Histology & Embryology Periodical

Department of Histology and Embryology

Third Faculty of Medicine, Charles University in Prague

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What´s up…

… in the month of December and January

Week 10:

Muscle tissue (lecture)

Types of muscle tissue (practical)

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Cells producing signaling molecules (lecture)

Week 14 and 15:

Nerve tissue & synapse structure (lecture)

Nerve tissue and its structure (practical)

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2nd Annual Conference

"Trends in developmental toxicology and teratology"

When: Wednesday **December 10**, 2014, from 9 am to 4.20 pm

Where: Radana Königová Conference Hall, dean´s office of the 3rd Medical Faculty

Please, come if you are interested in the topic, you can ask questions of the prominent Czech and Slovak scientists from the field of teratology, epidemiology

and developmental toxicology.
Hand-outs in English will be available!

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Holiday Concert of the Third Medical Faculty

When: Tuesday **December 16**, 2014 at **7pm**

Where: Military **Church of St. John of Nepomuk,** Hradčany (Prague Castle), on the corner of "Kanovnická" street and "U kasáren" street, take tram no.22, Brusnice stop

What: the quintessential **Czech Christmas baroque music** by **Jakub Jan Ryba**!

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Who is who II

MUDr. Tomáš Boráň
tomas.boran@lf3.cuni.cz

Just as a criminal returns to the scene of the crime, I, also, returned to the Third Medical Faculty as an assistant professor at the Department of Histology and Embryology. I graduated as an M.D. in 2005 from our Faculty and then worked for several years for the Institute of Experimental Medicine, Academy of Sciences of the Czech Republic.

My professional assignment is now shared between two institutions; the State Institute for Drug Control (SUKL) and the Third Medical Faculty. As for SUKL I'm involved, among other things, in the research on cellular therapies and tissue engineering. As for the Department of Histology and Embryology, I teach mostly foreign students of the magister program and the bachelor`s curriculum.

Due to the split in my professional activities I'm not always available on the Faculty grounds in person. Please send me an email with any issue you might encounter during our classes or if you would like to arrange a consultation with me in advance.

Tomáš Boráň

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MUDr. Zdeňka Zemanová, CSc.
zdena.zemanova@lf3.cuni.cz

To give you an idea about my qualification, experience and interests let me start from my professional beginnings. I was only an 8th semester med student when asked by the legendary prof. Borovanský to become one of his assistents and teach anatomy to the students of the 1st and 2nd semester.

News & Reminders

The Periodical of Histology and Embryology will **not** be published **in January**.
Look for a new issue in February, 2015 on: http://www.lf3.cuni.cz/en/departments/histologie/hep/index.html

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Word of the Year 2014: **Exposure**

Surely, you noticed the word of the year for 2013 chosen by the Oxford dictionary, "**selfie**". In the year 2014 they went lower key in Oxford and elected the word "**vape**" to become THE word. Whatever opinion you may have on e-cigarettes (the latest insight offers the December WHO bulletin by the epidemiologist of WHO, Dr. Peruga: http://www.who.int/bulletin/volumes/92/12/14-031214/en/) however Dictionary.com has chosen a little more exciting word chose Dictionary.com. As for this leading online dictionary the Word of the year 2014 is „**exposure**". Exposure means 1) the condition of being exposed to danger or harm, or 2) the act of bringing to public attention especially through media coverage; publicity". You may immediately think of the deadly public health issue of the latter half of 2014, the epidemic of Ebola disease in West Africa. Other meanings of the word „exposure" and more reasons why the word won over others in 2014 are available on http://blog.dictionary.com/exposure/.

After I graduated from medical school, there was no job for me as I was not loyal to the Communist party. The Czechoslovak Academy of Science was a more liberal environment than medical faculties at that time and I applied and was admitted as an aspirant. However, the unexplainable happend and I was sent by the decision of a clerk at the Ministry of Health or who knows who, to work as a dentist in a small town far, far away from Prague. I was lucky enough to have good friends who were able to bring me back to Prague. Back at the Academy, I was doing science in the field of embryology, specifically the morphology of kidneys. Then at the faculty I had the honor to work under the supervision of assistents Čihák, and Rychter, and assistent Jelínek and I became good at microsurgery, histology, imunohistochemistry, and physiology of kidneys. I have loved everything I have ever worked on (also, I´m passionate about arts, particularly music and painting). The political changes in 1989 allowed me to return to the Third Medical Faculty and teach again. And here I´m back again, hoping I can participate in all the good work of the faculty staff and our students.

