Tradition and the present state of developmental biology in Yugoslavia

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Yugoslavia has existed as an independent state since the end of the first World War. Before that time, several prominent scientists born in this part of Europe studied abroad, mainly in Austria, Italy and Germany. Some of them continued to live there and made valuable contributions to the science of these countries. After the war new universities, particularly medical schools, were founded. Scientists who were educated and active in research abroad were engaged to establish institutes of basic sciences at these universities. This time- and energy-consuming activity was incompatible with continuous and systematic research.

This was the destiny of Boris Zarnik, born in Ljubljana,Slovenia in 1883 (Fig. 1). He graduated and received his Ph.D. degree in 1904 from the University of Würzburg, Germany and was appointed as instructor at the Institute of Zoology, then headed by Theodor Boveri. During 11 years of teaching and research activity at this institute he made substantial contributions to the embryology of the marsupial Didelphys. In 1915, as associate professor, he moved to Istanbul, Turkey, where he was appointed as full professor and established the Institute of Zoology at the Faculty of Medicine.

In 1918 he accepted the invitation of the newly founded Medical Faculty of the University of Zagreb and was appointed full professor of biology, histology and embryology. He established the Morphological-Biological Institute, which in 1943 split into the Institute of Biology and Institute of Histology and Embryology. He was an outstanding teacher with a remarkable artistic talent and high competence in the histological technique. In teaching he paid special attention to embryology and made a fine collection of total preparation and histological sections of amphibian and avian embryos. Overburdened with teaching, organizing and other activities, he had to neglect research. Nevertheless, in 1928 he published a paper which is cited in the recent literature as the first successful attempt to obtain the transformation of the newt iris epithelium into lentoids in organ culture (see Juric-Lekic *et al.*, this issue).

His successor in the chair of biology, Zdravko Lorkovic (b. 1901), was a prominent scientist in the field of speciation. He introduced the concept of semispecies as a transitory category between subspecies and species. There is a «Lorkovic's Room» at the British Museum devoted to his work. Although he used some criteria of reproductive biology (copulation mechanism in Lepidoptera) in his research, he was not a developmental biologist. Nevertheless, he continued to give particular importance to classical embryology in his lectures and textbooks. At the age of 91 he is surely the oldest active biologist today.

Nikola Skreb and the "Zagreb school of mammalian embryology"

The period of continuous and internationally recognized research in developmental biology began in the early fifties. It was initiated by Nikola Skreb (Fig. 2). He first tried to continue Dalq's work on oogenesis but, working on bats, he was not able to confirm the hypothesis on bilateral symmetry in oocytes as far as it could be disclosed by cytological and cytochemical markers. His results were corroborated later on by other authors. Then he turned to the experimental analysis of the early postimplantation rodent embryo and, from the very beginning, focused his attention on the crucial period of gastrulation. Successively, young collaborators joined N. Skreb, not only in his own laboratory (Institute of Biology) but also in the Institute of Histology and Embryology and the Institute of Pathology, Faculty of Medicine, University of Zagreb. It thus became possible to give the original idea a broader scope and to attack the basic problem by a variety of methodological approaches. The

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Fig.1. Professor Boris Zarnik (1883-1945).

