

## SISSET50: trajectories of hemostasis and thrombosis in Italy 1970-2020

Giovanni de Gaetano,<sup>1</sup> Maria Benedetta Donati,<sup>1</sup> Americo Bonanni<sup>2\*</sup>

<sup>1</sup>Research Unit of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli (IS);

<sup>2</sup>Multimed Comunicazioni, Pozzilli (IS), Italy

\*Science Communication Officer

**Americo Bonanni (AB):** SISSET was founded in 1970. That was the year of Apollo 13, the famous “Houston, we have a problem,” the advent of long-distance dialing, the patenting of the computer mouse, and the legendary soccer match Italy vs Germany (4-3). It was also the year of the first New York City Marathon and the release of the movie *They Call Me Trinity*. The Nobel Prize for Literature went to Aleksandr Solzhenitsyn, while Julius Axelrod, Bernard Katz, and Ulf von Euler won the Nobel Prize in Medicine for their work on synaptic neurophysiology. Fifty years ago, Giuseppe Ungaretti and Jimi Hendrix passed away.

And SISSET was born.

The first SISSET Congress was held in November 1970 in Parma. A half-century has passed since then. The Society’s Board of Directors has asked Giovanni de Gaetano to provide a brief overview of SISSET’s 50-year history. We will also hear from Maria Benedetta Donati, who joins us here at the Marc Verstraete Auditorium of the IRCCS Neuromed in Pozzilli, Molise.

Let’s start with Giovanni de Gaetano...

**Giovanni de Gaetano (G):** Thank you. In July 1970, the International Society on Thrombosis and Haemostasis (ISTH) held its first meeting in Montreux, on Lake Geneva, after being established the previous year in Bath, England. SISSET effectively began in 1970, in parallel with the international society... The first SISSET Congress was held in Parma, organized by Prof. Dettori in November of that same year, and lasted only one morning - on a Sunday.

**AB:** Were you there?

**Maria Benedetta Donati (B):** Yes, we had been among the 200 attendees at the Montreux meeting, and we also participated in Parma after obtaining permission by Professor Coccheri, even though we were not yet SISSET members. Since then, we have journeyed alongside SISSET throughout these 50 years. For us, and for many others, SISSET has been the place, the environment, and the cultural hub where hemostasis and thrombosis have developed in Italy - and often internationally - over the past half-century. SISSET immediately aligned with the international wave of this emerging hematological field, which was becoming, albeit with some challenges, an autonomous science and discipline.

**AB:** Do you have any memories of that first SISSET Congress?

**G:** Yes, it was quite a strange feeling, because we didn’t know, except by name, either the Founders of the Society or the other participants, as we had gone abroad immediately after graduating in 1968. We remember this feeling well, because later, the Italian experts in hemostasis and thrombosis became very familiar to us. At the time of the Parma Congress, we were PhD students in Leuven, Belgium, in the laboratories of Professors Verstraete and Vermeylen. Collen was a young medical student like us. We remember, like in movie, the night before SISSET: we traveled in a sleeper car on the Brussels-Milan train, which was used to bring

Italian miners back home. Tickets were dirt cheap, but we will never forget the sound of those silicotic lungs accompanying us all night. We realized how privileged we were as migrants...

**AB:** What were the emerging topics of SISSET in its early years?

**B:** The focus was primarily on hemostatic issues. Bleeding was the predominant concern, with hemophilia and thrombocytopenia as its major dramatic representations. Cryoprecipitates were just starting to be discussed, and AIDS was still far away. Within SISSET, we were ourselves hematologists, but we were evolving into something profoundly new.

**AB:** Were you worried that SISSET’s scientific focus might be too narrow compared to hematology and other disciplines?

**G:** At the time, we used to say that blood goes everywhere, so no discipline or specialty could avoid interacting with us. The so-called “hemostatic balance” was starting to appear restrictive for many of us.

**B:** Indeed, a concept that began to develop - albeit embryonically - was that the factors and mechanisms of the hemostatic system did not only govern the balance between bleeding and thrombosis but also contributed to the pathogenic development of seemingly unrelated diseases, such as solid tumors and metastases. Thus, the two T’s - tumors and thrombosis - were born.

**AB:** An exciting intellectual and experimental challenge.

**B:** Yes, I remember at the ISTH meeting in Paris in 1975, our presentation on experimental tumors and thrombosis was confined to the last Friday afternoon in a poster session titled *Miscellanea*. Today, we have clinical trials on anticoagulants and tumors, and dedicated conferences on this topic, thanks largely to the pioneering contributions of many SISSET members.

