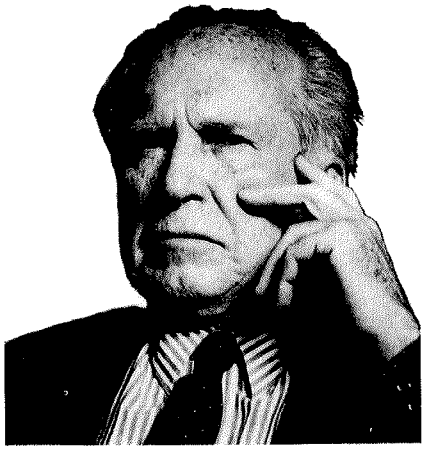

Prof. dr. Nikola Škreb
1920-1993

Our teacher Professor Nikola Škreb passed away after a short and acute period of fight with cancer on Wednesday, 3 March, 1993.

Professor Škreb was the founder and spiritus movens of the embryological school that he founded in Zagreb, and in which he developed asking interest in studies of the early mammalian embryo.

Nikola Škreb was born in Zagreb, Croatia, on 21 August, 1920. He was educated and studied at the Medical School of the University in Zagreb. His university education took place during the hard times of the Second World War, in the turmoil and sufferings of southeastern Europe. He finished his medical education in 1948 and started his research and teaching activities at the Medical School in Zagreb, first in the Department of Bacteriology and later in the Department of Biology where he worked till the very end of his life.

Professor Škreb's early studies of medicine run a very irregular course. The Second World War pressed him to interrupt his studies on two occasions: in 1942 and in 1944. He joined the resistance movement in Croatia very early. There, he was carried out the duties of doctor, though he had not yet finished his studies.

In spite of this first hand experience in practical medicine professor Škreb chose a basic medical discipline for his future professional occupation. A WHO fellowship took him to Paris and to Brussels, and finally motivated his transfer to the Department of Biology of the Medical School in Zagreb, where he entered the field of experimental embryology, which was closest to his medical training. The WHO stipend was used for studies first in Paris in the Collége de France with Professor Charles Deviller on fish embryology, and after that in Brussels with Professor Albert Dalcq on amphibian embriology.

At this time (1950) experimental embryology was still occupied with various animal species, whose development was extracorporal. Experimental embryology of mammals was still in its initial stages. Nikola Škreb was among the first to understand the importance of mammalian a embryology as way to understand better the embryonal development of man. He had courage to step in this unknown field, and stick with it all his life.

On the basis of his first results, reported at the embryological meeting in Pallanza in 1960, he proposed the hypothesis on the critical period of development of the rat embryo, which coincides with the period of the mesoderm formation. Before this stage he was able to observe the so called "all or none" effect: embryos were either totally

deleted, or showed no deleterious effects of various teratogenic agents, whatsoever. After this stage of mesoderm formation, Professor Škreb studied malformations in various parts of the embryo, caused by the application of noxious agents (heat shock, X-rays, mercury compounds).

The next phase of research was devoted to analysis of growth and differentiation in the rat embryo developing on various ectopic sites. The methodological approach most frequently used in the laboratory was the procedure of grafting of early rodent embryos onto different extrauterine sites. Rodent embryos develop there into tumorous masses composed of differentiated tissues, but spatially totally disorganised masses (experimental embryogenic teratomas). These studies of the developmental consequences in the embryo, when it was transferred to extrauterine sites, indicate again that its fate depended on its developmental stage: before mesoderm formation or after the mesoderm was present. The sites chosen were the chorio-allantoic membranes, the anterior eye chamber, and the space under the kidney capsule of the rat. These results proved the hypothesis of the critical developmental stage of the early rat embryo: the period of mesoderm formation.

Transplantation experiments carried out with the mouse embryo under the kidney capsule also yielded interesting results. A certain percentage of early mouse embryos did not give rise to differentiated cells, and they remained at the embryonal stage of development, which was partially dependent upon the genetic background of the mouse strain used. Such a tumorous mass of undifferentiated embryonal cells kept growing constantly until they killed the host mice, the recipients of such embryo transplants. The embryo-derived teratocarcinomas were so obtained displaying all the pathological characteristics of malignant tumours. Embryogenic teratocarcinomas and embryonal carcinoma cells attracted a lot of attention and research worldwide and provided new insights about mechanisms of regulation in embryonic and neoplastic growth. Ivan Damjanov and Davor Solter, two of Škreb's collaborators developed this field considerably further in their laboratories abroad.

