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An intense half-semester developmental biology course, as taught at Uppsala University, Sweden

LENNART OLSSON*

Institut für Spezielle Zoologie und Evolutionsbiologie mit Phyletischem Museum, Friedrich-Schiller-Universität Jena, Jena, Germany

ABSTRACT This intensive course, designed for advanced undergraduates and beginning graduate students, was first taught in 1995 at Uppsala University, Sweden, and consists of a half-semester (8-9 weeks) of daily lecture and laboratory sessions covering a broad range of topics and giving an overview of developmental biology and some of its applications. The labs introduce students to a diverse assortment of model systems. The course goals are to present a comparative view of animal development (gametogenesis, fertilization, gastrulation, neurulation, organogenesis), followed by lectures on cellular and molecular mechanisms that regulate development, such as induction mechanisms, cell adhesion and migration, cell-matrix interactions and genomic imprinting. The development of complex systems, such as the nervous system, limbs and flowers, is emphasized, including aspects such as malformations, homeosis and mutant analysis, reproduction and fertility problems, and the connection between development and cancer. Model organisms are emphasized, but evolutionary aspects receive due attention. Typically, during the first 5 weeks, a day begins with lectures in the morning and ends with labs or demonstrations and seminars in the afternoon. Wednesday afternoons are "free" to give time for reading. A theory test is taken at the end of this period. Then, students do supervised research for 3 weeks to give them a feel for what it is like to do "real science." Finally, students present oral and written reports on their projects. This is the only course students enroll in during this portion of the semester, so they are expected to devote full effort to it.

KEY WORDS: *Sweden, course, laboratory exercise, research project*

Background Information

Scholarly Interests of the Author

As with most developmental biology courses, this offering reflects—to some extent—the research interests of the author. My interests include neural crest and paraxial mesoderm development (cell migration, cell differentiation, pattern formation, fate mapping), and I am fascinated as well with the evolutionary aspects of development.

However, as many of the lectures are presented by specialists from the Uppsala-Stockholm region, a broad range of topics, with in-depth coverage are included (see below).

Representative Publications

FALCK, P., JOSS, J. and OLSSON, L. (2000). Cranial neural crest cell migration in the Australian lungfish, *Neoceratodus forsteri. Evol. Dev.* 2: 179-185.

OLSSON, L. and JACOBSON, C-O. Eds. (2000). *Regulatory Processes in Development: The Legacy of Sven Hörstadius (1898-1996).* Wenner-Gren International Series, volume 76, Portland Press, London. ISBN:1 85578 136 0.

OLSSON, L., FALCK, P., LOPEZ, K., COBB, J. and HANKEN, J. (2001). Cranial neural crest cells contribute to connective tissue in the anuran amphibian *Bombina orientalis. Dev. Biol.* 237: 354-367.

General Teaching Philosophy

This course is situated in the 3-4th year of the curriculum . It is elective, and most students who take it continue as graduate students – albeit not necessarily in developmental biology. The teaching philosophy is to give the students the opportunity to learn not only the pertinent facts about developmental biology, but also to expose them to a wide range of topics and researchers in developmental biology and in applied fields of research that rely on developmental biology to provide the underlying knowledge base (teratology, childhood cancer, etc.) The number of teachers is unusually high, and this is the only course of those I have been involved in for which I have had the opportunity to pay people from other departments and universities to come and teach. This gave me the freedom to design a series of lectures such that (1) I myself did not have to lecture on topics about which I have little clue,

***Address correspondence to:** Dr. Lennart Olsson. Institut für Spezielle Zoologie und Evolutionsbiologie mit Phyletischem Museum, Friedrich-Schiller-Universität Jena, Erbertstr. 1, D-07743 Jena, Germany. Fax: +49-3641-949-162. e-mail: b1olle@pop3.uni-jena.de

