Meet the Champions

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'Maintain Focus and Aim High'

An Interview with Dr. Chung Owyang, H. Marvin Pollard Collegiate Professor, Department of Internal Medicine, University of Michigan, Ann Arbor, Mich., USA

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Abstract

Dr. Owyang is an academic leader well known for his work in pancreatic physiology and pathophysiology. He has made considerable contributions to our understanding of the neurohormonal control of digestive functions. His identification of the novel 'CCK releasing peptide' changed our understanding of hormone secretion during feeding and provides the mechanism responsible for feedback regulation of pancreatic secretion. Over the years, Dr. Owyang has trained numerous researchers, many of whom have gone on to become leaders in gastroenterology. Answering Martin Fernandez-Zapico's questions, he emphasizes the importance of good mentorship for the development of a new investigator and gives us a glimpse of his life and work.

Dr. Chung Owyang

M.E.F.-Z.: What initiated you to work in pancreas research in the first place?

C.O.: When I joined the GI Fellowship Program at Mayo Clinic, I had the good fortune to work with Drs. William Go and Eugene DiMagno who were giants in the field of gut endocrinology and pancreatology, respectively. Dr. Go was a pioneer in gut hormones at that time. His laboratory was working on developing a reliable radioim-

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munoassay (RIA) of cholecystokinin (CCK), a major hormone responsible for post-prandial pancreatic stimulation. Because CCK shares significant structure similarities with gastrin, most of the antibodies used for RIA at that time were not very specific. Furthermore, the concentration of CCK in the circulation is very low. This created additional challenges to the development of a specific and sensitive RIA for CCK and has impeded the progress in our understanding of the physiology of CCK. Dr. Go offered me the opportunity to participate in this challenging research project. Working with Dr. DiMagno, I developed a dog model which allowed us to study the relationship between fasting and post-prandial pancreatico-duodenal pressures, pancreatic secretion and duodenal volume flow in the dog. This ignited my interest in exocrine pancreatic physiology. My earlier experience working with both Drs. Go and DiMagno piqued my research interest in the biology of CCK as it relates to gastrointestinal functions. Both of my mentors emphasized the importance of a good experimental design and a disciplined and multilayered approach. These are the principles that have guided my research career till today.

M.E.F.-Z.: You have pioneered the pancreas research in so many directions. At the end of the day, what has given you the most personal satisfaction?

C.O.: As a physician scientist, we can take a clinical question, go to the laboratory, find an explanation, return to the clinic and apply what we learned to address a clinical problem. This 'from bench to bedside' approach in research gives me the greatest satisfaction. For example, pain in chronic pancreatitis is one of the most difficult problems to manage. Human studies suggest that at least in some patients with chronic pancreatitis, pain is related to increased intraductal and pancreatic tissue pressure. We hypothesize that pancreatic ductal hypertension is secondary to pancreatic exocrine insufficiency. To test this hypothesis, we developed a rat model and showed that diversion of pancreatic juice from the duodenum stimulates CCK release and pancreatic enzyme secretion. On the other hand, intraduodenal administration of trypsin inhibits the release of CCK and pancreatic enzyme secretion. The increased plasma CCK levels and pancreatic secretion after diversion of pancreatic juice appears to be mediated by a trypsin-sensitive, CCK-releasing peptide secreted by the proximal small intestine. When trypsin is present, this peptide is cleared and inactivated. The protease-sensitive feedback mechanism also occurs in humans. This led to the use of pancreatic enzyme replacement to treat painful chronic pancreatitis. There is nothing more rewarding than taking a clinical issue to the laboratory, finding an answer and applying the information to improve clinical management.

M.E.F.-Z.: Based on your experience as mentee and mentor, can you comment on the value of mentorship for the development of a new investigator?

C.O.: The transition from a mentee to an independent investigator represents a tenuous and daunting time. Good mentorship during this period of career development perhaps is the most important determinant for success in academic medicine. Yogi Berra once said 'You've got to be careful if you don't know where you are going, because you might not get there.' This sentiment is especially true in the world of academic medicine. Good mentorship will provide guidance in shaping the goal as well as important advice on the requisites to get there. I was fortunate to have outstanding mentors during my formative years. Both Dr. DiMagno and Dr. Go are model mentors. They have always taken an active interest in the nurturing of young investigators and brought out the best in those around them. In addition to being mentors, they are also friends, always making time to discuss whatever issues arose regardless of whether they were personal or scientific. A new investigator is probably at the most vulnerable stage of his research career. A mentor's task is to provide important insight and perspective. Guidance regarding career choices and the skills needed to be successful are invaluable to a neophyte embarking on a career in academic medicine.

