IN MEMORIAM

Lauri Saxén (1927-2005) in 1997.

Dr. Lauri "Tupu" Saxén died last October (2005) at the age of 78. He was a physician, a scientist, a photographer, a naturalist, a great story-teller and a man who enjoyed science enormously. His name has become synonymous with the Finnish school of Developmental Biology, a school that focuses on reciprocal inductive interactions during vertebrate organogenesis. But many biologists probably don't know the full extent of his importance to the field. A few years ago, I had the occasion to outline some of his contributions which are so varied and important that it is difficult to believe that they are the work of one person, and I have included them in this brief eulogy. One could divide his scientific contributions into five categories: (1) the threshold hypothesis of amphibian metamorphosis; (2) the double-gradient hypothesis of primary embryonic induction; (3) the analysis of reciprocal induction during kidney development; (4) the integration of developmental biology with epidemiology and (5) the maintenance of a national infrastructure for science.

The threshold hypothesis for amphibian metamorphosis

In the mid-1950s, Saxén performed experiments documenting the existence of a pituitary-thyroid axis that functioned during frog metamorphosis. Moreover, on the basis of these experiments, Saxén proposed that the mechanism for coordinating the events of metamorphosis was the response of different tissues to increasingly large levels of thyroid hormones. Thus, early events (such as the formation of hindlimbs) necessarily occurred prior to later events (such as the regression of the tail). Such coordination allowed the frog to survive as it changed its shape and its biochemistry. This threshold gradient concept is still the major paradigm of studies on amphibian metamorphosis.

The determination of the neural axis: primary embryonic induction

In 1955, Saxén and Sulo Toivonen developed their "double gradient theory" for explaining the polarity of primary embryonic induction. Earlier experiments had shown that different parts of the notochord and different adult organs could induce different regions of the central nervous system in amphibians. The anterior region of the dorsal mesoderm (or adult guinea pig liver) could induce head formation, while the central region of the dorsal mesoderm (or guinea pig bone marrow) induced the ectoderm to form spinal cord. Saxén and Toivonen placed a brain inducer together with a spinocaudal inducer into amphibian blastocoels or between sheets of competent ectoderm. In addition to inducing spinal cord and forebrain structures, the dual implants also formed intermediate neural tube structures (such as midbrain and hindbrain) that neither did alone. Saxén and Toivonen interpreted these results in terms of two gradients, each arising from its specific inducer. These gradients were projected upon the competent ectoderm. A "neuralizing" agent acted along a dorsal-ventral gradient, while a "mesodermalizing" induction occurred along a gradient from posterior to anterior. The interaction of the two agents directed the fate of the target cells and the regional segregation of the neural tube. This hypothesis was subsequently tested in a series of ingenious experiments done by Saxén and his colleagues and it culminated in a paper in *Science* (1968), showing that the double gradient model worked on the cellular level. Contemporary developmental biology and the present-day research on posterior-to-anterior gradients of fibroblast growth factors and retinoic acid can be traced back to this model. In his historical account of Organizer research, Joseph Needham (1968) reflected that this work *"is assuredly the fourth fundamental experiment in this field"* and Viktor Hamburger (1988) noted that the collaboration done by Saxén and Toivonen *"left its mark on experimental embryology to this day."* This work is reflected in the present double gradient model for the specification of the amphibian axes, wherein a gradient of BMP specifies the dorsal-ventral axis and gradients of Wnt, Fgfs and retinoic acid specify the anterior-posterior axis. In a recent interview (Tyler *et al.,* 2003), Dr. Saxén reflected on this period of his life saying, *"It was a small group. It was a small and very modest laboratory, an old dark hole in the Zoology Department; but the atmosphere was absolutely great and the whole thing was great fun."*

