Advances in the study and treatment of liver diseases

Liver diseases are often underestimated despite being quite common and potentially having serious and even life-threatening consequences, especially in chronic cases. The most common causes of liver diseases are hepatitis viruses, excessive alcohol consumption, and obesity; congenital or autoimmune liver diseases are quite rare. Thanks to advances in medical research, diseases such as hepatitis B and C can be treated effectively. Fewer advances have been made in finding treatments for other diseases, particularly liver cancer.

Liver cirrhosis
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Since the liver plays a major role in the metabolism and in metabolic detoxification, it is exposed to a large number of harmful substances and pathogens. Although the liver cells (hepatocytes) have enormous regenerative capacity, strong toxins, long-term exposure to harmful substances and chronic viral infection can nevertheless lead to permanent damage to the hepatocytes and to cirrhosis, which is the irreversible replacement of healthy tissue by scar tissue (fibrosis). Patients with cirrhosis are at a high risk of developing liver cancer (hepatocellular carcinoma, HCC), which is the most common and most malignant type of liver cancer. HCC is one of the most common fatal tumours. It used to be a relatively rare type of cancer, but its incidence has more than doubled over the last decades.

Viral liver inflammation and liver cancer

Hepatitis C viruses (HCV) seen through the electron microscope.

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Chronic alcohol consumption and chronic inflammation caused by hepatitis viruses (hepatitis B, C and D) are the major causes of liver cirrhosis and liver cancer (with or without previous cirrhosis). In recent years, the study of the molecular mechanisms of these liver diseases has made huge progress, which has enabled the development of therapies for treating virus-induced inflammations of the liver. However, this is not the case for liver cancer, which, according to Prof. Dr. Peter Schirmacher, an internationally reputed pathologist and expert in this field, is a typical example of a tumour that results from the action of viruses, and from metabolic and inflammatory processes. Laboratory results from research into liver cancer have not yet led to a satisfactory transfer into clinical application (see also article entitled "A centre focusing on hepatocellular carcinoma research").

Around 500,000 people in Germany suffer from chronic infection with hepatitis C viruses (HCV). Worldwide, the numbers are much higher. According to the Robert Koch Institute, 100 to 130 million people have chronic HCV infection.

There is no vaccine against hepatitis C. However, there is reason to hope. A team led by Prof. Ralf Bartenschlager (Heidelberg) has developed a cell culture system that enables the propagation of HCV and that has also enabled the team, in cooperation with Prof. Thimme from Freiburg, to elucidate the key mechanisms needed for a successful immune response to this viral infection (see article entitled "Against chronic liver inflammation and liver cancer"). This raises hopes that a successful HCV vaccine will eventually be found. In Europe, chronic hepatitis C is the major cause of liver transplantation. However, the number of patients waiting for a transplant by far exceeds the number of transplantable livers. The early detection of the disease at a time when treatment with interferon and virus blockers is still likely to be successful is therefore paramount. Due to the variability of the virus, unfortunately many people do not respond to these drugs. However, over the past few years, new virus protease inhibitors have been developed and been shown to have a broader effect in combination with other therapies.

Hepatitis B viruses (HBV) seen through the electron microscope.

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The number of people with chronic hepatitis B virus (HBV) infections exceeds the number with chronic hepatitis C. The World Health Organisation estimates that between 300 and 420 million people have the disease worldwide; in Germany, the figures are between 300,000 and 650,000. The risk of infection with HBV is extremely high. However, an effective vaccine is available which, when administered during childhood as recommended by the Standing Committee on Vaccination, protects around 95% of people vaccinated against the possibility of acute infection. Successful treatment of chronic HBV infection is only possible through

transplants. That said, most patients respond well to antiviral drugs that help keep viral propagation at bay.

However, as the viruses tend to become resistant to the drugs, new therapeutic strategies are urgently needed. One such strategy is the use of Myrcludex B, a peptide drug developed by virologist Stephan Urban, which could potentially be effective against the worst of all viral liver diseases, i.e. chronic hepatitis D (see article entitled "Fighting hepatitis viruses with their own weapons"). At present, no effective therapy is available. Hepatitis D virus (HDV) infection only occurs in people who have also been infected with HBV, as the hepatitis D virus requires HBV for propagation. It is estimated that around 30,000 people in Germany, and around 10 million worldwide, suffer from HDV/HBV infections.

Acquired and congenital metabolic diseases of the liver

Fatty liver disease, which is not caused by viruses, has become common in industrial countries, affecting up to 20 percent of the adult population. Fatty liver disease can be due to many causes, but is commonly associated with excessive alcohol consumption, obesity, eating incorrectly or too much food, and lack of physical exercise. Left untreated, chronic non-alcoholic steatohepatitis (NASH) progresses into cirrhosis and liver cancer.

Reducing calorie intake or eating a balanced diet is often not enough to solve the problem. Effective drugs are unavailable, at least for the time being. However, over the past few years, researchers have come up with a number of promising therapies, including a bile acid-phospholipid compound. The biotech company Phenex from Heidelberg has developed drugs for treating NASH and other metabolic diseases of the liver that target the nuclear receptor FRX (Farnesoid X receptor). This receptor plays a key role in the regulation of the gall acid, lipid and carbohydrate metabolism. In January 2015, Phenex sold its FRX programme to the biopharmaceutical company Gilead Sciences who will advance the development of the compound into clinical development.

Congenital metabolic disorders such Wilson's disease, a recessive disease in which copper accumulates in tissue, are relatively rare but pose particular challenges. Sufferers must take drugs for life; in some cases, a liver transplant is the only way to save someone's life. New markers as early indicators that a particular medical therapy does not work are currently being tested at the Heidelberg University Hospital, which houses the largest centre for investigating and treating Wilson's disease in Europe.

Urea cycle defects are severe, life-threatening metabolic disorders for which liver transplants are the only life-saving therapy available. However, this type of treatment is unsuitable for newborns. The biotech company Cytonet has developed a liver cell therapy that can compensate the defect while a child is waiting for a transplant (see article entitled "Liver cell transplantation for the treatment of innate urea cycle defects"). The procedure is already undergoing clinical testing and the eventual aim is to place the procedure on the market. Cytonet's liver cell suspension has already been used to successfully treat adults with acute liver failure. Such new regenerative medicine approaches could potentially replace liver transplants, if not completely, then at least during the time a person is waiting for a transplant.

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