II Falk Gastro-Conference
Dresden (Germany), October 9–14, 2007

Falk Workshop
Mechanisms of Intestinal Inflammation
Dresden, October 9–10, 2007

Falk Symposium 161
Future Perspectives in Gastroenterology
Dresden, October 11–12, 2007

Falk Symposium 162
Liver Cirrhosis: From Pathophysiology to Disease Management
Dresden, October 13–14, 2007
Scientific Organizers

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Foreword

In the ongoing search for the causes of gastrointestinal disorders, scientists have increasingly focused on the molecular level. Their objective is to better understand the function of certain genes and the effects of molecular changes on physiology and pathophysiology, which, in turn, will enhance our understanding of gastrointestinal and hepatological disease entities. This, it is hoped, will provide the basis for novel therapy concepts leading to more adequate management of some challenging disorders. This applies not only to inflammatory bowel diseases but also to diseases of the liver, particularly, liver cirrhosis. The presentation of new data on genetic anomalies and on new approaches in the areas of physiology and pathophysiology provided a common theme through the presentations of the Falk Workshop and Falk Symposia at the II Falk Gastro-Conference in Dresden. Attending this international event were about 1100 participants from over 50 countries.

The scientific organizers arranged a sophisticated forum at which experts in their respective fields presented the newest data and experience on the etiology, diagnosis and treatment of inflammatory bowel diseases, liver cirrhosis and other gastroenterological and hepatological disease entities. Speakers discussed how these new data could be expected to provide the basis for future therapeutic strategies.
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Dresden, October 9–10, 2007

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Inflammatory bowel diseases – The interaction of genes and environment

Inflammatory bowel diseases (IBD) are complex disorders with a polygenic background. According to S. Schreiber (Kiel), however, the pathophysiology of ulcerative colitis and Crohn’s disease is fundamentally different: “Inflammatory bowel diseases are not a uniform entity. Hence, they react differently to different therapeutic strategies.” The genetic background has been especially well studied in Crohn’s disease: The NOD2 gene, with several defined polymorphisms, has long been known to be involved in the pathogenesis of this disease. “Crohn’s disease is an example showing that, even in polygenic disorders, the genetic background can be successfully elucidated,” S. Schreiber said. To date, eight susceptibility regions of the genome have been linked to the pathogenesis of Crohn’s disease. The candidate genes remain the object of study, but it has been shown that there is a high variance with hundreds of thousands of potential polymorphisms in some cases. Thus, even healthy persons may be carriers of polymorphisms associated with these disorders. “In the pathogenesis of Crohn’s disease, we have a number of ‘players’ but only a few have been recognized to date,” S. Schreiber noted (figure 1).
NOD2 is only one of the genetic factors implicated in the etiology of Crohn’s disease (S. Schreiber, Kiel)

Fig. 1

- Crohn’s disease and NOD2
- NOD2 contributes
- NOD2 major factor
- No contribution of NOD2
The IL-23 receptor – Does it play a protective role in Crohn’s disease and ulcerative colitis?

The identification of genes involved in the pathogenesis of the disorder is just part of the picture, said J. Cho (New Haven). Also of importance are the gene-gene interactions, although these are difficult to identify and study. One example is interleukin-23 (IL-23). Beside NOD2, the IL-23 receptor gene region is the genetic factor most strongly associated with Crohn’s disease. This example also underscores the potential importance of even small changes in the signal pathways. Research suggests that one variant of the IL-23 receptor may play a protective role with respect to the development of Crohn’s disease. Other variants, however, do not offer this protection. According to J. Cho, a fully “intact” IL-23 signal pathway is essential for the occurrence of intestinal inflammation. If, due to the presence of different alleles in the receptor gene, there are changes in the signal pathway, it would appear that the inflammatory reaction cannot be sustained. The IL-23 receptor, therefore, would seem to have a protective role. Interestingly, there is also an association between the IL-23R and psoriasis, which may explain the close association between the skin disease and IBD. There does not, however, appear to be any association between the IL-23R and other autoimmune disorders, such as rheumatoid arthritis or systemic lupus erythematosus (SLE).

Crohn’s disease due to lack of defensins?

A reduction in the synthesis of defensins, which act as the body’s own antibiotics, may play a role in the pathogenesis of Crohn’s disease, said J. Wehkamp (Stuttgart). He reported on findings of his own research that showed that especially the Paneth cells in the small bowel mucosa of patients with ileocecal Crohn’s disease produce remarkably small amounts of defensins. It was observed that, following inoculation of bacteria on agar dishes enriched with mucosal extracts from healthy subjects and from patients with ulcerative colitis, there was very little bacterial growth. A corresponding effect was not observed when the agar was enriched with a mucosal extract from Crohn’s patients, a phenomenon that J. Wehkamp ascribed to the reduced production of defensins in these patients (figure 2). The phenomenon may also result in changes of the barrier function, allowing increased penetration of microorganisms of the intestinal flora into the epithelium and lamina propria with subsequent persisting inflammatory stimuli.
Elucidation of these relationships may result in completely new therapeutic concepts. This also holds for the genetic factors, said W. Strober (Bethesda). There is, for example, evidence that NOD2 has a negative regulatory function, while certain gene polymorphisms, as in the case of the IL-23 receptor, may be protective with respect to the development of IBD. “These factors may also be the basis for novel therapeutic approaches,” W. Strober said.

Patients with ileoceleal Crohn’s disease produce remarkably small amounts of defensins (J. Wehkamp, Stuttgart)

Fig. 2

Intestinal bacteria on agar dishes

Enrichment with:

- Mucosal extract from healthy subjects
- Mucosal extract from patients with ulcerative colitis
- Mucosal extract from patients with Crohn’s disease

Nuding et al., Gut*, September 2007
Cytokine expression – Midpoint and lever in the pathogenesis of IBD

The midpoint and lever in the pathogenesis of IBD, said M.F. Neurath (Mainz), is the pattern of cytokine expression, especially of the various interleukins. Research has shown that many of the mediators of this system, including IL-12, IL-23, IL-17, IL-13 and IL-10, as well as other cytokines, such as interferon-gamma (IFN-γ) and the growth factor TGF-β1, are involved. In experimentally induced colitis, there usually is an initial significant increase in the expression of IL-12 and IFN-γ, followed by a more gradual increase in the expression of IL-10, paralleled by a decrease in IL-12. This is followed by an increase in IL-23, IL-17, IL-13 and TGF-β1, although longer-term there is overexpression only of the last two mediators (figure 3).
Interleukin-13: Its role is decisive

"After binding to their specific receptors, the cytokines activate the expression of certain gene patterns and in this way control the activity of the T effector cells," M.F. Neurath explained. In the longer term, however, it is IL-13 in particular that has central importance, said S. Fichtner-Feigl (Regensburg). In ulcerative colitis, IL-13 is the cytokine that is believed to play the decisive role in maintaining the chronic inflammatory reaction and in the induction of fibrotic processes. In addition, there are probably further factors involved in the etiology and pathogenesis, such as the nuclear orphan receptor RORγt, cited by D.R. Littmann (New York), or selective populations of natural T killer cells (NKT cells), whose role has been studied in depth by I.J. Fuss (Bethesda).
Intestinal microflora – An important pathogenetic factor

The effect of the intestinal microflora must also be included in the pathogenetic equation. There are different microbial populations colonizing the bowel that may have pathogenetic importance in IBD. “We have to identify the microbial antigens that trigger inflammatory bowel diseases,” emphasized G.W. Tannock (Dunedin).