**G:** I also want to point out that until the 1980s, the idea that coronary thrombosis was a significant cause of myocardial infarction was merely a hypothesis, even contested by many investigators in Italy, especially pathologists. The cultural climate both at Mario Negri Institute in Milan, where both of us were working at that time, and within SISSET, fostered the first GISSI study, involving Rovelli, Neri Serneri, Mannucci, and Benedetta herself, along with the entire Italian cardiology community. That study allowed cardiologists to witness firsthand that coronary thrombosis could be dissolved or reduced by streptokinase.

**AB:** What happened after streptokinase?

**B:** Streptokinase, in a way, paved the way for tPA (tissue plasminogen activator). Many will recall a heated session at the 1990 SISSET meeting in Bari, with Désiré Collen as the protagonist. However, thrombolytic therapy for myocardial infarction was later partly overshadowed by interventional cardiology, including angioplasty and stents.

**AB:** Did cardiologists become interested in other SISSET-related topics?

**G:** Yes, certainly. The experimental and clinical research con-

ducted in Italy on platelets and aspirin in the 1980s—continuing into more recent times with the so-called “aspirin resistance”—provided opportunities for a frequent dialogue with pharmacologists, cardiologists and neurologists. Low-dose aspirin as an anti-infarction drug was in fact developed in Italy. Studies on aspirin also helped shift attention toward the vascular wall, particularly the endothelium. At Mario Negri, the first human endothelial cell cultures had been developed in the Seventies and we recall the famous dilemma about aspirin inhibiting both platelet thromboxane and endothelial prostacyclin.

**B:** During the same period, Italian groups discovered von Willebrand Factor and Tissue Factor on human cultured endothelial cells. Years later, Tissue Factor transitioned from the vessel wall to circulating blood, with SISET members demonstrating its presence on metastatic tumor cells, platelets, neutrophils and macrophages. At the 1992 second SISET meeting in Parma, one presentation was titled: *No Cell is an Island*. Those were the years of cellular interactions, adhesive molecules, and transcellular metabolism.

**AB:** Were there international events where SISET presented these new ideas?

**G:** Yes, absolutely. The first ISTH meeting assigned to Italy was held in Bergamo in 1982, coinciding with the 100th anniversary of Giulio Bizzozero's first description of platelets. The main symposium was titled *Cellular Aspects of Hemostasis and Thrombosis: One Hundred Years After Bizzozero*. This truly marked the entry of cellular biology into hemostasis and thrombosis.

**B:** I would also like to recall that the prestige of SISET members later attracted other major international events to Italy, such as the Congress on Fibrinolysis in Venice in 1984, the ISTH Congress in Florence in 1997 with over 7,000 participants, the ISTH Subcommittee meeting in Venice in 2004, and, most recently, this year's ISTH Congress in Milan, which became virtual due to COVID. Additionally, organizations like the Mediterranean League have chosen Italy for several congresses and meetings. The European Thrombosis Research Organization (ETRO), to which several Italian laboratories had been admitted, celebrated in Rome, in 1997, the 25th anniversary of its foundation.

**AB:** The Nineties, the new era of genetics...

**G:** Yes, the Human Genome Project was a revolution, with an excitement comparable, perhaps, to the Colombo's discovery of America. SISET had always been deeply interested in genetic diseases, rooted in its hematological origins. Think of hemophilia and other rare diseases like Glanzmann's thrombasthenia or von Willebrand disease.

**B:** The novelty was that the molecular biology that emerged in those years fostered two major research areas: first, the identification of congenital mutant forms of coagulation factors. Let me highlight that the earliest observation dates back to 1958 and was described for fibrinogen by Imperato and Dettori in Parma. The second area involved genetic polymorphisms in platelets, fibrinolysis, and coagulation factors, which could partly explain the risk of ischemic diseases like myocardial infarction. Here too, SISET members made significant, sometimes pioneering, contributions.

**AB:** Beyond the work of individual members or small groups, what has SISET achieved as a society?

**G:** Since its foundation, SISET has excelled in educational activities, such as national courses held across Italy. Additionally,

over the past 20 years, SISET has produced numerous original guidelines on critical clinical and therapeutic topics.

**B:** Within SISET's cultural framework, independent initiatives have also emerged, complementing its activities. Examples include the Federation of Centers for Monitoring Antithrombotic Therapies (FCSA), established in 1989; the Platelet Study Group, formed 20 years ago; the Italian Association of Hemophilia Centers (AICE); the annual courses of the Menarini Foundation and the historic Schweitzer Center in Bari; and more recently, the Arianna Anticoagulation Foundation. This array of societies, groups, and initiatives demonstrates the widespread culture of hemostasis and thrombosis spread in Italy by SISET and underscores Italy's clear leadership on the international stage.

**AB:** What has been the relationship between SISET and the pharmaceutical and reagent companies?

**G:** The companies have always been supportive of SISET and its members, maintaining a fruitful, cordial, and highly respectful relationship. As far as I recall, there have been no unpleasant conflicts of interest.