MUDr. Zdeňka Zemanová, CSc.

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Endocrine disruptors I:
Introduction

- ✓ **Hormones** are signaling molecules that regulate physiological and behavioral activities.
- ✓ Hormones are produced by endocrine glands, transported through the circulatory system to the distant target organs.
- ✓ Hormones in target organs bind to cell receptors and consequently change the function of a cell

either slowly via genomic effect or rapidly without altering the genome.

- ✓ Hormones regulate expression of genes playing critical roles in guiding the development of embryonic organ systems.

VERSUS

- ➢ **Endocrine disruptors** are hormonally active substances that function as signaling molecules regulating physiological and behavioral activities.
- ➢ The main **routes of exposure** to endocrine disruptors are ingestion such as through food, water and contaminated dust, or inhalation, and exposure though skin from cleaning and personal care products. However the source of exposure "divers and vary widely around the world as some endocrine disrupting chemicals were banned decades ago while others recently with significant differences between countries."[1]
- ➢ Endocrine disrupting chemicals in target organs bind to cell receptors just like hormones and cause changes in the cell function.
- ➢ The most troubling thing about endocrine disrupting chemicals is their effect on developing organisms.

Once upon a time…

Dr. Theo Colborn was a well accomplished American zoologist – also an epidemiologist, toxicologist and water chemist – when she was invited to join the **Conservation Foundation** in 1987. The purpose was a research project on the Great Lakes on the border of the US and Canada. The Great Lakes are a unique ecosystem, and the largest compound of freshwater lakes on Earth, containing about one fifth of the worlds' surface freshwater by volume.[2] Dr. Colborn´s research resulted in a new field in science and scientific and human awareness. In her book "Great Lakes, Great Legacy?" she documented that **man-made chemicals** in the waters of the Lakes **that interfered with the developing organ systems** of the young of top predators of the Lakes. Such chemicals didn't affect the predator's babies directly, after being born, but rather through their mothers during prenatal development. In light of Dr. Colborn's research, an international, multidisciplinary panel of scientists **in 1991** in Wisconsin coined the term "**endocrine disruptors**". [3]

Dr. Colborn published a worldwide popular book "Our Stolen Future" in 1996 and also founded an organization that "focuses primarily on human health and environmental problems caused by low-dose and/or ambient exposure to chemicals that interfere with development and function, called endocrine disruptors"[4]. Even as an 87 year old woman Dr. Colborn has not given up on spreading the knowledge and awareness of chemicals in the environment.

[1]Diamanti-Kandarakis, E. et al. *Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement*. Endocrine Review, 2009. **30**(4). 293-342.

[2]U.S. Environmental Protection Agency. *Great Lakes* [online]. Last update: 7/5/2012. [Retrieved 12/01/2014]. Avalailable from: http://www.epa.gov/glnpo/basicinfo.html

[3] *Statement from the work session on chemically induced alterations in sexual development: the wildlife/human connection*. 1991. [online]. [Retrieved 11/28/2014]. Available from: http://endocrinedisruption.org/assets/media/documents/wingspread_consensus_statement.pdf

[4]TEDX: The Endocrine Disruption Exchange. [online]. [Retreived 11/29/2014]. Available from: http://endocrinedisruption.org/about-tedx/about

Give me a definition…

The International Programme on Chemical Safety, part of the World Health Organization (WHO) adopted the term endocrine disruptors and defined them as **"exogenous substances that alter function(s) of the endocrine system and consequently cause adverse health effect in an intact organism, or its progeny, or (sub) populations."**[5]

> *Because of the shared properties of the chemicals and … hormones,* ***no endocrine system is immune*** *to endocrinne disrupting chemicals.*[1]

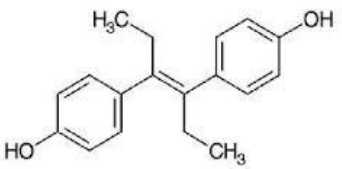
Evidence supporting the endocrine disruptor hypothesis is derived from studies in wildlife living in contaminated environments, studies of livestock foraging on phytoestrogen-containing plants, laboratory animal studies, and reports of increasing rates of health effects in hormonally sensitive tissues including tumors of the testes, breast, and prostate, birth defects that affect the reproductive tract (hypospadias and cryptorchidism), and diminished semen quality. [6]

So what are we talking about here, really?

