Table 1.2) and are overweight or obese. Apart from family history (of fatty liver, T2D, or premature cardiovascular disease) and possibly age and gender, all risk factors for NAFLD are related to the complications of over-nutrition. They include insulin resistance, fasting hyperglycemia, glucose intolerance or T2D, one or more elements of atherogenic dyslipidemia (Table 1.2), and metabolic syndrome; the latter includes arterial hypertension.

The gender profile of NAFLD is age dependent. It is more prevalent in 20–40-year-old men than women [65, 70], but the prevalence in postmenopausal women increases so that most studies demonstrate an approximately equal gender prevalence after the age of 50 years. The relatively lower prevalence in younger women is similar to the protective effect of estrogens against the onset of

Table 1.2 Metabolic associations of NAFLD and NASH*

Central obesity (waist:hip ratio ≥0.85 in women, ≥0.90 in men; waist circumference** ≥94 cm in European men, ≥90 cm in Asian men, and ≥80 cm in European and Asian women)
Overweight (Body Mass Index (BMI) ≥ 25 kg/m^2 in European people, ≥22.5 kg/m^2 in Asian people)
Obesity* (BMI ≥ 30 kg/m^2 in European people, ≥25 kg/m^2 in Asian people)
Insulin resistance, even without glucose intolerance
Glucose intolerance (fasting hyperglycemia, impaired glucose tolerance – prediabetes)
Type 2 diabetes mellitus*
Atherogenic dyslipidemia (any one or more of: low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol, or hypertriglyceridemia)
Arterial hypertension
Metabolic syndrome* (International Diabetes Federation definition is central obesity plus two or more of the above features)
Family history: type 2 diabetes, fatty liver disease, or premature cardiovascular disease

*These features are strongly associated with NASH.
**This is the definition of the International Diabetes Federation: other definitions are more liberal.

cardiovascular disease before the menopause. However, while several studies have found equal gender prevalence of NAFLD in children, one recent cohort study found the condition was more common in girls (16% versus 10%) related to their greater adiposity [85]. (NAFLD in childhood is discussed in Chapter 15.)

Who gets NASH?

The factors associated with severer forms of NAFLD, such as NASH and cirrhosis, are increasing age, more extensive obesity, glucose intolerance or T2D, and the number of components of metabolic syndrome [9, 38, 39, 41, 43, 47, 50, 51, 65, 66, 85]. It is unclear whether the biological effects of aging increase progression to NASH or fibrotic progression to cirrhosis, or whether age is a surrogate indicator of duration of fatty liver disease [86]. Clinical experience and published evidence are that patients often present with cirrhosis complications in the sixth, seventh, eighth, and ninth decades of life [46], but there is often a history of lifelong overweight or obesity that may have resolved at the time of presentation [80]. Some patients give a suggestive or definite history of fatty liver for longer than one decade. More long-term studies are required to establish the separate effects of age and disease duration on severity and liver complications of fatty liver disease, such as HCC (Chapters 16 and 17).

The reproducible relationship between the severity of metabolic disorder (diabetes and three, four, or five components of metabolic syndrome) and NASH is consistent with the lipotoxicity concept of NASH pathogenesis (see Chapter 5). It indicates either that one or more of the metabolic abnormalities cause or result from NASH, or that the liver disease and the metabolic complications are separate manifestations of common pathogenic pathways. Aspects such as adipose inflammation and adipose "failure" or dedifferentiation, particularly with resultant hypoadiponectinemia (strongly associated with severer forms of NAFLD), have been proposed, as recently reviewed [39, 50, 51, 54, 56]. The pathogenesis of NASH is discussed in more detail in Chapter 5.

