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FATTY LIVER DISEASE: TURNING THE TIDE

A progressive and potentially life-threatening condition previously associated with alcoholism is becoming more common — even in non-drinkers.

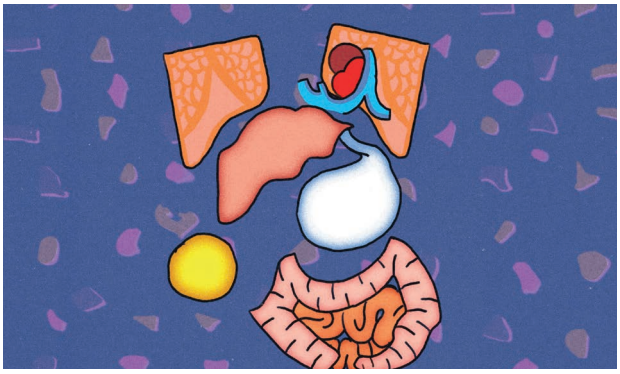
BY LIAM DREW

In July 1980, Jurgen Ludwig and colleagues at Mayo Clinic in Rochester, Minnesota, published the first article to identify non-alcoholic steatohepatitis (NASH) (J. Ludwig *et al. Mayo Clin. Proc.* **55,** 434–438; 1980). At the time, steatohepatitis — an inflammation of the liver that is accompanied by the aberrant accumulation of fat — was thought to be caused by excessive alcohol consumption. But the Mayo study described 20 people with fatty and inflamed livers — none of whom was a heavy drinker. Most had some liver scarring, also known as fibrosis. Three of the patients had cirrhosis, liver damage that results from such scarring. The study also noted that "most patients were moderately obese, and many had obesity-associated diseases".

Although now regarded as a landmark study, the Mayo article had little impact at first. The medical community continued to accept that in people who were not alcoholics, a fatty liver was a benign condition, and that patients with obesity-related diseases had other, greater, concerns.

Throughout the 1980s and 1990s, however, researchers at Mayo Clinic, as well as a small number of other liver specialists such as Oliver James and Christopher Day at Newcastle University, UK, argued that non-alcoholic fatty liver disease (NAFLD), of which NASH represents a moderately advanced stage, was a serious condition in its own right. Epidemiological studies confirmed that obesity and other features of metabolic syndrome — including high blood pressure and insulin resistance — were the main risk factors for NAFLD. And as those two decades became witness to a worldwide epidemic in obesity, doctors came round to the importance of NAFLD — especially as they encountered greater numbers of people with advanced liver disease who were neither alcoholic nor affected by viral hepatitis. NAFLD is now viewed as a considerable health issue, and it affects about 25% of the US population.

NAFLD is a progressive condition. The mildest form is defined as an accumulation of fat in the liver with little or no associated inflammation. But if chronic inflammation ensues, the diagnosis becomes NASH. The presence of NASH substantially increases a person's risk of developing cirrhosis or a type of liver cancer called hepatocellular carcinoma, as well as their chances of experiencing a serious cardiovascular event. Up to 30% of people with NAFLD will go on to develop NASH. Yet questions remain about the pathology of NAFLD and, in particular, why the condition progresses to NASH, and then to cirrhosis or cancer, in only certain people.



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The prevalence of NAFLD is assumed to track trends in obesity and diabetes, although historical levels must be inferred owing to difficulties in diagnosing the condition. Liver biopsy is required to unequivocally identify the presence and severity of NAFLD. Major research initiatives are seeking easy-to-measure factors in blood that correlate with the disease, and others are refining ultrasound techniques to assess liver health. Advances in non-invasive diagnostics will facilitate both the broad monitoring of liver health and the development of drugs for NAFLD.

Weight loss and exercise can reverse mild cases of NAFLD and, possibly, NASH. However, the appreciation that the more advanced stages of NAFLD represent a serious condition, coupled with the well-known challenges of sustaining lifestyle changes and weight loss, have made drug development a priority. The multifaceted nature of NAFLD means an array of compounds is under investigation. Lipid metabolism, insulin resistance, metabolic stress, inflammation, cell death and fibrosis are all essential elements of this condition, and drugs that target each are on trial.

NAFLD now has the attention of the medical and research communities, but it still needs better means of diagnosis, management and treatment.

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