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Fig. 1. Young female cone of Norway spruce, as seen by scanning electron microscopy. *A course project involved the attempted cloning of new MADS-box genes from Norway spruce. In plants, MADS box genes have functions similar to HOX genes in animals. (Picture kindly provided by Annelie Carlsbecker)*

although I think they belong in the course, and (2) I could often get people to come who are both real experts in their fields and very busy. Such people often see their lectures as a way of attracting prospective graduate students, which has also proven to be correct. The laboratory exercises and demonstrations are important both because they give the students the opportunity to develop manual skills and get to know new techniques or new applications of "standard" methods. Students also learn to appreciate the efforts and skills involved in some of the classical experiments performed by the pioneers of "*Entwicklingsmechanik*." We use amphibian embryos to do extirpation and transplantation experiments, and encourage students not only to develop their own experimental design, but also to "re-enact" for example "Einsteck" experiments. There is quite a lot of time set aside for the labs, so the students have time to discuss the experiments among themselves and with the teachers. The research projects are even more "hands-on," and the idea is to expose students to "the real world" of science. To that end, students are also encouraged to take part in research seminars and journal clubs. The most important aspect of working with a small research project in a research group is to expose the students to how one plans and performs experiments, including how to deal with the common phenomenon of an experiment that "doesn't work." Although this can be a tough school, the research projects are the most popular part of the course, even if – as sometimes happens – the student has no proper results after 3 weeks. Obviously, the idea behind having research projects does work. Although the students have studied at least 3 years and have heard a lot about experiments and their interpretations in lectures, they themselves have done mostly "cookbook" experiments. The opportunity to do something more "real" is thus met with great enthusiasm.

General Features of the Course

The course grew out of part of a zoology course, and was originally called "Animal Development." Later, in 2000, we introduced plant development, which had previously been taught in a plant physiology course, as one of the modules. The name of course was then changed to Developmental biology. The course is taught to approximately 15 senior-level undergraduate biology majors or graduate students without previous education in developmental biology. Prerequisites for enrolling are at least 2 years of basic courses in Natural Sciences. Biology courses should include Cell Biology, Genetics and Gene Technology, Structure and Physiology of Organisms, Faunistics and Floristics, and Ecology. Chemistry courses typically include General, Physical, Organic and Inorganic Chemistry as well as Biochemistry. Two graduate students are employed to help with the labs.

Uppsala University has a 2-semester system. The spring and fall semesters are each 17-18 weeks long. Having successfully completed the first 2 years, biology majors can choose from a large variety of about 40 advanced courses in different biological subjects. Most of these courses are half-semester courses, like our Developmental Biology course, and the idea is that the students take two courses each semester, one after the other. As courses are taken one at the time, the students are given an intense, full-working-week exposure to developmental biology for 8-9 weeks. Typically, for the first portion of the course (approx. 5 weeks), a day begins with lectures between 900 and 1200, and ends with labs and/or demonstrations and seminars between 1300 and 1600. Wednesday afternoons are "free" to give time for reading. A theory test is taken at the end of this period. Then students do supervised research projects in a research group for 3 weeks. The project part gives a feel for what it is like to do "real science." Finally, students present oral and written reports on their projects. The supervisors are in the audience, and the idea is that the student gives a presentation (maximum 15 minutes), which is then followed by questions and comments from fellow students and from the teachers. Typically, the fellow students have tougher comments than the teachers. In the evening, we have a party.

Information Content: Course Outline

Lectures cover the Following Topics (Typically 3 Hours for Each Topic):

1. Introduction: Developmental phenomena and how to explain them
2. Oogenesis, spermiogenesis
3. Fertilization and cleavage
4. Fertility and fertility problems in humans
5. Early development and axis specification in *Drosophila*
6. Early development and axis formation in amphibians
7. Ectoderm development and derivatives
8. Mesoderm development and derivatives
9. Endoderm development and derivatives
10. Development of the neural crest
11. Development of the nervous system
12. Cell interactions during nervous system development
13. Cell death and signaling pathways during development
14. Cell adhesion in development
15. The extracellular matrix
16. Regulation of gene expression
17. Epigenetics in development
18. Imprinting and pediatric oncology
19. Primordial germ cells
20. Sex determination and sex reversal

21. Stem cells
22. Transgenic animals: Models for development and disease
23. Implantation and placentation
24. Structure and function of the placenta
25. Mechanisms of teratogenesis
26. Introduction to the plant
27. *Arabidopsis*, the model plant
28. Development of the flower
29. Evolution of flower development
30. Plant growth regulators

