Meet the Champions

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Never Conclude with a Negative Result, Explore All Possibilities before Changing Your Hypothesis

An Interview with Dr. Catherine Figarella, Former Director Groupe de Recherche sur les Glandes Exocrines, Faculté de Médecine, Marseille, France; Active Member of the Board of the French Cystic Fibrosis Association: 'Vaincre la Mucoviscidose'

Martín E. Fernández-Zapico

Schulze Center for Novel Therapeutics, Division of Oncology Research, Mayo Clinic, Rochester, Minn., USA

Abstract

Dr. Catherine Figarella is a world expert in the isolation and characterization of human exocrine pancreatic proteins (enzymatic and non-enzymatic ones). She was a pioneer in the identification and characterization of the numerous zymogens present in pancreatic juice. In particular, her discovery of a peculiar behavior of one of the main proteolytic zymogens: human trypsinogen 1, which was more readily activated into active trypsin than human trypsinogen 2 and trypsinogens of other species led her to propose that a premature intracellular activation of this zymogen may play a role in the pathogenesis of chronic pancreatitis. She demonstrated that a similar phenomenon may occur in cystic fibrosis (CF) and has applied this knowledge of pancreatic zymogens to follow the evolution of the pancreatic disease in CF. With this brief but keen biographical article Dr. Figarella shares her life experience as an innovative medical and biochemical investigator of human exocrine pancreatic function.

Dr. Catherine Figarella

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

C.F.: When I entered my third year of medical school I simultaneously attended a course in biological chemistry. The course was given by Prof. Pierre Desnuelle at the faculty of Sciences-St Charles, in Marseille. I did well and at the end of the year Prof. Desnuelle suggested that I could join his research laboratory. I declined his invitation because my first idea was to become a physician, and I pursued my medical studies. However, at the end of the sixth year, already married and mother of two little girls, the hospital work became too much for me and I returned to see Prof. Desnuelle and asked him to welcome me to his laboratory.

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Martín E. Fernández-Zapico, MD
Schulze Center for Novel Therapeutics, Division of Oncology Research
Gonda 19-216
Rochester, MN 55905 (USA)
E-Mail fernandezzapico.martin@mayo.edu

His first question was: 'Are you really sure that you want to do scientific research? You have to know that this choice offers only two possibilities: either too little work or too much work.' I agreed without being sure he was right! But he was! Scientific research was much more demanding than I had imagined. After this introduction, Prof. Desnuelle kindly accepted me to his lab under the condition that I was willing to work on their main topic, which was the study of pancreatic enzymes in various animal species. One of the recent topics was the delineation, in friendly competition with Hans Neurath, of the mechanism of conversion of pancreatic proteolytic zymogens into active enzymes by the phenomenon of limited proteolysis. The fact that the cleavage of a single protein bond in a protein may induce a transconformation allowing biological activity is now known to play an important role in a great number of biological processes.

I agreed to the idea and I proposed, as a physician, to work on human pancreatic enzymes, which were largely unknown, especially the number and characteristics of human pancreatic zymogens. In June 1960, I submitted my MD thesis, a review about pancreatic enzymes, and joined Prof. Desnuelle's laboratory in September as a PhD student.

M.E.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?

C.F.: My first personal satisfaction came from the fact that I contributed to establish a link between biochemistry and medicine (which was not so evident 50 years ago) since my scientific research in the pancreatic field was nearly always devoted to humans (with the exception of a few experimental studies on rats at the very beginning of my career). During the course of my PhD, Prof. Henri Sarles who was a gastroenterologist particularly involved in chronic calcifying pancreatitis, offered me to join his INSERM Research Unit on Digestive Pathology to create a new group on pancreatic research. This allowed me both to develop a fundamental biochemistry work on proteins of normal and pathological human pancreatic juice, and to relay these results to the clinical findings in chronic and acute pancreatitis, and later in diabetes. I was helped in this work by the invaluable collaboration of Dr. Odette Guy, a biochemist from Prof. Desnuelle's laboratory, and other skilled coworkers. Another very rewarding aspect was to interact with many foreign physicians who came for fellowships in the Hospital Department of Gastroenterology of Prof. Sarles and in our research group, and to establish stimulating personal relationships.

Second, I also found a profound personal satisfaction in this field of research because all the new directions which were opened up by our findings were extremely exciting! It is therefore difficult to choose the one which has given the greatest satisfaction! It is perhaps, more particularly, our work on the characterization of the different pancreatic zymogens of human juice, and mainly of the two trypsinogens, their behavior and their implication in chronic pancreatitis and cystic fibrosis (CF). As is well known, trypsinogens are physiologically converted into trypsins at their entrance into the duodenum where they meet enterokinase. Subsequently, the generated trypsins activate their own zymogens and all the other zymogens. Our comparative studies in vitro on the activation of the purified trypsinogens by different trypsins and cathepsin B, a lysosomal proteinase, have shown a very peculiar behavior of the main trypsinogen, trypsinogen 1 or cationic one, compared to trypsinogen 2 (or anionic one) and trypsinogens of other species. In all cases, the human trypsinogen 1 was converted into trypsin much more faster than the human trypsinogen 2 and trypsinogens of other species. In addition, at acidic pH (pH 5) which is a pH very close to the pH of lysosomes, human trypsinogen 1 can be fully converted into active trypsin, in the absence of any added proteinase [Figarella C, et al: Biol Chem Hoppe Seyler 1988;369 Suppl:293–298].