**AB:** Over the years, SISET has evolved. How has this change been reflected in its congresses?

**G:** SISET congresses have become increasingly interdisciplinary and international. They maintain a high scientific level while offering opportunities for younger researchers to present their work. The success of these events lies in their dynamic structure, integrating basic science with clinical applications.

**B:** Yes, and I would add that SISET congresses have always been inclusive, welcoming both established professionals and early-career researchers. These events not only disseminate knowledge but also trigger collaborations and mentorship.

**AB:** Looking ahead, what do you think are the future challenges for SISET?

**G:** The main challenge is to continue evolving in step with scientific progress while maintaining its identity. SISET must also keep addressing emerging health issues, such as the interplay between coagulation, inflammation, and cancer, as well as thrombosis in the context of infectious diseases like COVID-19.

**B:** Another challenge is to nurture the next generation of scientists. SISET must remain a vibrant space for young people, offering them opportunities to grow and contribute to advancements in hemostasis and thrombosis.

**AB:** Any closing thoughts?

**G:** SISET has a rich history that has always been deeply intertwined with its members' contributions and initiatives. Its strength lies in its collective vision, which has enabled it to adapt and lead in a constantly changing field.

**B:** I agree. SISET has made Italy a significant player in the global hemostasis and thrombosis community. Its legacy is not just in its past achievements but in its ongoing commitment to innovation and collaboration.

**AB:** A final question: How can we imagine the next 50 years of SISET?

**B:** That's a million-dollar question, as they used to say... Let's try to imagine some answers, even if they might seem a little vague and unclear.

**G:** First of all, in 1970, life expectancy at birth in Italy was 71.5 years. Now, in 2020, it is 83.5 years—a gain of 12 years. By 2070, life expectancy is projected to reach 89.5 years, an additional six-year gain. SISET will undoubtedly contribute to achieving and perhaps overcoming this predicted increase. But more

importantly, SISSET must work to extend the hope of life without disability, a healthy life currently just shy of 70 years.

**B:** Many SISSET congresses will be held using communication tools that will evolve and proliferate over the next half-century, irrespective of situations like COVID-19. However, even though today we are not physically present in Baveno, we hope that the handshake, the embrace, the nervous walk to the podium, and the shared moments at the evening table will never disappear.

**G:** We are already moving towards personalized medicine. This trend will only grow, and by 2070, everyone might have a tailored prevention, diagnosis, and treatment program. Each individual could have a unique "hemostatic balance," allowing effective thrombosis prevention and treatment without increasing the risk of bleeding. This might sound like a dream, but it's possible we'll finally separate the two sides of the hemostatic balance. Another balance that could be optimized concerning thrombosis is that between inflammation and immunity. Furthermore, more attention will likely be given to lifestyle, nutrition, environment, and culture over pharmacological interventions.

**B:** Gene-environment interactions will be studied in depth; epigenetics, still in its infancy today, will see maximum development. It might become possible to replace missing or defective genes and modify the expression of normal genes through diet or other measures. These will also be the years when artificial intelligence and big data will enable innovative analyses of information currently limited or overly predictable. The preference will be for 1,000 data points on a single individual rather than one data point on 1,000 individuals. SISSET will provide increasing contributions to 21st-century experimental and clinical research.

**G:** Controlled, randomized clinical trials, which have illuminated recent decades but are not without methodological and ethical limitations—since they often are far from everyday reality—will no longer be the gold standard in medicine. We'll move out of the statistical night where all patients are "black" and are treated as indistinguishable. Instead, there will be a focus on caring for healthy individuals, what we like to say, in Italian, *La Cura dei Sani*.

Probably, healthcare will finally center on communities for both health promotion and the management of milder or early-stage conditions. Hospitals, in turn, may no longer be organized by specialty departments. Instead, as we used to feel as children on carnival rides, the experience will be about holistic care: you could enter the hospital at any point and be treated as a whole person.

**B:** Indeed, the focus will shift from diseases to the patient—or rather, the person—viewed holistically, with each one being unique. This individuality, even among apparently healthy people, will form a new basis for epidemiological studies, striving to define, as in mathematics, the least common multiple and the greatest common denominator of health and the risk of losing it.

**G:** These are dreams and visions. But let us conclude by paraphrasing a thought from *The Prophet* by Gibran: "We may offer our experience to those who come after us, but we cannot foresee their thoughts, for they already dwell in the house of tomorrow, which we cannot visit, not even in our dreams."

**AB:** Thank you, Giovanni de Gaetano and Maria Benedetta Donati. And to all of you, enjoy the continuation of the XXVI SISSET Congress 2020 in Baveno!