As is the case with genetic studies, however, the situation is highly complex, especially because of connections with other disease entities, particularly the chronic inflammatory forms of arthritis R. Duchmann (Frankfurt) said. The intestinal microflora may be the missing link between these disorders. According to M. Boirivant (Rome), it also appears to be centrally involved through the bowel’s own immune system in the regulation of tolerance and in general bowel homeostasis.

In this connection, one must also not overlook the so-called toll-like receptors (TLR), said S. Rakoff-Nahoum (New Haven). The TLRs play an important role in direct association with the defensins in the immune defense against infections and inflammatory processes in the bowel. There are both TLR-dependent and TLR-independent inflammation mechanisms. The interaction with the commensal microflora appears to be important for a healthy equilibrium in the bowel and for maintaining normal bowel function. It appears that individual TLRs may be activated and in such situations participate in repair mechanisms and epithelial regeneration (figure 4).
Toll-like receptors play an important role in maintaining the barrier function in the bowel (S. Rakoff-Nahoum, New Haven)
Epithelial Barrier Function in Inflammatory Bowel Disease

Chair:
L. Mayer, New York
D. K. Podolsky, Boston

Toll-like receptors maintain the barrier function
According to E. Cario (Essen), the toll-like receptors (TLRs) not only have the function of maintaining the barrier function of the intestinal mucosa, but they also control the immune system and contribute to assuring that homeostasis is maintained between the intestinal microflora and the mucosa. This is especially true for TLR2, as has been shown by E. Cario’s own research. TLR2, however, could also represent a new target for pharmacological measures aimed at influencing mucosal damage and IBD.

The barrier function, however, is not controlled by TLR alone. According to J.-D. Schulzke (Berlin), other factors, in particular, interleukin-13, are active. This mediator is especially important in ulcerative colitis, in which it disturbs the barrier function and stimulates apoptosis of epithelial cells. These effects are mediated through the phosphatidylinositol-3-kinase signal pathway.

Transcription factors control the inflammatory process in the bowel
Equally important is the NFκB pathway, said M. Pasparakis (Cologne). The transcription factor can be stimulated by different proteins (figure 5).

Another transcription factor that is important for the pathogenesis of IBD is XBP1 (X-box binding protein 1), which appears to be synthesized by the endoplasmatic reticulum as a reaction to stress, said A. Kaser (Innsbruck).

The transcription factor controls the function of the Paneth cells and in this way affects the synthesis of defensins. It thus exerts an influence over the intestinal antimicrobial function and is also involved in the regulation of the inflammatory status in the bowel. Disturbance of XBP1 results in spontaneous enteritis according to findings reported by A. Kaser.
The NF-κB signaling pathway

NF-κB activating stimuli

NEMO

Phosphorylation of IκB

Ubiquitination of IκB

Proteasomal degradation of IκB

NF-κB responsive genes

Cytokines, chemokines
Adhesion molecules
Acute phase proteins
Anti-apoptotic proteins

Fig. 5

The NF-κB signaling pathway influences the maintenance of the barrier function (M. Pasparakis, Cologne)
Regulatory T cells play a central role in ulcerative colitis

Intestinal inflammation is not controlled by mediator substances alone, but, according to A. Kitani (Bethesda), in ulcerative colitis, regulatory T cells play a decisive role. The regulatory T cells, however, are affected in their activity by various mediators (figure 6). Here, said G. Monteleone (Rome), we are dealing with a whole bundle of mediator substances, which can also interact with and affect one another. How complex this regulatory system truly is and how many individual mediators are involved, was made clear by R.S. Blumberg (Boston), who reported his studies on carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) isoforms.

In describing the carefully balanced interaction of pro- and anti-inflammatory cytokines, F. Powrie (Oxford) explained how this serves to control the regulatory T cells, which in turn regulate the T effector cells. In animal experiments, the regulatory T cells protect against inflammatory reactions. If the activity of these cells is suppressed, as may occur in response to pro-inflammatory cytokines, inflammation may develop and lead ultimately to ulcerative colitis.
Regulatory T cells (Treg) control intestinal inflammation in association with T helper cells (Th) and mediators (A. Kitani, Bethesda)
Crohn’s disease and ulcerative colitis: Dysbalance of the immune system

It is generally accepted today that immunological changes ultimately underlie the development of Crohn’s disease and ulcerative colitis, said W. Strober. This dysregulation can affect both the inborn and the acquired immune system and practically always results in an imbalance in the activity of the effector cells and regulatory T cells. “The interplay of these two cell types decides whether or not a chronic inflammatory reaction will occur,” W. Strober emphasized (figure 7).

Environmental factors and bacteria from the physiological intestinal microflora may trigger the effects of this dysbalance and may be important in making the inflammation chronic. These processes, in the case of Crohn’s disease, lead to activation of Th1 or Th17 cytokine expression patterns, while in ulcerative colitis the relationship between T1 helper cells (Th1) and T2 helper cells (Th2) is decisive. An exact elucidation of these relationships, W. Strober believes, would open completely new vistas in the treatment of IBD.
Homeostasis in the bowel represents a balanced interplay between effector cells and regulatory cells (W. Strober, Bethesda).
**Inflammatory bowel diseases: Changes in cytokine expression**

According to C.O. Elson (Birmingham), an altered pattern of cytokine expression is the basis of the persisting inflammation in Crohn's disease. The pro-inflammatory cytokines interleukin-12 and interleukin-23 are particularly important. Common to both is the protein p40 but they stimulate different signal pathways. Both, however, result in an imbalance between regulatory cells and effector cells in which pro-inflammatory signals dominate. In ulcerative colitis, on the other hand, T2 helper cells and interleukin-13 released from the natural killer cells (NKT cells) play a de-
cisive role in disease development. The complexity with which this system is regulated was illustrated by C. O. Elson with the example of IL-12, which represents an entire family of mediators (figure 8).

The different cytokines are controlled by genetic factors. To date, more than 200 genes have been identified that are involved in the regulation of this system. They affect the degree to which the cytokine pattern is expressed and thus exert a direct influence on the relationship between effector cells and regulatory cells (figure 9).

The activity of effector cells and regulatory T cells is controlled by a variety of different T helper cells, which, in turn, are controlled by cytokines (C. O. Elson, Birmingham).
Better understanding of the disease as the basis for new therapy options

A central objective of research into IBD is to better understand the mechanisms that underlie the chronic inflammation, said A. Stallmach (Jena). “Our mission for the future cannot simply be to identify more and more genes that might be involved in the disease process. Instead, we must more closely study the function of the genes that we already know and learn to understand them better,” A. Stallmach said. “This is the only way to develop new and possible causally oriented therapy options.”

