

Major advances in gastroenterology and hepatology over the last 25 Years: Review of 25th UEG Week Anniversary Session

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Introduction, Michael Farthing¹

As United European Gastroenterology (UEG) celebrates 25 years as a major provider of international conferences, postgraduate education, a leading communicator of discovery science and an advocate of high-quality clinical practice across Europe, it seemed right to review our achievements in gastroenterology and hepatology.

In 2014, UEG commissioned a survey of the impact of gastrointestinal (GI) and liver disease in Europe with the intention that this should guide future healthcare planning and research. The presentations in the 25th UEG Week Anniversary Session have updated that work, focusing on the major advances that have been made in the treatment of inflammatory bowel disease (IBD), Hepatitis C virus infection (HCV), *Helicobacter pylori* (*H. pylori*), gastro-oesophageal reflux disease (GERD), the treatment of childhood diarrhoea and the diagnosis and treatment GI cancer. The extraordinary technical advances that have been made in GI endoscopy and laparoscopic surgery are also discussed.

In addition to the impact survey, UEG also undertook a scenario planning exercise to further understand the range of possibilities for the delivery of care in GI and liver disorders. During the final part of the anniversary session we, like a fortune-teller, gazed into a 'crystal ball' and imagined how healthcare professionals in our disciplines would deal with the challenges ahead.

Antibodies in inflammatory bowel diseases, Julian Panés²

The introduction of the monoclonal antibodies (MAbs) in the treatment of IBD represented a true revolution. MAbs have provided new effective and safe modes of therapy, but also brought to the field of IBD new paradigms for drug dosing, the redefinition of therapeutic targets, and completely changed the design of drug development programmes.

Initial studies with infliximab for treatment of Crohn's disease or ulcerative colitis generated enthusiasm for its efficacy, but it became apparent that some patients did not respond or lost response during therapy.

One of the early reasons identified for this problem was the development of anti-drug antibodies. It became clear that the pharmacokinetics of MAbs is complex, with many factors, in addition to immunogenicity, affecting drug clearance and drug concentration at target tissue, including leakage of antibody into the gut lumen, target abundance, and drug degradation by metalloproteinases at sites of inflammation.

The development of therapeutic MAbs has also introduced the use of objective measures of disease activity and severity, both for patient selection and as an outcome measure. It is also informing the selection of therapeutic targets in studies and clinical practice, showing that endoscopic remission is associated with superior long-term clinical outcomes.

Hepatitis C virus: Discovery and extinction, Michael Manns³

HCV causes chronic hepatitis which might result in liver cirrhosis, hepatocellular carcinoma, liver transplantation or death. Globally, more than 100 million people are chronically infected. The discovery of HCV in 1989 led to the development of hepatitis C antibody testing (anti-HCV) and subsequently HCV RNA measurement, viral genotype and subtype determination. This blood-borne infection was caused by blood and blood products until anti-HCV blood product screening was introduced in 1990. At present, major risk factors are unsafe injection drug use and unsterile medical procedures, in particular in countries with a high HCV prevalence. The interplay between basic research and clinical medicine led to the development of diagnostic tests and HCV therapies that for the first time enabled a cure of a chronic viral infection in man. Milestones of this development are virus discovery, the establishment of diagnostic tests, the identification of the HCV life cycle and the development of an in vitro replicon system that paved the way towards direct-acting antiviral agents (DAAs). Therapeutic developments had already started in 1986 with the use of recombinant interferon alfa when the disease was still called non-A, non-B hepatitis and the virus had not been discovered. Cure rates gradually improved over the years

due to higher doses and longer durations of interferon alfa, the addition of ribavirin, the use of long-acting pegylated interferons (PEG-IFN) and finally DAAs. Three different classes of DAAs target three different steps in the HCV replication cycle: the NS3/4 protease, the HCV polymerase and the NS5A protein, which is unique for HCV infection. In 2014, the first all-oral interferon-free regimen became available and in 2017 combinations of two or three DAAs have allowed for the cure of HCV infection close to 100% for all genotypes and all patient populations, including decompensated liver disease in 8–16 weeks and almost without any side effects. As of today HCV is still a major global health burden. The discovery of HCV and the subsequent development of diagnostic tests and HCV therapies was a masterpiece of modern translational medicine that should facilitate global HCV eradication.

***Helicobacter pylori*: The Nobel bug, John Atherton⁴**

The landmark description of *H. pylori* by Robin Warren and Barry Marshall in their letters to the *Lancet* in 1983 heralded a revolution in the understanding and practice of gastroenterology. Most peptic ulceration – particularly duodenal ulceration – is an infectious disease caused by a bacterium that is acquired in childhood and carried lifelong. A simple combination of antibiotics (usually with a proton pump inhibitor) not only heals ulcers but prevents their recurrence: it cures the disease. Even more significantly, gastric adenocarcinoma – until recently the second biggest cancer killer in the world – is also largely an infectious disease. As *H. pylori* prevalence is falling so, dramatically, is the incidence of gastric cancer. This is one of the biggest public health successes of our generation.