In 1968. Professor Škreb in collaboration with Anton Švajger introduced another original experimental method for separation of different embryonal cells: germ layers, and their individual analysis. In the preface of the first issue of the monograph "Development in Mammals" it was pointed out that the embryo surgery worked out in the laboratory of Professor Škreb was one of the achievements which revolutionized studies of early mammalian development. The major results from application and work with this technique were impressive. It was possible to penetrate further into the analysis of this critical stage of embryonic development. A technique was developed for isolation of particular germ layers, which were afterwards transplanted under the kidney capsule. In this way it was possible to study and start to understand their "differentiative potentialities". The most general conclusion of these experiments indicate that practically all the tissues arise from the primary ectoderm. So the results provided evidence to consider the classical theory of germ layers, as having only a limited value, and can be accepted only with great restrictions.

Still another and unfortunately last methodological approach used in Professor Škreb's laboratory was *in vitro* cultivation of early rodent embryo. This work was initiated towards the end of his active duty as Chairman of the Department of Biology of the Medical School in Zagreb, as our teacher and professor of Medical Biology for the first year medical students, but these experiments were carried on very successfully long after his retirement in the year 1985.

The method of *in vitro* cultivation of mouse or rat embryo under conditions referred to as the organ culture method has already provided, and is promising to provide, interesting results, because one can analyze the conditions necessary for differentiation of cells and tissues in chemically defined media without serum and protein supplementation. After two weeks of cultivation in such "serum-free" conditions there is no morphogenesis, but one can observe terminal differentiation of the major tissue types. By selective addition of a single or a combination of well defined serum protein factors to the growth medium results were obtained on the requirements of various types of tissues for their differentiation factors.

The basic idea of Professor Škreb's research during four decades generated a number of new ideas and research approaches carried mainly by his students and collaborators. So for a number of years parameters of rat fetal growth and weight were monitored *in vivo* in relation to various factors including genetic background. Regulatory mechanisms of liver regeneration were studied after partial hepatectomy. Developmental mechanisms active in morphogenesis of the posterior part of mammalian embryo are being studied, as well as transformations of one type of embryonic cells into another type, as is the case in metaplasias and transdifferentiation. Early attempts to obtain molecular parameters of differentiation in mammalian development used electrophoresis in polyacrylamide gels to study protein changes during organogenesis, as well as in neoplastic growth in mammals and plants. These were early results which indicates that quantitative protein changes in developing systems were neither sufficient nor adequate indicators of cell differentiation, because the final protein pattern indicative of cell differentiation appears in different organs (particularly the brain) long after birth, when all the organs have already long acquired their morphological characteristics.

Professor Škreb's continuous research interest in mammalian embryology was supported with numerous research grants either from Federal and Croatian science foundations or from the United States of America - Joint Board on Scientific and Technological Cooperation. The United States Department of Health, Education and Welfare supported, through its National Institute of Child Health and Human Development, three successive research projects, headed by professor Škreb as the principal investigator: Cytological and Biochemical Studies of Early Mammalian Embryos (1971-1975); Experimental Analysis of Early Rodent Embryos (1982-1985); and Functional Analysis of Postimplantation Mammalian Embryo (1986-1989).

Professor Škreb took advantage of numerous visits with scientists and to laboratories in

France, Belgium, and United States, USSR, Poland, Denmark, Sweden and Great Britain. It must be stressed, however, that each and every result published by him and his co-workers was produced entirely from work carried out in his modestly equipped laboratory in Zagreb, Croatia, in the Medical School and its Department of Biology on Šalata.

Nikola Škreb participated in many scientific meetings. At many of them he attended as a distinguished invited speaker: Paris (1974), Nutley (1975), London (1975), Minneapolis (1978), Toulouse (1979), Boulder (1987), Hamburg (1990) and Dubrovnik (1991). There were also two extended study visits: to Sloan Kettering Cancer Center in New York and the Mammalian Research Centre in London.

Professor Škreb was member of several international scientific societies: International Embryological Institute in Utrecht, International Society of Developmental Biologists, Society for the Study of Differentiation and International Society for Differentiation.