As an example, A. Stallmach cited new data on the role of the defensins, which might potentially lead to the development of therapy strategies with which to boost the bowel’s defenses against penetration by bacteria from the intestinal flora. “We know that the bacterial flora is important even though we have yet to identify a specific pathogen that is responsible for Crohn’s disease or ulcerative colitis (figures 10–12).”
Esophagus and Stomach
Chair:
P. Malfertheiner, Magdeburg

Carcinogenesis with Helicobacter pylori has a genetic background
A genetic background is to be sought not only for the IBD but also for the development of gastric carcinoma, E.M. El-Omar (Aberdeen) said. This hold also for carcinogenesis developing on the foundation of a Helicobacter pylori (Hp) infection. “There are genes that apparently protect some patients suffering from an infection with Hp, while other genetic constellations trigger carcinogenesis in such cases.”

The first barrier that protects the stomach against colonization by bacteria is the gastric acid secretion. The production of gastric acid, however, must be precisely regulated. If too little acid is produced, there can be problems with the absorption of iron, calcium, vitamin B₁₂ and other nutrients from the food. “If too much acid is produced, however, patients are at risk for damage to the esophagus, the stomach and the small bowel,” E.M. El-Omar warned.

A mucus layer protects the stomach from “self-digestion”. Further defense mechanisms cited by E.M. El-Omar include the secretion of bicarbonate, the high polarity of the surface epithelial cells and the tight junctions between neighboring epithelial cells (figure 13).

Parietal cells may be lost as a consequence of Hp infection
Whether gastric acid is produced in excess depends on whether the stomach has been colonized with Helicobacter pylori. Hp infection results in inflammation of the gastric mucosa and, initially, an increased production of gastrin, which, in turn, triggers secretion of gastric acid from the parietal cells. If the inflammation becomes chronic, there is risk of duodenal ulcers; severe inflammation of the gastric corpus, however, leads to reduced ability to produce gastric acid. The parietal cells atrophy and this results in achlorhydria. “This is a significant risk factor for the development of gastric carcinoma,” said E.M. El-Omar (figure 14).
**Fig. 13**
Structure of the acid-producing gastric glands (E.M. El-Omar, Aberdeen)

**Fig. 14**
Helicobacter pylori infection results in destruction of the parietal cells (E.M. El-Omar, Aberdeen)
Reflux esophagitis: Proton pump inhibitors lifelong or endoscopic therapy?

Conversely, excess production of gastric acid promotes the development of reflux esophagitis. The prevalence of gastroesophageal reflux disease (GERD) stands at 10–12% of the population in the Western world. “According to data from the Federal Statistical Service, about one in three persons surveyed in Germany reports suffering from reflux symptoms,” emphasized K. Caca (Ludwigsburg; figure 15).

"These patients often require lifelong administration of proton pump inhibitors since the tormenting heartburn nearly always quickly returns once medication has been discontinued," K. Caca continued. In his opinion, a potential alternative is endoscopic therapy. The implantation of a biocompatible polymer has been shown to be unsuccessful due to resulting serious adverse effects. On the other hand, radiofrequency application has resulted in symptomatic improvement, although the precise mechanisms of action have not yet been elucidated. In addition, some endoscopic suturing techniques have been shown to be helpful, K. Caca said, although there is a lack of long-term data on these methods (figure 16).

Fig. 15

Prevalence of symptomatic reflux disease in Germany

The German National Health Interview and Examination Survey (GNHIES):

n = 7124 (18–79 years)

Source: Federal Statistical Service 2004

Nocon, Labenz, Willich 2006

One in three persons in Germany reports reflux symptoms

(K. Caca, Ludwigsburg)
Endoscopic techniques offer an alternative to pharmacological GERD therapy (K. Caca, Ludwigsburg)

- Radiofrequency application (Stretta)
- Injection/Implantation (Enteryx, Gatekeeper)
- Suture techniques (EndoClinch, Plicator, Esophyx)
Dyspepsia – The worldwide prevalence stands at 25 percent

Even more common than GERD is the condition known as functional dyspepsia, whose prevalence worldwide has been estimated at an average 25%, said H. Mönnikes (Berlin). The current ROME criteria differentiate between a “post-prandial distress syndrome” in which postprandial feeling of fullness and early satiation predominate, and an “epigastric pain syndrome” that is characterized by epigastric pain and burning. Of pathogenetic importance, H. Mönnikes explained, are an altered sensory and motor function, visceral hypersensitivity, psychological stress, a reduced acid clearance and also infection with H. pylori and inflammation.

The diagnosis of functional dyspepsia is still generally made by exclusion of other disorders, such as GERD or IBD. Increasingly, however, there are positive diagnostic options available, such as the H2- and 13C breath tests. Therapy consists in changes of lifestyle, smoking cessation and transition to smaller, more frequent meals with avoidance of any irritating foods. Depending on the predominant symptoms, patients with feelings of fullness may benefit, for example, from use of prokinetic agents. If excess acid production is an issue, proton pump inhibitors may be used. Patients with pain may benefit from antidepressants. According to H. Mönnikes, an Hp eradication should also be considered.
Cholesterol – A double-edged sword
A normal cholesterol balance is of decisive importance for health, said D.E. Cohen (Boston): “We have learned in recent years that the LDL cholesterol level should be much lower than had long been thought to keep cardiovascular risks low.” On the other hand, cholesterol serves as the substrate for steroid hormones and it is an important component of cell membranes. As a result, it is synthesized in practically every cell of the body.

Cholesterol is broken down only in the liver and is then excreted with the bile. About 50% of biliary cholesterol and bile acids, D.E. Cohen explained, are re-absorbed from the bowel into the enterohepatic circulation. Only about 0.4 grams are lost each day with the stool. “This is the same rate at which cholesterol is synthesized in the liver: This regulates the cholesterol balance” (figure 17).

Fig. 17

Bile acids are re-absorbed through the enterohepatic circulation
(D.E. Cohen, Boston)
Transport proteins must be regulated
The bile salts are absorbed and transported by means of specific transport proteins. According to a hypothesis proposed by A.W. Wolkoff (New York), the subcellular localization of the bile salts directly regulates their function. The microtubuli are involved in the transport function. The importance of this process should not be underestimated since the same transport proteins are involved in the absorption and distribution of pharmacological agents. Disturbances in the function of this system can have consequences for the individual uptake and metabolism of drugs.