The group of molecules identified as endocrine disruptors is highly **heterogeneous**. From a physiological perspective, the Endocrine Society recognizes an endocrine-disrupting substance as "a **compound,** either natural or synthetic, **which**, through environmental or inappropriate developmental exposures, **alters the hormonal and homeostatic systems** that enable the organism to communicate with and respond to its environment"[1].

Endocrine disruptors includes industrial solvents and lubricants and their byproducts (polychlorinated biphenyls - PCBs, polybrominated biphenyls - PBBs, dioxins), plastics and plasticizers (bisphenol A, phthalates), pesticides and fungicides (methoxychlor, chlorpyrifos, DDT, vinclozolin), and pharmaceutical agents (DES). Natural chemicals found in human and animal food (*e.g.*, phytoestrogens, including genistein and coumestrol) can also act as endocrine disruptors. [1]

Diethylstilbestrol (DES)



Hormonally-active chemicals were first shown to have effects on developing humans in the early 1970s, when **vaginal adenocarcinoma**, a rare cancer, was shown to be linked to **fetal exposure** to diethylstilbestrol (DES). During the 1950s, the mothers of these young women had been given DES, a synthetic estrogen, in an effort to prevent miscarriage and preterm delivery. In November 1971 the FDA banned DES in the USA for use by pregnant women[7]. In Europe the ban was delayed as long as 12 years.[8]

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[5] WHO library. *State of the science of endocrine disrupting chemicals 2012*. [online]. [Retreived 11/29/2014]. Available from: http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/

[6] Teratology primer. Kavlock, R. J. Can Chemicals in the Environment That Affect Hormone Function Disrupt Development? In: Teratology Society, 2010. Teratology Primer, second edition [online]. 9 July 2010 [Retreived 11/29/2014]. Available from: http://connection.teratology.org/p/cm/ld/fid=6

[7] Calle, E.E. et al. *Diethylstilbestrol and the risk of Fatal Breast Cancer in a Prospective Cohort of US Women.* American Journal of Epidemiology, 1996. **144** (7). 645-652. [online] . [Retrieved 12/2/2014]. Available from: http://aje.oxfordjournals.org/content/144/7/645.full.pdf

[8] European Environmental Agency. *Late lesson from early warnings: The precautionary principle 1986-2000.* Published 01/09/2002. ISBN: 92-9167-323-4. Available from: http://www.eea.europa.eu/publications/environmental_issue_report_2001_22

DDT

Isomer **o, p - DDT**, binds, in experimental animals, to estrogen receptors and **feminizes** hormonally sensitive tissues while the DDT metabolite **p,p - DDE demasculinizes** development by binding to and inhibiting the androgen receptor. [6]

Pesticide DDT was banned in the USA in 1972 and that saved the national symbol, the bald eagles, from extinction[9].

DDT was banned in many European countries in the early 1970s and banned from the entire EU in 1986[10].

However, DDT is still used in many countries of the third world as a malaria prevention despite of its´ decreasing effectiveness and extreme toxicity[11].

Bisphenol A (BPA), a plasticizer, is now the subject to intense process of evaluation and re-evaluation on the both sides of the Atlantic. If you feed a little child by bottle play it safe and go glass or BPA free: http://www.niehs.nih.gov/health/topics/agents/sya-bpa/index.cfm

In the next issue:

Endocrine disruptors II: Atrazine

[9] U.S. Fish and Wildlife Services. *Bald Eagle*. Last update 03/18/2013. [online]. [Retrieved 11/29/2014]. Available from: http://www.fws.gov/midwest/eagle/recovery/biologue.html

[10] EFSA. *Opinion of the scientific panel on contaminants in the food chain on a request from the commission related to DDT as an undesirable substance in animal feed.* The EFSA Journal 2006. 433. 1-69. [Online]. [Retrieved 11/30/2014]. Available from : http://www.efsa.europa.eu/en/efsajournal/doc/433.pdf

[11] Toxipedia [online]. DeCarvalho, J. P.DDT. Last updated: 05/03/2013. [Retrieved 12/02/2014]. Available from: http://www.toxipedia.org/display/toxipedia/DDT

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Repetitio mater studiorum….

… Myoepithelial Cells

"Good fences make good neighbors."[12]

Q: Myoepithelial cells are:

? Smooth muscle cells that acquired characteristics of epithelial cells or

? Epithelial cells with characteristics of smooth muscle cells?

