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What's up….

What is May (besides time for love) but the right time to finish the module "Cellular Basis of Medicine"! Yes, only one more course, course six "**Connective tissue; Blood and Immunity**" and your exams await to become the perfect example of the old adage "*Finis coronat opus"*!

In the previous five courses we studied three basic types of tissue; epithelial, muscle, and nervous. So at this point, you are expected to be completely knowledgeable about them, both in **theory and practice**. In other words, you should now be able to recognize any slide of the tissues listed above through microscope lenses and talk about nearly everything you see.

In the sixth course we will address the subject of connective tissue, including blood and lymphatic tissue plus the corresponding organs focusing primarily on the immunological topic. Our histology practices and lectures will teach you about cells and tissues involved in the body defense with an emphasis on **morphology,** as is typical in the histology science.

There is a lecture and practice about **cartilage & bone tissue** in the course six. Why is that, you may ask? Well, what about bone marrow? Is not that an organ of hematopoiesis? We will find out together in the coming course!

Last but not least, brush up what you have learned from a lecture and practice about "**Barriers & Phagocytosis**" several weeks ago as that has a lot to do with immunity, too.

Reminders….

- You will find several new slides in your exam slide boxes. Along with the 50-piece basic set, there is now an extra set of slides from reproductive organs, immune system, placenta & fetal membranes, and brand new slides of appendix and liver.
- Your "work book" is the very clue for the coming practical exam. Do not neglect the **electronographs** and their detailed description! Your ability to explain the images taken with an electron microscope is an essential part of your practical exam! Make sure you do not join the long line of students who have had to reappear due to underestimating the electronographs!
- There is a continuing opportunity for your individual microscope practices!

Mondays & Wednesdays,
3,15 – 4,45 pm, room no 318

- Individual consultations are possible. Please, get in touch with your tutor.

Do not miss this!

Students' Scientific Symposium will be held on **May 27, 2014**! If you cannot make it for the entire day, don't miss at least the opening lecture "Our inner time" by **prof. RNDr. Helena Illnerová, DrSc.**, an internationally acclaimed physiologist and biochemist. Prof. Illnerová was the first to recognize that melatonin of the pineal gland is produced under control of a biological clock in the

brain. Circadian rhythm is her life-long scientific interest and passion, and the fact that professor Illnerová gives a lecture at the 3rd Medical Faculty is our great honor and your unique opportunity to listen to a world class scientist!

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During the first week in June, as a closing part of the module "Cellular Basis of Medicine", two **integration conferences** will be held. We've chosen attractive lecturers and thought-provoking subjects (one for all, RNDr. Michal Dubovicky, Ph.D. about Neurobehavioral teratology), and hope you will be leaving the Module motivated for your further learning!

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Neurobehavioral Development & Developmental Neurotoxicity

It was time when fetal injuries were assumed to have a manifestation of structural birth defects. It applied to all body systems including the central nervous system hence neurological effects would not be taken notice unless the brain was visibly abnormal.

Today, neurodevelopmental disorders include brain damage as well as autism, attention-deficit hyperactivity disorder (ADHD), a spectrum of learning disabilities such as dyslexia or dyscalculia and other cognitive impairments.

As the research of developmental neurotoxicity have pushed ahead, and one of the reasons is that prevalence rates of autism spectrum disorders and ADHD seem to be increasing worldwide[1], scientist nowadays even talk about the "global, silent pandemic of neurodevelopmental disorders"[2]. It the USA, disorders of neurobehavioral development affect 10-15% of all births[3]!

The causes are only partly understood though. **Genetic factors** seem to account about 30-40% of all cases of neurodevelopmental disorders, typically a trisomy 21[2]. The majority of the culprits are therefore non-genetic and include;

- **Environmental toxins and chemicals**
- **Drugs,** both medicinal and recreational
- **Nutrition** such as deficiency of folic acid or iodine in maternal diet or postnatal nutrition, e.g. iron supplementation in baby formula[4]
- **Metabolic disorders** such as diabetes mellitus or phenylketonuria
- **Infections**, e.g. congenital toxoplasmosis, rubella or syphilis
- **Immune dysfunction**, e.g. an immune reaction against brain tissue following streptococcal infection in infants and toddlers such as PANDAS [5] or Sydenham's chorea
- Trauma and congenital **injuries** causing e.g. cerebral palsy
- **Deprivation** (sensory or maternal)
- Antenatal **stress** and **anxiety**

