Lionel Bueno - The creative scientist and the gentleman

N. Vergnolle, Vassilia Theodorou

tions to the pressure at the EGJ. So far, the separation of the two sphincter components can only be corrected surgically. Transient LES relaxations (TLESRs) constitute another major reflux mechanism. Reflux reduction by means of inhibition of TLESRs is feasible, e.g. with GABA-B receptor agonists. However, widespread use of this therapeutic principle is hampered by side effects of the available drugs. The obesity epidemic clearly is a pivotal factor in the worldwide increase in the prevalence of GERD. The bulk of the available evidence suggests that the most important mechanism is the increased abdomino-thoracic pressure gradient that is associated with obesity. Some types of bariatric surgery have been shown to reduce reflux, but other procedures may induce reflux. Impaired esophageal motility and delayed acid clearance have long been recognized as playing an important role in the pathophysiology. The available evidence strongly suggests that the impaired motility is not simply the consequence of reflux and reflux esophagitis. However, until today no effective prokinetic therapy for the esophagus is available. It thus remains a challenge to develop treatment modalities other than pharmacological inhibition of acid secretion and surgical fundoplication.

Friday, 5 June 2015
13:15–15:00 Hall A
PL-02 Lionel Bueno Memorial - Pharmacological treatment below the diaphragm

001

Lionel Bueno - The creative scientist and the gentleman

N. VERGNOLLE and V. THEODOROU†*
**Centre de Pathophysiology de Toulouse Purpan, Toulouse Cedex, France and and †Inra Centres, Science ⁊Impact, Toulouse, France*

Abstract: Lionel Buéno was born July 9, 1945 in Angers, France. He graduated in biochemistry in 1969 from the National Institute of Applied Sciences (INSA) in Lyon and the following year he was appointed to a permanent position as young researcher in the French National Institute of Agronomic research (INRA). Lionel then moved to Toulouse following his mentor Yves Ruckebush who headed the Physiology Department of the Veterinary School of Toulouse. Very rapidly he created his own group of 'Digestive pathophysiology' in this department this was the beginning of a brilliant career in the field of gastroenterology. In 1982, he left the Veterinary School to head the Pharmacology and Toxicology INRA Unit. He managed this Unit with an exemplary scientific efficiency up to 1996. In 1999 he participated to the creation of a new group called Neuro-Gastroenterology and Nutrition INRA located at the same site. Lionel's group had a major impact on the International stage as indicated by the quantity and quality of his scientific publications. Lionel also excelled as a mentor, he trained a number of GI scientists who have pursued highly visible academic and industrial careers. He retired from administrative and scientific supervision in 2010 but he continued his activity as an emeritus Professor until he suddenly passed away on Saturday evening, January 24th, 2015. The early part of his career as a collaborator with Yves Ruckebusch, was devoted to the understanding of the digestive physiology of ruminants. A number of seminal papers between 1970 and 1975 describe short chain fatty acid production in the rumen and its effect on motility of the compound stomach and duodenum. In 1978, his career took a decisive turn after meeting Jacques Frexinos, Professor of Medicine at the University of Toulouse, who was also the Head of the Gastroenterology Department at the Rangueil Toulouse Hospital. From that time onwards, he devoted his career to the understanding of functional gastrointestinal disorders and particularly irritable bowel syndrome. He was helped in this endeavor by his close friend and long-term scientific collaborator, Jean Fioramonti. Together they published more than 200 papers. Lionel was a true pioneer and visionary. He provided insights into the mechanisms underlying brain-gut interactions and the pathophysiology of IBS, helping to steer current thinking towards concepts of visceral hypersensitivity, neuro-immune interactions and impairment in intestinal barrier function. He was convinced that peripheral rather than central mechanisms provided the trigger for IBS symptoms and was very much in favor of the theory that low-grade intestinal inflammation was a causative factor in IBS. In this scientific continuum from bench to bedside, Lionel advanced the translational approaches recognizing the importance of relevant animal models and advancing the methodologies necessary for the understanding of IBS the pathophysiology. His research outputs in Neurogastroenterology have been widely recognized by the international scientific community but also the national community of gastroenterologists. To give just a few examples; Lionel was the first researcher in basic sciences to be elected as President of the French Gastroenterology Society in 2004. Two years later, he received an international award from the American Gastroenterology Association, the 'sustained achievement in digestive sciences'. Lionel is dearly missed as a mentor and colleague. The neurogastroenterology community will continue to pay every day a tribute to his legacy.

