



EASL Recognition Awardee 2020: Prof. Giovanna Fattovich

Antonio Craxi*

Department of Internal Medicine, University of Palermo, Palermo, Italy

Since 2006, the Recognition Award of the European Association for the Study of the Liver has been given to women and men who have been instrumental in shaping clinical practice, research and academic teaching of hepatology in Europe. Giovanna Fattovich definitely fulfills all the criteria for such an illustrious award.

Giovanna Fattovich was born in 1949 in Venice, where she grew up. In 1944 her Italian parents fled with her baby brother in a mass exodus, their home in Zadar (Zara) was destroyed by bombing. Dalmatia, the land of origin of her family, has been disputed between the Austro-Hungarian empire and Italy through the centuries. It was an Italian protectorate between 1915 and 1944. However, when Italy lost its influence after World War II, 350,000 Italians were forced to come back to Italy as refugees from Dalmatia and Istria. Her family settled in Venice, where one more brother was born, while Giovanna's father, an economist, supported by his wife, a teacher, managed to become the Administrative Director of the Municipal lagoon navigation company. Her family and ancestral history are in my opinion essential to understand her strong willpower and dedication to work, but also her curiosity and passion.

At the age of 17, she applied to the American Field Service organization, being selected thanks to her adaptation and communication skills for a year of exchange schooling in the USA. Her parents were very open minded since at that time it was unusual for an Italian girl to go abroad for such a long time. She was assigned to a family in Santa Ana California and graduated at Santa Ana Valley High School. This year had a major influence on her life, outlining the importance of exchange student programs. She still has a strong link with her "adoptive" family in the US.

Once back to Italy, she elected to study Medicine at the University of Padua. At that time more than 90% of medical students in Padua and elsewhere were males. During the last 2 years of medical school, she became involved in hepatology, both bedside and in the laboratory. This was a lively time when she joined other young colleagues such as Alfredo Alberti, Flavia Bortolotti, Giulio Diodati and Federico Tremolada under the mentorship of Prof. Giuseppe Realdi, the chief of the Liver Research Unit of Padua University. Some of their names have also left a major and durable imprint on the field of liver diseases. The group was then at the leading edge of liver research, being particularly active in the field of hepatitis B with the first observations on the relationship between the distribution of HBV antigens in



hepatocytes, HBV replication and the histological and clinical features of liver disease and its subsequent course. Her MD thesis (1974) on "A RadioImmunoAssay test for HBsAg" was at the time a rather advanced project!

After graduation, she stayed in Padua as a volunteer in the Liver Research Unit laboratory to pursue her craving for research but also the uncertain possibility of a university position. Meanwhile, she supported herself by working part-time as a general practitioner on a rather punishing schedule mitigated only by hope and enthusiasm for research. She got married to Maurizio (an anesthesiologist, willing to share family duties as very few Italian men would have done back in the '70s!) and her first son Matteo was born in 1976, to be followed in 1984 by Massimo. Eventually in 1978, she got a Fellowship position and in 1981 became Clinical research assistant at the Department of Clinical Medicine, University of Padua, her dream became reality after years of volunteering.

She continued her laboratory research on the immunological mechanisms underlying chronic viral hepatitis within the Liver Research Unit directed by her mentor Giuseppe Realdi, progressively shifting the focus toward clinically oriented research

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* Corresponding author. Address: Department of Internal Medicine, University of Palermo, Palermo, Italy.

E-mail address: Antonio.craxi@unipa.it.

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issues. Giovanna was also interested in studies on the immunoregulatory function of the suppressor T lymphocytes and the cellular immune response to viral antigens in acute and chronic HBV infection. From these studies, elements emerged that allowed researchers to trace a new interpretation of the pathogenesis of chronic liver disease associated with HBV. Treatment of chronic hepatitis B in the '80s was still in its infancy, with IFN- α as the only available tool to contain HBV replication, while tests for HBV replication had low sensitivity. Capitalizing on her knowledge of immunological mechanisms, she hypothesized a possible therapeutic role of levamisole, an immunomodulatory agent, in chronic hepatitis B and translated this into a double-blind placebo-controlled trial, to be published in *Gastroenterology* in 1986.¹ Although levamisole definitely was not enough to obtain HBV control, the pattern was set for a long line of studies on the effects of boosting innate and adaptive immunity for HBV cure.

Giovanna, possibly due to her family background, has always had a meticulous (non-Italian?) no-limits attitude to work. Capitalizing on her clinical work starting in the '70s, by the '80s she had already amassed a huge collection of data from patients with chronic viral hepatitis carefully followed on the ward and in the outpatient clinic, at a time when effective treatment for HBV and HDV were practically non-existent. The major focus of her research in that period was thus the natural history of chronic hepatitis B and B/D. She single-handedly managed to describe the disease course and outcomes of chronic hepatitis B, mostly unmodified by treatment, for the first time in a Western population. Some of these papers are still considered as a reference to assess the spontaneous course of liver disease in Western patients, mostly HBeAg-negative patients bearing HBe minus HBV variants.²⁻⁵

