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The Finnish tradition of developmental biology

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Finland is a country with a relatively vast area but sparse population. During most of its history it has been under the rule of other countries: in the 12th century it became part of the Kingdom of Sweden and this lasted until 1809 when it became an autonomous Grand Duchy of the Russian Empire. Its independence dates from 1917. For nearly three hundred years there was only one university, which was founded in 1640 in Turku, a city also known as the site of Finland's oldest Bishop's See. In 1828 the University moved to Helsinki, which in 1812 had become the new capital of the Grand Duchy.

In the 18th century and the first part of the 19th century, all biological studies at the University of Turku were carried out in the Linnean tradition, and several of the professors had been students of Linnaeus. There was little or no room for experimental biology, and even the Cuvierian comparative anatomy was established as late as the 1840's. General zoology and anatomy reached an international level in Finland in the middle of the century, especially through the works of Professors Alexander von Nordmann, the discoverer of *Diplozoon paradoxum,* and E.J. Bonsdorff. However, there were no signs of interest in developmental biology, in spite of the fact that K.E. von Baer, the famous founder of modern descriptive embryology, worked as nearby as the Academy of Sciences of St. Petersburg. Physicians and anatomists published some descriptions of congenital malformations, but this did not arouse any general interest in studying their possible origins.

Developmental problems were approached more directly during J.A. Palmén's time. Palmén, who had become Professor of Zoology in 1884, is best known as an ornithologist and an evolutionist; in fact, he was the first prominent scientist in Finland who made Darwinism the focus of his lifework. In 1883 he published a morphological study on paired genital ducts of certain insects, in which both developmental and evolutionary aspects were taken into consideration. Influenced by Haeckelian ideas, he regarded these two aspects as closely linked.

Palmén never studied the development of vertebrates, but encouraged several of his students to undertake embryological research. The first of these pioneers of Finnish embryology was Hjalmar Grönroos. He was born in 1863 and graduated in 1886, whereafter he continued his studies in the School of Medicine. Soon his interest in anatomy and embryology took him to Tartu (Dorpat), Estonia, and then to Tübingen, Germany, where he was received by an able but now forgotten embryologist, A. v. Froriep. Grönroos stayed in Tübingen for several years, studying early Urodelan development. One of his first publications (1890) was also presented as his doctoral dissertation in Helsinki, and in 1896 Grönroos obtained the degree of Doctor of Medicine in Tübingen. After several difficult years he finally obtained the Professorship of Anatomy at the University of Helsinki in 1904, which he held until his retirement in 1928.

The most important embryological studies of Grönroos dealt with cleavage and gastrulation of Urodeles. In a meticulous description of the cleavage of newt eggs (1890), he not only described various aspects of the cleavage process, but tried to show, comparing different cleavage types in amphibians, that the holoblastic egg of Anurans was derived from more primitive, meroblastic eggs and that a partial cleavage would thus be the original type for all vertebrates. Grönroos continued his studies with eggs of *Salamandra maculosa* (1896), with more cautious conclusions on phylogenetic derivations. He also wanted to

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describe the gastrulation process of the salamander embryo, but only a couple of preliminary notes were ever published (1898). A paper on the homologies of cleavage furrows (1899) was Grönroos' last one as an embryologist; at the end of the 1890's he had turned to pure anatomy, especially to studies on the brachial muscles of primates. None of his students became true embryologists, although descriptions of congenital malformations were published at the School of Medicine from time to time. Yrjö Kajava, Professor Extraordinary of Anatomy from 1921-1925, even wrote a book on various malformations (in Finnish), and some descriptive studies were published, such as the work of Eino Suolahti (1926) on the development of human larynx during the fetal period.