Labs (Selection, all labs are not given every year)

1. Development from egg to tissues (Microscope slides)
2. Regeneration in planarians
3. Sea urchin fertilization and development
4. Experimental embryology of amphibians (axolotl, frog)
5. Chicken development
6. Development of cartilage, bone and muscle in the chicken: immuno- and histological stainings
7. Mammal embryology - organ culture
8. Genomic imprinting
9. Patterns of cell division
10. Floral pattern mutants

Demonstrations

1. *In vitro* mouse preimplantation development
2. Mouse oocyte dissection, oocyte microinjections

Subjects for research projects (examples)

1. Do somitomeres exist?
2. Development and function of the hypochord in the amphibian embryo
3. Cranial muscle development in *Ambystoma mexicanum*
4. Are cranial neural crest cells differentiated already before or during migration in *Ambystoma mexicanum*?
5. Does pH influence the timing and/or sequence of ossification in metamorphosing frog larvae?
6. Isolation of a neurotrophin from Amphioxus (*Brachyostoma* sp.)
7. Expression and distribution of laminins and heparan sulfate/heparin proteoglycans during early mouse embryogenesis
8. Analysis of cell-extracellular matrix interactions during early muscle development
9. Developmentally regulated cell proliferation.
10. Mechanisms of transcriptional regulation
11. Cell cycle regulation during *Drosophila melanogaster* embryogenesis
12. Screening for genes with a potential role for the development of muscular dystrophy
13. The effects of severe hypoxic stress on cell survival and gene expression
14. Analysis of mammalian silencing mechanisms
15. Characterization of chromatin organization in the Imprinting Control Region (ICR) of H19/Igf2 using *in vitro* chromatin templates.
16. Characterization of an insulator function in the Imprinting Control region of H19/Igf2.
17. Does the hypoxia-inducible transcription factor EPAS-1 play a role in the organ of Zuckerkandl of the human fetus?
18. Do gonochoristic species show the same sex difference in preoptic GnRH-ir cell numbers as sequential hermaphrodites?

Tests

The Swedish system has only three grades; fail, pass, and pass with honor. Typically, passing grades correspond to having at least 50% (pass) or 75% (pass with honor) of the maximum points on the test or tests. It is fairly easy to pass, but not very many pass with honor. In cases where a student is on the borderline between two grades (i.e., almost but not quite over the limit to a higher grade), the quality of the report (written and oral) of the research project can tip the balance positively (but not negatively). In this course, there are two tests. One 1-hour developmental anatomy test after 2 weeks, where students are given the task of explaining slides of different embryos and embryonic stages (up to histogenesis) which they have been studying during these two weeks, and a 4-hour theory test covering the textbook as well as the lectures. Here, the questions are typically of the essay type. I have collected good test questions in a “question bank,” from which the core test questions are drawn. I also ask the guest lecturers to supply questions related to the material that they have actually covered in their lectures. This practice developed because I think there is some basic knowledge that students should be able to explain (the questions in the bank), and in addition I want the test to reflect the shifting contents of the more research-oriented lectures. I sometimes rewrite the questions submitted by the guest lecturers because they are too difficult. The specialist may ask questions which he/she finds interesting, forgetting that their specialty is typically a very small part of the material that the students need to learn. This practice has also evolved over the years. In the beginning, I did *not* change these questions, and the test became very tough indeed, and it also did not really reflect the core knowledge in the field. Guest lecturers are given the choice of either correcting the answers themselves, or of providing me with the correct answers. There has been an approximately even split between the two strategies over the years. Unfortunately, I have the feeling that some lecturers want to see the answers written by the students before they decide exactly what is needed to get the full number of points on a question. This is a dubious strategy. Examples of typical questions are given below.