However, all is not perfect. *H. pylori* has lived in our stomachs at least since humans emerged from Africa, and most likely throughout our evolution. As we have co-evolved with it, our physiology and immunology have adapted to its presence. Without it, our stomachs are, on average, more acidic and *H. pylori*-free humans more frequently develop complications of GERD – Barrett's oesophagus and oesophageal adenocarcinoma. *H. pylori* also stimulates a regulatory immune response and the lower level of this in *H. pylori*-free individuals may explain why some allergic diseases, notably childhood asthma, are more common in those who are *H. pylori* negative. Avoidance of gastric cancer is likely to greatly outweigh these considerations: an *H. pylori*-free individual is likely to be a healthier individual – but not one who is at reduced risk of all diseases.

Endoscopy: A technical revolution, Paul Fockens⁵

The impact of the advances in flexible gastrointestinal endoscopy in the past 25 years on patients with GI disease, has been larger than any other development in our specialty. Thinking back, patients with acute ulcer bleeding were scoped to identify the cause of bleeding and then went for surgical therapy. Nowadays endoscopy is both the first and second line of treatment in any ulcer bleeding. Patients with a dysplastic Barrett's oesophagus all used to go for esophageal resection because of 'invisible' cancers in 40%. Now they are diagnosed and treated endoscopically with mucosal resection and/or ablation. Stones in the common bile duct (CBD) were an indication for open surgical exploration, a technique that in 2017 hardly any surgeon still masters and ERCP (endoscopic retrograde cholangio-pancreatography) is taking care of 99% of CBD stones now. Another bright example is that large flat colonic polyps were either missed (and became interval cancers) or went for surgical resection with considerable morbidity and mortality. In 2017, we detect them and more than 90% can be treated endoscopically. Gastroenterology and hepatology are larger than GI endoscopy alone, but high definition GI endoscopy has become a most important technique for detection and treatment of early neoplastic changes in the GI tract and has replaced surgery in multiple other areas, reducing the burden for our patients.

Treating diarrhoea in children: A global life-saver, Sibylle Koletzko⁶

Diarrhoea is the cause of death in 1 out of 10 children dying under the age of 5 worldwide. In 2015, diarrhoea killed 1400 young children per day, or 526,000 per year (UNICEF, One is too many. Ending child deaths from pneumonia and diarrhoea, November 2016). Diarrhoea is most deadly in the poorest places in the world such as sub-Saharan Africa and South Asia. Many children could be saved through rather basic interventions.

The younger the child, the greater is the risk that fluid and electrolyte losses will lead to health-threatening dehydration. Fluid losses from diarrhoea and vomiting can be as high as three times the circulating blood volume. The type of dehydration – isotonic, hypotonic or hypertonic – is independent of the causative organism (viral or bacterial), and in all three situations treatment with oral rehydration solution (ORS) is safe and effective. ORS was developed after the discovery of the coupled co-transport of sodium and glucose in the enterocytes. In the presence of glucose or galactose, sodium is more effectively taken up from the intestinal lumen by the SGLT1 transporter. Water then passively follows the

sodium influx. Since 2004, UNICEF and the World Health Organization have promoted low-osmolality ORS and zinc, in addition to continued feeding, but little progress has been made in the broad implementation over the last decade, with only 2 out of 5 affected children being treated with ORS. Besides improving accessibility, particularly in rural areas of poor countries, education of health care providers and parents is crucial for implementation of good diarrhoea management. Preventive measure such as providing clean water, promoting breast feeding and a vaccination programme against rotavirus infection will further decrease the deadly burden of diarrheal diseases.

