Editorial

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Celui qui cherche la vraie science doit la pêcher là où elle se trouve
Michel de Montaigne 1533–1592

The first time I heard of Didier Lebrec was in 1981 after an article had appeared in the *New England Journal of Medicine* entitled "Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study" [1]. At that time, I was working in Gustav Paumgartner's group at the University of Munich. We were planning to perform a study to test sclerotherapy for the prophylaxis of first variceal bleeding in patients with large esophageal varices [2]. With this new and provocative paper in mind, we discussed whether we should treat the conservative arm with propranolol.

There was a meeting on cirrhosis and its complications in London. Jean Pierre Benhamou was one of the chairmen and Didier Lebrec one of the speakers. Gustav told me to contact Benhamou to get more information on the value of non-selective β-blockers (NSBB) for the treatment of portal hypertension. I met Didier Lebrec in the hotel lobby and asked to meet Jean Pierre Benhamou. When I told him what I wanted he said: "*You should ask me, I am the one who performed the study*". We decided against propranolol in the second arm. It was difficult for us to accept the rationale of treating these patients with an NSBB. We were afraid that the hemodynamic reaction would be impaired in case of bleeding, the kidney function would deteriorate, etc. Later on, a second study performed by Andrew Burroughs at the Royal Free Hospital in London was published [3]. The authors found no difference in rebleeding after esophageal hemorrhage between the control and propranolol groups, so we were happy about our decision. But today, it is clear that we were wrong. Three decades after the first report that oral treatment with NSBB decreases portal pressure, these drugs are still the treatment of choice for the prophylaxis of first variceal bleeding and rebleeding, together with the ligation of varices. The conclusions of the prestigious Baveno consensus meetings, where Roberto de Franchis gathered experts in portal hypertension, have continuously confirmed this [4]. Although the participants have aged, NSBB are as topical as ever. What other indication for a drug has remained unchanged for 30 years? Very few! The treatment of portal hypertension is

an example of how new treatments must remain in synch with clinical practice to span decades.

The story behind this achievement is closely connected to an assumption made by a young French hepatologist at Hôpital Beaujon in Clichy, Paris. When he read a paper showing the portal pressure reducing effect of somatostatin, Didier hypothesized that splanchnic hyperperfusion might be present in patients with cirrhosis, increasing portal hypertension by an increase in portal tributary blood flow. Didier thought that this dynamic component might respond to drugs that decrease the portal tributary blood flow. He chose an NSBB [5], which reduces cardiac output on the one hand, while possibly causing an unopposed splanchnic alpha-adrenergic reaction on the other hand. As a result of working from 1973 to 1974 as a Fulbright postdoc with the cardiologist Jay N. Cohn at Georgetown University, Washington DC, Didier had learned about the importance of the systemic circulation. Furthermore, early in his career, he had learned to measure the hepatic venous pressure gradient (HVPG), which reflects portal pressure [6]. He was also the first hepatologist in Europe to perform transvenous (transjugular) liver biopsies [7,8]. With these skills and this expertise, it was easy for Didier to measure HVPG in the portal vein in humans and to confirm his hypothesis. His group performed an elegant study showing that continuous administration of propranolol leads to a sustained reduction in the HVPG and heart index without affecting hepatic blood flow [9]. Later, they used animal models of cirrhosis using microspheres to prove that during portal hypertension, splanchnic blood flow is indeed increased while the hepatic blood flow, which is a fraction of splanchnic blood flow, is not [10]. Thus,

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Editorial

Didier Lebrec and Roberto Groszmann [11] identified an important paradox in the pathophysiology of portal hypertension and cirrhosis: namely that while vasoconstriction is present in the liver, vasodilatation is observed in the splanchnic and systemic vascular system.

Over time, numerous clinical trials published in the most prestigious journals [12,13] have proven that Didier's treatment of portal hypertension with non-selective β-blockers was correct.

Today, new findings are often generated by mass screening techniques that can generate new findings and associations that may be of great clinical importance. This is possible thanks to the revolution in biostatistics and may become the subject of further research on function [14,15]. Didier's approach, however, was completely the opposite. His hypothesis was based on an educated guess. He then worked to prove the hypothesis by performing hemodynamic measurements and controlled clinical trials, one at a time. Few scientists are competent and lucky enough to identify a new treatment that is accepted worldwide and used for decades.

During his nearly 40 years at Hôpital Beaujon in Paris, where he was also Director of Research at the National Institute of Health (INSERM), Didier Lebrec trained 34 fellows from France and 28 from other countries in Europe, America, and Asia. Two of these were members of my group. They came back with new ideas, new methods, and wonderful memories for the rest of their lives of this large family where clinical research and "*savoir vivre*" were shared in Paris. Together with these young co-workers and the members of the Liver Unit in Clichy (Richard Moreau and so many others), the group made an enormous contribution to our knowledge on portal hypertension, especially on the endogenous factors involved in the control of arterial tone in cirrhosis [16,17]. Even today, we do not fully understand why there is an impaired response to vasoconstrictors in the dilated vessels [18]. Didier and his group have shown that NOS upregulation [19], partly due to bacterial translocation [20] may be one reason. Last but not least, the group showed that there is a significantly augmented inflammatory response to LPS in cirrhosis as compared to controls [21]. This was the basis of Didier's last large randomized controlled study – which was again hypothesis driven – namely by treating cirrhosis with the anti-TNF molecule, pentoxifylline [22].

Didier Lebrec was not only involved in research in hepatology, he also looked after his patients, postdocs at Hopital Beaujon, and the community of hepatologists worldwide. He was a scientific committee member and president of the French Association for the Study of the Liver, scientific committee member of the European Association for the Study of the Liver (EASL) and president of the International Association for the Study of the Liver (IASL). He has been in the editorial boards of all the highly ranked international journals in the field of liver disease and he was associate editor of the *Journal of Hepatology*. Today, he is still the editor in chief of the *European Journal of Gastroenterology and Hepatology*.

What qualities are needed for such a career? There are no standard answers, but the most important are ideas, a passionate interest and a structured approach, as well as a sincere and unbiased attitude when analyzing raw data, self-confidence, and a good team.

When I visited Didier in March 2013, he was still working in his office on the first floor of the Pavillon Abrami, Hopital Beaujon, surrounded by photos of friends he had met at the many research meetings he had attended around the world, and by walls of books, journals, and papers. Didier has followed his path over a period of four decades, and a visit to his office is a proof of this: a living, active, working space allowing creative scientific thoughts based on the solid foundations of scientific exchange and the highest level literature from worldwide experts.

Didier Lebrec was born in Paris as the third of six children. His father was a member of the famous Ecole Polytechnique, one of the *grandes écoles* in France. In the French tradition, Didier was sent to the prestigious Lycée Louis-le-Grand. Fortunately for hepatology, Didier did not become a *polytechnicien*, but began studying medicine, met his mentor, Jean Pierre Benhamou, and started his 40-year journey.

He is the father of two sons and one daughter and the grandfather of five grandchildren. All the members of his large family live in Paris and the close *banlieu,* enjoying life in this cultural centre of Europe. But Didier also has close connections with the New World, he has been happily married for 20 years to his wife, Dale, who has her roots on the East Coast of the US.

When I visited Didier, he showed me a photo of the garden that he and Dale had created in their country house in the Perche, near Chartres. Today he spends more and more time there, studying the different plants, trees and bushes, looking at other gardens in the area, then adapting the garden, choosing plants that will thrive in the local terrain, just as he has done throughout his career in the field of hepatology and portal hypertension.

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