Fig. 1. *The main building of the University of Helsinki, designed by C. L. Engel around 1830, after the University had been transferred from Turku to Helsinki.*

Wilhelm Roux had begun his experimental work on amphibian embryos in the early 1880's, and somewhat later Hans Spemann joined the field in which he was to become the sovereign master, crowned with the Nobel prize in 1935. Roux's work did not go unnoticed among Palmén and his students. In the 1890's K.M. Levander, a young zoologist, wrote several articles about Weismann's germ plasm theory, Roux's experiments and other similar problems. In 1903 Erik Nordenskiöld, another student of Palmén's, gave a lecture at the meeting of Vanamo, the Finnish biological society, on «developmental mechanics or experimental zoology», a trend which, as he asserted, had spread rapidly and aroused considerable interest everywhere. In this lecture he expressed his skeptical views on the possibilities of purely anatomical research to solve problems related to the regulation of development. He emphasized the importance of experiments on lower and simpler animals, but he himself never ventured to do experimental work, though during the first two decades of this century he made valuable contributions to the understanding of development and reproduction in acarids, before devoting himself entirely to the history of biology. At that time another student of Palmén's, Harry Federley, began experiments to solve an interesting problem in invertebrate development. As early as the turn of the century he had, in his unpublished Master's thesis, addressed the question of whether the so-called biogenetic law of Haeckel —that ontogeny is a recapitulation of phylogeny— would be valid in moth larvae. After a careful comparison of the different stages, Federley had come to the conclusion that, at least in the order Lepidoptera, the biogenetic law could not be applied without restrictions: it was not possible to make phylogenetic conclusions on the basis of ontogeny alone. In order to make full use of his living material, Federley kept moth cocoons at different temperatures for various periods of time. With these experiments Federley was able to show that changes in temperature influenced the structure of the wing scales of the moths emerging from the cocoons. He published his results in 1906 as the first doctoral dissertation in Finland in which a biological problem had been treated with purely experimental methods.

Federley did not stay in developmental biology, but moved towards genetics, a field in which his work has been widely recognized. His publication on hybridization of some *Pygaera* moth species, for example, was considered a «splendid achievement», to use the words of Wilhelm Johannsen. If Henry Mor-