Gastrointestinal cancer treatment goes personal, Thomas Seufferlein⁷

For many years, 5-fluorouracil (5-FU)-based chemotherapy was the mainstay for the treatment of GI tumours, achieving moderate results. Over recent years, this has substantially changed. New chemotherapeutic agents have been introduced. Furthermore, based on data from signal transduction research, so-called targeted agents have been developed that address specific properties of a given tumour such as the Epidermal Growth Factor receptor or the human epidermal growth factor receptor 2. Now, there is a plethora of drugs that target the majority of signalling network components in cancer. Large-scale tumour sequencing has also developed rapidly over the past years and allows us to identify the molecular alterations in a given tumour. These approaches revealed that apart from the conventional pathological classification there is a novel molecular classification of cancer. Using such a classification, a whole cancer entity such as pancreatic or colorectal cancer is reclassified into subgroups according to their specific molecular profile. This allows, in principle, the tailoring of the treatment to the alterations present in the particular subgroup. Apart from the tumour itself, the tumour stroma and the host are also increasingly the focus of therapeutic approaches. Antiangiogenic agents targeting the nutrient supply of tumours have been in use for many years in GI oncology. Recently, immuno-oncology has achieved tremendous results – also in certain GI cancers. After many years of searching for a master tumour antigen the inhibition of immunological checkpoints is now at the forefront of interest. Using so-called checkpoint inhibitors targeting the programmed cell death protein 1/programmed death ligand-1 system, surprising results could be achieved in subgroups of tumours, e.g. in colorectal cancer with microsatellite instability. Here, almost all heavily pretreated patients with metastatic colorectal

cancer achieved long-term survival when their tumour exhibited this molecular feature. Consequently, this treatment was approved for this subgroup by the Food and Drug Administration and the European Medicines Agency. Thus, there is very exciting progress in the field and we are well on the road to a personalized treatment of GI malignancies. There are of course unresolved issues to tackle. First of all, not all tumours with a given mutation respond to a specific targeted drug. Here we need a better understanding of tumour heterogeneity. Furthermore, we have to find ways to make immunologically ‘cold’ tumours (alas, the majority of GI cancers) accessible to the immune system.

Gastroesophageal reflux disease: Reducing acid and complications, Rebecca Fitzgerald⁸

The widespread availability of proton pump inhibitor (PPI) therapy has revolutionized the treatment of gastroesophageal reflux disease (GERD). This class of drugs was first discovered in 1975 and in the 1980s they were shown to be superior to H₂ receptor antagonists. In 1996 Omeprazole became the world’s biggest selling pharmaceutical and by 2004 over 800 million patients had been treated worldwide.

For patients presenting to Gastroenterologists, diagnosis of reflux symptoms has become much more sophisticated. Reflux and motility assessment has been transformed by ambulatory pH tools including wireless probes, multi-probe pH catheters, spectrophotometers to detect bile reflux and impedance-pH monitoring, which is currently considered to be the most accurate and detailed method to assess gastroesophageal reflux. Patients can now be sub-categorized into GERD, NERD (non-erosive reflux disease) and reflux hypersensitivity, permitting a more personalized treatment approach.

When required, anti-reflux surgery is largely laparoscopic with a number of endoscopic modalities available including magnetic sphincter augmentation and transoral incisionless fundoplication.

In 2017 GERD presents a global economic burden. The challenge is to ensure that PPIs are not over-used – this is not only economically important but essential to avoid long-term complications, particularly in the elderly, and to ensure that patients are appropriately investigated for complications such as pre-malignant Barrett’s oesophagus.

Laparoscopic surgery: A diagnostic and therapeutic success, Mario Morino⁹

In April 1989, Jacques Perissat presented at the Sages Congress in Louisville the video of a laparoscopic

cholecystectomy. K.A. Forde, Sages' President, defined that moment as 'a singular event that changed the history of surgery perhaps for all time.' In the following years, abdominal surgery was stormed by the so-called laparoscopic revolution: all abdominal surgical procedures were performed by laparoscopy by an international group of enthusiast minimal invasive surgeons.

The reason for such a huge success was the undeniable advantages of laparoscopy: reduced pain, quicker recovery, shorter postoperative ileus, shorter hospital stay, better cosmesis, and a better early quality of life. These advantages were self-evident to every patient. Randomized controlled trials were difficult to perform: for some procedures such as cholecystectomy, fundoplication, Heller myotomy, bariatric, IBD resections, adrenalectomy, splenectomy, etc. patients were reluctant to accept randomization, favouring laparoscopic access.

Oncologic digestive surgery was a different story. The typical advantages of laparoscopy were related to early postoperative courses; surgeons and oncologists were sceptical of long-term results. But in the years 2000–2010 robust RCTs confirmed that laparoscopy was superior to open surgery in terms of early clinical results without affecting long-term disease-free survival in colorectal cancer. These data prompted the diffusion of oncological procedures: nowadays, laparoscopy represents 50% of colorectal oncological surgery worldwide, while hepatic resections, partial and total

gastrectomies and distal pancreatic resections are steadily gaining popularity.

After 25 years of continuous advances in minimal invasive surgery including robotics, transanal, 3D, etc. we can affirm that the surgical trend towards a reduction in the trauma of surgical access represents one of the major revolutions of surgery and will continue in the near future as a consequence of technical, technological and clinical progress.

Watch the full recording of the session via UEG Week 24/7. <https://www.ueg.eu/anniversary-session-recording/>

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