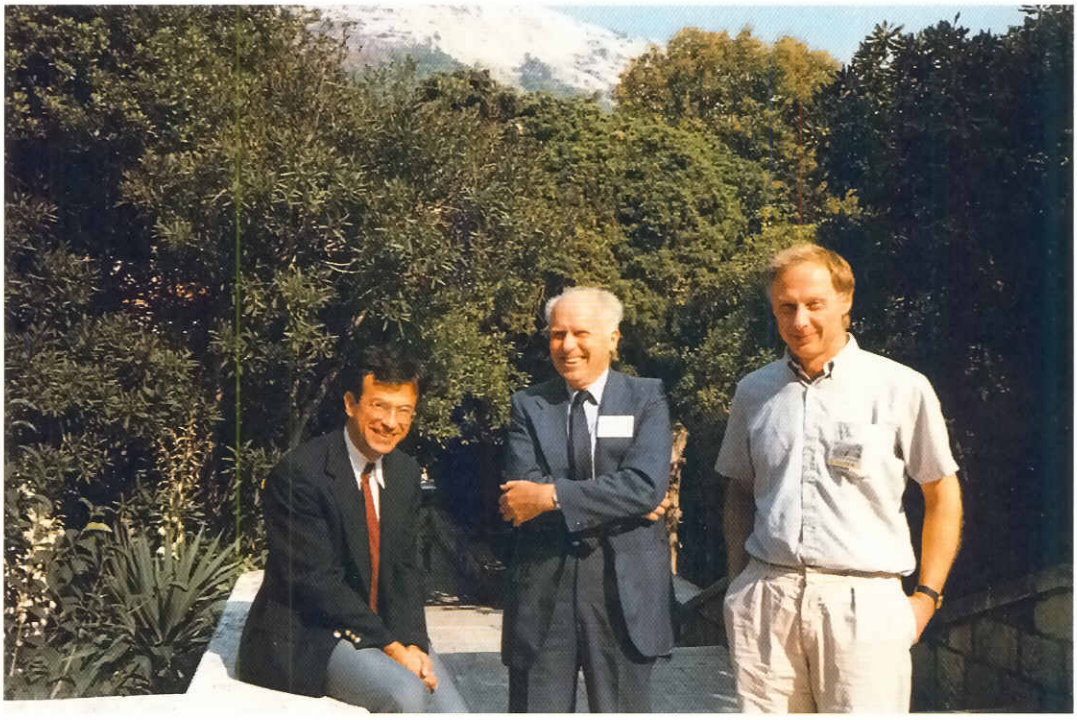
research in this field is still continuing, in the same old, good building, with the active participation of the pioneer who obviously neglects the fact that he has been retired for 6 years.

If one looks back at the scientific achievements of N. Skreb from the very beginning of his commitment to mammalian embryology up to the present time, three decisive qualities come clearly into view: 1) the choice of experimental mammalian embryology as a most promising field of research, 2) the choice of the gastrulation period as the crucial stage of early development which was still insufficiently understood at that time, and 3) the persevering continuity of work on the same basic problem. He first applied the techniques of teratology (exposure to x-rays and heat-shock) to early postimplantation rat embryos and found that a considerable increase in the rate of malformed fetuses occurred when the embryos were exposed at the beginning of gastrulation (initial mesoderm formation). Almost all further research was focused on this "critical" stage of development with the aim of disclosing the nature of the sudden change in the reactivity of embryonic cells.

The next step was the analysis of growth and histological differentiation after transfer of embryos to ectopic sites (with Bozica Levak). In these conditions embryos developed into tumorous masses composed of adult tissues distributed in a chaotic way (experimental teratomas). It was shown that the degree of differentiation within these tumors depended on both the initial developmental stage of the transplanted embryo (before or after the critical period) and the environment created by the host tissue (anterior chamber of the eye, kidney capsule, chick chorioallantoic membrane).

After transplantation of mouse embryos at the gastrulation stage under the kidney capsule (with Ivan Damjanov and Davor Solter, Fig. 2) not all embryonic cells underwent differentiation into adult tissues but displayed a fast, uncontrolled and locally expansive malignant growth resulting in teratocarcinomas composed of undifferentiated cells. This finding led to further experiments the results of which, together with those of L.R. Stevens on teratomas in mice, initiated the very fruitful research on teratocarcinomas done by many authors around the world.

As at the end of 1968 Anton Svajger and Bozica Levak-Svajger (Fig. 3) succeeded in separating germ layers of rat embryos, microsurgery in early embryos was introduced as a new and promising experimental approach in mammalian embryology. By applying it in combination with the transplantation method it was shown that the embryonic ectoderm isolated immediately prior to or