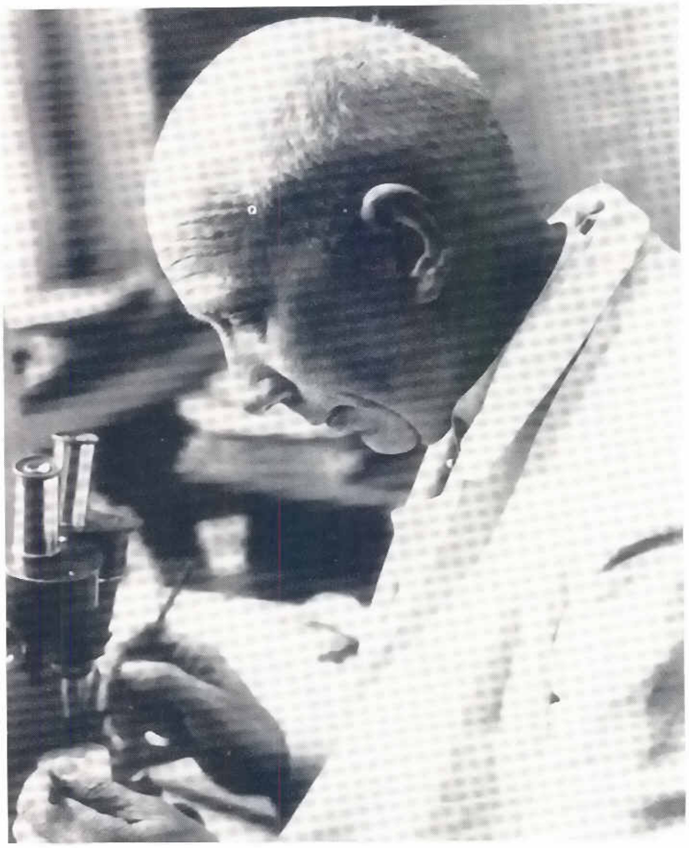

Fig. 2. *Gunnar Ekman (1883-1937).*

gan and his school had not made fruit flies the overwhelming protagonists of all genetical research for the future years, Federley might have become even more prominent. In 1913 he provided definitive proof of the individuality and continuity of chromosomes in Lepidopterans, demonstrated at the same time in Dipterans by Morgan and his school. In 1915 Federley became the first Docent in Genetics in Finland, and in 1923 he received the position of Professor Extraordinary at the newly established Department of Genetics where he was at first the only member of the staff. He soon founded a flourishing school, especially with his students Esko Suomalainen, who later became Federley's successor in Helsinki, and Tarvo Oksala, who was to occupy the first Chair of Genetics at the University of Turku. His understanding of the importance of developmental biology may be seen in what he wrote as early as 1918, when a new private Swedish university was being founded in Turku. Federley stressed the necessity of traditional zoology and botany as the basic subjects of life sciences, but he added that a professorship in biology should be established and directed to some special field of modern research: «If we only take the scientific point of view into consideration, the choice could hardly fall on disciplines other than developmental physiology and genetics, including evolutionism».

Federley's wishes were not fulfilled. Åbo Akademi in Turku has only one Chair in Biology, not specifically oriented towards experimental sciences, and though there are three Departments of Genetics (in Helsinki, Turku and Oulu), there is not a single ordinary Chair of Developmental Biology in any Finnish university.

It was Gunnar Ekman, also a student of J.A. Palmén, who established the tradition of developmental biology in Finland. In the 1919's it seemed that experimental embryology would advance on a broader front, as Alexander Luther had also become acquainted with the appropriate techniques and started promising work. Luther was one of the closest associates of Palmén, and the relationship was strengthened by the fact that he married Palmén's niece. Born in 1877, he had begun a fine zoological career as a specialist on Turbellarians and published a number of articles on other fresh and breakwater animals. After extensive anatomical work on Selachians, Luther spent two years, from 1912 to 1914, in Spemann's laboratory in Rostock, where he was the first foreign student of Spemann, a fact which the great developmental biologist remembered with warmth. Thanks to Luther, in 1922 Spemann was invited to act as a Corresponding Member of the Finnish Society of Sciences.

From 1916-1925 Luther published some experimental studies on the development of frog limbs, eyes and ears, and he even tried to apply the transplantation technique to lamprey embryos, but it seems that experimental embryology, after all, was not the field where he felt most at home. He had become Professor Extraordinary of Zoology in 1918 and the Head of Tvärminne Zoological Station after Palmén's death in 1919. Once more, the

