

'In a Certain Sense Dr. William Osler Has Been My Best Mentor'

An Interview with Prof. Tadashi Takeuchi

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Abstract

Tadashi Takeuchi is a Professor Emeritus of the Tokyo Women's Hospital University, one of the founders of the Japan Pancreas Society and first Editor-in-Chief of its official journal. His research contributed enormously to the understanding of the role of gastrointestinal hormones in pancreatic physiology as well as disease. In this interview, Professor Takeuchi discusses the importance of mentorship during career development.

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

T.T.: I started studying the pancreas in 1960 on the ward and in the laboratory of the First Department of Internal Medicine at the University of Tokyo, where I was fortunate to work in a very conducive and productive environment with many good mentors. My first patient with pancreatic disease was a woman with periarteritis nodosa, and she died of acute pancreatitis while on steroid therapy. That event sparked my interest in the etiology of pancreatitis. During my research on the causes of pancreatitis, at the suggestion of Dr. Masayuki Oda, I tried to create an animal model of acute pancreatitis in the dog. I injected several different bile acids, which are the main ingredients of bile, into the pancreatic duct at low pressure to confirm the bile reflux theory that Claude Bernard and Opie had proposed. I later found that pan-



creatitis could be induced by injection of contaminated bile, but not by sterile fresh bile, and that the cholate conjugates taurocholate and glycocholate induced only mild, edematous pancreatitis, whereas deoxycholate, which is present in a high percentage of patients with biliary tract infections, induced severe pancreatitis associated with

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1424-3903/07/0076-0393\$23.50/0

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hemorrhage or necrosis. In addition, I discovered that *Enterococcus* produced free cholic acid from conjugated bile acids and that *Clostridium welchii* generated deoxycholate from cholate.

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

T.T.: I moved to the Department of Medicine of the National Cancer Center Hospital in Tokyo in 1964. There it was my responsibility to set up the Pancreas Unit, and I engaged in clinical work and pancreatic research with Dr. Kaneo Ishii, the Chief of the Medical Division. At that time, any given pancreatic disease was diagnosed only by measuring serum amylase levels, performing barium contrast studies of the stomach to exclude other causes and evaluating the patient's symptoms. Pancreatic cancer was usually inoperable by the time it was diagnosed, and we could only provide terminal care. In addition, these diagnostic tools enabled us to differentiate pancreatic cancer from the patients with chronic pancreatitis. Shortly after that I performed the pancreozymin-secretin test (according to the method of Sun and Shay) at the National Cancer Center Hospital for the first time in Japan as a pancreatic exocrine function test, and it was subsequently widely applied to the diagnosis of chronic pancreatitis and pancreatic cancer in many hospitals in Japan. It was eventually approved as the gold standard for examination of the exocrine function of the pancreas. That spurred the interest in pancreatology among gastroenterologists in Japan, and the small study group on examination of the exocrine pancreas gradually grew larger. Finally, the Japan Pancreas Society was organized to discuss the pancreas as a whole in 1985, and I became the founding editor of its official journal *Suizou*.

From 1966 to 1968, I was a research fellow in Biochemistry at the University of Pennsylvania and Clinical Research Center of Philadelphia General Hospital (Director: Dr. Darwin J. Prockop), which allowed me to meet and interact with many people in the Gastroenterology Unit including Dr. Frank Brooks as well as Dr. William Chey, who was working in the laboratory of Professor Harry Shay at Temple University in Philadelphia and was also studying the exocrine pancreas. In August 1973, Professor William Chey and Professor Frank P. Brooks held a symposium on 'Recent Advances in Gastrointestinal Hormone Research' in Rochester, New York, and I was invited to attend. The symposium was the first in the world to focus on gastrointestinal hormones. We later developed precise radioimmunoassays for classic hormones, such as secretin and cholecystokinin, in the laboratory of

Tokyo Women's Medical College, and we made many discoveries concerning the relationship between the exocrine pancreas and gut hormones. That made me proud, and it was a source of great personal satisfaction that many physicians were able to train through hard work in this research as well as the busy clinical service. It was a great pleasure to have many excellent coworkers.

I should mention that my other sources of personal satisfaction are that I am still actively engaged in fostering young investigators and supporting pancreatic meetings as a result of establishing the Pancreas Research Foundation of Japan in 1993.