Presentation, clinical features, and associated disorders

These aspects have been well covered in the first edition of this book [10, 73] and in standard texts, informative original articles, and reviews [9, 11, 41, 43, 69]. Chapter 8 recapitulates these aspects from the point of view of assessment in primary care. In brief, most patients with NAFLD either have no symptoms or have symptoms, like fatigue and right upper-quadrant abdominal discomfort, that are nonspecific. The diagnosis comes to light from finding an enlarged liver on clinical examination, abnormal liver tests not explained by alcohol or other liver disorders in someone who is overweight or who exhibits elements of metabolic syndrome, and/or the finding of increased echogenicity and

other features of fatty liver (Chapters 8 and 9) on ultrasonography. It is increasingly common to consider NAFLD as the diagnosis in persons with obesity and/or T2D who present with complications of cirrhosis or HCC (Chapters 16 and 17). In such cases, there may be clinical features (spider nevi, hard liver edge, splenomegaly, ascites, etc.) that clearly indicate the presence of cirrhosis and its complications, and the diagnosis of NAFLD–cirrhosis is suspected by the presence of risk factors and the exclusion of alcohol and other liver diseases. More recently, the importance of fatigue, which is unrelated to disease severity, impaired quality of life including falls, and possible cognitive impairment have been the subject of attention for people with NAFLD, and this aspect is expanded in Chapter 11.

NAFLD is often diagnosed during assessment or continuing care of patients with diabetes (particularly T2D) (Chapter 6), dyslipidemia, and cardiovascular disease (Chapter 7). It may come to light by the presence of abnormal liver tests in someone for whom cholesterol-lowering "statin" therapy is strongly indicated. As discussed in more detail in Chapters 8 and 26, this is not a contraindication for the use of statins; the presence of metabolic syndrome with NAFLD at any stage (including NASH and cirrhosis) usually provides a strong indication for their use as cardioprotective agents. Whether they may actually benefit liver histology in NASH is discussed in Chapter 26.

In addition to the metabolic associations with NAFLD and NASH that are likely to be etiopathogenically related, some other disorders are associated with NAFLD through their co-association with obesity. In most cases, there are as yet insufficient data to appreciate whether this association is more common than would be expected for a cohort of obese subjects, since NAFLD is so common in obesity. Examples include polycystic ovarian syndrome (in which NAFLD is typically mild), sleep apnea, hypothalamic–pituitary disorders (NASH is often severe), and major psychiatric disorders treated with antidepressants and certain groups of antipsychotic agents which promote weight gain. Another common association that has clinical significance is with colonic polyps and colorectal carcinoma (CRC) (Chapter 17); NAFLD is associated with more polyps, polyps with greater malignant potential, a higher rate of CRC, and worse outcomes from treatment of CRC. The implications for screening are self-evident, particularly among persons aged 40 years or older (they should be subject to colonoscopy). Finally, obese and diabetic patients have a high rate of gallstones; so do patients with NAFLD. It is common to have patients referred for continuing hepatic discomfort or liver test abnormalities after a cholecystectomy when the patient's history of prior biliary colic is unconvincing. It is clearly better to make the correct diagnosis before surgery, so as to either avoid unnecessary surgery or to perform a liver biopsy at surgery (some surgeons are reluctant to do this even when the surface of the liver appears nodular), so prior planning and patient consent are important.

Can we prevent NAFLD?

The statement recently appeared in an article published in a leading hepatology journal that "there is no current management to prevent NAFLD" [87] (top of p, 1621). While all must concede that we face monumental challenges in contemporary society to reverse or ameliorate the obesity and diabetes epidemics (and hence NAFLD) [39, 51], this statement ignores evidence that properly conducted lifestyle interventions impact the incidence of T2D among those with prediabetes for at least 10 years [88]. Further, direct evidence that lifestyle interventions can reverse NAFLD is now increasing (these data are summarized in Chapters 12 and 22) [89–92]. The public health measures that could impact on central obesity and its complications (which include metabolic syndrome, T2D, and NAFLD) in children and adolescents have been reviewed [93]. The view of the editors is that NAFLD (and therefore NASH) was rare before 1970 and its onset now is no more inevitable than is death from cardiovascular disease or lung cancer (both of which are falling in many countries), particularly given current understanding of the risk factors. However, prevention of NAFLD will be effective on a population basis only when contemporary societies are persuaded

to become more physically active and to eat less, as well as to select more prudent food choices (Chapter 22).