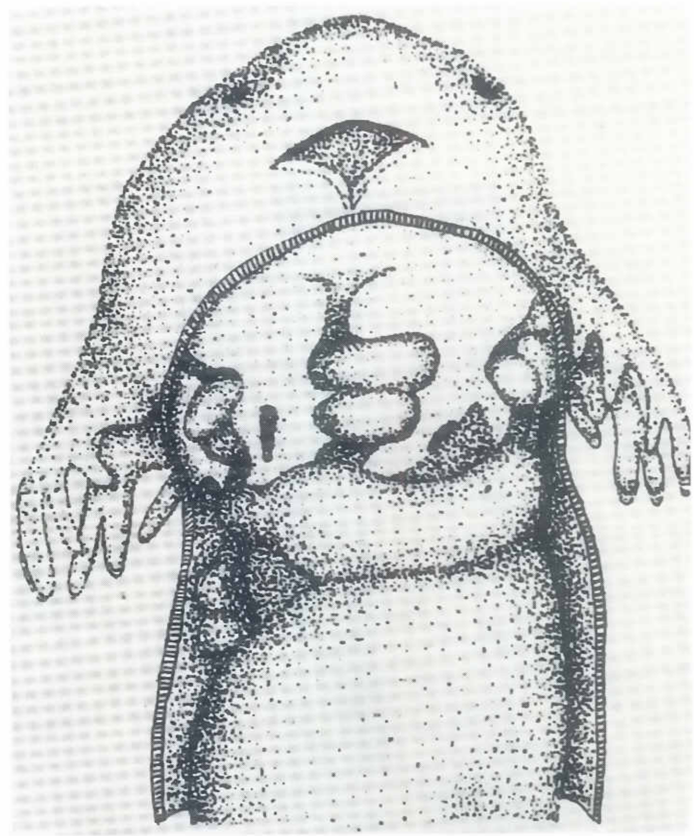

Fig. 3. *Result of the classic experiment by Ekman in 1924 in which splitting of the heart primordia resulted in the development of the three separate pulsating hearts (from G. Ekman, Neue experimentelle Beiträge zur frühesten Entwicklung des Amphibienherzens. Commentationes Biologicae. I. 9: 36 1924).*

lower water animals lured him, and after a long and fruitful career he summarized his studies on Turbellarians in a great monograph the last part of which was published in 1963, when Luther was 86 years old.

Thus, there was only Gunnar Ekman to promote the experimentalist tradition. During his school years he had prepared a beautiful collection of stuffed birds; he even made anatomical preparations of different organs of animals. This interest led him to zoological studies, and soon after completing his Master's degree he became an assistant in zootomical exercises at the Department of Zoology. Ekman received at least one impulse to experimental embryology in this work when he noticed that the shark under preparation lacked a branchial opening. Soon afterwards he wrote his first scientific paper on this subject (1910).

Early in the second decade of this century, Ekman decided to learn developmental mechanics abroad and chose the laboratory of the well-known experimentalist H. Braus in Heidelberg. In 1913, after three active spring seasons, he was able to show in his doctoral thesis that the ectoderm has a decisive role in the development of gill pouches of frog embryos. Ekman published some papers on the development of the lens of *Hyla arborea* and the gastrulation of *Rana esculenta*, but then concentrated his efforts on the development of the heart. His publications from the years 1921-1929 are now classics and were cited in standard textbooks well up to the 1960's. Most of the experimental work was done in Spemann's laboratory in Freiburg, which Ekman visited several times in the 1920's. His favorite experimental animal was the frog *Bombina*, later also *Rana fusca*, both species not found in Finland.

In his first article, Ekman was able to show the relative totipotency of the amphibian heart rudiment by demonstrating that