Dysregulation of the bile fluid may cause cholestatic liver diseases
Functions of the bile include stimulation of “exocrine” lipid secretion, the elimination of cholesterol, the facilitation of lipid absorption from the food, the promotion of protein and carbohydrate digestion and the distribution of immunoglobulins and antioxidants in the bowel, said M.C. Carey (Boston). Phospholipids make up about 22% of the human bile fluid. Bile salts make up about 68%, including cholate, chenodeoxycholate and deoxycholate. According to M.C. Carey, normal secretion of bile fluid is essential for maintaining homeostasis and for the metabolic, biophysical/chemical and immunological health of the organism. Disturbances of this function lead to gastrointestinal disorders such as cholestatic liver diseases or the development of gallstones.
Gallstones form as a result of the hepatic hypersecretion of cholesterol

The prevalence of gallstone disease, said F. Lammert (Bonn; since January 1st, 2008 in Homburg), stands at 10–20% in Europe and the United States. In Germany alone about 190,000 cholecystectomies are performed annually due to this disorder. Cholesterol gallstones are present in about 90% of cases. This is explained by the pathogenesis of gallstones, which primarily develop as a result of hepatic hypersecretion of cholesterol combined with reduced motility of the gallbladder. About 2% of patients suffer from black pigment stones that consist predominantly of bilirubin, while about 10% of patients have calcified brown pigment stones (figure 18).

In most cases, gallstones consist mainly of cholesterol (F. Lammert, Bonn/Homburg)

Fig. 18

Gallstones: Classification

Schafmayer et al. BMC Gastroenterol (2006)
Coming soon: The individual lithogenic signature?
Although studies of twins have provided evidence for a genetic predisposition, environmental factors appear to be decisively involved in the development of gallstones, F. Lammert said. Factors that promote the formation of gallstones include, for example, high-calorie and low-fiber diets, physical inactivity, overweight and a metabolic syndrome but also precipitous weight loss and estrogen substitution. Based on understanding of these genetic and environmental factors, it may be possible in the future to construct a kind of individual “lithogenic signature”. Persons with identified high-risk constellations could be offered prophylactic treatment, such as ursodeoxycholic acid or, in special cases, even prophylactic cholecystectomy.

Don’t forget carcinoma of the papilla of Vater
Work-up of diseases of the bile ducts must not overlook bile duct carcinoma, W. Kimura (Yamagata) warned. Not infrequently affected is the papilla of Vater. Here, two different types of carcinoma must be differentiated: The pancreaticobiliary type and the intestinal type. In the case of the latter, survival after resection is better than with pancreaticobiliary carcinoma of the papilla (figure 19). Other potential disorders of the bile ducts, said S. Jonas (Berlin), include congenital malformations and dilatations of the bile ducts due to cysts, bile duct diverticula, stenoses and also leakage secondary to injuries.

Fig. 19

Carcinoma of the papilla of Vater
(W. Kimura, Yamagata)
Candidate genes for chronic pancreatitis have been identified

This also applies to the genetic background of chronic pancreatitis, a disease entity that shows clear increased frequency in some families. It long remained unclear, however, which genes might facilitate development of this disease, said H. Witt (Berlin). Research has identified several candidate genes, mutations of which may favor the development of chronic pancreatitis. “We are speaking here both about new friends and also about some old kids on the block,” H. Witt said. As example, he cited SPINK1, a pancreatitis gene, some mutations of which are known to be associated with idiopathic chronic pancreatitis: “Based on present knowledge, these represent the strongest single risk factor for developing the disease” (figure 20).

The molecular machinery behind the secretion of pancreatic enzymes is better understood

As with IBD, research into disorders of the pancreas has increasingly focused on study of the molecular interactions. It is now well known that the pancreatic enzymes are synthesized in the rough endoplasmatic reticulum and then pass through the Golgi apparatus, where they are packed into secretory vesicles. These vesicles are then transported along the microtubuli of the cytoskeleton to the cell membrane where, guided by a network of actin filaments, they dock on the membrane and fuse with it, allowing the enzymes to be released from the cell. “This last step is carefully controlled by intracellular messengers,” reported J.A. Williams (Ann Arbor). The molecular machinery of enzyme production in the pancreas is increasingly well known, as are the regulatory signals that follow it.

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**Serine Protease Inhibitor, Kazal Type 1**

1. **SPINK1 appears to trigger chronic pancreatitis (H. Witt, Berlin)**

**Autophagia – Autocannibalism from within**

By comparison still mostly unknown is the process of autophagia, as J.L. Iovanna (Marseille) observed. The phenomenon of autodigestion in the pancreas appears to be induced by stress reactions. “We are dealing here with a kind of autocannibalism,” J.L. Iovanna explained. The process involves formation of invaginations in the membrane which finally bud off to form autophagosomes, which fuse with lysosomes and are themselves digested within the cell. Parallel to this, the cell organelles deteriorate and the cell practically dissolves from within. According to J.L. Iovanna, it is known that the phenomenon of autophagia is triggered by the transmembrane protein VMP1 (vacuole membrane protein 1). How this protein is regulated, however, remains unclear.
Acute Pancreatitis: Mortality on the decline

Significant progress can be reported in the area of acute pancreatitis. About one-half of all cases are caused by choledolithiasis but, as G. Adler (Ulm) observed, “another 30% are due to chronic alcohol abuse.” Other, less common causes include obstructions due to carcinoma, as well as drug reactions and hypercalcemia. The diagnosis is made on the basis of clinical symptoms and the increase in serum lipase concentrations. Close monitoring of the patient is crucial, G. Adler noted. Mortality associated with acute pancreatitis has declined, not least because of improvements in intensive care (figure 21).

Fig. 21

There has been a significant reduction in mortality associated with acute pancreatitis (G. Adler, Ulm)
An argument for an early return to enteral nutrition

Patients with severe acute pancreatitis can often be re-started on enteral nutrition at an early point. Studies addressing this question have clearly shown a reduction in the risk of infection and also of the general complication rate. Whether antibiotic prophylaxis is generally indicated remains controversial.

Paradigm shift necessary in our understanding of the disease

Speaking in Dresden, D.C. Whitcomb (Pittsburgh) argued for a paradigm shift in our understanding of the pathogenesis of chronic pancreatitis. He cited three reasons: "First, we are increasingly coming to recognize that complex genetic factors trigger the development of pancreatitis. Second, we have learned that development of the disease involves a variety of cell types and that significant changes have already occurred even before the pancreatitis becomes manifest. Third, we have observed in our patients quite divergent mechanisms of disease development that merge in chronic pancreatitis as a common final pathway" (figure 22).

D.C. Whitcomb therefore argued for a more careful differentiation of the disorder as it developed in each individual case. Progress in the diagnosis and therapy of chronic pancreatitis will in his view depend especially on the development of genetic tests and on the measurement of biomarkers, an area that is currently under intense investigation, said C.D. Logsdon (Houston).

Fig. 22

1 Diagnosis of chronic pancreatitis: Histology (D.C. Whitcomb, Pittsburgh)
The future of endoscopy in gastroenterology

Significant progress has also been made in the field of endoscopy, said M. Classen (Munich). Progress is reported for two different spheres. First, it has been possible to examine increasingly small cavities, such as the small pancreatic ducts. Second, more and more therapeutic interventions have become routine using a method originally confined to diagnosis. “The therapeutic importance of endoscopy should continue to increase,” according to the assessment of J.F. Riemann (Ludwigshafen; figure 23).