At the individual level, highly motivated and well-informed patients with fatty liver frequently lose weight and resolve both liver test abnormalities and imaging evidence of steatosis [89–92]. An emphasis in this book will be to consider ways to achieve this reversal of NAFLD (see Chapters 8, 11, 12, and 22), and thereby the anticipated prevention of adverse health outcomes from liver disease, cardiovascular disease, and common (insulin resistance-related) cancers.

Reversibility of NASH: perspectives on lifestyle, obesity interventions, and drug therapy

NASH is reversible. Liver outcomes after bariatric surgery provide the strongest support for this contention; the evidence is reviewed in Chapter 13. Organized lifestyle intervention programs could also reverse NASH, but there is sparse histological evidence to support this proposal [90, 91]. However, lifestyle intervention programs that involve a behavior-based change in both food intake (and dietary balance) and physical activity have relatively high rates of success in the short term for improving anthropometric and metabolic indices, as well as liver biochemistry tests, typically serum alanine aminotransferase (ALT) levels [89–92]. Most studies have been for only 3 or 6 months, and there are very few outcome studies as long as 2–3 years after the intervention. The recognition of an "archiving effect" from diabetes intervention studies [88], which employed similar programs approximately 10 years ago, is encouraging. However, we need more data before concluding that longer term efficacy against NASH can be achieved by lifestyle intervention.

Enthusiasm may also need to be tempered by the observation that more than 7% loss of body weight may be needed to reverse NASH [90, 91]: this is a lot to achieve and maintain for someone with a Body Mass Index (BMI) of 35 kg/m^2 or more. Further, those who shed weight often regain it: a Japanese study noted that a change in BMI of as little as 1 kg/m^2 was sufficient to precipitate onset of or cause regression of NAFLD [94]. Another daunting recent observation is that the amount of physical activity that "protects" against the development of fibrotic NASH may be substantial. Thus, in the large cohort of patients studied in the NIH NASH Clinical Research Network, only "regular vigorous exercise" was associated with less fibrosis in NASH [91]. The criteria of regular vigorous exercise are more rigorous (and less attainable) than the minimal requirements suggested in guidelines for physical activity or fact sheets of health authorities, such as that of the US Centers for Disease Control [95]. The importance of dietary factors (Chapter 22) and physical activity (Chapter 12) is given detailed attention in this book, and the clinical implications for primary care physicians are outlined in Chapter 8.

As inferred already, many patients with NAFLD, and particularly those with NASH, have morbid obesity (BMI >40 kg/m^2 for Europeans and >35 kg/m^2 for Asians), or have severe obesity (BMI >35 kg/m^2 for Europeans and >30 kg/m^2 for Asians) with metabolic syndrome or T2D. Because of shortened lifespan and generally refractoriness or recidivism to other weight-lowering measures, patients with NAFLD in these weight categories should be considered for bariatric measures. There is some debate about which surgical approach is the most effective and acceptable [96–98], and preferred procedures vary between surgeons and countries. On the other hand, there is little doubt that contemporary approaches (when they achieve weight loss) not only reverse NASH in the vast majority (>75%) of cases [96–98], but also are safe for the liver. In this respect, results are quite different from those observed with jejuno–ileal bypass, which was associated with steatohepatitis and some instances of fatal liver failure, as reviewed by Bode and Bode in the first edition of this book [99]. The evidence that liver fibrosis is reversed after bariatric surgery is more contentious [96–98]. However, the overwhelming concern about bariatric surgery is cost and availability. Chapter 13 provides an excellent overview of all the issues about surgical measures to combat obesity and NASH.