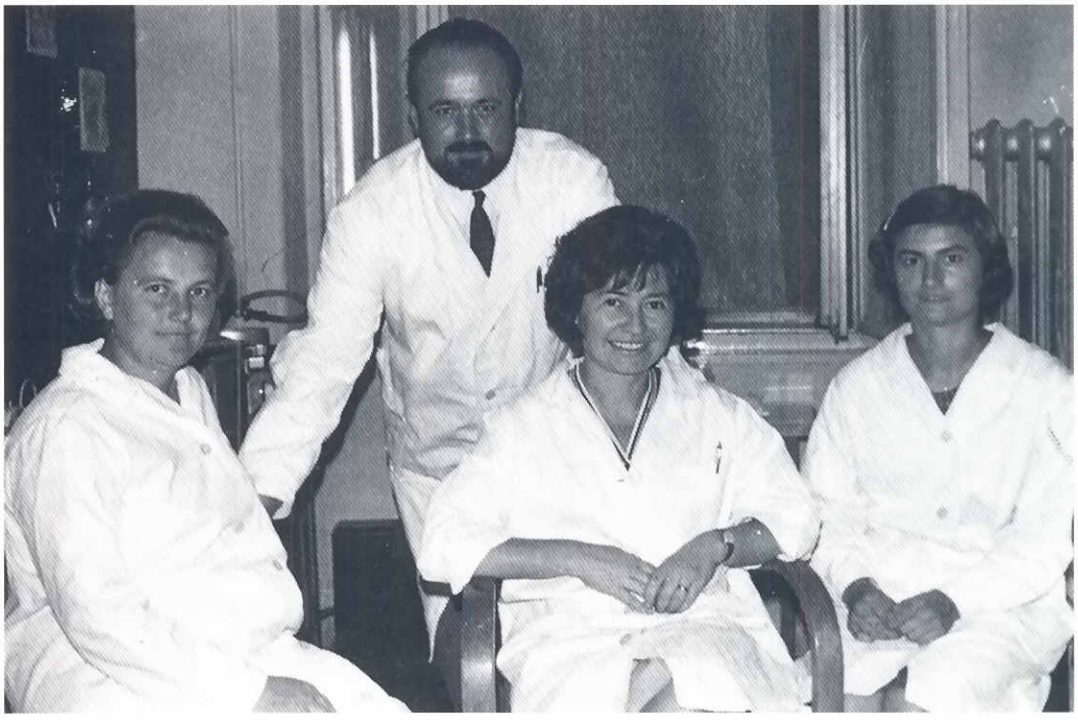
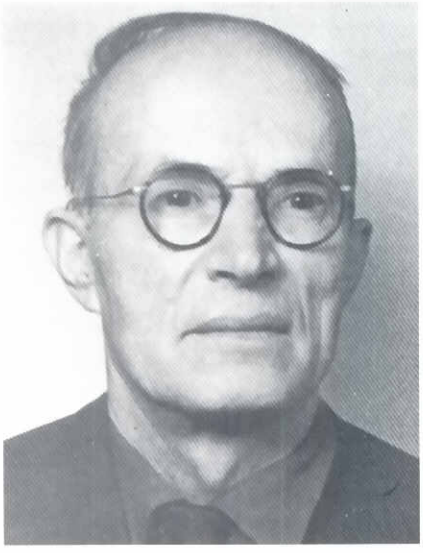


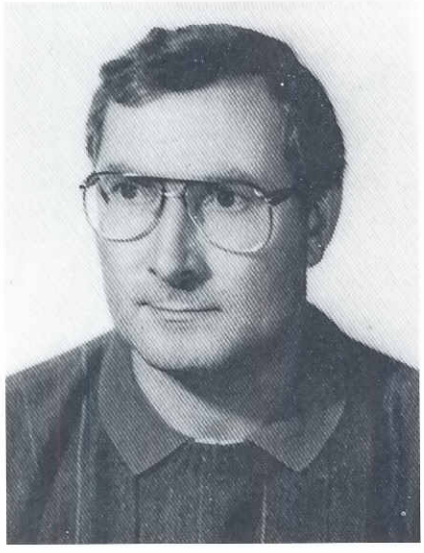
Fig. 2. Professors Nikola Skreb, Ivan Damjanov (left) and Davor Solter (right) in 1986.

Fig. 3. Professor Anton Svaiger and Professor Bozica Levak-Svajger (center) with two laboratory technicians in 1970.

at the onset of gastrulation has the capacity to differentiate into tissue derivatives of all three definitive germ layers. As gastrulation progresses, the ectoderm loses the capacity to differentiate into endodermal derivatives and differentiates only into ectodermal and mesodermal tissues. Together with the blastocyst injection experiment of R.L. Gardner, the labeling of ectodermal cells by R. Beddington and the tracing of ectodermal cell lineages by K.A. Lawson, these experiments contributed a great deal to the concept of the early ectoderm as the source of all cells which build the embryonic body.

