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Editorial

Diego and Giorgina Vergani: The two hearts of translational autoimmunity

A B S T R A C T

Since the publication of the first textbook on autoimmune diseases in 1963, the knowledge in the field has exponentially grown into numerous tracks of research, particularly at benchside. Systemic and organ-specific autoimmune diseases, as in the case of the liver, have witnessed notable advances in terms of epidemiology, genetics, effector and regulatory mechanisms, and ultimately treatment. While the available tools for communication have provided accelerating progress rates, we recognize that key opinion leaders continue to provide significant contributions to the field. The present issue is dedicated to celebrate Giorgina Mieli-Vergani and Diego Vergani as two of the finest examples of excellence in autoimmune liver diseases and the broader field of autoimmunity. Diego and Giorgina are extremely well-liked Colleagues who fully represent the translational efforts between laboratory research and clinically relevant questions in the practice of pediatric liver diseases and autoimmune hepatitis.

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1. The early days

Giorgina Mieli was born in 1946 in Como, where her parents had moved during the war. Her2 father, who was from an Italian family that had expatriated to Alexandria, Egypt, in the second half of 1800, had moved to Italy in his twenties and become a very successful entrepreneur in silk manufacturing. Her mother, whose father had died in the World War I when she was only 2, came from a family of musicians. Giorgina is the fifth of seven children. She attended primary and secondary school in Como, at the Orsoline Institute. Diego Vergani was born in Capiago-Intimiano (Como), Italy, in 1946, third of four children. His father was a countryside general Practitioner and his mother a housewife. Diego's father lost his voice as a consequence of surgery for laryngeal cancer when Diego was 14 and Diego would later follow his father to help communicate with patients or to fulfill forensic duties. The young Diego demonstrated a strong personality and the capacity to obtain what he wanted, using negotiation without being aggressive. While on vacation at the age of three, he met a famous Italian comedian named Macario who, after observing his behaviour, stated “Diego: I break, but I do not bend”, which remains an apt definition of his personality. Diego attended elementary school in the small town of Capiago-Intimianobetween 1952 and 1957, where he was one of the few fluent in Italian, though he would use the local dialect to relate to other children and create long-lasting friendships. These are indeed renewed every Christmas when all elementary schoolmates and their teacher, Maria Maspero Locatelli (who is now over 90 years of age), gather for a party.

2. The high school years

Giorgina and Diego met as classmates at high school in the Liceo Classico Alessandro Volta in Como where they sat at opposite sides of the classroom and were quite different in terms of motivations and literary preferences. Giorgina never liked going to school and found it much more interesting and productive to learn from books during the summer vacation and from the various pieces of art collected by her uncle and aunt. After meeting Toscanini at the age of three, Giorgina developed a love for music and played the violin. She also loved riding horses and practiced classic ballet dance from the age of 6 until the age of 11, when she became taller than the other girls and was only given male parts. Diego was also not particularly fond of school and often did not attend, preferring to walk in the woods, and ride his bicycle or motor bike on the country roads and montains around the Como Lake. In 1966 during the disastrous flood of the Arno River, which killed over 100 people and damaged or destroyed pieces of art and books, Diego hurried to Florence where he helped recovering hundreds of ancient precious books from the mud, transferring them by the truckload to a monastery in the surrounding area.

3. The medical school years

Giorgina decided to become a physician at the age of 12 and never changed her mind, despite her parents tried to convince her otherwise, as there were no doctors in the family, and attended the local hospital as an observer when she was 14. She had experienced a long hospital admission when she was 5 due to severe thrombocytopaenia after smallpox vaccination. She fully recovered

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and has vivid memories of that period and the love her father showed her during that time. After high school, both Giorgina and Diego enrolled in the University of Milan Medical School in 1966 and became close during their second year, when Giorgina had a car accident with a prolonged hospital stay. During that time, Diego helped her to understand physiology, biochemistry and general pathology and allowed her to brillantly pass exams after being discharged. This period and the sharing of several common interests (including art, music, trekking, and good wine) grew into a solid relationship that led to their marriage in 1972. While on their honeymoon, Diego had to start his military service and was sent to Florence where Giorgina followed him for the three months of military medical school. The years in medical school also include the 1968 student protests and both Diego and Giorgina shared the views of a peaceful opposition to the old academic system.

