Obituary

Shmuel Shaltiel

First published online 11 December 2002

Part I: by Giorgio Semenza[1]

Shmuel stemmed from an old Spanish Sephardic family (a Shmuel Shaltiel is buried in Toledo's old Jewish cemetery), who had reached prominence in Gerona before los Reyes Católicos in 1492 expelled – or forced to convert to Christianity – all Jews and Muslims who were in Spain. Shmuel was proud of his Jewish tradition and culture, which I, a goy, could not fully fathom, but I am told by knowledgeable friends, that he was a scholar.

The emigrated Shaltiels kept speaking Spanish (i.e. the one of the 15th century, the so-called 'ladino') and became an outstanding part of the highly cultivated, large, flourishing Jewish community in Salonika. In the twenties the Spanish premier of the time, Primo de Rivera ('el dictador'), granted the possibility of obtaining the Spanish passport to those emigrated Sephardites who had kept speaking ladino in the country of emigration, in spite of the more than four century elapse. Shmuel's grandfather made use of this possibility ('You never know'), and I remember Shmuel showing a copy of his grandfather's Spanish passport in a slide during a lecture in Spain. This passport would save their lives.

In 1940 Mussolini – against the suggestions of his generals, contrary to the good sense, and *without* informing the German ally – attacked Greece from southern Albania, vastly underestimating the will and the capacity of the Greeks to put up an efficient resistance in the difficult and inaccessible mountains of the Epirus. ('We'll break Greece's neck in a couple of weeks'.) Actually, the Greeks fought back and occupied part of southern Albania. The Italian setbacks compelled the Germans to come to rescue by occupying Yugoslavia first from north to south, and then Greece itself. Very soon the Jewish were rounded up and sent to annihilation camps. The cultivated, flourishing Jewish community of Salonika was no exception: its more than 50 000 Sephardites were sent to Bergen-Belzen, the Shaltiels among them.

Shmuel, then a 6 year old boy was with his father, and

[1] ETH-Zentrum, Postfach 35, CH-8092 Zurich, Switzerland and Dipartim. di Chimica, Biochimica e Tecnologie per la Medicina, Università di Milano, Via Saldini 50, I-20133 Milano, Italy. E-mail address: semenza@bc.biol.ethz.ch

0014-5793/02/$22.00
doi:10.1016/S0014-5793(02)03787-0

remembered for his life with gratitude a young SS who dared to give him 'Wasser' which he needed badly, when the crammed train stopped in the sun for hours. In the Lager of Bergen-Belzen in the evenings, after the daily labours, his father would tell him: 'and now we make the homework for school'. At this time the unexpected happened. The Spanish authorities (the Consul in Athens or Salonika, or perhaps even Franco himself, I don't know) requested that the Jewish families with Primo de Rivera's Spanish passport had to be sent back. The Shaltiels were, therefore, among the few who were saved. As Shmuel used to say with a bitter smile, 'I have 50 000 controls'.

I came to know Shmuel and his wife Sarah (who was to die of cancer a few years before him) rather well when they spent half a year in our lab in Zurich. They had most uncommonly vast interests and gifts in history, literature and arts. (Sarah, during their previous stay in the States, taught young Americans to write in good English style; later, in Israel, she succeeded to learn Swedish by herself, in order to read Selma Lagerlöf – quite a feat, I can assure you!) But – and this is the rare quality that made the basis of our friendship – they were easily approachable by everybody in the lab, always ready to help in biochemistry and other matters. Their natural generosity and equilibrium, in spite of the hardships in their lives and the difficulties (I assume) in working and growing in career in a country in perennial state of war and with limited financial resources made it natural for them to forget and forgive. I never heard a negative judgement from them, rather words of understanding and objectivity – nor, for the matter, any word less than positive *about* them. They soon became 'old friends' to each member of my group.