Attempts to treat NASH pharmacologically have been based on the concept that it is a disorder of hepatic lipid partitioning associated with insulin resistance. It was conceived that the hepatocellular injury and fibrosis that distinguish NASH from simple steatosis were separately mediated by inflammation and oxidative stress. It now seems, however, that the inflammation and oxidative stress could be consequences of hepatocyte injury in fatty livers subject to lipotoxicity, rather than its cause. Furthermore, steatosis and liver inflammation both play roles in the development of insulin resistance, as well as its consequence. This may explain why agents such as metformin (which is ineffective [Chapter 24]) and pioglitazone have not been as effective as anticipated. Among insulin sensitizers, pioglitazone is the most promising agent, possibly better in the higher daily dose of 45 mg/day (Chapter 24). However, it seems to benefit only about one third of patients, particularly those without diabetes [35], and there are minimal if any effects on fibrosis [100–103]. Further, pioglitazone would need to be given long term, if not indefinitely, with accompanying weight gain and concerns about cardiac and bone safety in the long term. Together with cost, these issues countermand the introduction of pioglitazone as therapy for NASH; it has still not "hit prime time" [102].

Among anti-inflammatory, anti-oxidant, and hepatoprotective agents, pentoxyphylline and vitamin E have produced interesting but sometimes conflicting results. Most studies are small, with the exception of the Piven study [35, 104]; the design of that study may have been under-powered to detect significant effects of both vitamin E and pioglitazone, and only the vitamin E arm achieved statistical significance (40% reduction of NAFLD activity score by ≥2 points vs. 20% in placebo controls). The evidence is considered more fully, together with practical implications, in Chapter 25.

Attention is now turning to lipid-modifying agents (particularly ezetimibe) [72, 105], including the nuclear receptors that control these pathways, such as farnesyl X receptor (FXR) [106] (Chapter 26). Other agents of interest are those that improve diabetic control, such as glucagon-like peptide 1 (GLP-1) agonists (liraglutide and exenatide) and dipeptidylpeptidase-4 (DPP-4) inhibitors (sitaglipin and vildagliptin) [107–109]. In selected patients, these agents have transformed the management of T2D, with discontinuation of the need for insulin, restoration of appetite control, and healthier body weight. Inhibition of apoptosis is another novel approach to therapy [13]. Thus, while at present there is no pharmacological therapy for NASH, there is hope that effective agents will be developed as more is learned about the pathobiological basis of this disease. An excellent summary of the current landscape of drug treatment of NASH and the future prospects is contained in the concluding three chapters of the book, Chapters 24–26.

Multiple choice questions

1. Which of the following statements about NAFLD is (or are) correct?

- **a.** The diagnosis of NASH can be made with risk factors for NAFLD and the presence of raised serum alanine aminotransferase (ALT).
- **b.** Any alcohol intake in the previous week excludes the diagnosis of NAFLD.
- **c.** Increased hepatic echogenicity with posterior attenuation of the ultrasound signal in a nondrinker with type 2 diabetes is strong evidence of NAFLD.
- **d.** Both hepatitis B and hepatitis C virus infections can cause NAFLD.
- **e.** Tamoxifen use has been associated with fatty liver disease.

2. Which of the following statements about complications and clinical outcomes of NAFLD is (or are) correct?

- **a.** NAFLD does not decrease life expectancy.
- **b.** Alcohol may interact with obesity and type 2 diabetes to increase the risk of cirrhosis.
- **c.** Risk of death from colorectal cancer is increased with NAFLD.
- **d.** NASH increases risk of stroke.
- **e.** NAFLD pathology is often worse in women with polycystic ovarian syndrome.

3. Which of the following statements concerning management is (or are) correct?

a. Bariatric surgery reverses NASH pathology in two thirds or more of cases.
b. At least 12–15% reduction in body weight is required to improve liver tests during dietary interventions.
c. A diabetic diet and 100 minutes of aerobic training each week will normalize liver pathology in 2 years in most patients.
d. The risk of drug-induced liver injury from statin use is increased when NASH causes "hepatic dysfunction" (abnormal liver tests).
e. Metformin is the drug of first choice for NASH, followed by pioglitazone if liver pathology does not improve in 6 months.

Answers are to be found after the Reference List.

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Answers to multiple choice questions

1. c, e
2. b, c, d
3. a