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There is a strong evidence that industrial chemicals widely disseminated in the environment are very important contributors to the number of neurobehavioral disorders[6]. You can guess the very reason; literary no person living on the Earth can escape them. And there is another factor; the number of recognized toxins harmful to the developing brain is growing in an astonishing pace[2]. Dr. Grandjean from University of Odense, Denmark and dr.Landrigan from the Harvard School of Public Health, Boston, MA, USA, in their study published in 2006 listed six known industrial chemicals toxic to the human developing brain (besides 201 industrial chemicals

neurotoxic to adult human individuals); **lead, arsenic, methylmercury, polychlorinated biphenyls, toluene and ethanol**. During the 7 years since 2006 the number of industrial chemicals recognized as toxic for human neurodevelopment has doubled. In other words, 12(!) new chemicals were identified and confirmed of causing developmental neurotoxicity since 2006.[2]

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Let's talk about several examples of industrial chemicals and their effects to make sure everyone is on the same page:

Mercury is a heavy metal that can be absorbed through skin or mucous membranes, inhaled or ingested. The most toxic forms are organic forms, such as methylmercury. Mercury can cause both, acute or chronic poisoning. The worst case scenario of poisoning is documented from the Minamata Bay, Japan. A chemical factory was, for decades (1932-1968), releasing methylmercury in the industrial wastewaters into the bay and the sea. The toxin accumulated heavily in shellfish and fish, and resulted in mercury poisoning of the population. Only in 2001 (!) over 2000 victims recognized, around 10 000 financially compensated. Symptoms were worse among children exposed in utero than in their mothers – mental retardation, cerebral palsy, blindness etc. Developmental toxicity occurs at much lower exposures than the concentrations that affect adult brain function, and the neurological deficits from low-level prenatal exposures are still detectable at the age of 14 years[2].

Lead exposure is illustrative because many studies

suggest that the effect of lead neurotoxicity are probably permanent and that no safe level of exposures to lead exists[7]. Lead exposure in early childhood is associated with reduced school performance and with delinquent behavior later in life [2].

Fetal alcohol syndrome; maternal consumption of alcohol even in very small quantities has been linked to growth impairment, facial dysmorphism, and neurobehavioral adverse effects in offspring such as reduced IQ, impaired executive functions and social judgment, seizures or ADHD. [7]

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The newly recognized developmental neurotoxins should draw our close attention as they include **manganese** (exposure in drinking water or airborne manganese concentration of children living near manganese mining causes impaired intellectual and motor functions[8]) and **fluoride** (in raised concentrations in drinking water), and mainly, a number of **pesticides**. There is a number of studies suggesting that acute pesticide poisoning in childhood might lead to lasting neurobehavioral deficits.[2]

"The presumption that new chemicals and technologies are safe until proven otherwise is a fundamental problem"

Grandjean & Landrigan[2]

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A fetus is not well protected against chemicals. The placenta does not block the passage of many environmental toxicants from the maternal to fetal circulation, additionally, many chemicals are transferred to the infant through breastmilk. For example, a recreational drug **methamphetamine** accumulates more in the fetus than in her mother[6].

Generally speaking, drugs are designed to have biological effects, no surprise that some drugs exposures are teratogenic. While vitamin A or, another retinoid, 13-cis-retinoic acid for acne treatment are known teratogens however to limited to a certain number of possible victims,

antiepileptic drugs are prescribed daily to about 1% of the US population (~ 3 million people)[6]. An antiepileptic drug valproate is a strong teratogen that causes neural tube defects and "**fetal valproate syndrome"** however needed vitally by many, pregnant, women.

Similar situation applies to **antidepressants** during pregnancy. The risk of major depression among women is highest during childbearing age with an estimated prevalence of up to 20% during pregnancy[9]. SSRIs (selective serotonin reuptake inhibitors) account for over 80% of antidepressant prescriptions in the USA and although all the SSRIs share similar mechanism of action, their chemical structure and pharmacokinetic properties vary, and each may affect the developing fetus differently[9]. Data on human teratogenity associated with maternal SSRI use during the first trimester of pregnancy are inconsistent[9] therefore the question still exists; do not treat depression and face possible adverse reproductive outcomes (premature delivery, low birth weight, intensive care admission) or do treat depression with possible teratogenic effect on the newborn?

