

The Most Important Role of the Mentor Is to Guide the Mentee in Finding Own Solutions to Problems

An Interview with Prof. Henri Sarles

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Abstract

In this interview for *Pancreatology*, Professor Henri Sarles shares his life experiences as clinical expert and scientist in pancreatic research. He is a pancreatologist recognized worldwide for his contribution to the understanding of pancreatic diseases. In particular, he led the way in the pancreatitis field with the characterization of pathogenesis of chronic pancreatitis.

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

H.S.: I was born in 1922 near Paris but later lived in Marseille. I started research after my medical studies, at the end of the war. I had a degree in biochemistry (pre-historical biochemistry of the fifties). At this time, research possibilities in Marseille were extremely poor because the economic situation was very bad. In my hospital, an average of 2 people died each day of starvation in the 2 last years of the war. It was only after 1950 that research possibilities increased and became satisfactory under de Gaulle's government. I became interested in the relationships between diet and pathology. Under our difficult working conditions the only way to make honest medical research was to do statistical epidemiology limited to simple data such as age, sex and nutritional data



Prof. Henri Sarles

calculated by the excellent dietitians working with us. Chronic (calcified) pancreatitis, a previously rare disease, became frequent at the same time as cholesterol gallstones almost disappeared, before recurring when diet became normal again. To study these problems, I selected two groups of patients with an indisputable diagnosis: (1) acute pancreatitis proven by surgery and (2) chronic pan-

creatitis proven by calcified calculi visible on radiography. The literature at this time was full of papers on the so-called 'chronic relapsing pancreatitis', a mixture of all cases of pancreatic diseases and other diseases, and it was assumed without any serious proof that the recurrence of acute pancreatitis was the cause of chronic pancreatitis. A reason for disagreement between the different authors was that the same word was used with different meanings. In an effort to understand and be understood, I organized in a symposium in Marseille with 30 European pancreatic pathology specialists to define the words *acute* and *chronic* pancreatitis. This classification that was widely used was outdated but at the time it allowed different authors to speak the same language. For studying the relationship between acute and chronic pancreatitis, I compared the two groups of patients previously selected and perfectly defined. Unexpectedly, the first attack of chronic pancreatitis occurred 13 years earlier than acute pancreatitis. This proved that acute pancreatitis could not be the cause of chronic pancreatitis and contradicted the common assumption, which although unproven was admitted nevertheless by many as a religious faith. This simple work paid for invitations and travels abroad and attracted to my service and my laboratory a number of young researchers from many countries.

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?

H.S.: A collaboration of basic scientists with clinicians having a scientific culture and able to focus on unexplained findings began. One part of our work has been a statistical study of the nutritional conditions of pancreatitis patients. In the most frequent form of pancreatitis, alcoholic pancreatitis, on the contrary to what is observed in liver cirrhosis, patients were found to have a higher fat and protein intake than matched controls. Experiments in rats and dogs confirmed that high fat and protein intakes modify the secretory response of the pancreas to alcohol. Tropical pancreatitis in India (Kerala) is not observed after short-term starvation, which causes kwashiorkor, as observed in Hungary during the war but after long-lasting malnutrition. Experiments in rats showed that mother rats receiving a low-protein diet compatible with survival give birth to pups secreting a pancreatic juice hyperconcentrated in protein, as observed in alcoholic rats fed a protein-rich diet. This suggests that protein-insufficient diets of the mother are probably responsible for the disease.

Morphological studies on chronic pancreatitis using an optical and ultrastructural microscope with three-di-

mensional reconstruction of pancreatic ducts thanks to serial sections allowed distinction between two types of chronic pancreatitis lesions: (1) lesions due to duct obstructions preexisting to chronic pancreatitis (small tumors, oddities, scars), and (2) lesions observed most frequently in two conditions: alcoholism in adults and malnutrition in tropical countries (India). Such pancreatitis, mostly nutritional, is characterized by the presence in the ducts of protein plugs that later calcify, forming stones. Lesions of ducts range from atrophy of the basal membrane in contact with plugs to strictures. These lesions are fairly similar in alcoholic and tropical pancreatitis. This pancreatitis is a lithiasis.

Biochemical studies of pancreatic juice have shown different modifications in chronic pancreatitis, compared to normal, that might play a role in stone and plug formation at the origin of ductal lesions: hyperconcentration of secretory protein (although the output is decreased due to pancreatic lesions), a manifold increase in lactoferrin concentration, decreased concentration of citrate and of a previously unknown protein discovered in pancreatic calculi, called PSP (pancreatic stone protein), a name later changed for lithostathine. It represents about 6% of protein secreted by acinar cells. This protein is the major protein constituent of pancreatic calculi from which it can be easily purified upon extraction by citrate dissolution. Lithostathine can prevent calcium carbonate crystal formation. As its concentration is decreased in pancreatic juice from chronic pancreatitis, it should play a part in this disease characterized by the presence of calcified stones. But a similar decrease is observed in alcoholics without pancreatitis. Therefore, another agent of lithogenesis is necessary. The most probable candidate is lactoferrin, which is greatly increased in chronic pancreatitis. My retirement and the lack of interest of the French research administration to solve this problem explain why research was stopped in this field. Research is frequently driven by the fields of interest of industrial laboratories.