Giorgina's 1971 MD dissertation was on the use of thermography for the diagnosis of breast cancer and she became board certified in Pediatrics in 1974 and Immunology and Allergy in 1977. After graduation she worked in the De Marchi Pediatric Hospital in Milan with Professor Giuseppe Masera, a consultant haematologist whose main interests were leukaemia, thalassaemia, and childhood solid tumours. During her years in Milan, Giorgina witnessed the introduction of prednisone/vincristine in the treatment of acute lymphoblastic leukaemia, which transformed this condition from 100% mortality to 90% full remission. Giorgina also worked for 6 months with Ferdinando Gianotti, who had named an acrodermatitis associated with hepatitis B virus infection, and met Alex Mowat, a Scottish paediatrician interested in liver disease, that visited the Center. This experience together with frequent occurrence of obscure liver abnormalities in children with malignancies and thalassaemia redirected her interest to paediatric hepatology, a subspecialty that was nearly unknown at the time.

In a parallel fashion, Diego's 1971 MD dissertation was on the radiological treatment of nasopharyngeal cancer and he became board certified in Internal Medicine in 1976 and Immunology and Allergy in 1979. Between 1973 and 1976 Diego worked as a Registrar at the Ospedale Luigi Sacco in Milan, in the department of internal medicine. A large number of his patients were young drug addicts, all of whom were either positive for the ‘Australia antigen’ or had other types of hepatitis from sharing needles. He learned how to perform liver biopsies and read histology from Gaspare Jean, a colleague with a keen interest in hepatology, and became aware of liver pathologies that were largely enigmatic at the time. This experience led to his interest in liver immunopathology and the decision to join a center of excellence for one year.

4. Moving to London

By the end of 1976, Giorgina and Diego shared the developing interest in liver diseases and started browsing international centers of excellence. There were only two paediatric hepatology centres worldwide, one in Paris led by Daniel Alagille and one in London led by Alex Mowat. By early january 1977 they moved to London (Fig. 1), where Diego would work at the adult Liver Unit led by Roger Williams. Both Giorgina and Diego started in the laboratory, which was a new experience for them, and initially had limited clinical involvement, mainly represented by the Saturday case discussions led by Roger Williams and Alex Mowat. Giorgina was working on lymphocyte cytotoxicity in autoimmune hepatitis using peripheral blood lymphocytes cultured with rabbit hepatocytes. In those same years, Zinkernagel reported that histocompatibility antigens were crucial to detect T cell cytotoxicity [1,2], an observation thatinspired Giorgina to attempt autologous cytotoxicity using lymphocytes and hepatocytes from the same patients. Both her supervisors Malcolm Cochrane and Adrian Eddleston tried to dissuade her but she persevered, obtaining biopsies from King's and other hospitals. Giorgina succeeded, producing a number of papers on autologous cytotoxicity in autoimmune hepatitis, hepatitis B, alpha 1 antitrypsin deficiency, and cystic fibrosis [3–6]. Diego in the meantime was starting on a project on drug induced liver disease, particularly hepatitis following the administration of halothane. He was able to demonstrate a cellular sensitization to halothane altered liver cell membrane and published this in the Lancet a few months later [7]. He went on to show with Giorgina and Alfredo Alberti that patients with halothane-induced liver failure had circulating antibodies to halothane altered hepatocytes that were able to inflict damage. These findings were published in the New England Journal of Medicine and ultimately led to the discontinuation of the use of halothane as an anaesthetic [8].

Fig. 1. Diego Vergani and Giorgina Mieli-Vergani pictured at Kew Gardens in 1978, a year after they arrived in London.

In view of the success in the lab, both Giorgina and Diego were asked to stay longer and Diego was offered a tenure position as Lecturer in Immunology in the Department of Immunology at King's College Hospital in 1978. There he was deeply involved in undergraduate and postgraduate teaching and in research, which was not limited to the liver. One of many outcomes of his teaching activity was the publication of the textbook ‘Basic and clinical immunology’ which was co-authored by Mark Peakman, one of his early PhD Students. Diego collaborated on research projects with David Pyke, an active leader in diabetes care, who had collected the largest series of identical twins concordant or discordant for type 1 diabetes. In one of his first research projects, based on the knowledge that concordance for diabetes occurs mostly