Fig. 23

Endoscopy continues making inroads into the therapeutic sphere (J.F. Riemann, Ludwigshafen)
“Endoscopy Centers” – Coming to your neighborhood?
Endoscopy continues to evolve from a purely diagnostic to a therapeutic discipline. Natural orifice transluminal endoscopic surgery (NOTES) has already provided an alternative for a number of open or laparoscopic surgical procedures, such as cholecystectomy. In addition, the introduction of capsule endoscopy has made the “black box” of the small intestine accessible. “We can endoscopically examine practically the entire small bowel,” J.F. Riemann noted. He described the capacity for endoscopic ultrasound as a particularly important advance.

In the area of early diagnosis of cancer J.F. Riemann expected an even greater role for endoscopic techniques in the future, which may also see advances in methods such as virtual colonoscopy. Endoscopy requires an increasingly interdisciplinary approach and he expects that, like the current “Abdomen Centers”, “Endoscopy Centers” will begin to be established.
Gastric cancer – Main risk factor is *Helicobacter pylori*

Much more common are gastrointestinal lymphomas. Here, according to W. Fischbach (Aschaffenburg), it is important to distinguish between MALT lymphomas (mucosa-associated lymphoid tissue) and large B-cell lymphomas. An important cause of MALT lymphoma is colonization of the stomach by *Helicobacter pylori* (Hp).

“About one percent of Hp-positive patients develop MALT lymphoma,” W. Fischbach said. “*Helicobacter pylori* thus is the most important risk factor for gastric cancer,” M. Ebert (Munich) added. Carcinogenesis develops on the basis of chronic gastritis and atrophy leading to intestinal metaplasia, dysplasia and, finally, manifest malignant disease. *Helicobacter pylori* promotes development of chronic gastritis, as well as of atrophy and the development of intestinal metaplasia (figure 24).

Despite declining incidence figures, gastric cancer remains the fourth-most common malignancy worldwide, M. Ebert noted. Due to the current demographic development, an increase in prevalence can be expected.
Helicobacter pylori is a crucial trigger in the development of gastric cancer (M. Ebert, Munich)
Increasing incidence of pancreatic carcinoma

That disease entities that develop in the gastrointestinal tract can have consequences throughout the body was illustrated by M. Otsuki (Kitakyushu) based on the example of the pancreas. His own findings suggest that one-third of patients with chronic pancreatitis develop diabetes mellitus within eight years of diagnosis. As is the case with gastric carcinoma, increasing numbers of patients with pancreatic carcinoma can be expected, said R.M. Schmid (Munich), although, unlike with gastric cancer the growth is due to an increase in the incidence of the disease. The prognosis of the disease is very poor, with a five-year survival rate of only 4%. The increasing incidence seems to be due to general progress in cancer therapy, because of which patients more frequently survive other tumors only to then develop pancreatic carcinoma, R.M. Schmid said.

Ductal adenocarcinoma is present in 90% of patients, but in a vast majority of cases is first diagnosed in an advanced stage. At that time, a complete resection is rarely feasible and there is often infiltration into neighboring tissue and metastasis of the lymph nodes, peritoneum and liver.

A genetic predisposition to pancreatic carcinoma is well documented. In fact, the risk of developing this tumor is five times higher in persons with a first-degree relative who has been diagnosed with cancer of the pancreas. Further risk factors include chronic pancreatitis, smoking and obesity, R.M. Schmid said (figure 25).

Positive family history, obesity and smoking are the most important risk factors for pancreatic carcinoma (R.M. Schmid, Munich)
Hepatocellular carcinoma – Risk factors are many and varied

One of the most frequent gastrointestinal tumors, said H.E. Blum (Freiburg), is hepatocellular carcinoma (HCC; figure 26). Although the process of carcinogenesis leading to HCC is increasingly well understood, this has not translated into any significant improvement in survival rates in recent years. Like pancreatic carcinoma, this tumor often first becomes symptomatic in an advanced stage and this significantly delays diagnosis.

The most important risk factors for HCC, said H.E. Blum, are chronic hepatitis, developing on the basis of a viral infection, alcohol-induced damage or damage due to other toxins, such as the aflatoxins. However, the metabolic syndrome should also be seen as a risk factor for HCC, since it can lead to non-alcoholic steatohepatitis (NASH), subsequently to liver cirrhosis and, finally, HCC.

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Hepatocellular carcinoma – Incidence

![Hepatocellular carcinoma Incidence Map](image)

1 Hepatocellular carcinoma is especially prevalent in Asia and in parts of Africa (H.E. Blum, Freiburg)
Multiple steps on the path to colon carcinoma

There are also multiple steps in the carcinogenesis of colon cancer, said C.R. Boland (Dallas). With these tumors as well there is evidence that viruses, especially the polyoma viruses, may be involved in the malignant transformation of cells (figure 27). There are some differences with respect to certain disease entities in tropical regions, said R.K. Tandon (New Delhi). As examples, he cited sprue, pancreatitis and intestinal infections, which, because of hygienic conditions in developing countries, are a more significant health concern than in Europe or North America. However, even in the tropics, disease entities more typical for Western industrialized countries are becoming more frequent, such as metabolic syndrome, reflux esophagitis, diverticular disease and last but not least also the inflammatory bowel diseases, R.K. Tandon said.

Fig. 27

Colon cancer develops on the basis of adenomas as an intermediate stage (C.R. Boland, Dallas)
Falk Symposium 162
Liver Cirrhosis: From Pathophysiology to Disease Management
Dresden, October 13–14, 2007

Pathomechanisms of Fibrogenesis (1)
Chair:
S.L. Friedman, New York
D. Häussinger, Düsseldorf

Fibrogenesis – A highly complex process
Current data suggest that the pathogenesis of chronic liver diseases is just as complex as that of IBD. Cytotoxic agents, said H.W. Jaeschke (Kansas City), lead to apoptosis, to programmed cell death, with reduction in cell size, fragmentation and destruction of the cells, or to necrosis, which typically begins with swelling of the cell and its subsequent destruction. Which pathway is ultimately taken depends not least on the energetic status of the tissue. There are also overlaps between the two mechanisms, whose final stretch, however, is comparable and ends with cell demise. Both processes also activate the hepatic stellate cells and the development of liver fibrosis (figure 28).

Liver fibrosis is based on cell demise – whether by apoptosis or necrosis (H.W. Jaeschke, Kansas City)
Liver and bowel diseases are closely linked

The close connection between diseases of the liver and bowel is clearly seen in the example of primary sclerosing cholangitis (PSC): In about 70% of cases, patients also suffer from an IBD. Conversely, about 3–10% of patients with IBD also develop PSC, said D.K. Adams (Birmingham). A link between the liver and bowel as organ systems is seen in the expression of homing receptors for lymphocytes, which occur physiologically only on the bowel, in the endothelial cells of the liver: Thus, T cells that are activated in the bowel can also be recruited in the liver and lead to inflammatory processes in that organ. In fact, memory cells may migrate between the liver and bowel for a period of years, though they ultimately settle in the liver. Similar mechanisms may also explain the development of extraintestinal complications in IBD (figure 29).