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

T.T.: It is true that mentorship is important to foster new investigators, but we do not have enough time for laboratory work because of the recent need to spend more time in clinical education to train physicians in gastroenterology. Nevertheless, in my opinion, research-minded doctors are good clinicians, and good clinicians are good researchers. I also recommend spending as much time in the laboratory as possible and spending time with good mentors because young investigators are often greatly influenced by their mentors. Good mentors should have enough experience to provide supportive advice, proper direction and encouragement to investigators. Based on my experience, a good chemistry between the mentor and mentee is key for a successful development.

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

T.T.: Throughout my career as a physician, I have received a great deal of advice from numerous mentors and my seniors. It is hard to single out the best advice I ever received, but I indirectly received advice from Dr. William Osler (1849–1919). When I was a research fellow at Philadelphia General Hospital and the University of Pennsylvania, I saw the relics of Dr. William Osler, the old autopsy table and the instrument used by him in Osler Memorial Hall at Philadelphia General Hospital, and I was impressed very much by his achievements. Ever since that experience the words in his books have greatly affected my thinking. So, I would say that in a certain sense Dr. Osler has been my best mentor.

As for the young people, gastroenterology is full of practical science, and it is attractive because it provides an opportunity to experience both the art and the science of medicine. Some physicians are not satisfied with rou-

tine work alone, such as performing gastrointestinal endoscopy or sonography, and pancreatic research would be a suitable source of satisfaction for them because it is a research field full of potential. In fact, since gastric cancer is a common disease among the Japanese population, there are many endoscopists in Japan that become interested in pancreatology, and the membership of the Japan Pancreas Society has been increasing as a result. Clinical research should be planned with a view to its clinical usefulness 5–10 years later, and pancreatic research should be performed from the same perspective. Some physicians became aware of research topics as they engaged in practice and became interested in conducting research. It has not been uncommon for such occasions to lead to a superb study, learning that Zollinger-Ellison syndrome or Verner-Morrison syndrome, for example, was discovered in this manner.

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

T.T.: The most important problem within pancreatic disease is pancreatic cancer. Most of the pancreatic cancer patients that I saw 40 years ago survived only 3–6 months. Despite the subsequent development of diagnostic imaging techniques, such as CT, MRI and MRCP, it is still difficult to detect small pancreatic cancers only 1–2 cm in diameter. Moreover, despite various therapeutic methods such as nutritional support or chemotherapy, survival time is no more than 2–3 times longer than it was 40 years ago. We need to study pancreatic cancer based on its specific characteristics of being able to grow with a poor blood supply, unlike liver cancer, and I hope that a new tumor marker as sensitive as the marker for prostate cancer can be developed. I expect knowledge from basic research will be able to solve these problems.

As for pancreatitis, severe acute pancreatitis is now being treated by means of multidisciplinary therapies including gastroenterology, cardiology, nephrology and re-

spiratory therapies. Together these combined regimes have contributed to the decrease in the mortality rate of this disease. However, the mechanism of development of acute severe pancreatitis is still unknown. Also, the earliest stage of chronic pancreatitis has not yet been identified. Work from my colleagues proposed the new concept of autoimmune pancreatitis based on the clinical evidence obtained by ERCP study [Yoshida K, et al: *Dig Dis Sci* 1995;40:1561–1568], and a great deal of other evidence concerning autoimmune pancreatitis has recently been reported. However, further characterization of its pathogenesis is needed.

Finally, since the pancreozymin and secretin used in exocrine pancreatic function tests are biological substances extracted from bovine tissue and they are no longer produced because of the risk of Creutzfeldt-Jacob disease, it is hard to obtain those substances to perform the tests. It will be necessary to develop sensitive exocrine pancreatic function tests in order to detect the early stage of chronic pancreatitis.

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

T.T.: Space for discussion of clinical and research work to inspire young investigators is needed in a journal like *Pancreatology*. Not only publication of interesting case reports but reviews on the concept of disease and commentaries on statistics and epidemiology are needed to interest readers in clinical pancreatology through clinical cases. I take for granted that the quality of the publications is adequate, but an effort should be made to invite good papers from presentations at meetings. Commentaries by basic scientists and articles on the history of pancreatology, such as gastrointestinal hormone research, I believe will stimulate young investigators' interest in this research field.

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