For the CNS, the period of vulnerability starts during the first trimester and last through adolescence. And while the effects of various factors on the developing brain are usually not life-threatening, a proper neurobehavioral development is not less important than e.g. cardiac defects. It is our minds and mind setting what navigate us through the life!

Charles Vorhees [7]

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What do you remember...

…. cells of connective tissue

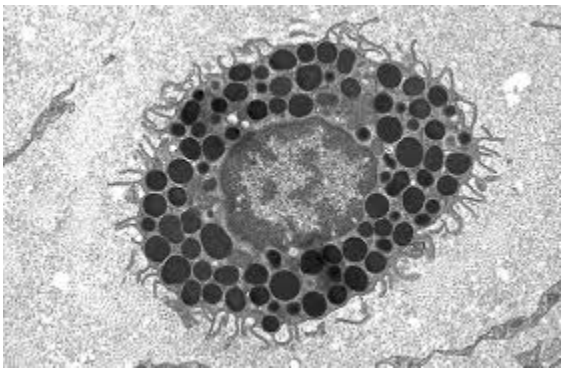
The principal cell of connective tissue is …. (1).

Macrophages of the connective tissue derive from their precursors called … (2).

Monocytes live in circulating blood for about … (3). Stained with HE, monocytes have basophilic cytoplasm containing azurophilic granules i.e. (4), and have (5) on the surface.

Despite of the presence of small, dense granules with lysosomal enzymes, monocytes are classified as agranulocytes [10].

Mast cells have their origin in … (6) and differenciate in … (7). Their major activity is to produce …. (8), store them and release at the time of mast cell activation. The mediators found in the mast cell granules include; …. (9).



Three Second Anagrams:

Connective tissue macrophage: **SITOCITEHY**

Cells that secrete all sort of fibers and ground substance in connective tissue: **BIBLOSFARTS**

The characteristic of a cell of taking on a color different from that of the dye with which it is stained: **ROTMASEHACIM**

A mediator, a biogenic amine, causing edema in a tissue and skin reaction such as itching and redness: **METASHINI**

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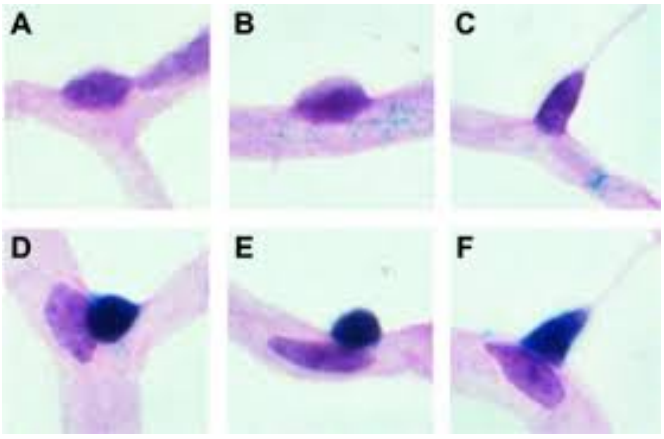
Pericytes are … (10) cells with their origin in embryonic or postnatal vasculogenesis or angiogenesis. The vascular pericytes are mesenchymal stem cells residing in sites called (11). Pericytes operate long …(12) over the surface of **endothelial cells**. Endothelial cells and pericytes are in a close touch via …. (13 a,b) and several of other functional connections. Function of pericytes reflect these interactions; … (14) and many others. The various functions further

indicate the pathology in which the pericytes are involved; hypertension, diabetic retinopathy, Alzeiheimer's disease, multiple sclerosis, pericyte-derived tumors and vasculopathies. [9]



Picture: Pericytes at branches (A,D), pericytes on straight capillaries with broad contact to endothelium (B, E), and migrating pericytes (C,F) [11]

Q: Name the **basic tissue types**. How many are they?

A/Q: Yes, there are four basic types of tissue; epithelium, connective tissue, muscles and nervous tissue. Where **blood** belongs to, anyway?

A: Blood is considered a type of connective tissue.

Q: Which leucocyte is the most abundant in a smear of peripheral blood?

A: Neutrophils are the most frequent, followed by lymphocytes, monocytes, eosinophils and basophils.