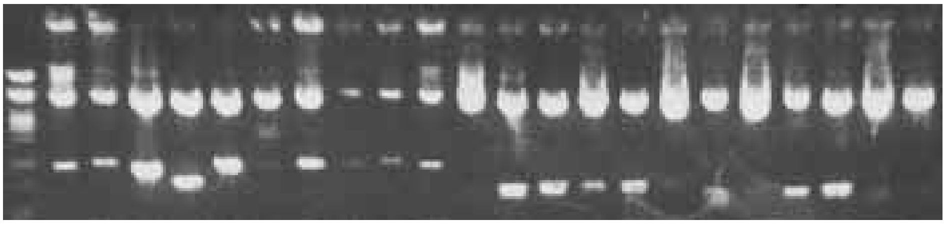

Fig. 2. New MADS box genes from Norway spruce cloned with PCR techniques. *The PCR products were cloned into a vector, and the picture shows an agarose gel with ethidium bromide-stained DNA where the vector and insert have been separated. The smaller bands are potentially new genes. (Picture kindly provided by Annelie Carlsbecker).*

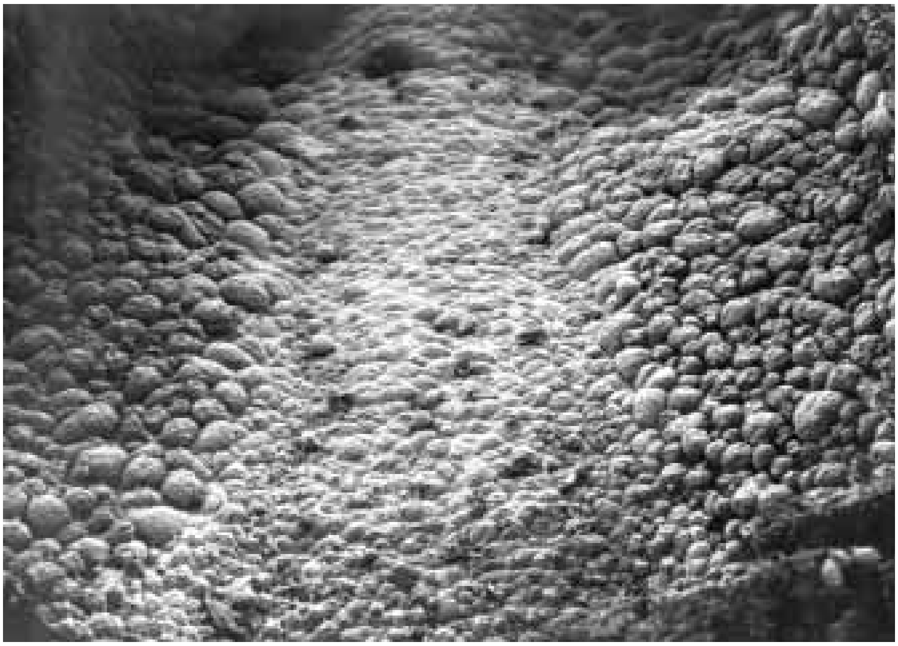

Fig. 3. The relatively unknown morphogenesis of the notochord in the Mexican axolotl studied in a student research project. *Here the view is from inside the embryo, using the scanning electron microscope. (Picture kindly provided by Joakim Eriksson).*

Fertilization

Describe (briefly) the fertilization process in mammals.

Gastrulation

Describe and compare gastrulation in amphibians and birds.
What are the major differences?
Which structures have the same function?
Drawings are encouraged!

Organogenesis

The mesoderm gives rise to a number of different organs, and parts of organs, in the vertebrate embryo. What are these mesodermal derivatives, and how do they form?

Cell Adhesion

Explain the concept "differential cell adhesion." Give an example illustrating the importance of differential cell adhesion for the development of an organ, and an example where the molecular mechanisms are well known.

Regulation of Gene Expression

Discuss the various strategies employed by regulatory transcription factors and DNA regulatory sequences in order to provide the variety and complexity of gene regulation which is necessary for development, giving theoretical and/or actual examples where possible.

Axis Formation

In the fruitfly *Drosophila melanogaster* the anterior-posterior patterning of the embryo is regulated in a hierarchical fashion. Which classes of genes are involved in this, and which main roles do the different types of genes play?

Limb Development

The development of vertebrate limbs is beginning to be understood in some detail.

How are the dorsal-ventral, proximal-distal and anterior-posterior axes established in the chicken embryo?

Epigenetics, Genomic Imprinting

Define epigenetics (a) and the different modes of epigenetic inheritance (b). List at least two different biological processes which are believed to require epigenetic inheritance for normal development (c).