Epithelial-mesenchymal interactions in mammalian kidney development

Following postdoctoral research with Clifford Grobstein, Saxén shifted his focus to look at the inductive tissue interactions between the epithelium and mesenchyme during mouse kidney organogenesis. Saxén spearheaded the effort to determine how the kidney formed and his ability to separate the various phenomena of kidney development (growth, mesenchymal condensation, aggregation, polarization) allowed for the rapid progress in this area once molecular probes were made possible. His 1982 volume, *Organogenesis of the Kidney,* summarized the phenomena that would have to be explained on the molecular level. Moreover, Saxén was largely responsible for training those people who did do the molecular analysis of kidney development. As late as 1997, he continued to direct molecular studies in this area. Saxén also formulated some of the key principles of epithelial-mesenchymal induction (such as the distinction between instructive and permissive interactions and the ideas of community effect) that are still being used today.

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Teratology and developmental epidemiology

Lauri Saxén was trained as both a scientist and a physician. This integration of medicine and developmental biology is often overlooked, but it may be one of his most enduring contributions to biology. Saxén was a central figure in setting up the *Finnish Register of Congenital Malformations* and for establishing the parameters whereby pediatricians would be trained to recognize congenital anomalies. This database has become one of the major resources for teratological research. The *Finnish Register* allowed the temporal and geographic comparisons necessary for showing whether or not oral contraceptives, sauna use, oral polio vaccination during pregnancy, video display terminals, or fallout from the Chernobyl nuclear accident caused birth defects in Finland. (In these five instances, the register clearly demonstrated that they did not cause birth defects—a very important set of findings!) Having knowledge of background incidence across a wide area and long timespan is critical in providing accurate assessments of whether a particular compound or practice is teratogenic. The Finnish database is unique in this respect.

Establishing and maintaining scientific infrastructure

Lauri Saxén is largely responsible for coordinating the infrastructure that has led to a remarkable scientific Renaissance in Finland. In addition to his scientific achievements, Saxén has also been a very active and successful administrator. He was president of the Finnish Culture Foundation (1977-1987), the Finnish Medical Society (1982-1988) and the Finnish Academy of Sciences (1983-1992) during the critical years when Finland's scientific infrastructure was being formed. Saxén also presided over the founding of the Institute of Biotechnology in 1989 at the University of Helsinki, one of the first Centers of Excellence in biology. Such institutes of excellence and the major effort to promote biology and biotechnology between 1988 and 1995 were applauded by the European Molecular Biology Organization in what *Nature* called "a glowing report."

Saxén always appreciated a scientist's immediate environment as well. He described his Wetterkulla Medical Center as a *"semi-serious organization, but it was a haven for many Finnish biologists"*. Originally a manor house in Hame, it was the place where he and Sulo Toivonen went to write *Primary Embryonic Induction* (1962). *"Its unwritten operational principles,"* said Saxén in an interview (Lehtonen, 1999) were *"to secure tranquil reading and writing surroundings for a scientist, to provide an inspirational atmosphere for the innovative mind and to offer a moment's relaxation for the frustrated man."* (Women, too, would enjoy this refuge, as membership of the Finnish Society for Cell and Developmental Biology expanded enormously). I went to work in the Saxén laboratory in 1990. One of the reasons I came then was because it was a time when the techniques of molecular biology were beginning to be applied to those questions of morphogenesis that Lauri Saxén thought interesting. But there was another reason as well: at the party held when I was leaving, I remarked that I had thought Tupu was going to retire at the end of that year. Tupu hit his forehead with his palm, looked at me wide-eyed and exclaimed, *"I forgot!"* The real reason was that he was having too much fun coordinating the research, and the new techniques were enabling him and his students to answer the questions that they had been pursuing for decades. As he said in the Tyler *et al.* (2003) interview, *"You should be in research as long as it is fun… And I hope young people will come to be devoted to research can also feel that it is great fun, almost a privilege, to do experimental work"*. Finally, Lauri Saxén intimately participated in the renewal of this journal, *The International Journal of Developmental Biology,* in 1989, and its current prestige is due in large part to the inspiring impetus which he contributed during this time.

Scott Gilbert
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