This very fast conversion of trypsinogen 1 led us to the hypothesis that in chronic pancreatitis the liberation of a tiny amount of trypsin which is not immediately blocked by the secretory trypsin inhibitor could be responsible for a premature activation of pancreatic zymogens. Indeed we observed in the juice of patients with chronic pancreatitis several signs of this premature activation: a free proteolytic activity, a partial denaturation of pancreatic proteins, and an alpha 1 proteinase inhibitor-chymotrypsin complex. Moreover an insoluble protein of 14,000 molecular weight identified by others in precipitates and pancreatic stones of pathological pancreatic juices was shown to be a proteolysis product. It originates from the action of traces of trypsin on a soluble secretory glycoprotein of 19 kDa of unknown function present in the juice. The discovery in 1996 by Whitcomb and coworkers of a genetic mutation on the trypsinogen 1 in hereditary pancreatitis was therefore of personal satisfaction since it comforted our hypothesis! This mutation prevents the trypsin 1 to be autolyzed, showing that some trypsin molecules could be generated in vivo certainly due to the very fast conversion of the zymogen.

This phenomenon may also occur in CF where the pancreatic histological lesions are close to those observed in chronic pancreatitis, except for the fact that they are more generalized. A thorough collaboration with Prof. Jean-Pierre Chazalette, who was in charge of more than 300 CF patients at the Renée Sabran Hospital in Giens, and Dr. Jacqueline Carrère allowed us to study the behavior of serum immunoreactive trypsin in serum samples from CF patients and obligate heterozygotes for the CF gene. Our biochemical studies showed a release of active trypsin in blood of CF patients, resulting in premature activation of trypsinogen within the CF pancreatic gland [Carrère J, et al: Biochim Biophys Acta 1989;993:137–142].

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.F.: Mentorship is certainly essential, and a good mentorship relies upon both scientific and human qualities. Tremendous drive and energy as well as diplomacy are demanded from her/him. I remember Pierre Desnuelle telling me that when he entered the laboratory of Claude Fromageot (a leading French biochemist in the 1930s) he was told that 'there are two possibilities when you get extraordinary results: either it is a small discovery or a big error' and Fromageot added: 'I must tell you that the more frequent is a big error!'

The new investigator's research project must be chosen in common agreement between mentee and mentor, and the results should be discussed regularly but without pressure from the mentor. The mentor has to accept negative results especially when these results were obtained after they have been duly verified by the mentee. Mentee and mentor must clearly understand the difference between a hypothesis and a dogma! A hypothesis is very useful to pursue research but when the results do not fit, it has to be rejected.

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 pancreatic research?

C.F.: I have certainly received much good advice during my career since I never hesitated to contact scientists more specialized than I on different aspects of my research. But it is perhaps from Prof. Hans Fritz, a brilliant specialist of kinins and kininogenases, that I received the best advice: 'never conclude with a negative result before having explored all the possibilities'. This may be illustrated by an anecdote. Contrary to Hans Fritz, I was not convinced of the presence of a kallikreinogen in the human pancreatic juice. This zymogen, when converted into kallikrein, has the same effect as trypsins on specific synthetic substrates and despite many assays I was unable to detect a trypsin-like activity outside the two trypsinogens after chromatographic separation of the proteins of the juice. I was therefore very tempted to conclude to the absence of a kallikreinogen in human fluid and told it to Hans. But he replied: 'you have not finished your investigations, you have to look for a hypotensive effect of activated pancreatic juice!' It should be recalled that both kallikreins and trypsins are releasing kinins from kininogens, but when injected into the blood, trypsins are immediately blocked by the alpha-2-macroglobulin inhibitor and therefore unable to produce a hypotensive effect. On the contrary, kallikreins are not inhibited and may produce a hypotensive effect. So, I decided to make the experiment! I convinced a surgeon (who was my husband!) to help me, and I went with him and a young investigator in a laboratory of experimental surgery to look for a hypotensive effect of injected activated pancreatic juice in an anaesthetized dog. Different samples of human pancreatic juice before and after activation by bovine trypsin were injected into the femoral veins of dogs and the arterial blood pressure was recorded. To my great surprise, a very strong hypotensive effect was observed with the activated juice! Further experiments using the same pharmacological assay allowed us to purify and characterize human pancreatic kallikreinogen.

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

C.F.: Curiously, pancreatology is a word restricted to the study of exocrine pancreatic function. Basic and clinical studies on the exocrine pancreas and pancreatic secretions may be pursued for a better understanding of the pathophysiology of pancreatic diseases and especially for the prevention and early diagnosis of pancreatic cancer. However, I think that the relationship between the exocrine and endocrine pancreas is worthy of study. Langerhans islets are dispersed in the pancreatic tissue and it is difficult to think of an absence of exchange between the two tissues.

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

C.F.: Besides continuing to publish short and good-quality articles from serious scientists as well as reviews, opening up to some frontier research might be interesting. I would also suggest a larger diffusion, such as institutional bibliolinks by INSERM or CNRS in France.