Fig. 29

Gut and liver: What is the link?

Enterohepatic recirculation of lymphocytes
– Lymphocytes primed in the gut recirculate through the liver
– Memory cells are long-lived and will continue to recirculate for many years
– The chance of responding subsequently to modified-self or foreign antigens in the liver is increased

Model to explain the connection between liver and bowel diseases (D.K. Adams, Birmingham)
Inflammation – A double-edged sword

Activation of the immune system can be a double-edged sword in liver diseases. According to U. Spengler (Bonn) this can be seen in the case of infection with the hepatitis C virus, to which the organism responds with inflammatory reactions. The damage to the liver appears to be due more to the activation of the immune system than to replication of the virus itself. The inflammation is especially important in the acute phase of the infection in order to eliminate the virus. If this is unsuccessful and the persisting activation of the immune system leads to chronic hepatitis, this opens the door to the development of liver fibrosis and, ultimately, liver cirrhosis (figure 30).

Fig. 30

A defect in the cell-mediated immune reactions allows for increasing viral load in cases of hepatitis C infection (U. Spengler, Bonn)
Cytokines also play a central role in liver diseases

Intestinal bacteria that cross the bowel wall by translocation and reach the liver through the enterohepatic circulation may, as in the bowel, trigger inflammatory processes, which, mediated by cytokines, may affect the function of the hepatocytes. Analogous to the situation in the bowel, cytokines play a central role in inflammatory processes in the liver. For example, in non-alcoholic steatohepatitis (NASH), involvement of interleukin-6 and tumor necrosis factor alpha (TNF-α) has been documented. “These two substances, however, do not only mediate inflammation in the liver,” C. Trautwein (Aachen) observed. Their synthesis is triggered by high-calorie, high-lipid diet and they are also centrally involved in the development of insulin resistance. There is resulting increase in blood glucose levels, with a parallel development of inflammation in the liver. Closely associated with these processes is an elevated triglyceride level (figure 31).

\[ \text{Fig. 31} \]

High-fat diet triggers increased cytokine expression

\[ \text{Increased expression of IL-1β, IL-6 and TNF-α due to high-calorie, high-lipid diet} \]
\[ \text{(C. Trautwein, Aachen)} \]
**Pathomechanisms of Fibrogenesis (2)**
Chair:
A.M. Gressner, Aachen
F. Lammert, Bonn/Homburg

**Dysbalance of cytokines**
The enormous importance of cytokines and chemokines in the development of liver fibrosis was illustrated by R. Weiskirchen (Aachen). Besides a number of pro-inflammatory cytokines, such as IL-12, IL1-β, TNF-α and IFN-γ, there is also a group of anti-inflammatory cytokines, such as IL-4, IL-10, IL-13 und IL1-Ra. Of decisive importance is their overall effect especially on the hepatic stellate cells, which, in response to excessive activation, transdifferentiate to myofibroblasts and participate in the fibrotic process of the liver. When the pro-inflammatory cytokines predominate, inflammation becomes manifest. There are further cytokines which, based on this inflammatory reaction, open the way for fibrosis. This second step is probably also characterized by a dysbalance of cytokines. The development of fibrosis is promoted by TGF-β, TNF-α, and growth factors such as PDGF (platelet-derived growth factor) and by IL-1 (figure 32).

**Fig. 32**

**Cytokines in liver fibrogenesis**

**Inflammation**
- PRO-
  - IL-1β
  - IL-12
  - TNF-α
  - TGF-β
  - IFN-γ
  - IL-18
- ANTI-
  - IL-4
  - IL-10
  - IL-13
  - IL1-Ra
  - sTNF-α-R

**Fibrosis**
- PRO-
  - TGF-β
  - TNF-α
  - PDGF
  - bFGF
  - ET-1
  - IL-1
  - IGF-1
- ANTI-
  - HGF
  - IFN-γ
  - IL-10
  - BMP-7

The development of liver fibrosis is controlled by cytokines (R. Weiskirchen, Aachen)
**Fibrogenesis – There is also a genetic component**

There is, in addition, a clear genetic component in fibrogenesis, added F. Lammert (Bonn; since January 1st, 2008 in Homburg). When confronted with toxins in the liver, the result may be a "fibrotic response". This latter phenomenon, however, may range in severity, as shown by a study of 1157 patients with chronic hepatitis C infection. In the study collective, there were patients who very rapidly developed fibrosis, while others showed only an intermediate response or in whom only a very slow fibrotic transformation could be observed (figure 33).

**Can we expect a “fibrosis fingerprint”?**

That some patients apparently synthesize and deposit excessive extracellular matrix (ECM) would seem to be due to hereditary factors. This would explain the observed differences in disease progression. What is certain, however, is that this is not a monogenic phenomenon. It is much more likely that we are dealing with complex interactions between multiple genetic factors.

**Fig. 33**

*The development of fibrosis shows wide individual differences (F. Lammert, Bonn/Homburg)*
factors, the disease process being also influenced by environmental factors such as diet and possible viral infections (figure 34). Hence, it may be possible in the future to identify the genetic determinants and then, using new technologies such as genomics, proteomics and glycomics, predict the individual patient’s risk for developing liver fibrosis.

Fig. 34

Liver fibrosis: Complex trait

- Environmental factors (e.g. diet, virus)
- Multiple genetic risk factors (polygenic trait)
- Gene × gene interaction (epistasis)
- Interaction between genetic and environmental factors

Genetic risk factors

G × E interaction

Environmental factors

Peltonen & McKusick Science (2001)

Fibrogenesis is also a complex process consisting of interactions between genetic and environmental factors (F. Lammert, Bonn/Homburg)
From NASH to progressive liver fibrosis
Such capabilities would be of especial relevance to patients with NASH, who would clearly benefit from a reliable estimate of their relative risk that an existing metabolic syndrome would progress to NASH with complications such as cirrhosis, liver failure and hepatocellular carcinoma. In the majority of patients with metabolic syndrome, the disease does not progress past the stage of hepatic steatosis, while 20% develop NASH with subsequent progressive hepatic fibrosis.

C. Hellerbrand (Regensburg) proposed a new model for understanding the progression of fibrosis in NASH. In his three-hit hypothesis, he postulates that, in addition to steatosis, inflammation represents a second “hit” in which lipid oxidation leading to oxidative cell damage and cell demise may be responsible. The inflammation would seem to be a necessary but by no means sufficient cause in itself for the further progression to liver fibrosis. Here, C. Hellerbrand suggests that the loss of hepatoprotective adiponectin, or, in some cases, the presence of bacterial products such as LPS, may represent the third “hit” required for the development of fibrosis. It is possible that the process is analogous in both NASH and alcohol-induced steatohepatitis (ASH).

