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OBITUARY

Uri Seligsohn, MD (1937–2022)

Uri Seligsohn, one of the most distinguished leaders of the modern era of hemostasis and thrombosis passed away on January 29, 2022, at the age of 84. He was born on February 6, 1937, in Tel Aviv, Israel. His father and grandfather were highly respected patent attorneys and built one of the most successful intellectual property firms in Berlin, Germany. Despite this, his family decided to flee Germany as the Nazis imposed their antisemitic laws, barring them from appearing in court, arriving in Palestine under the British mandate in 1934.

Uri attended Hebrew University Medical School and Hadassah Hospital in Jerusalem from 1957–1963 and received his M.D. in 1964. He trained in medicine and hematology at Sheba Medical Center, Tel Hashomer, leading to his appointment as professor of hematology at Tel Aviv University in 1982. From 1979–1993 he was the director of the Institute of Hematology at Ichilov Hospital and from 1993–2005 first chairman of the Department of Hematology and then director of the Institute of Thrombosis and Hemostasis at Sheba Medical Center. He founded and directed the Amalia Biron Research Institute of Thrombosis and Hemostasis, Tel Aviv University and Sheba Medical Center, from 2002 until 2018.

Uri was a charismatic leader, even in childhood when the other children called him "The Prince." As an adult he was universally admired for his medical and scientific brilliance, his mentorship, and his integrity. As a result, he held numerous leadership positions in the World Federation of Hemophilia, the European and Mediterranean League against Thrombotic Diseases, the European Hematology Association, the Israel Society of Hematology and Blood Transfusion, the American Society of Hematology, and the International Society on Thrombosis and Haemostasis (ISTH). Education was a very high priority for Uri, and in addition to serving as vice dean of the Sackler Faculty of Medicine at Tel Aviv University and founding director of its School of Continuing Education in Medicine, he served as chair of the educational committee of the ISTH for several terms. He was also a terrific writer and editor, and served as co-editor of *Williams Hematology* for several editions (see photo). One of us founded the Israeli Society of Thrombosis and Haemostasis with Uri and developed an Israeli training program with him in the field of thrombosis and hemostasis. He was very devoted to the ISTH mission and ultimately served as chair of the ISTH Council and president of the 1995 ISTH Congress in Jerusalem.

Uri was recognized by his peers by numerous awards, including the Ham-Wasserman Lecture award for Distinguished Research in Hematology, American Society of Hematology; the ISTH Esteemed Career Award; the ISTH Robert P. Grant Medal; the Sheba Prize for lifetime achievement; and election to the Israel Academy of Sciences and Humanities.

Uri served with distinction in the Israel Defense Forces, commanding field hospitals in Israel's 1967 and 1973 wars, rising to the rank of lieutenant colonel, and assuming command of a medical battalion. Shmuel Bernstein, one of his comrades in the 1973 war, described him as having the respect of the doctors who served under his command as well as the respect of his superior officers for his excellent judgment, ability to accomplish his goals, and calm demeanor, even under great pressure. He also participated in the planning to

set up showers outside of Ichilov Hospital in Tel Aviv during the 1991 Gulf War in case Israel was attacked with Scud missiles carrying poison gas and casualties needed to be decontaminated before they entered the hospital, in order to protect the patients and staff inside the hospital.

Uri was also a master clinician who cared for innumerable patients with a wide spectrum of hematologic disorders. He and his mentor, Dr. Bracha Ramot, recognized that Israel was home to multiple Jewish communities that had lived in isolation in other countries for extended periods of time, with intra-group marriage very common, leading to their having a relatively high percentage of recessive genetic disorders. Thus, in addition to his expertise in caring for patients with the sex-linked forms of hemophilia,[1–8] he developed expertise in managing large cohorts of patients with factor XI deficiency,[9–14] factor VII deficiency,[15–23] combined factor V and VIII deficiency,[24–34] and Glanzmann thrombasthenia.[35–39] As a result, in addition to his pioneering basic research on these disorders he became a world leader in their clinical management. His patients revered him for his expert care, his compassion, and his devotion to them. To show their appreciation they invited him to their homes and one of us had the pleasure of accompanying Uri on a visit to a family that included several children with Glanzmann thrombasthenia in Kafr Kanna in the Galilee, in which the family showered us with course after course of delicacies.