It is not surprising that the method of culture *in vitro* could not be avoided as the next approach. Using a modified organ culture method it was shown that in serum- and protein-free media the early rat embryo can grow and differentiate to a degree which is much inferior to that in ectopic grafts, but nevertheless some tissues could easily be recognized. Various general or selective effects were





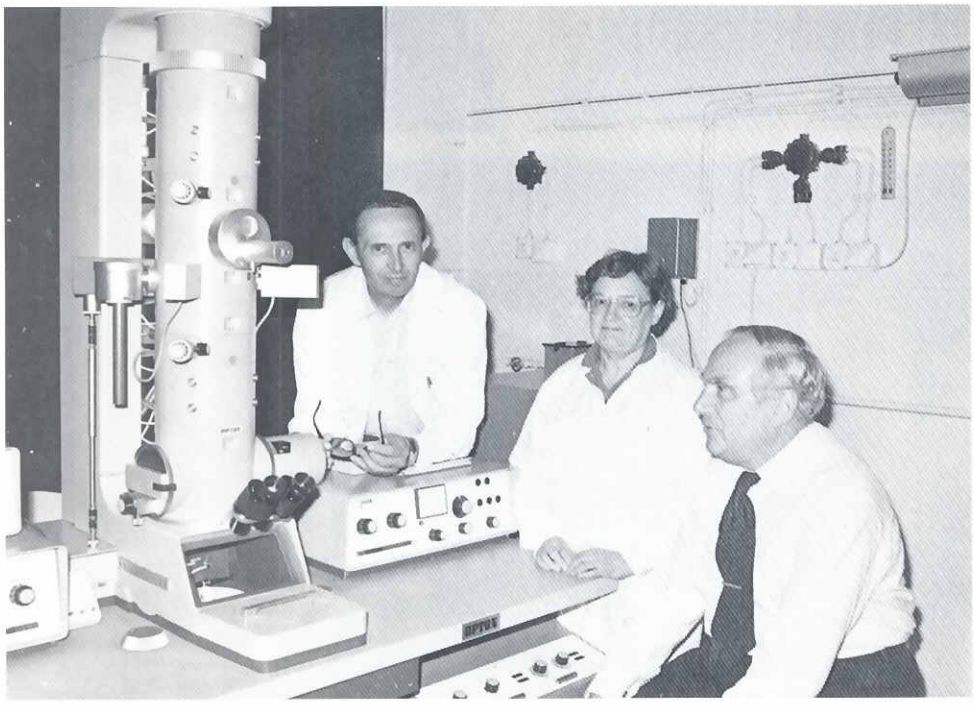


Fig. 4. (Left) Doctor Petar Martinovic (1897-1984) in 1975.

Fig. 5. (Right) Professor Ivica Kostovic in 1987.

Fig. 6. Professor Zvonimir Devide with his collaborators Mercedes Wrischer and Nikola Ljubesic (from right to left) in 1991.

observed when the culture medium was supplemented with cAMP, RA, NGF, bovine albumin, transferrin, etc. The most impressive result obtained so far was the significant increase in differentiation of atypical lens cells (lentoids) in the serum-free medium supplemented with transferrin.

This is the story of the continuous work of N. Skreb and his group in exploring the early rodent embryo: the same period of development for forty years!

Another branch of research in N. Skreb's laboratory was introduced by Drasko Serman. By using the method of polyacrylamide gel electrophoresis he analyzed the protein inventories in developmental systems, particularly during organogenesis in mammals as well as during neoplastic growth in animals and plants. His results indicate that quantitative changes in whole proteins in a developing system are not reliable and sufficient indicators of the level of cell differentiation.

Diversity of topics

Small teams work in several institutes at the universities in Zagreb, Rijeka, Split and Ljubljana. Sometimes their research program belongs to the borderline between developmental biology and other disciplines. As a result, a great diversity of topics is investigated which can only be partly listed here: ultrastructural aspects of cytodifferentiation, secondary body formation in tailed mammals, differentiation of lentoids from atypical sources in various experimenal systems with mammalian embryos, differentiation of the elastic cartilage and of the adipose tissue, develop-

ment, regression and anomalies of the notochord of human embryos and fetuses, stereological analysis of the human placenta, endocrinological and immunological aspects of reproduction and development, differentiation of the APUD system, regeneration phenomena in hydra, human brain gangliosides in development, growth factors and proto-oncogenes in embryogenesis and oncogenesis, biophysical aspects of morphogenetic movements.

This diversity of topics is reflected in the contributions to this issue and in the list of references in this article.