Role of bile acids in bacterial translocation
Besides their role in the digestion of lipids and the absorption of fat-soluble vitamins, the bile acids also play an important role in the physiological relationship between the host and the bacterial microflora of the bowel. The bacteriostatic function of many bile acids has long been known, said A. Moschetta (Santa Maria Imbaro). If, as a result of liver cirrhosis, there is reduced secretion of bile acids, there may be excessive bacterial overgrowth in the small bowel with bacterial translocation into the tissue of the host, which ultimately impacts its survival. Beside the direct effect of bile acids on bacteria, there is a recently discovered indirect effect in that bile acids bind to the nuclear farnesoid-X receptor (FXR). This results in the expression of genes that repress intestinal bacteria.
Cell Response to Chronic Liver Injury

Chair:
D. Lebrec, Clichy
M. Pinzani, Florence

Progenitor cells control regeneration

The development of chronic liver diseases is countered by the ability of the liver to regenerate. This is based on progenitor cells that can differentiate into both biliary and hepatic cells (figure 35). "Whether and to what degree the progenitor cells are activated depends on the type of damage and the severity of the disease," explained T. Roskams (Louvain). "The control mechanisms for these processes are currently only imperfectly understood." Growth factors such as TGF-α and β, and the hepatocyte growth factor (HGF) appear to be involved and there is evidence that the autonomic nervous system may also play a role. Findings from animal experiments suggest that especially oxidative stress can stimulate the cells to differentiate.

Liver progenitor cells:
CK7, CK19, OV6, OV1, Chrom A, NCAM
subpopul: CD34, c-kit, flt-3, thy-1, sca1, CD133

Fig. 35

1 Hepatic progenitor cells (T. Roskams, Louvain)
Stellate cells are involved in fibrogenesis
According to C. Kordes (Düsseldorf), the hepatic stellate cells also belong to the progenitor cells and under culture conditions differentiate to myofibroblasts. They synthesize actin and extracellular matrix proteins and are centrally involved in the process of fibrogenesis. “The control mechanisms are not yet adequately understood,” C. Kordes said. In addition, these cells may represent a further cell type with undifferentiated progenitor properties. Independent of this process, the hepatic stellate cells are probably also involved in the development of portal hypertension due to their role in sinusoidal remodeling and increase in intrahepatic resistance, said V. Shah (Rochester). In the absence of adequate nitric oxide, the cells become more contractile and tend toward migration and proliferation.

Oxidative stress forces angiogenesis
It is especially oxidative stress that is responsible for increased expression of pro-angiogenic growth factors such as PDGF, said M. Fernández (Barcelona). The expression of growth factors, for example, promotes the formation of new blood vessels, a development that can also be involved in the creation of collateral vessels as a result of portal hypertension. Anti-angiogenic treatment strategies, as are already routine in cancer therapy, may prove helpful in the treatment of portal hypertension.
Inflammation – A *sine qua non* of liver fibrosis

Fundamental to the development of liver fibrosis is inflammation of the liver, as D.A. Brenner (La Jolla) explained (figure 36). The activation of hepatic stellate cells occurs directly through the Kupffer cells, which in their turn open the way for fibrogenesis (figure 37). S.L. Friedman (New York) characterized the activation of the hepatic stellate cells as the “main event” on the path to liver fibrosis. S.L. Friedman’s own work in this area centers on the role of the Krüppel-like factor 6 (KLF6). S.L. Friedman explained that this factor appears to be involved in the molecular

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1 Inflammation of the liver, liver fibrosis and liver cirrhosis
(D.A. Brenner, La Jolla)
Fibrosis develops on the basis of inflammation (D.A. Brenner, La Jolla)
regulation of the stellate cells. Paradoxically, it is synthesized after damage to the liver, when the stellate cells multiply. Although first believed to be a tumor suppressor, it is currently thought that there are different splice variants of this factor, some forms of which stimulate proliferation, while others inhibit it. Also remarkable is the increased synthesis of KLF6 in various malignant tumors, S.L. Friedman noted: “In this regard we need more intensive research into hepatocellular carcinoma” (figure 38).

Fig. 38

**Hepatic stellate cell activation – A central event in liver fibrosis**

Normal liver

Activated hepatic stellate cells with fibrosis

† **Hepatic stellate cells and development of fibrosis (S.L. Friedman, New York)**
Fibroscan – The elasticity of liver tissue can be measured

Determination of the elasticity of liver tissue using the Fibroscan method as a means of estimating the degree of liver fibrosis was described by M. Beaugrand (Bondy). In this method, ultrasound is combined with a low-frequency pulse wave emitter to produce elastic shockwaves in the liver, their pulse echo being used to determine the degree of fibrosis. The method has been tested in several pilot studies and its diagnostic value is currently being tested in a multicenter study in patients with chronic hepatitis C and patients with liver fibrosis. There are also current studies in progress assessing the value of the method in the work-up of portal hypertension and esophageal varices, M. Beaugrand added. According to M. Pinzani (Florence) there is intense research focusing on other non-invasive and valid methods for estimating and assessing the progression of the fibrosis.

Serum markers should indicate the degree of fibrosis

Significant progress has been made in diagnosing and monitoring liver fibrosis, said D. Thabut (Paris). While liver biopsy remains obligatory, a focus of intense research has been to develop alternatives to this invasive modality. At present, work is focusing on several serum markers. Especially promising is measurement of serum concentrations of components of the extracellular matrix. Another potentially useful track would be detection of cytokines that trigger the fibrotic process. Further studies are needed to determine the diagnostic value of these various markers.
Is there hope that fibrosis can be reversed?

Just as there are cytokines that trigger the development and progression of fibrosis, there are also mediators that protect against fibrogenesis. Examples include IFN-α and IL-10. This would suggest, in principle, that regression of fibrosis is possible, said H.E. Wasmuth (Aachen). “Getting fibrotic tissue to regress will probably take longer than it took to develop in the first place,” H.E. Wasmuth said, cautioning against exaggerated hope. More work will need to be done to better understand the complex interaction of the numerous involved mediators before it will be possible to reliably exert any external influence. “Fibrosis regression will certainly be possible clinically someday. But in the meantime there is still a lot of research to be done,” H.E. Wasmuth concluded (figure 39).

Fig. 39

Reversibility of secondary biliary fibrosis after drainage of the common bile duct

Secondary biliary fibrosis due to compression of common bile duct

30 Months after decompression of common bile duct


Regression of liver fibrosis seems to be within the realm of the possible (H.E. Wasmuth, Aachen)
Clinical Management of Portal Hypertension (1):
Pre-primary and Primary Prophylaxis

Chair:
J. Heller, Bad Neuenahr-Ahrweiler
F. Wong, Toronto

Portal hypertension: The most frequent complication of liver cirrhosis

Increased intrahepatic vascular resistance should always be suspected in patients with liver cirrhosis, said J.-C. García-Pagán (Barcelona), and this forms the basis for portal hypertension. “Portal hypertension is the most frequent complication of liver cirrhosis,” observed G. Garcia-Tsao (New Haven; figure 40). This leads in many cases to the formation of esophageal varices, which may bleed and contribute greatly to these patients’ high morbidity and mortality (figures 41 and 42).
The risk of bleeding increases with the formation of esophageal varices (G. Garcia-Tsao, New Haven).