Uri joined Sam Rapaport's lab in the 1970s, and his research resulted in a series of elegant papers with Sam, Bjarne Østerud, and John Griffin studying the activation of factor VII.[40–43] One of us also had the great pleasure of collaborating with Uri on studies of patients with Glanzmann thrombasthenia, applying each new technology as it became available. While Israeli patients with Glanzmann thrombasthenia were indistinguishable based on their clinical symptoms and their abnormalities in platelet aggregation, clot retraction, and even polyacrylamide gel electrophoresis, they could be differentiated based on immunoblotting into those likely to have defects in αIIb or β3.[44,45] As monoclonal antibodies to αIIbβ3 became available they provided a method to rapidly diagnose the disorder and to study carriers of the disorder,[46] as well as to analyze antibodies made by patients in response to platelet transfusions.[47] This then led to an international collaboration to help families that wanted prenatal diagnosis in which patients from Israel traveled to London to undergo fetal blood sampling and platelet analysis with the monoclonal assay.[48,49] After the DNA sequences of the αIIb and β3 genes and the genes of related receptors were determined, it was discovered that αIIbβ3 was closely related to another integrin receptor αVβ3, sharing the same β3 subunit. Analysis of αVβ3 on the platelets of Glanzmann thrombasthenia patients further helped differentiate those with defects in αIIb vs β3, defined the relative contributions of αIIbβ3 and αVβ3 to platelet interactions with vitronectin and fibrinogen, and provided insights into the biogenesis of the receptors and the role of the receptors in trafficking both fibrinogen and vitronectin.[50,51] Uri's group went on to devise a simple method to assess patients' αVβ3 expression using transformed β-lymphocytes.[52]

Dr. Peter Newman, who pioneered the use of the polymerase chain of platelet mRNA to identify genetic defects affecting platelets, joined the collaboration, leading to the identification of the major DNA abnormalities in the affected populations in Israel.[50] Uri and his colleagues then developed methods to rapidly identify these DNA abnormalities in urine, thus obviating the need to obtain blood samples,[53] and they went on to identify and analyze a number of additional DNA abnormalities in Glanzmann thrombasthenia patients in Israel, Jordan, and India, providing important insights into αIIbβ3 structure, function, and biogenesis.[54–68] With Coen Hemker's group Uri also studied the impact of Glanzmann thrombasthenia on thrombin generation and later Uri studied the impact of recombinant factor VIIa on enhancing thrombin generation in the presence of Glanzmann thrombasthenia platelets.[69,70]

Having data on whether αIIb or β3 was responsible for causing Glanzmann thrombasthenia made it possible to perform prenatal diagnosis using chorionic villus samples, which can be obtained at ~11 weeks of gestation compared to 18–20 weeks for fetal blood sampling. Drs. Deborah French and Alok Srivastava joined the collaboration and performed prenatal diagnosis by gene linkage analysis.[71,72] As the specific DNA abnormalities were identified, prenatal diagnosis could be performed using direct polymerase chain reaction analysis of chorionic villus samples. Uri also directed his research to population genetics, identifying and dating founder mutations, and using the information to trace Arab and Jewish ancestry.[55,73]

With David Ginsburg, Uri deciphered the cause of the mysterious combined factors V and VIII deficiency syndrome, discovering a novel transport mechanism in protein biogenesis.[24–30,32–34] Uri and his colleagues also studied the molecular biologic basis of factor XI deficiency among Ashkenazi, Roman, and Iraqi Jews; French Basques; and Arabs, again defining and dating founder mutations.[74–85] He also studied the impact of factor XI on thrombin generation,[86] platelet-associated factor XI,[87] the role of disulfides in factor XI activation,[88,89] and the impact of acquired factor XI antibodies in patients with factor XI deficiency.[90,91] Presciently, he reported the protective effects of factor XI deficiency on ischemic stroke[92] and deep vein thrombosis,[93] which provided crucial genetic support for the ongoing development of inhibitors of factor XI as antithrombotic agents.[94]

At the center of Uri's world was his wonderful and tight-knit family. His wife Hani has played important roles in the Habima National Theatre, and his children Yael, Gabi, and Danny are each accomplished in their own professional fields. Together, and with their children's own families, they enjoyed exciting travel, including a memorable trek in Nepal. Uri and Hani also enjoyed the cultural life of Tel Aviv, including the theater, the opera, and the symphony. Uri Seligsohn leaves an enormously rich legacy, with every institution, patient, student, peer, and friend that he touched enriched by his creativity, warmth, and absolute commitment to the highest values and ideals of academic medicine.

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