003

Bench to bedside

R. C. SPILLER
University of Nottingham, Nottingham Digestive Diseases Centre, Nottingham, UK

Abstract: Lionel Bueno was a great colleague and an enthusiastic basic scientist who started many lines of enquiry in the field of Neurogastroenterology. This lecture will describe examples of how Lionel's basic science studies have led to changes in understanding of clinical problems. His group early on showed mast cell involvement in stress-induced visceral hypersensitivity. Using the model of maternal deprivation they also showed that stress induced hypersensitivity was associated with increased nerve mast cell interaction and increased permeability. Subsequent work supported the idea that mast cell hyperplasia and activation could account for the known link between psychological stress and changes in gut function and in particular increases in gut permeability. These findings have translated well to human studies. The demonstration that real life stress increased small bowel permeability which could be inhibited by the mast cell stabiliser, disodium cromoglycate confirmed the importance of mast cell activation. Subsequent clinical trials of H1 receptor antagonists, ketotifen and ebastin showed promise in patients with irritable bowel syndrome. Lionel also made the observation that faecal extracts from IBS patients contained proteases which acted via PAR2 receptors to induce visceral hypersensitivity in mice. Subsequent studies showed that these proteases are mostly endogenous and that increased levels correlate with urgency. Early studies in Lionel's laboratory with rodents showed that 5HT3RAs reduced response to colorectal distension, subsequently shown in humans to reflect enhanced compliance. Clinical trials confirmed that a major part of the benefit of both alosetron and ondansetron in IBS with diarrhoea is on urgency. Recently noninvasive, patient acceptable techniques for assessing GI physiology using MRI have been developed. The constriction of the small bowel and abnormal colonic response to feeding has thrown new light on the pathophysiology of IBS-D which may assist the assessment of future therapies.

004

Novel therapeutic targets

J. TACK
Department of Clinical and Experimental Medicine TARGID, Leuven, Belgium

Abstract: Most gastroenterologists perceive the gastrointestinal motility and functional disorders as 'underserved' in terms of available treatment options. This probably relates to the symptom-based nature, the underlying heterogeneous pathophysiology, the high risk-benefit ratio requirements and, for many conditions, the lack of well-established regulatory and trial design track. In the aftermath of lack of success with prokinetics, reflux inhibitor and TRPV1 antagonistic drugs for refractory gastroesophageal reflux disease, the field of (functional) symptomatic esophageal disorders is currently in low activity state. For functional dyspepsia, prokinetics are considered a valid treatment approach, although prokinetic studies recently tend to focus on (diabetic) gastroparesis first. The last few years saw negative studies with 5-HT4 agonists and ghrelin and motilin receptor agonists, but ongoing studies continue to investigate these drug classes in diabetic gastroparesis. For functional dyspepsia, studies in Europe are currently investigating itopride, a mixed dopamine-2 receptor antagonist/cholinesterase inhibitor, a Japanese

Kampo medicine (Rikkunshito) and acotiamide, a mixed muscarinic antagonist/cholinesterase inhibitor. A new patient-reported outcome measure was developed and validated for these studies. In the lower GI tract, IBS with diarrhea is the target for recently completed studies with the poorly absorbed broad-spectrum antibiotic rifaximin (a retreatment trial) and with eluxadoline, a mixed mu/delta opioid agonist. Both studies, presented as abstract, showed statistically significant gain in responder rates of up to 10% over placebo. A world-wide phase 3 clinical trial program in women with IBS-D is ongoing with ibodutant, a selective neurokinin-2 receptor antagonist. Constipation (either in chronic constipation or in IBS-C) is the target for ongoing studies with a novel guanylate cyclase agonist (plecanatide), and an ileal bile acid transport inhibitor (elobixibat). Stu-dies with peripherally restricted mu opioid receptor antagonists in opioid-induced constipation are ongoing or have recently been concluded. Finally, several investigator-initiated studies in IBS are ongoing, including studies with analgesic agents (e.g. duloxetine, pregabalin), anti-inflammatory/anti-allergic agents (ebastin, mesalamine), dietary interventions (FODMAP and other diets), pre- and probiotics and faecal microbiota transplantation. It is conceivable that at least some of these novel therapeutic approaches may become available for clinical practice in the near future.