No wonder that Shmuel served at the Weizmann Institute in various important duties that carried a lot of responsibility; e.g. as the Dean of Ph. Curricula, and others. No wonder, also, that he has been such a motivated, objective, constructive Editor of FEBS Letters. He knew the importance of publication for a young scientist at his/her beginnings, and the importance for the journal to be selective and fair. He often corresponded with the authors, suggesting extra experiments or different interpretations or improvements in the text.

We have lost a friend, a first-class biochemist, and a scholar.

Part II: by Edmond Fischer[2]

I first met Shmuel in November of 1963 when my wife Bev and I arrived in Haifa by boat. It was our first visit to Israel where we already had very good friends (including Ephraim Katchalski/Katzir and Michael Sela with whom I was to work) and we had decided to bring a car with us so that we could see as much of the country as possible: Israel was not very large at that time. The trip we were supposed to take from Genoa along the Dalmatian Coast was canceled at the last minute so we had to take a Turkish boat from Naples, which turned out to be one of those great maritime disasters second only to Trafalgar. Anyway, here we were in Haifa on a very stormy evening, waiting for them to unload our car because, dumb as we were, we thought that all we would have to do is buy a road map and follow the signs all the way to Rehovot. Of course, in those days, there was no map, no freeway, no road sign, no service station and God knows where we would have ended had we attempted to make the trip on our own. But then, on the pier way down below us, we saw a fellow with a smile from here to there waving frantically at someone (we didn't know who) until we finally realized that he was waving at us. It turned out to be Shmuel who had come to our rescue and, I must say, never Savior was received with more gratitude. It was midnight by the time we went through all the formalities, raining like crazy, and Shmuel drove us through impossible roads all the way to Rehovot. This was the beginning of a wonderful friendship with Shmuel who later spent two years (1964–1966) in Seattle as a Post Doc after completing his thesis with Patchornik and Arieh Berger.

His visit turned out to be an unforgettable pleasure and experience. A pleasure, first, because Shmuel was the epitome of the scholar: the real Renaissance Man, speaking five languages absolutely fluently, widely read and solidly versed in the arts, literature and music. In the lab, once in a while, he would hum a passage of a concerto or symphony, or sing an aria from an opera – in fact, with a nice voice. And then, of course, he was a first-class scientist with a vast knowledge, meticulous and demanding in the lab. He worked on the structure and function of pyridoxal 5′ phosphate in phosphorylase. This coenzyme is bound covalently as a Schiff base and essentially impossible to remove under non-denaturing conditions. But after systematically testing hundreds of conditions, he and Jerry Hedrick came up with what they called a 'deforming agent' in the form of an imidazole/citrate/cysteine mixture with which they could liberate the coenzyme under the mildest of conditions. Shmuel was so excited about the rapidity of the process (half-life of 3.5 min) that a few months later, during a Symposium at a Federation Meeting in Atlantic City in which I was describing his work, and carried away by his enthusiasm, I spoke of this 'incredibly fast' reaction. Until I noticed the next speaker who was seated in the front row and who was looking at me with an amused and sardonic smile. It was Manfred Eigen, ready to talk about his new T-jump procedure that measured reactions in a millionth of a second.

The unforgettable experience came when it was time to publish our first paper, and anybody who has ever written a manuscript with Shmuel would know what I'm speaking about. Every word, every sentence was meticulously analyzed and every statement scrutinized as to its scientific validity and any other possible interpretation. In fact, I often accused him of taking into account the Talmudic implication of any statement made. He argued every point as if his life depended on it but those heated discussions usually ended with a fat joke that triggered his explosive laughter.

While Shmuel was spending most of his time in the lab, his wife Sarah who was as gentle and endearing and bright as could be worked on a Bachelor of Arts degree in English, which she completed in two and a half years when it ordinarily takes four.

Shmuel and Sarah were the most faithful and considerate of friends. They will be sorely missed.