Mechanisms behind Teratogenesis

Retinoic acid and other retinoids are powerful teratogens. This is hardly surprising to a developmental biologist. Explain why we expect retinoic acid to be a teratogen in the light of its role in normal development.

And Finally, Two Questions on Mammalian Development, with Clear Answers provided by the Lecturer (Mariann Wide)

Placentation

Question: The blastocyst of domestic animals (such as cow, pig, etc) has a characteristic development from eclosion (disappearance of the zona pellucida) to the establishment of the placenta. Can you describe this development?
Answer: dramatic elongation of the blastocyst (trophoectodermic) with minor development of the embryonic disc. Histotrophe nutrition, recognition of pregnancy are the major roles of this elongation. There is no implantation per se, but an attachment (so-called central implantation) to the surface epithelium of the uterus, and a primarily epitheliochorial placenta formation.

Sex determination

Question: A number of factors are involved when a mammalian fetus develops from the sexually indifferent stage into a male
A. Which factors?
B. Where (in which tissues) are they expressed?
C. What are their specific effects?
Answer:
A. Y-chromosome, SRY-gene, TDF, AMH, testosterone (+hCG),
B. Pre-Sertoli cells, Sertoli cells, Leydig cells (+ placenta),
C. Müllerian duct regression, male secondary sex characteristics.

Experiences with Students from Diverse (International) Backgrounds

The course was originally intended for advanced undergraduates from Sweden, but in 1995 Sweden joined the European Union (EU), and Swedish students proved to be very keen on studying abroad (in countries where courses are given in English or a Scandinavian language). Through student exchange programs (such as ERASMUS), the number of foreign students from EU countries increased dramatically, partly because we started to give advanced courses in subjects such as biology in English. The

Developmental Biology course has had relatively many foreign students (3-5 out of 12-16), maybe because it still is uncommon for the subject to be given as a course in its own right (rather than as part of a Zoology course). Sweden has strong links with North America for historical reasons. More than 20% of the Swedish population emigrated in the 19th and early 20th century, mostly to the United States, in particular to the Great Lakes region, where the climate is similar to that of Sweden. Many Swedes have relatives in North America, including myself. Exchange programs exist with many US and some Canadian universities. In addition to advanced undergraduates from Western Europe, Australia and North America, some of our beginning graduate students from either (mainland) China or India in the developmental biology department have taken the course. These students typically have a background in biochemistry/molecular biology rather than organismic biology or zoology. My experiences with foreign students are necessarily impressionistic and based on relatively few individuals, but I want to give a few comments anyway. First, of course, individual level and direction of interest are the most important factors determining how well students do in the course. Second, differences in the educational systems of different countries shine through. The most obvious difference is in how much laboratory experience students have. The Swedish system is lab intensive and may be a bit weak on the theoretical side. Students from other Scandinavian countries, Germany, and Holland seem to have a background similar to that of the Swedes – maybe with stronger theoretical backgrounds. Students from Australia and the United Kingdom, however, have less lab experience, and students from southern Europe, especially (Spanish and Greek students have taken the course), seem to have had more theory and a lot less practical experience. They also are the only ones who sometimes have insufficient English knowledge. North American students have very different educational experiences (and skill levels) depending on which university or college they come from. Some foreign undergraduates have apparently never experienced this type of intensive course before and complain that it takes up most of their time. However, Swedish students have that complaint as well, although they are used to the system. The course simply covers a lot of ground in a relatively short time. The graduate students often do well on the theory test, reflecting that they have more experience studying and that they generally are preselected on the basis of theory tests. Somewhat to my surprise, the "slide test," which tests knowledge of developmental anatomy, is surprisingly difficult, not least for the graduate students. This reflects, I think, that their training is in molecular biology, and also that it is easy to underestimate the difficulty of learning to decipher "descriptive" histological information. The ability to make a mental 3-dimensional model out of serial sections varies widely among individuals, regardless of educational level.