Four years ago a Swiss-American group published that they could not confirm our conclusions on lithostathine. I proposed a collaboration to try to confirm or to invalidate our results. They refused. Newer studies from researchers working in our laboratory reproduced our results. Since this time, using X-ray analysis, they were able to give the tridimensional structure of lithostathine and to show that the molecule isolated from pancreatic juice and having this structure could prevent calcite crystal formation. I assume that the molecule isolated by the Swiss-American authors was not lithostathine or was de-

graded. A possible assumption is that the hereditary modifications of trypsinogen recently described could lead to lithostathine inactivation and be responsible for its precipitation.

In alcoholics, in tropical pancreatitis and in some forms of hereditary pancreatitis, pancreatic calculi are mostly a build up of calcite and of still active lithostathine (inhibiting calcium carbonate crystal growth). But in another form of hereditary pancreatitis, calculi are built up from a degraded form of lithostathine, no longer active on crystals. At the beginning of this disease, calculi are X-ray-transparent because they contain no calcium carbonate. When the disease progresses they are covered with a shell of calcium carbonate (bull's eye). It would certainly be interesting to compare the compositions of calculi in the different hereditary defects presently described.

One of the contributions of our group was to explore the effects of ethanol on pancreatic secretion in an attempt to understand why alcoholism may cause a calcified chronic pancreatitis. The study performed in dogs showed that a unique ethanol injection can decrease or stimulate pancreatic secretion, depending on the dose. These two effects are mediated by the vagus nerve. In animals receiving large ethanol doses for months, these two mechanisms disappear and uncover stimulation at the level of the pancreas. This is also observed in rats and might account for the increased protein concentration in the pancreatic juice of alcoholics.

The work of our laboratory was not limited to alcoholic pancreatitis. In collaboration with us, Prof. G Hage discovered the first physiological mechanism inhibiting pancreatic secretion: after a meal-induced stimulation, the injection of fatty acids in the jejunum inhibits secretion, this being transmitted by cross-circulation. Since this time the humoral mechanism of fat inhibition has been described by others.

I was also interested by a rare disease that became more frequent during the war: benignant Vaterian stenosis or odditis or papillitis. As some developed in the hours or days following an intense emotion (for instance being locked in the cellar after the house was bombed) we compared our odditis patients with patients presenting with cholesterol main bile duct stones having the same symptomatology. Intense stresses generally due to the war were significantly more frequent in the immediate past of odditis patients. In some of our patients, stress causes an immediate increase of the resistance of the Oddi sphincter to bile flow. In dogs, odditis similar to human lesions were produced by chronic irritation of the right splanchnic nerve.

This effect is suppressed after section of the right vagus and of the right splanchnic nerve, suggesting a nervous cause for odditis.

These studies were done by researchers from Marseille and more frequently by foreign post-graduate collaborators or professors in sabbatical year. If I was responsible for the direction of this multidisciplinary research, many ideas and conclusions came from researchers who I cannot mention in such a paper. But there was always a long discussion and the different conclusions came more frequently from the group than from an individual.

Approximately half of my time has been dedicated to gastroenterology. Associated with research, this allowed to keep contact with suffering men. This was also a good part of my life. I always tried to teach students to limit drugs and examinations to what is necessary for their patient and, if possible, not painful. I think that a well-done interview can be just as useful as sophisticated investigations. I tried to teach that examinations are not done as a matter of curiosity but for the sake of the patient. For this purpose I tried to teach the young and less young students and physicians that semiology, that was well known in France and Germany but tends to be forgotten, may be useful for the diagnosis. Indeed, it needs more brain effort than prescribing 10 exams and 6 drugs. A computerized study of pancreatic symptoms has been done using an extensive list of symptoms described as precisely as possible. It led to a simplification of pancreatic symptomatology by suppressing useless data and allowed 80% exact diagnosis of chronic pancreatitis.

In conclusion, I tried to associate human care of patients and good research, based on findings in humans. If it is necessary to continuously improve techniques, it is also necessary to keep in contact with patients. At the present time, we need physicians who know human symptomatology well and are able to inspire research in collaboration with different specialists.

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

H.S.: Mentors are evidently necessary (1) for young researchers at the beginning of their carrier for choosing the knowledge necessary or useful for the type of research they would like to do; (2) for everybody at every stage of their carrier to open their minds and help them perceive as deeply as possible in the understanding of their subjects; (3) to be skeptical and not to admit unproven ideas

even when they originate from 'well-known' authors, the opinion of authors being sometimes not based on the value of their work but on fashionable empty papers coming from powerful groups, and (4) to help other researchers and not to be envious of their success.

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

H.S.: Everything that is not or not yet well known, particularly when it is not on a currently fashionable subject, giving complete freedom to the researcher but judging them on their results, helping them if they produce good

work, suppressing their grant if they were sterile, and not supporting civil-servant pseudo-researchers as in France for 50 years.

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

H.S.: To choose good original articles even or preferably if they come from yet unknown authors. The purpose of research is to understand ideas that are not understood or not well understood. Really new ideas frequently hurt well-established people.