Academician Škreb published the results of his research work with his collaborators in leading scientific journals and Proceedings of important international Symposia. Among those, there are two perhaps which have to be singled out for their importance, both from 1975: Roche Symposium on Teratomas and Differentiation, Nutley NY, USA and Ciba Foundation Symposium on Embryogenesis in Mammals, London, UK. Both the contributions are compacted reviews of the most important results provided by Nikola Škreb, and they are frequently quoted as the crucial literature for understanding the mechanisms of early mammalian development and the border area between embryonic and neoplastic mechanisms of growth and differentiation.

Besides all of his scientific engagements described previously, the late Professor Škreb was also very active in numerous social and expert activities in Croatian institutions, as well as in European and international organizations. Nikola Škreb devoted a lot of energy in 1962 to unite all the biologists scattered in different organizational units of the University in Zagreb into the Institute of Biology, University of Zagreb. He was serving it as Director, for the major part of its existence. This organizational effort, though only temporary, provided a feeling of joint identity for our biologists, and equipped their laboratories with some of the most important research equipment. At the Medical School in Zagreb he founded and ran the Fund for Scientific Work, which enabled effective acquisition of some major and expensive pieces of equipment, by contributions from various scientific projects. He was member of the Biological Committee of the Council for the Scientific Research of Croatia, president of the Commission for the Organization of Scientific Work at the University of Zagreb, and of the Federal Council for Science in former Yugoslavia and its Commission for International Communications. Professor Škreb wanted very much to introduce the importance of biological sciences to expert and general public, and with this goal he published articles in *Liječnički vjesnik* and the *Medical Encyclopaedia*. In 1971 he launched the column "Science" in the daily newspaper *Vjesnik* and published the book *Problems of Contemporary Biology*. He was member of

Hrvatskog liječničkog zbora (Croatian Medical Association), Croatian Physiological Society, Croatian Biological Society, and Croatian Naturalist Society. As the President of the Croatian Naturalist Society he organized in 1985 the celebration of 100th Anniversary of founding of the Society. At the Medical Faculty he was Professor of Medical Biology, and served as vice-dean, and president of the Council. As a teacher he was very effective in communicatin with his students and collaborators. He knew how to stimulate in his students interest and enthusiasm for his ideas. He knew how to be a good friend for them, a trustworthy mentor in their efforts towards M.Sc. and Ph.D. theses.

He, was among the founders and the first president of the European Developmental Biology Organization. Perhaps his role and contribution in starting EDBO is worth mentioning here. Professor Škreb participated at all the scientific meetings organized by the European group of scientists dedicated to embryology which later on became known as the European Developmental Biology Organization (EDBO, 1978). Professor Škreb was elected the first president of EDBO in Berlin and served this position for four years. The first hint about the EDBO came from the late Professor Alberto Monroy. Later, during the Sorrento Conference in 1974, Professors D. Newth and M. Abercrombie carried further the informal discussions with many scientists including Professor Škreb. In 1976, many national societies of developmental biologists in Europe were formed, and they nominated their representatives to constitute the Provisional Board. Professor Škreb was elected as the representative of the individual members on the Board. At the second Board Meeting on the occasion of the XIIIth International Embryological Conference in Berlin 1978, the new Constitution was adopted. Finally, the definitive Board was elected and Professor Škreb was elected President of the EDBO Board.

For his scientific work he was elected member of the Academy of Sciences and Arts in Zagreb (1979), and Honorary Member of the Croatian Medical Academy, Zagreb. He was awarded the "Ruđer Bošković Award" for science in 1970, and the Award for his Lifetime Scientific Opus in 1979. The multifaceted activities of professor Nikola Škreb, his impressive international scientific figure and significant achievements for his people and his country were honoured with the highest awards and still other acknowledgements. In 1986 the International Conference on "Embryonic Origins and Control of Neoplasia" was organized at the Inter-University Centre in Dubrovnik in honour of academician Nikola Škreb. Many of the most prominent scientific figures in this field from Europe and America attended this meeting and honoured the work and achievements of Nikola Škreb.

Towards the end of 1991, in the turmoils of war and agression against Croatia, a special number of *The International Journal of Developmental Biology* was edited by Professor A. Švajger and published in Spain to describe research in various areas of developmental biology in Croatia and to celebrate the nestor of this research, academician Nikola Škreb, who managed to raise this research to a high international level.

It was indeed an exceptional privilege and honour to have had the opportunity to

work with, to know and to appreciate the unique personality of Nikola Škreb, to fight with Nikola in many battles, including the last one which nobody can win.

Draško Šerman

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