The natural course of virally induced liver disease was bound to stay as the dominant theme of her subsequent professional career as a researcher, even more so when the onset of HCV as an identifiable entity made clear the overwhelming role that viruses had at that time as determinants of cirrhosis and hepatocellular carcinoma (HCC). In fact, by the beginning of the '90s, Giovanna had realized that only large-scale data collections performed by a multinational approach involving many hepatology units throughout Europe could originate sound blocks of clinical knowledge in the rather heterogeneous area of chronic viral hepatitis. Thus, she became strongly involved with EUROHEP (European Concerted Action on Viral Hepatitis), an MHR4 EU community networking project lead by Prof. Solko W. Schalm, creating a strong and durable linkage between Padua and Rotterdam. The periodic meetings at various European locations held by the EUROHEP network produced an atmosphere of collaboration and friendship between the various participants (Giuseppe Realdi, Stephanos Hadziyannis, Françoise Degos, Piero Almasio, Jose Maria Sanchez-Tapias, Erik Christensen and many others), that kept the group active over more than a decade. Collecting and analyzing big data on multinational networks is standard practice today, but was definitely a major innovation 30 years ago, at a time when computing facilities were few and isolated, the worldwide web non-existent and data exchange done by surface mail or fax. A huge body of work started with the preparation of the data collection sheet of patients with cirrhosis B and subsequently C for the EUROHEP subproject on the natural history of viral cirrhosis. Giovanna still remembers

that: 'The design of the study was discussed painstakingly and collegially during several meetings of the EUROHEP group with clinicians, epidemiologists and statisticians. Some centers preferred to send us the completed paper forms and others as files to be transferred by mail on floppy disks. Giuliano Giustina, then a PhD student, took all data and transcribed them in Excel format on a PC's hard disk (512 megabyte!), but I used to bring home kilograms of printed paper in order to double check the correct transcription of data and to work on the analyses over the weekends. The Centers were repeatedly contacted for clarification and for any missing data. Data elaborations were done using "prehistoric" statistical programs running on a PC and produced innumerable printouts and survival curves. What a difference from today, when researchers can do their analyses on a smartphone!'

The EUROHEP team produced, mostly with Giovanna as the driving force, a significant number of multicenter European studies on the course of cirrhosis due to HBV, to HDV and later to HCV.⁶⁻¹³ Treatment of chronic viral hepatitis at all stages of disease was also a major focus of the group. The evaluation of the efficacy and tolerability of various antiviral drugs as well as of both viral and host factors that influence the response to therapy, provided fundamental information, recognized internationally, for adequate clinical and therapeutic management. Since Giovanna Fattovich was identified as the proponent of a major proportion of EUROHEP's cooperative efforts, she was invited to report on studies conducted in Caucasians patients at the NIH conference on HCC in 2004. The ensuing publication in *Gastroenterology*,¹⁴ which ranks highest in terms of citations among her works, was based in addition to the EUROHEP results on an enormous and painstaking work of systematic revision of the literature on the incidence and risk factors of HCC done in collaboration with Francesco Donato, Professor of Hygiene at the University of Brescia.

In 2010 Giovanna spent a brief, fruitful period as Visiting Professor at the Division of Gastroenterology and Hepatology and Clinical Pathology, University of Geneva, hosted by Francesco Negro in his direct laboratory. Working in a pleasant atmosphere fostered by Franco's well-known hospitality and friendliness, she worked on the role of genetic polymorphisms in determining response to IFN in chronic hepatitis C.¹⁵

When, at the end of the '90s, the Liver Research Unit in Padua changed its asset due to Prof. Realdi's move to Sassari, Giovanna transferred her academic appointment as an Associate Professor to Verona, a nearby city without the strong hepatological tradition of Padua. There she continued her hard clinical and research work, and dedicated much time to teaching medical students and residents. Of this period at the University of Verona, which was somewhat problematic for her further career development, she remembers in fairness: 'In retrospect I am happy with the Veronese experience even if it was difficult and what remains is only a memory. I had to divide myself between clinical activity, teaching and research. The preparation of the internal medicine classes in particular required an important commitment. The Veronese environment was not saturated with hepatologists like Padua and therefore I was able to work well. I have been able to involve various gastroenterologists with hepatological interest from neighboring hospitals in multicenter antiviral therapy studies. Numerous Paduan patients preferred to continue being followed in Verona possibly as a result of dedication and empathy'.

Although somewhat marginalized by a persistent self-defensive attitude of the local academic establishment, favoring the selection of native candidates over true merits, Giovanna, away from her native group, managed nonetheless to establish fruitful cooperations with other research groups in Verona and published original contributions on molecular mechanisms underlying anemia induced by ribavirin therapy¹⁶ and on hepatic iron metabolism.¹⁷ The lack of opportunities for career progression proportionate to her massive achievements effectively halted her career and led to a somewhat early retirement in 2015.

Her personal life is nowadays full and certainly more relaxed. While she still spends her energy as a volunteer physician in charity organizations, Giovanna takes time to travel, to go mountain trekking with her husband, and to play with three grandchildren ranging from 1 to 3 years.

When I asked Prof. Realdi what feature of Giovanna's career should be stressed more, he promptly quoted the ability to build her entire research curriculum, after its first phase, on her own, through intelligence, hard work, and her ability to establish and maintain contacts with other researchers, as well as her resilience and modesty. To attest to the latter, I also have to say that Prof. Solko Schalm, when requested to produce some pictures of the EUROHEP team, had trouble finding a good one because Giovanna was always at the back of the scene!

Thus, at a time when EASL attributes Giovanna Fattovich one of its highest honors, we must thank her for the privilege of working with her. She has shown us the way to constant, sound, credible clinical research and, most of all, the value of cooperation.

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