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OBITUARY

Prof. Theodor M. Fliedner (1 October 1929–9 November 2015): haematopoietic stem cell and radiation biology and pioneer

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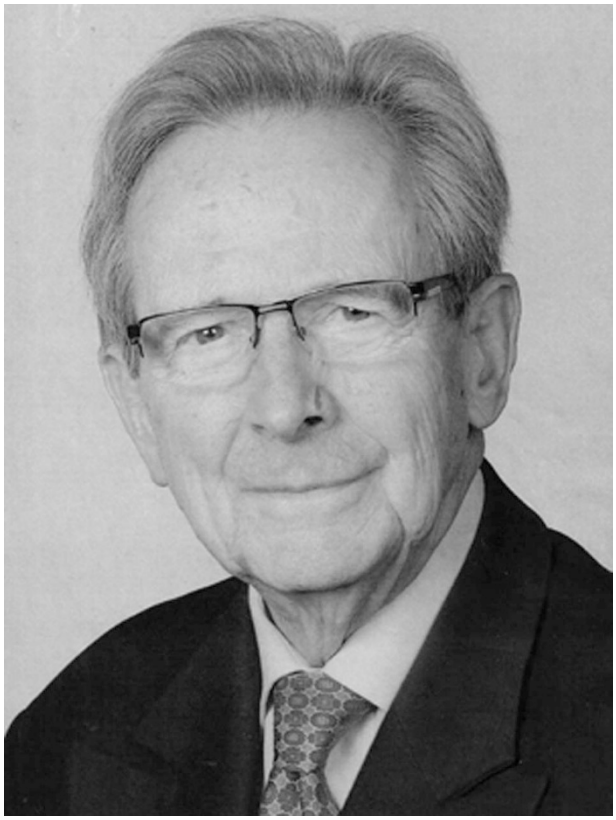

Prof. Theodor M. Fliedner, a pioneer in haematopoietic stem cell and radiation research, died in Ulm, Germany, on 9 November 2015. Ted was a man of charisma and extraordinary vision. He was born in 1929 in Hamburg and studied medicine at the Universities of Göttingen and Heidelberg. Throughout his life Ted had a strong interest in radiation biology and transplantation. His doctoral dissertation was 'On the pathogenesis of acute bone marrow atrophy in rats after whole body irradiation with fast electrons', and as a young physician he established a radiation haematology research unit in the Czerny-Hospital in Heidelberg. In 1957 he went to the US for 6 years, where he studied at the Brookhaven National Laboratory with Eugene P Cronkite. At that time haematopoietic stem cells were postulated but had not been proved nor identified. Ted tackled the question by studying bone marrow transplants in dogs given high doses of nitrogen mustard. He was able to show that a large proportion of haematopoietic stem cells were in the resting stage of the cell cycle. Later, Fliedner and colleagues developed techniques to restore haematopoiesis by auto-transfusion of frozen bone marrow cells.

In 1963 Prof. Fliedner returned to Europe to become the Director of a EURATOM Institute for Radiation Haematology Research affiliated with the Faculty of Medicine, University of Freiburg. He and his team studied the behaviour of resting haematopoietic stem cells in rats using a model of continuous ^{3}H-thymidine infusion. They were able to distinguish resting and dividing stem cells and their progeny, and postulated that the resting stem cells were attached to the bone marrow endothelium. This prescient observation is the basis of much of the current research into the so-called *stem* cell *niche,* a field most people think was only recently invented. Their model was also applied to other settings such as high-dose radiation exposures and leukaemia. These experiments in rodents and dogs required a continuous 24– 48 h ^{3}H-thymidine infusion and the team often spent nights and weekends in the laboratory. Fliedner typically stayed on and was always a cheerful sight at the team breakfast the next morning.