Saturday, 6 June 2015
13:30–15:00 Hall A
PL-03 Microbiome: What does it do to your health

001
Basic aspects
P. BRIGIDI
University of Bologna, Bologna, Italy

Abstract: With 1014 bacterial cells, the intestinal microbiota is the richest and most diverse of the human microbial ecosystems. The comprehensive genome of these bacteria contains 150 times more genes than the human genome and provides the host with essential physiologic and metabolic functions we have not evolved by our own, actively contributing to nutrient digestion and immune system homeostasis. Indeed, the gut microbiota is often referred to as a forgotten organ, comparable to the human liver for both total weight and metabolic capability. Alterations of the health-associated gut microbiota profile, in terms of relative abundance of the present bacterial species, have been linked to local and systemic diseases, such as inflammatory bowel disease, colorectal cancer, irritable bowel syndrome, obesity, type II diabetes, metabolic syndrome, and allergies. As a consequence, the composition of the gut microbiota is being increasingly recognized as an important risk/protection factor for these disorders, as well as crucial in determining the probability of success of nutritional/pharmaceutical strategies implemented to prevent or treat them. Moreover, the recent literature points out how the microbiota might be involved in previously unthought-of aspects of human life, such as behavioral traits and neurological disorders, as demonstrated by the increasing research interest in the so-called gut-brain axis. Due to the inability to cultivate the large majority of intestinal bacteria, the study of the gut microbiota cannot prescind from the most updated Next Generation Sequencing (NGS) techniques that ensure a comprehensive view of the gut microbiota profile from the compositional point of view, through the analysis of the bacterial 16S rRNA gene sequences, or integrating functional and compositional information when applying a metagenomic approach. In both cases, advanced bioinformatics and statistical tools are needed to translate the sequencing output in a microbiota description with a clear functional and metabolic significance.

002
Sensory-motor function
M. SIMREN
Department of Internal Medicine, University of Gothenburg, Gothenburg, Sweden

Abstract: In the human body a complex community of microbes is present (collectively referred to as the microbiota), and the vast majority of these can be found in the gastrointestinal (GI) tract. The concentration of microbes increases continuously along the gut, and the composition also differs, with predominantly Gram-positive bacteria in the upper GI tract and mainly Gram-negative microorganisms and anaerobes in the colon. During recent years, culture-independent techniques have dramatically increased the possibilities to study the role of the gut microbiota in health and disease, which has led to substantial progress in our understanding about the role of gut microbiota in diseases with disturbed sensorimotor function, such as irritable bowel syndrome (IBS). The gut microbiota has a crucial role in the development and functionality of innate and adaptive immune responses, but also in regulating gut motility and intestinal barrier homeostasis. This microbiota normally has a balanced composition that confers health, and disruption of this balance (dysbiosis) confers disease susceptibility. Moreover, several animal models, as well as clinical observations, have demonstrated that altered immune function and inflammation in the gastrointestinal tract, as well as gastrointestinal infections and gastrointestinal dysbiosis, affect motility and sensitivity of the gut, two of the key pathophysiological factors in IBS. By altering the gut bacterial milieu with anti- or probiotics in different animal models, researchers have demonstrated how gut microbiota changes can lead to altered gut sensitivity and motor function. Few human studies have investigated the effect of gut microbiota alterations on GI sensorimotor function, but in IBS, a disease in which visceral hypersensitivity and altered motor function are considered to be key pathophysiological factors, gut microbiota alterations have been demonstrated, as well as some associations between gut microbiota composition and gut sensorimotor function. However, more research is needed to fully understand the role of gut microbiota alterations in the development of disturbed GI physiology in man.

003
Clinical implications
F. AZPIROZ
University Hospital General Vall d'Hebron, Autonomous University of Barcelona, Barcelona, Spain

Background: The colon provides a dedicated niche for human microbiota, that metabolizes unabsorbed substrates releasing a vast amount of metabolites that influence the host.
Methods: Sensations originating in the gut in the absence of a structural cause depend on three factors: luminal content, gut function and sensitivity. The methodology to measure these parameters has become available for experimental studies in humans, both healthy subjects and patients with digestive complaints. In normal conditions, meal ingestion induces cognitive sensations (satiation and fullness), that depending on the characteristics of the meal and the digestive response may have a pleasurable dimension. By contrast, a large proportion of the general population presents digestive symptoms, such as abdominal bloating, distension, discomfort, and constipation or diarrhea, with no detectable abnormalities by conventional diagnostic methods. Some data indicate that these symptoms are produced by a combination of abnormal content, altered gut function and visceral hypersensitivity.
Results: Recent data indicate that microbiota might influence these three factors. Indeed, meal residues entering the colon are metabolized by microbiota with a modification in gut content and release of gas, which has been frequently associated with various complaints such as bloating and flatulence. Conversely, diet may modify microbiota composition. Microbiota may exert modulatory effects on gut function, both motility and barrier functions. A clear example has been shown in the experiments with pre- and probiotic treatment, which modify microbiota, and accelerate intestinal transit. A set of interesting data indicate that microbiota influence visceral sensitivity. Indeed, modulation of microbiota induces visceral hypersensitivity and visceral pain perception in rodents.
Conclusion: By modulating gut content reflexes and sensitivity intestinal microbiota may influence gut perception, both functional gut symptoms in patients, as well as pleasant sensations in normal conditions.