In other words;

Never **L**et **M**onkeys **E**at **B**ananas.

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Answers:

1. Fibro**blast**
2. Monocytes
3. One to three days, cca 12-100 hours
4. Lysosome
5. Microvilli
6. Bone marrow
7. Connective tissue
8. Mediators of inflammation
9. Histamine, heparine, proteases, chemotactic factors, leukotriene C, TNF α, certain interleukins and prostaglandins
10. Perivascular
11. Niche
12. Cytoplasmatic processes
13. a. gap juctions, b. tight juctions
14. vessel stabilization, regulation of vessel tone and maintenance of tissue homeostasis, proteosynthesis, immunological defense

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Eponyms

"Havers's and Volkmann's canals"

Contrary to the usual proximity of these name, Havers and Volkmann were no close buddies. Neither contemporaries, nor countrymen. In fact, besides their interest in medicine, they had very little in common. Despite of all above, every student of anatomy knows the two names well. But what do we know about the real people behind the names?

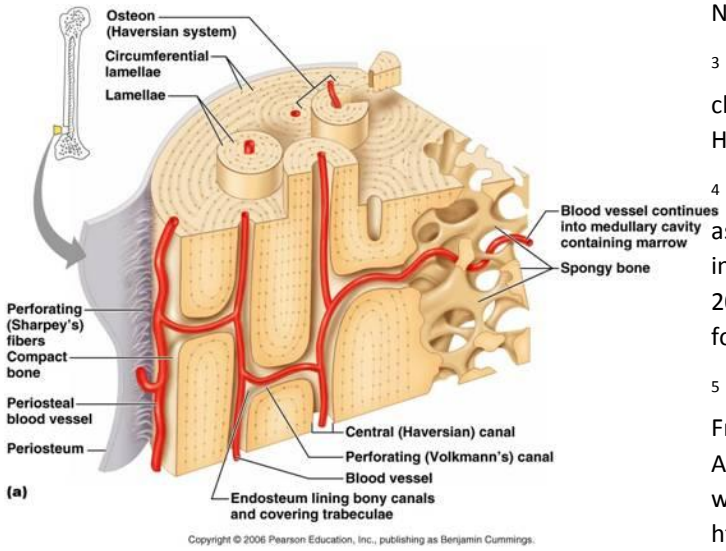
Clopton Havers (1657 – 1702)

The year 1657, the year when Clopton Havers was born, was just another year of the 17th century that introduced coffee to France and chocolate to London [12]. Very little is known about Havers' first

years and his education except for a few facts such as that he was born in the county of **Essex in England**, and after spending a couple of years at the University of Cambridge, he gained his MD title in **Utrecht, Netherlands**.

Havers, shortly after his graduation, became a „Licentiate of the Royal College of Physicians“ and was able to practice in London. He made a study of anatomy his special interest and delivered papers and lectures on the topic of osteology to his fellows in the College. Havers was a true pioneer in osteology and it was not accident that he named his most original work ***Osteologia nova***. In his publication he observed and described both longitudinal and transversal „Pores“ with the help of an „ordinary magnifying Glass“[13]. He believed that the canals contained „**medullary oil**“ althgough it *„doesn't detract from the merits or the originality of his observations at a time when the dissemination of scientific knowledge was of necessity restricted. Nor must we minimise the importance of his discovery of the penetrating periostal fibres afterwards known as Sharpey's fibres*“[13].

Havers remains a man who, *„while in the active practice of his profession, produced a work that breathed a new spirit of experiment and speculation into the study of osteology*“ [12].



Alfred Wilhelm Volkmann (1801-1877)

A.W. Volkmann was born 99 years after Havers's death, in the great town **Leipzig, state of Saxony, Germany**, never travelled far, worked and died in **Halle, Saxony-Anhalt, Germany**.

During his long life, Volkmann became a **professor of physiology and pathology** interested particularly in nervous and optic system.

And he was probably no old mossback considering that he became also a **professor of semiotics**, a very fresh science at that time.

Volkmann was evangelical and passionate about his religious opinion, spending much of his time lecturing against materialism and dualism, i.e. the mind-body problem. Well, it's a matter of preference. However, we hope that he took a weekend in his busy life and visited the beautiful nearby **Elbe Sandstone Mountains** in southern Saxony….[14] as you may, too in the coming summer!

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