Developmental neurobiology

This is another fruitful field of reseach in Zagreb, carried out at the "Drago Perovic" Institute of Anatomy, Faculty of Medicine. In 1974 the neuroanatomy section was founded as a separate unit by Ivica Kostovic who still heads it as the principal investigator (Fig. 5). The main topic of research is the normal structural development of the human brain (particularly telencephalon, thalamus and basal ganglia) from the early fetal to the adult age, as well as anomalies of development. The research is based on the Zagreb collection of human brains (see Kostovic *et al.* in this issue). A broad international cooperation including joint projects with several institutions in Europe and the USA has been established. Recently the Croatian Institute for Brain Research was founded.

Development in plants

The research in botany at the Faculty of Science and Faculty of Agriculture was previously almost exclusively restricted to taxonomy, phytogeography and phytocenology. After the second World War the «Ruder Boskovic» Institute for research in basic sciences was founded. In 1953 the first electron microscope in the country was installed there and Zvonimir Devide began research on ultrastructure of the plant cell. A few years later a small team was formed and research became concentrated on the differentiation of the plant cell, especially plastids (Fig. 6). Particular mention should be made of the valuable collaboration of this small unit with other teams who need electron microscopy in their research. At the Institute of Botany (now Institute of Molecular Biology), Faculty of Science, Sibila Jelaska introduced the method of cultivation of plant cells *in vitro* and research is currently being carried out on regeneration and organogenesis in plant tissues, influence of hormones, growth factors and exogenous factors on developmental processes.

The lonely rider: Petar Martinovic

Petar Martinovic was one of the pioneers of experimental biology in Yugoslavia. Born in 1897 in Podgorica (Montenegro), he graduated from Syracuse, NY, USA (agriculture and zoology) and spent several years in laboratories in the USA and England. He had a turbulent life in which he had to overcome many difficulties. He neglected his academic career and worked in different institutes and laboratories. Since 1949 he was director of the Division for tissue and organ culture of the "Boris Kidric" Institute for Nuclear Sciences in Belgrade, Serbia. He was an inquisitive person with many ideas and it is therefore very difficult to summarize in brief his manifold scientific interests. His first and continuous interest was concentrated on the methodology of transplantation and cultivation *in vitro*. He used these methods predominantly for endocrinological studies in rats and chicken but also for experimental studies of fetal and postnatal oogenesis and spermatogenesis in rats. He transplanted the embryonic chick forebrain region before the establishment of circulation, made heteroplastic graftings between rat and chick embryos, but his most spectacular experiment was the transplantation of the whole head between chick embryos belonging to different strains. Some of these chimeras lived for years after hatching. Several young scientists from other laboratories in the country were trained by Petar Martinovic in methods of culture *in vitro* and transplantation.

Brain drain

As in other basic sciences, the "brain-drain" is one of the problems facing developmental biology in this country. Some prominent developmental biologists, born and educated in this country live and work abroad: Pasko Rakic (Yale University, New Haven, CT), Ivan Damjanov (Jefferson University, Philadelphia, PA) and Davor Solter (Max-Planck Institute, Freiburg, Germany). Fortunately, they have not forgotten their native country and collaboration with them and their support help us to overcome many difficulties that we meet in our work.

Teaching of embryology

The teaching of embryology at the universities in this country is influenced by the fact that there are no chairs or institutes specialized in this subject and the fact that there are few scientists involved in research in developmental biology. The classical embryology of experimental animals is included in the subject General Biology, while descriptive human embryology is a part of the combined subject Histology and Embryology, according to the tradition in Central Europe. Textbooks are compiled from those written in foreign languages. Recent achievements and concepts in developmental biology are gradually being introduced into teaching.

At the end of this presentation I cannot fail to mention tradition again and to remember our ancient teachers. As founders of institutes and organizers of teaching *ab ovo* they almost completely renounced reseach. They did not leave us long lists of publications. But we still look with admiration at their fine collections made for the teaching purposes. I can hardly believe that the beautiful preparations and illustrations were made by a full professor (B. Zarnik) almost 70 years ago. And my own professor (Vjekoslav Duancic, 1906-1976), besides having written the first textbook of human embryology in Croatian, established a fine collection of human embryos and fetuses as well as a rich collection of serial histological sections of early human embryos which is still used today for teaching and research in descriptive human embryology. Today, in the era or "publish or perish", the memory of such devoted teachers deserves reverence.

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