[2] Department of Biochemistry, 357350 University of Washington, Seattle, WA 98195-7350, USA. E-mail address: efischer@u.washington.edu

Part III: by Rony Seger[3]

I first met Shmuel Shaltiel when I applied for M.Sc. and Ph.D. studies in the Feinberg Graduate School at the Weizmann Institute of Science. Among other procedures, I was pleased to be invited for an interview by the young, powerful Dean of the Graduate School. As in many other meetings to follow, I was extremely impressed by Shmuel's broad knowledge and wit, and therefore proceeded to learn more about his research, aiming at doing my Ph.D. studies under his supervision. Indeed, the excellent impression from Shmuel the Dean was backed up also by his scientific achievements, which at that time were already remarkable. During his post-doctoral studies with Ed Fischer and the first few years in the Weizmann Institute of Science, Shmuel studied the glycogen phosphorylase, which served as a model for enzymatic regulation. His finding of the conformational changes, which may be induced by covalent modification or by reversible modifications of glycogen phosphorylase, later on became a model for the regulation of enzymatic activity in general. One of these enzymes, which also participates in the regulation of glycogen phosphorylase, is the cAMPdPK (PKA), which is composed of two catalytic (2C) and two regulatory (2R) subunits. Shmuel mapped its catalytic pocket within the catalytic subunit, and the information on the structure of the ATP binding site was later used as a prototype for general ATP mimics inhibitors of many protein kinases. In addition, Shmuel was famous for the development of hydrophobic chromatography that enabled the development of the reverse phase HPLC. These techniques are used today for many applications, such as protein purification and identification, which earn an estimated $1.5 billion a year worldwide.

I joined Shmuel's lab in 1983 and decided to work on the kinase splitting membranal proteinase (KSMP) that had been identified in the lab a few years prior to my arrival. While studying the intracellular localization of the catalytic subunit of PKA, it was noticed that in the mucus of small intestine this subunit is cleaved by a specific proteinase, which was later shown to specifically cleave also kinase domains of other protein kinases. An intriguing feature of this enzyme turned out to be its unique recognition of the native form of the cleaved kinases only. Thus, the KSMP could serve as a useful tool for detecting the native conformation of protein kinases. Studies on KSMP strongly indicated that protein kinases are not only similar in their amino acid sequence, but also in their native conformation. Moreover, the fact that KSMP recognizes acidic amino acids in the C terminus of the kinases indicated also the importance of acidic cluster at the C terminus as a conformational element which is essential for the activity of many protein kinases and in particular that of the catalytic subunit of PKA. The studies on KSMP, that continued in Shmuel's lab for many years, showed that this protein is encoded by the gene of Meprin β, a membrane metallo-endoproteinase of the astacin family. This enzyme family has been implicated in the degradation of polypeptides that contain a cluster of acidic amino acids decorated with hydrophobic residues, such as many protein kinases but also bioactive peptides as gastrin. Finally, localization studies of KSMP indicated that it is abundant in the plasma membrane. In a work that was published only after Shmuel's death, this localization was found to be regulated by OS-9, which was identified by Shmuel as an ER-to-Golgi transport protein of KSMP and of other proteins in many tissues and organisms.

The fact that the kinase specific KSMP is localized in the plasma membrane and its catalytic side is directed towards the extracellular milieu, raised the possibility that kinases, and in particular PKA, may be functional not only inside cells but may also have extracellular functions. Work in Shmuel's and in other laboratories have indicated that indeed PKA may be found at the external surface of the cell membranes as an ectoenzyme and has specific extracellular substrates. Moreover, Shmuel showed that upon physiological stimulation of blood platelets with thrombin, the platelets selectively release ATP and PKA that specifically phosphorylate plasma proteins such as vitronectin. Vitronectin is present in the circulation as well as in the extracellular matrix, and was shown to promote cell adhesion, cellular spreading and is involved in the activity of plasminogen and PAI-1. The binding of vitronectin to PAI-1 stabilizes the inhibitor in its active (inhibitory) conformation and, as such, inhibits plasminogen activation. Shmuel showed that following binding to PAI-1, the conformation of vitronectin is modified in a way that allows it to undergo phosphorylation by PKA, which in turn separates the two proteins, leading to PAI-1 inactivation and consequently to fibrinolysis. Thus, the extracellular phosphorylation by PKA acts as a physiological regulatory device that converts vitronectin from an antifibrinolytic agent that secures that no fibrinolysis occurs as long as it is not desirable, into a profibrinolytic factor that initiates the solubilization of blood clots and the dissolution of the debris that are not needed any more.