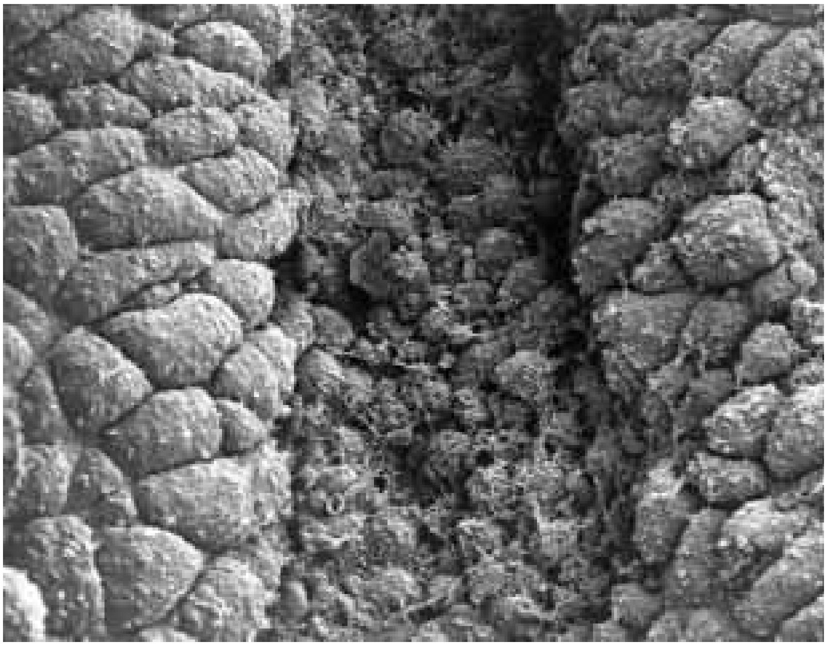

Fig. 4. Close up of the central area of Fig. 3. *The large notochord precursor cells on both sides can be seen, moving towards the center. (Picture kindly provided by Joakim Eriksson).*

The mix of graduate and undergraduate students, people from North America, different parts of Europe as well as India and China, is very good for a lab-intensive course like this. When students spend about 30 hours a week together, they get to know each other and learn from each other's skills. Graduate students can share their enthusiasm and skills, as well as their views on what life in the research lab is like.

Textbooks for Assigned Readings

We have shifted back and forth between Gilbert's *Developmental Biology* and Kalthoff's *Analysis of Biological Development*, usually using whichever book is in the most recent edition.

Many lecturers provide handouts of the illustrations they use (when not in the textbook). Nowadays, I give a lecture course using PowerPoint presentations, which are then made available on a (protected) course homepage.

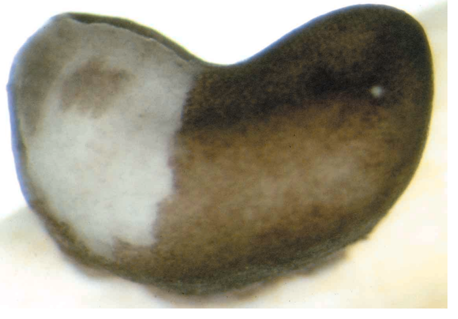

Fig. 5. The anterior part of a frog embryo with the epidermis removed, revealing the migratory streams of cranial neural crest cells (the dark streams on top of much paler cells). *Experimental embryology techniques, such as extirpation and transplantation of organ primordia, are taught using amphibian embryos. Amphibian eggs and embryos survive the rough treatment that inexperienced students give them and heal remarkably well.*

The department has bought 16 copies of the *Atlas of Descriptive Embryology* by W. W. Matthews (1986), which are used during the study of microscope slides (first 2 weeks of the course).

Visual Aids

To give a feel for the dynamics of early development, I use video clips of development in different animals: Fink, R. (ed.), "A Dozen Eggs: Time-Lapse Microscopy of Normal Development," 1991, Society for Developmental Biology (USA). In addition, I have (time-lapse) videos of salamander and chicken development. The salamander film in particular is splendid. It shows, in Germanic detail, the development of a *Triturus* newt in dorsal, ventral and side views. And, yes, it was produced by the Institute for Scientific Film in Göttingen, which has a homepage in German and English at http://www.iwf.de. A video (VHS format) tape can be bought for 25 Euro. The catalogue number is E 350, and the title "*Triturus alpestris alpestris* (Salamandridae) - Embryonic Development."