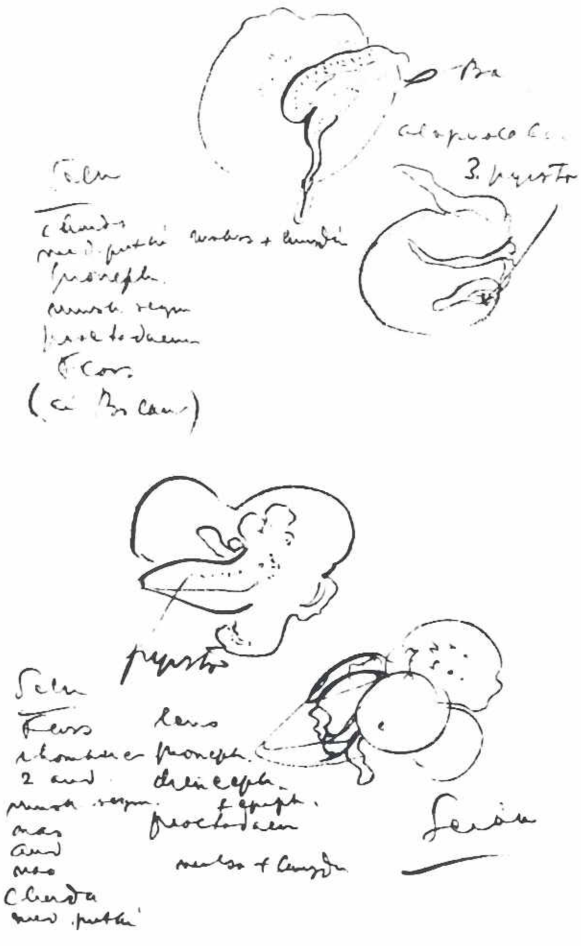

Fig. 5. *Two examples of* sandwiches *in which ectoderm is exposed to the combined action of a «neuralizing» and «mesodermalizing» inductor. Well-developed tails are seen, with myotomes and fins. Microscopic analysis reveals structures belonging to all three regions of the CNS (from the original record of Sulo Toivonen, 1954. Published in L. Saxén, Two-gradient hypothesis of primary embryonic induction.* Med. Biol. 56: *293-289. 1978).*

Fig. 4. *Sulo I. Toivonen (b. 1909).*

a functioning heart will develop from one single heart rudiment (right or left side), and that a rudiment split lengthwise will give rise to two functioning hearts with a circulation in both of them. Furthermore, he found that a 180° rotation of the anteroposterior axis of the heart rudiment of an early stage did not interfere with normal development of the heart, which meant that the main axis had not yet been determined at the stage with a neural plate or recently closed neural tube. Ekman was later able to divide the heart rudiment into as many as five different parts, which all developed into functioning tubular hearts, and he could grow small tubular hearts in an epidermal vesicle starting from a mere fraction of the original heart rudiment.

During the early 1930's Ekman, who had been named Professor Extraordinary of Experimental Zoology in 1928, grew increasingly interested in the problem of primary embryonic induction. He made an extensive study on the inducing capacity of the upper blastoporal lip of *Triturus* gastrula cut into two halves, and found that there was no essential difference between the inducing capacities of a full blastoporal lip and half a one. In these experiments, however, Ekman's role was not a pioneering one as it had been in the case of heart development. The induction studies were firmly in the hands of the German school led by Spemann, Otto Mangold and Johannes Holtfreter. Ekman's promising career ended in October 1937, when he unexpectedly died of an appendicitis at the age of 53.

Gunnar Ekman was a versatile biologist who in several articles published in Finnish wanted to spread knowledge of the latest developments in his science. He was vividly interested in the theoretical questions of biology, especially in the biological aspects of man and society, and in the relationship between development and heredity. His work in these fields, expressed for instance in the 140-page treatise «Über Entwicklung und Vererbung» (1930), has fallen into oblivion, but the experimentalist tradition he promoted is alive and flourishing.

Of Ekman's many students practically nobody wanted to follow him to the difficult and uncertain field of embryological experimentation, even though he switched from German frogs to domestic newts and their gastrulae. It was nearly by chance that Sulo Toivonen, a 27-year old graduate student and assistant at the Department of Zoology, started collaboration with Ekman in the spring of 1936. Toivonen learned the appropriate techniques and began to work on his thesis on heterogeneous inductors. Bautzmann, Holtfreter, Spemann and Mangold had reported in 1932 that the «organizer» need not be alive in order to have an inducing effect on the gastrula ectoderm, and in the following two years Holtfreter had made an extensive investigation of the distribution of inductive agents in different animal tissues. Thus, the question whether different heterogeneous inductors would have specifically different effects was an urgent one, especially as it seemed that these «abnormal» inductors might shed some light on the chemistry of the normal induction process.

Toivonen worked together with Ekman during the spring of 1937 —the egg-laying period of *Triturus vulgaris* lasts for only four to six weeks in southern Finland— but in October Ekman suddenly died. Toivonen was now alone promoting developmental biology in Helsinki, and he succeeded in this task. He published his preliminary results in 1938, and in December 1940 his thesis «Über die Leistungsspezifität der abnormen Induktoren im Implantatversuch bei Triton» for the Ph.D degree was accepted. His main results were that there would be three different types of primary induction, archencephalic, deuterencepahlic, and spinocaudal, each caused by qualitatively different inductors. Similar results had been obtained independently by H.-H. Chuang, and later the names of Chuang and Toivonen were often mentioned together as the main protagonists of the «qualitative hypothesis», as contrasted with the «quantitative hypothesis», according to which a single inducing agent would cause different inductions when present in different quantities. Chuang had been working in Germany in the 1930's and later returned to China, but due to political circumstances it was not until 1963 that Toivonen and Chuang met at an International Conference of Embryology in Helsinki.