While working on the phosphorylation sites of vitronectin, Shmuel showed that in addition to the phosphorylation by PKA, this protein undergoes a phosphorylation also by CKII and by PKC that were both shown to operate extracellularly. As it turned out, these phosphorylations also seem to have physiological consequences as PKC phosphorylation was shown to modulate plasminogen activation, while the phosphorylation by CKII was found to modulate cell spreading. Indeed, this phosphorylation was shown by Shmuel to increase vitronectin-mediated cell adhesion via the integrin $\alpha_v\beta_3$, but not via the $\alpha_v\beta_5$ integrin. Whereas both the phospho and non-phospho analogs of vitronectin trigger both the $\alpha_v\beta_3$ and the $\alpha_v\beta_5$ integrins to equally activate some intracellular signaling, only the phosphorylated analog of vitronectin induced cell adhesion that was mediated specifically by $\alpha_v\beta_3$ and the PI3K-AKT/PKB pathway. These experiments actually suggest that extracellular CKII phosphorylation is important for the effect of vitronectin on cell adhesion. Interestingly, phosphorylation of vitronectin was not the only example for a substrate for extracellular phosphorylation. Just a few years before his death, Shmuel showed that pigment epithelium-derived factor (PEDF) that was formally known as anti-angiogenic guardian of ocular function, is functional and phosphorylated also in the plasma. Recent data that are now in process of publication indicate that indeed, PEDF is phosphorylated in the plasma by PKA and CKII, and these phosphorylations are required to regulate the anti-angiogenic ef-

[3] Department of Biological Regulation, The Weizmann Institute of Science, 76100 Rehovot, Israel. E-mail address: rony.seger@weizmann.ac.il

fects of PEDF. Taken together, all these processes provide evidence for the existence and necessity of extracellular phosphorylation, which has been doubted over the past years by many investigators.

Based on all the above achievements, Prof. Shmuel Shaltiel was very well esteemed by the local and international scientific community. At the Weizmann Institute of Science he served over the years as acting president, Dean of the Feinberg Graduate School, Chairman of the Scientific Council, Head of the Department of Chemical Immunology and of the Department of Biological Regulation. In Israel, Shmuel served as a member of the National Planning and Budgeting Committee of the Council for Higher Education. He was awarded the Hestrin, Landau, Weizmann Prizes, and the very prestigious Rothschild Prize for his highly regarded research on cardiovascular disorders and the control of blood-clot dissolution (fibrinolysis). He won the Analytical Biochemistry Prize, awarded by the European Society of Analytical Biochemistry, and was elected Honorary Member of the American Society of Biochemistry and Molecular Biology. He was a Scholar in Residence at the US National Institutes of Health, and a Visiting Professor in UC Berkeley. However, dearest to his heart were his large number of students who continue to follow his scientific path. About three years ago his former and current students organized a very successful scientific gathering on his 65th birthday. A memorial symposium day will be held at The Weizmann Institute of Science on May 2003, a year after his death. May his name remain in our hearts forever.

Note from the Editorial Office

Professor Shmuel Shaltiel passed away on April 5th, 2002. He served on the FEBS Letters Editorial Board from 1989 until the end of 2000, and edited over 1100 manuscripts during this time period. To honor his memory and years of service to FEBS Letters, we asked the above colleagues to reflect on Professor Shaltiel's life and scientific career.