A: The precursor myoepithelial cells throughout all the glands and locations has still to be confirmed[13]. With more certainty we can speak of the **mammary gland**; analysis of its ultrastructure demonstrate the presence of three types of epithelial cells; **luminal cells, myoepithelial cells and basal pale cells**, which may represent the precursor of myoepithelial cells[13]. Functionally, myoepithelial cells are a **hybrid** of both smooth muscle cells and epithelial cells[14]. Like smooth muscle cells, they express actin and myosin and exhibit contractile properties. Like epithelial cells, they express intermediate filaments (keratins) and have cadherin-mediated cell-cell junctions.

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"True or False?"

Q1) Typical locations of myoepithelial cells include:

Sweat glands

Mammary glands

[12] Adriance.M.,C., Inman, J.L., Petersen, and O.W., Bissell M. J. *Myoepithelial cells: good fences make good neighbors*. Breast Cancer Research, 2005. 7 (5).

[13] Sopel, M. *The myoepithelial cell: its role in normal mammary gland and breast cancer*. Folia Morphologica, 2010. 69 (1) p 1-14.

[14] Ross, Michael H. a Pawlina, Wojciech. Histology: a text and atlas: with correlated cell and molecular biology. 6.ed. Baltimor, MD USA: Lippincott Williams & Wilkins, a Wolters Kluwer business, 2011. ISBN: 978-0-7817-7200-6.

Salivary glands

Lacrimal glands

Iris of the eye

Q2) Myoepithelial cells are easily identifiable in a routine **H&E specimen.**

Q3) Myoepithelial cells in the alveoli and ducts of the mammary gland response well to **oxytocin**.

Q4) Myoepithelial cells play an important role, besides others, in correct **polarity** of epithelial surface.

At the center of your being you have the answer; you know who you are, and you know what you want.

Lao Tzu (604 – 531 BC)

A1) True. There are two basic myoepithelial cell types: ductal & acinar.

A2) True. However sometimes myoepithelial cell are hard to identify.

A3) True. Oxytocin is a more potent promoter of smooth muscle contraction than is ADH. [13]

A4) Importantly true, see below.

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Q: Can you name some of the myoepithelial cells connections and interactions?

A: **Hemidesmosomes** to the basement membrane. **Desmosomes** with both luminal cells and other myoepithelial cells. **Gap junctions** and **cadherin-cadherin** interactions with other myoepithelial cells.

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Myoepithelial cells in mammary glands are involved in the glandular morphogenesis and **tumor suppression**.

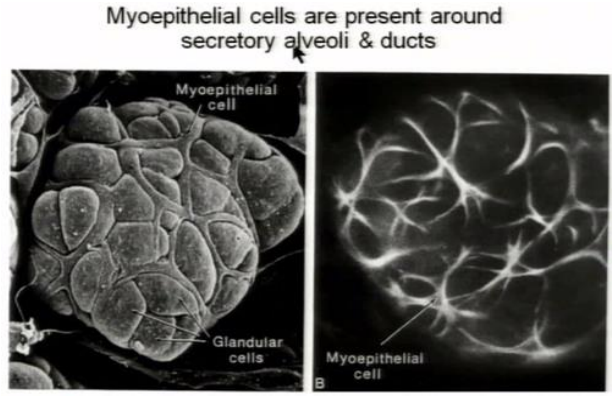

Figure 1. Source: http://quizlet.com/20863897/microanatomy-flash-cards

Progression of carcinoma "involves alteration of the entire organized structure of the breast..... loss of apicobasal polarity, collapse of the glandular structure, disappearance of normal myoepithelial cells and disruption of the basement membranes" [12]. Although the mechanism and details are still unknown, it's clear that myoepithelial cells in the breasts do more than just contractility, and that they are, along with the basement membrane they produce, more than just a "fence" between luminal cells and stroma of connective tissue. As a natural cancer suppressor secreting suppressor proteins limiting cancer growth, invasiveness and neoangiogenesis, myoepithelial cells make for an important target of further cancer research.

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Ebola

The recent deadly outbreak of Ebola disease in the West Africa is caused by a virus that was identified and named 38 years. In 1976 in a small village of Yambuku in Zaire, now Democratic Republic of Congo, several dozens of people got sick and were quickly dying of fever and loss of blood. The symptoms resembled hemorrhagic fever but tests ruled out viruses such as Lassa, Marburg and dengue as the cause, as well as a common infection, yellow fever. The mysterious disease was spreading rapidly.