The War delayed scientific work, and the main debate on the qualitative and quantitative hypotheses did not take place until the late 1940's and early 1950's. Toivonen, together with Taina Kuusi, a young biochemist, analyzed the nature of the heterogeneous inductors and found that the «archencephalic inductor» was thermostable, soluble in petroleum ether, and dialyzable, whereas the «spinocaudal inductor» was insoluble in organic solvents, thermolabile and non-dialyzable. Kuusi's conclusions were that the archencephalic factor might be connected to the RNA-rich granular fractions of the inducing tissues, and the spinocaudal agent seemed obviously to be a protein.

Fig. 6. *Lauri Saxén (b. 1927).*

In 1952, Toivonen became Professor Extraordinary of Experimental Zoology. This meant tenure, but no great laboratory facilities. Actually all work was done in rather primitive conditions in three small rooms in the basement of the old Zoological Museum. In 1960 a new building with more spacious rooms and better laboratory equipment was inaugurated for the Department of Physiological Zoology. At that stage Toivonen's team, the «Scuderia» as we used to call it, already included several young scientists, such as Lauri Saxén, Tapani Vainio, Juhani Kohonen and myself.

Saxén had joined Toivonen in the early 1950's. Together they experimented on the combined effects of two different inductors, the «archencephalic», or «neuralizing» liver, and the «mesodermalizing» bone-marrow, and found that the strength of the «deuterencephalic» induction depended on the relative amounts of these two inductors. On the basis of these experiments, now considered classic, Toivonen and Saxén formulated a «two-gradient hypothesis» according to which there are two basic factors not only in heterogeneous inductors but also in normal primary induction: a neuralizing agent and a mesodermalizing agent, which in different combinations determine the nature of the induction result. In 1962 they reviewed primary embryonic induction in amphibians in their monograph «Primary Embryonic Induction».

At that time the tradition was firmly established. The death of Tapani Vainio in a car accident in 1965 was a great loss, but work went on. Somewhat later the Department of Pathology, at the Medical School, obtained rooms in a new laboratory building. There Saxén, who was a pathologist by training, established a laboratory of his own, having become Professor Extraordinary in 1967. Kohonen went to the University of Turku, continuing his work, and I stayed, until the early 1980's, with Toivonen at the Department of Physiological Zoology —where the somewhat unofficial Laboratory of Experimental Embryology had its headquarters— widening the field with work on chick embryos which I had learned to operate under Koki Hara in Hubrecht laboratory, Utrecht, in 1965. New people poured in, often fully aware that embryological research would not bring them permanent or even temporary jobs. There were several medical students and graduate students in Saxén's team, and a few biology students who worked with Toivonen and me, and the contacts between the «Old Lab» and the «Pathology» always remained close.

When Toivonen formally retired in 1974, it was apparent that not only his students but even their students had acquired the highest academic degrees and senior teaching positions, and that many new fields had opened for developmental biology in Finland. However, he continued his research work as if nothing had happened, trying to answer the question of penetration of different inducing factors through various filters. On his 80th birthday he promised to continue his seasonal operations every spring as usual, as if more than fifty years of continuous work with newt embryos had not been enough. The continuity of the Old Lab may not last, but there is no question about the continuity of the tradition. This shows eminently what splendid fruit can be harvested through the tenacity and courage of single scientists like Gunnar Ekman and Sulo Toivonen, when they have the insight, skill and passion needed for lasting results.

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