In 1967 the new Ulm University was inaugurated with Ted Fliedner as the youngest of eight founders. He became the director of the Department of Clinical Physiology and later the dean of the Theoretical Faculty of Medicine. His research group, staffed by associates from Europe and elsewhere, focused on characterizing haematopoietic stem cells, especially after total body radiation in dogs. The team showed that large numbers of haematopoietic stem and progenitor cells could be collected by continuous flow centrifugation, frozen and stored for a future transplant. Like most dedicated scientists Fliedner was often the *volunteer* for these experiments, hooked up to the centrifuge for hours. This pioneering work led to the use of high-dose therapy and autotransplants to treat cancer.

Fliedner was concerned that radiation accident victims and transplant recipients would be at substantial risk for infections because of profound granulocytopenia. In 1969 two brothers with a severe combined efficiency syndrome arrived at the Haematology Clinic in Ulm. Five siblings had died of uncontrolled infections in the preceding few years. The team kept them in a germ-free (gnotobiotic) environment over 2 years, at which time they received successful bone marrow transplants and survive today. The team used this experience to develop an isolation tent (Life-Island) where adults with acute leukaemia were successfully treated and transplanted.

Prof. Fliedner is perhaps best known internationally for his work on evaluating victims of radiation accidents. He chaired a European Consortium of Experts that developed the 1981 publication *Manual on the Acute Radiation Syndrome*, which is widely used today. In it he described the MEROPOL (MEdical TREatment ProtocOLs for Radiation Accident Victims) system for classifying injuries, estimating dose and selecting interventions. Also, quite remarkably, he developed a database of radiation accidents over 800 detailed reports—a valuable resource indeed for physicians interested in radiobiology.

In 1973 Ted attended a meeting in the US National Institutes of Health (NIH) in Washington, where the *War on Cancer* programme was being developed. On returning home he convinced the Ministry for Research and Health to establish a similar programme in Germany. The current German multi-centre acute lymphoblastic leukaemia and Hodgkin disease study groups are outgrowths of this effort.

Fliedner, with Prof. Ludwig Heilmeyer, created the International Research Institute Schloss Reisensburg. Their vision was to develop an international scientific meeting centre from these historically important medieval ruins. When the centre was completed Fliedner and Heilmeyer hosted many meetings, including the first meeting on prognostic factors in acute leukaemia in 1973 attended by Emil Frei, Joseph Simone, David Galton, James Holland, Jean Bernard, Emil Freireich, Georges Mathé, Donald Metcalf and Robert Gallo. Prof. Fliedner also created an Institute of Clinical Occupational Medicine in Ulm.

In 1974 Prof. Fliedner was appointed a Director General of the World Health Organization (WHO) and chaired the WHO European Advisory Committee on Health Research. In 1983 he was appointed President of the University of Ulm. He established a *Science City* at the University to foster collaboration with research-based industry.

Prof. Fliedner received many honours. He was a member of the Academies of Sciences in Heidelberg and Milano, Foreign Member (Academician) of the Academy of Medical Sciences of Ukraine, Honorary Member of the American, Italian and Hungarian Societies of Haematology, and Honorary Doctor of Medical Sciences of Mahidol University, Bangkok (Thailand), the Medical University of Debrecen (Hungary) and of the LB-University of Uppsala (Sweden). He held the Mechtild-Harf-Award of the Deutsche-Knochenmark-Spender-Datei (DKMS).

Ted Fliedner was a man of vision, highly respected in the international scientific community, with many friends and colleagues worldwide. His evangelical attitude and passion for research quite probably reflected the missionary work of his forbearers. He especially favoured open, critical discussions in his garden (in summer of course; he was a grill master). Many people who knew him only superficially saw him as stern and sometimes uncompromising. But this was not his real character. During the 1968 student protests in Germany he arrived at the University seminar room one morning to find the students and technicians sitting on the conference table rather than in their chairs. When he politely inquired why, they said they were *protesting*. He asked: Protesting *what*? They said they weren't really sure. His response: *OK. I agree. Now let's get back to work*. (One is reminded of a line from the 1966 protest song *For What It's Worth by Stephen Sills: There's something happening here/What it is ain't exactly clear*).

Ted is survived by his wife, five children and six grand-children. The haematology and radiation biology research communities have lost a pioneer and great scientist. He will be missed.

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