Esophageal varices contribute greatly to the high morbidity and mortality in patients with liver cirrhosis (G. Garcia-Tsao, New Haven).
Screen for esophageal varices in every patient with liver cirrhosis

For this reason, it is crucial to diagnose portal hypertension as early as possible, emphasized R. de Franchis (Milan). Whether these patients have already developed varices should, in his opinion, be determined endoscopically: “Endoscopy is the best currently available screening method.” Endoscopic examination is indicated in every patient diagnosed with liver cirrhosis. If the patient has not yet developed varices, a follow-up endoscopy should be performed after two to three years. In patients with small varices, the interval should be shorter, such as after one to two years, R. de Franchis recommended. A shorter interval is, in his opinion, also advisable in patients with alcoholic liver cirrhosis and in those with severely reduced liver function.

If large varices are found, primary prevention of bleeding should be performed

If endoscopic examination reveals large esophageal varices, measures aimed at primary prevention of bleeding are indicated, said P. Calès (Angers). Options include non-selective beta blockers and band ligature of the varices. P. Calès recommended initial use of band ligature only when there are contraindications to the use of beta blockers.

The most commonly used pharmacological agent is propranolol, usually given at a dose of 80–160 mg once a day. The dose selected should not drop the resting pulse frequency by more than 20–25%, but in no case under 55 beats per minute. If this treatment is followed, patients can expect a ca. 50% drop in the risk of experiencing a first variceal hemorrhage.
Clinical Management of Portal Hypertension (2): Complications of Cirrhosis

Chair:
J. Bosch, Barcelona
R. Wiest, Regensburg

A.K. Burroughs (London). Because a large number of cirrhosis patients suffer from bacterial infections, antibiotic treatment should always be considered, A.K. Burroughs said: “Antibiotics help further reduce mortality” (figure 43).

Bleeding esophageal varices – The prognosis is now better

The prognosis for patients with bleeding esophageal varices has gotten better in recent years. “We’ve gotten better in managing the bleeding but we still have work to do in our efforts to reduce intrahepatic pressure in order to further minimize the risk of variceal bleeding,” said A.K. Burroughs.

Fig. 43

Acute variceal bleeding – Prophylactic antibiotics and mortality

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Prophylactic antibiotics in variceal bleeding reduces mortality (A.K. Burroughs, London)
Prophylactic antibiotics should be considered

Even a prophylactic course of antibiotics should be considered, said A.K. Burroughs. In his experience, this measure further reduces the rate of bleeding and so indirectly reduces patient mortality. Should bleeding nevertheless occur, the next step is to consider the indication for sclerotherapy or band ligature. Survival rates are comparable with both methods. A.K. Burroughs considers the use of fibrin glue to be an emergency measure but he cites as a further alternative the placement of a transjugular intrahepatic portosystemic stent shunt (TIPS).

After variceal bleeding: Don't delay secondary prevention

Patients who have experienced a first episode of variceal bleeding have a ca. 70% chance of recurrent hemorrhage within the next two years, said D. Lebrec (Clichy): "Mortality reaches 30%". For this reason, secondary prevention should be started as soon as possible: Depending on prior therapy, treatment with a non-selective beta-blocker, band ligature or even a combination of both measures may be indicated. Therapy can significantly reduce the risk of recurrent bleeding (figure 44).

Fig. 44

Beta-blockers for the prevention of variceal rebleeding: A meta-analysis

![Graph showing beta-blockers vs controls in terms of rebleeding rate and survival rate](image)

*Beta-blockers as secondary prevention reduce the risk of recurrent variceal bleeding (D. Lebrec, Clichy)*
Ascites significantly reduces survival rates

Another serious complication of liver cirrhosis, said F. Wong (Toronto), is ascites, which develops in about 10% of cirrhotic patients. This complication is to be understood as evidence of decompensation and is associated with a significant reduction in patients’ life expectancy.

“The survival rate after two years stands at only 50%,” F. Wong noted. Regarding treatment, she argued for sodium restriction, diuretics and TIPS placement with the additional administration of albumin and vasopressin. Beyond these, there are several new agents in the pipeline.

TIPS improves survival

If the ascites proves refractory to therapy, further complications threaten, said A. Cárdenas (Barcelona). These include a spontaneous peritonitis and, as A. Gerbes (Munich) added, the hepatorenal syndrome (HRS). This is characterized by a significant worsening in renal function, complications in the cardiovascular system and exaggerated activation of the endogenous vasoactive system. According to A. Gerbes, HRS can rapidly lead to complete renal failure and represents an acute life-threatening condition for patients.
With regard to the extent to which the prognosis can be improved with TIPS, data have been contradictory, said M. Rössle (Freiburg). A current meta-analysis comparing TIPS with paracentesis, however, does show advantages for TIPS and significant improvement in transplant-free survival. Reasons for the earlier non-uniform data, M. Rössle said, relate to differences in surgical technique and in inclusion and exclusion criteria for the studies. Based on current data, he sees a clear survival advantage in patients undergoing TIPS placement.

Besides the hepatorenal syndrome, patients are also at risk for a hepatopulmonary syndrome, said P. Schenk (Vienna). This complication is also associated with a very poor prognosis. It is considered an independent prognostic factor and is associated with a high risk of mortality. The prevalence of hepatopulmonary syndrome in the literature is given as 4–32%, P. Schenk said.

**Hepatic encephalopathy**

A further complication often experienced by cirrhosis patients is the development of hepatic encephalopathy, said D. Häussinger (Düsseldorf). The underlying cause of this disorder is a swelling of astrocytes induced by elevated systemic ammonia levels and the use of benzodiazepines but also by hyponatremia and pro-inflammatory cytokines.
MELD score forms the basis for liver transplantation registration

Organ transplantation forms the final therapeutic option in patients with liver cirrhosis. Because of the limited availability of donor organs, waiting lists as a means of prioritizing patients for transplant are unavoidable. In the United States, said D.M. Heumann (Richmond), the severity of the disease is determined using the MELD score (Model for End-Stage Liver Disease): “The MELD score is an answer to limited organ availability, but it is not a satisfactory one.” For example, it remains unclear how the MELD score correlates with the chances of survival after the transplantation.

In December 2006 the MELD system was also introduced in the Eurotransplant nations, said A.O. Rahmel (Leiden). According to initial experience, this has led to a significant reduction in mortality in patients on the waiting list.

Future research should target portal hypertension

Hepatologists are confident that the future will see further progress in the treatment of liver diseases, said J. Bosch (Barcelona). Highest priority, however, should be progress in the therapy of portal hypertension. J. Bosch hopes for the formulation of new targets and the establishment of innovative therapy options.
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