with its constituent blood and lymph vessels, immune cells, and both intrinsic and extrinsic nerve terminals.

A number of factors relevant to the pathogenesis of liver disease can disrupt gut-barrier integrity (Table 3-1). These include ethanol, inflammatory mediators like interferon gamma and TNFα, proteases released from mast cells and neutrophils, and a number of drugs(237). It has been postulated that an overgrowth of gram-negative bacteria, allied to impaired gut barrier function, allows whole organisms – through a process called *translocation* – and/or the gram-negative bacterial component lipopolysaccharide (LPS), endotoxins and other bacterial products to gain access to the portal system(238). While translocation has been repeatedly demonstrated in a host of animal models, its demonstration in man has proven much more challenging due, in large part, to the limitations of currently-available assays(239).

The immune response in the liver: In liver disease, an overgrowth of gram-negative bacteria, allied to impaired gut barrier function, allows whole organisms, through the process called translocation, and/or lipopolysaccharides (LPS) to gain access to the portal circulation(237). In the liver, they then activate the inflammasome complex, resulting in a cascade of pro-inflammatory cytokine production which ultimately leads to liver injury and may be especially important in the progression from steatosis to steatohepatitis and, ultimately, to fibrosis(240).

Summary: While many details remain to be resolved and more work in humans rather than in animal models needs to be performed, a framework incorporating the gut microbiome, the gut barrier, and the immune responses in the intestinal mucosa and the liver has emerged to explain how microbes in the gastrointestinal tract might play a role in the pathogenesis of NAFLD.

c. Current Medical Treatment of Non-Alcoholic Fatty Liver Disease

Current medical treatment for NAFLD is essentially dependent on life-style interventions and modifying the various components of metabolic syndrome: obesity, type 2 diabetes mellitus, insulin resistance, dyslipidaemia, and hypertension. Drug development for NAFLD has been hampered by the condition's heterogeneity, leading to lack of agreement on hard end-points, as well as a relative lack of good biomarkers that could act as surrogate end-points for use in clinical trials.