Dr. Peter Piot always dreamed about exotic adventures and helping the poor, and he ignored a bit of advice from his professor at a med school: "There is no future in infectious diseases, they all have been solved".

In September 1976 Dr. Piot worked as a junior at a laboratory of the Institute of Tropical Medicine in Antwerp in Belgium when a special package arrived from Zaire.

Zaire is a former colony of Belgium once called Belgian Congo. In the days of fall 1976, the epidemic affected locals as well as a group of Flemish nuns at a mission in the area, all of them fully vaccinated.

Two of the nuns were transported from Yambuku to the capital Kinshasa which started the epidemic on a very large scale. Blood samples of the nuns were transferred to the lab of Dr. Piot and before long the samples were shipped to one of the few safe laboratories, to the CDC lab in Atlanta specialized in hemorrhagic fevers. However, before the sample transfer Dr. Piot´s boss, Dr. Steffano Pattyn and his team was able to exclude all then known viruses and take an electronogram of the virus unknown. It was a wormlike virus and huge (as huge as viruses go, 14 000 nanometers), about the size of the **Marburg virus** discovered in a German laboratory nine years earlier. CDC confirmed, using Marburg antibodies unavailable in Antwerp, that the virus was different from Marburg. It was truly a new virus.

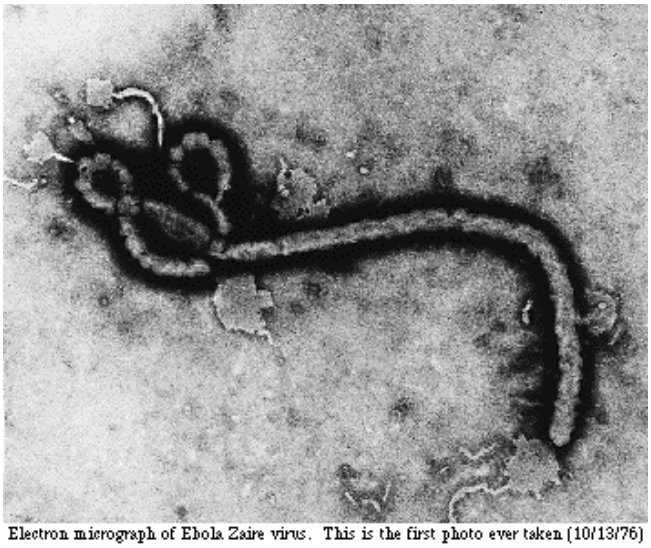

Figure 2: The first electronogram take at CDC October 13, 1976.
Source: http://www.microbiologybytes.com/virology/Filoviruses.html

An international team started to gather in the epicenter of the epidemic, in Yambuku. **Yambuku** was also the first suggestion for the name of the new virus. Dr. Piot in his 2012 memoire "No Time to Lose: A Life in Pursuit of Deadly Viruses" recalls that this proposal was opposed with an argument that it would stigmatize the village as had happened before, e.g. in the case of Lassa virus which emerged in the town of Lassa in Nigeria in 1969. Another suggestion came to name the virus after a river. The obvious option would have been the Congo River but another virus of a similar name already existed; Crimean-Congo hemorrhagic fever virus. So the scientists looked at a small map pinned of the wall in a room where they "were drinking their Kentucky bourbon" that late night and on the map the closest river to Yambuku was called Ebola, meaning "**Black River**" in the local language Lingala. "It seemed suitably ominous", Piot writes.

And so, Ebola joined the list of viruses named after a feature of their geographic origin; **West Nile virus**, **Marburg**, **Coxsackie** (a town in the New York state) or **Hendra** virus (a suburb of Brisbane, Australia). The latest virus of this tradition was discovered and officially named only during the last year; Middle East respiratory syndrome coronavirus – **MERS**-CoV. [15]

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Merry Holidays And Happy New Year 2015

The Internal Newsletter, Third Faculty of Medicine, Charles University in Prague.
Editorial Board:
MUDr. Klára Matoušková, MPH – editor
klara.matouskova@lf3.cuni.cz
MUDr. Lucie Hubičková-Heringová, Ph.D.
MUDr. Eva Maňáková, Ph.D.

Full text available at:
http://www.lf3.cuni.cz/en/departments/histologie/hep/

[15] Livescience. *How Ebola Got Its Name.* 10/09/2014 [online]. [Retrieved 11/27/2014]. Available from: http://www.livescience.com/48234-how-ebola-got-its-name.html