M.E.F.-Z.: What is the best advice you have received during your career? What is your advice to the young investigators who are beginning in the field of pancreas research?

C.O.: The best advice I received from my mentors was to maintain focus and aim high. Frequently there is a risk that new investigators will get too diffuse and stray from their primary goals. Dabbling in multiple areas will hamper one's ability to focus and develop the in-depth expertise needed to make significant contributions to medicine. It is also important to set your goals high. One should carefully choose an area that has important biological or clinical significance and use state-of-the-art techniques to address the question. It is important to maintain focus on long-term goals as the achievements of a physician scientist will be considered as a whole rather than a series of isolated events, such as papers, presentations or grant applications. This advice has helped to guide my research throughout my career.

During the last 30 years, I have had the good fortune to mentor over 40 postdoctoral trainees, many of whom have gone on to become leaders in gastroenterology in

their own right. As a mentor it is always important to remember a few simple rules: treat your mentees as you were (or wanted to be) treated, recognize the full spectrum of their needs, guard against conflict of commitments, and never be selfish. With these things kept in mind, the mentoring of junior investigators as they build and flourish in their careers can be an extremely rich and rewarding experience.

M.E.F.-Z.: What do you think are the big questions that need to be answered in pancreatology?

C.O.: Significant advances in pancreatic research have improved our understanding of the pathophysiology of pancreatitis and pancreatic cancer. However, these basic observations have yet to be translated into improvements for the prevention, diagnosis and treatment of these pancreatic disorders. We need to think outside the box and take advantage of newer research tools including genomics and proteomics and large population genetic studies. Prevention and treatment of acute pancreatitis remain elusive. Much of these rely on better understanding of molecular and cellular signals regulating ductal and acinar cell function. Genome-wide studies reveal genetic factors which may predispose patients to the development of acute pancreatitis or influence its severity. At a cellular level, stress in the endoplasmic reticulum can lead to the accumulation of unfolded proteins and the initiation of the unfolded protein response resulting in inflammation and cell death. This is a promising area that may reveal potential targets leading to prevention or treatment. Research in proteomics and computer modeling provide new insights into zymogen granular membrane architecture and help to identify new protein regulating secretion and ion flow. Abnormalities in these pathways may permit intracellular activation of pancreatic enzymes leading to pancreatic injury. Information from such studies may provide therapeutic targets for prevention or treatment of acute pancreatitis. The quest for non-invasive methods for the diagnosis of early chronic pancreatitis continues. Studies using proteomic technologies report distinct protein profile patterns in the serum of patients with chronic pancreatitis. These potential biomarkers may provide a simple and convenient way to diagnose chronic pancreatitis. However, the diagnostic sensitivity and specificity of this approach remains to be determined. A number of studies provide evidence that chronic pancreatitis pain has an important central component similar to that reported in other chronic pain disorders. Electrophysiology studies consistently demonstrate enhanced activities in the insular, anterior cingulated gyrus and cortical somatosensory area, suggesting chronic pancreatitis is associated with neuroplastic changes in the CNS. These observations provide a new paradigm for pain management in chronic pancreatitis.

The pathogenesis of pancreatic carcinoma still remains unclear. Somatic genetic research has identified major tumor suppressors and oncogene in pancreatic cancer. Unfortunately, these findings have yet to be translated into therapeutic approaches. Recent studies on chromatic dynamics reveal new and attractive targets to induce epigenetic changes in pancreatic cancer cells. New information gained on DNA methylation and chromatic-mediated inactivation of tumor suppressor genes may be used to develop new therapeutic tools for pancreatic cancer.

Current imaging technologies are still too insensitive to detect pancreatic cancer early enough for curative resection. An attractive approach may be to use a strategy to image biomarkers for pancreatic cancer based on regions of chromosome amplification. This approach has the potential of detecting dysplastic changes when the pancreatic neoplasm is still in its formative stage.

M.E.F.-Z.: What do you think is the major need that a journal like *Pancreatology* should fill?

C.O.: *Pancreatology* must position itself to be the go-to journal for investigators and clinicians interested in pancreatic biology and disorders. The editor should aggressively solicit original papers from authorities in the field. Rapid review and publication will help. Publishing translation research can be a special niche. This is a void currently not well covered by other journals. Bridging the gap between basic science research and clinical papers may be an important mission for *Pancreatology*. This may render the journal highly attractive to both basic scientists and clinicians alike.