Histology & Embryology Periodical

Department of Histology and Embryology
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Welcome!

We are happy to have you here, at our

Department of Histology & Embryology
of the Third Faculty of Medicine,
Charles University in Prague!

We are sure you are equally excited, all set to sink deep into the lectures, textbooks, microscopic images and new pieces of knowledge in surprising contexts. We hope to bring you a different view of the world, a view you might have never seen, a thrilling microscopic and nanoscopic perspectives that will prepare you for your further clinical adventures!

Who is Who

MUDr. Eva Maňáková, Ph.D.

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MUDr. Maňáková has years and years of experience at the Department. She completed her medical studies at our Faculty back when it was called Medical Faculty of Public Health (Lékařská fakulta hygienická, LFH UK). After the graduation she joined the team of doc. Václav Janout, CSc. at the Department of Histology, LFH UK. Her Ph.D. thesis regarded the development of pancreas in vivo and under certain experimental conditions. She soon specialized in methods of histology, both basic and advanced, and later broadened her knowledge with the fields of histochemistry and immunohistochemistry. Her area of expertise is experimental embryology and toxicology.

While practicing science, MUDr Maňáková has been educating medical students in the years preceding their clinical teachings, making sure they master the basics. The classes and credits on pathology would be difficult and real understanding of many clinical topic would be allusive otherwise. She authored a textbook called Methods in Histology. MUDr. Maňáková also contributed significantly to the translation of an excellent textbook "Histology" by a German professor Lüllmann-Rauch.

Since 2001 she has been in charge of the Czech Teratology Information Services (CZTIS) with its headquarters right at our Faculty. MUDr. Maňáková has published many articles in both, Czech and foreign scientific journals, and has been invaluable resource to our students. Ignore her advice at your peril!

Lucie Hubičková-Heringová

MUDr. Lucie Hubičková – Heringová, Ph.D.

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I´m also a graduate from the LFH UK moved with the same institution and I stayed for my postgraduate program. My mentor for postgrad was Professor Richard Jelínek who also served as the head of the Department of Histology and Embryology at that time. I worked with Prof. Jelínek and for the Department ever since. Teratology and developmental toxicology was Professor's Jelínek continuing theme. Our current research honors his legacy and goes on with the theme, using the chicken embryos as a model organism. Since 2001 I've been working for the office of CZTIS. If you need to talk to me, send me an email or look for me in my office, room no. **326**, or in the lab, 5th floor room no. **520.**

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University lecturers in theoretical subjects such as histology, physiology or biochemistry are not professional teachers and their greatest interest lies in science. Your educators are no exception! Besides passing our knowledge and experience on to you we are involved in our scientific projects, publications and grants regarding embryology and teratology!

Therefore, we want to welcome and thank the senior student volunteers on our team! There are thirteen of them and the majority of them have returned to serve their second year! They will be present for practicals and the individual sessions, always ready to help to get orientated throughout slides and discuss any histology or embryology issue with you.

*

Karen Vávrová

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Karen is an accomplished and experienced laboratory technician and you can trust me, there are not many like her around anymore! Each and every slide we use during our histology practicals is made on the spot, to be precise, it's Karen who makes them! She knows all too well how much work it is to make a single slide, how many steps and hours it takes, therefore don't get upset with her if she insists on being gentle with them! Keep the slides, as well as your working place, clean and orderly. There are certain, not that many, rules regarding handling slides for light microscopy during our practicals, please honor them! Karen will be happy to assist any of you in case you need her assistance. You will find her in room no. **322**, right next to our classroom.

Lucie Hubičková-Heringová

MUDr. Ondřej Balík

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Assistant

I joined the Department because I'm excited about teaching! Although I may switch to a clinical field of practice one day for now I'm excited to be here, on the academic ground. I love music, I like to read and think things over, I have a dog and in my short life I've probably tried all the sports you can imagine. You will find me in room no. **311** during the hours of my consultations. Besides the given hours I would be happy to share my time with you as much as my other duties will allow me to. My ideal in teaching is to search for the true meaning of the given information and to evoke your critical thinking. And by the way, I'm not a fan of exaggerated self-opinion and sloppy generalizations!

Michal Skála

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The Secretariat of the Department of H&E, 3rd Medical Faculty, Charles University in Prague

I'm 32 years old. Curiosity and interest in different jobs and environments have brought me to the Department of Histology and Embryology at the Third Faculty of Medicine. My intention is to do my best to help you, our students, to reduce the paperwork and administrative burden. When not at the Faculty, I make my living as a freelance translator. I'm a computer geek and the best way to reach me is to shoot me an email. Also, you will find me in the secretariat during the office hours posted on the door. I like philosophy, peanuts in chocolate and I collect "Random Acts of Kindness stories." - make sure to send at least one to me! They can take any form; a video, text or a picture… I would be happy to try to help you with just about anything only, please, give me a sufficient notice! Good luck with your studies!

MUDr. Klára Matoušková, MPH

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I've associated with the Department of Histology and Embryology since 2003, my 5th semester at the Faculty. Professor Richard Jelínek, the head of the Department at that time, made me so excited about embryology and teratology (not saying his sacred influence made me an A student) that I passed a course he tutored and ever since stayed in touch - with him, with the field of reference, and our Department. I'm an editor of this Periodical, it was in fact my crazy idea one day during my morning yoga practice. Please, contact me with any thoughts, opinions or even contributions. I always thought I would give it the first kick and then someone else would do the work – not there yet. During your two semesters we don't meet in person. I live in Denver, CO

with my American husband and our two little Czech-American boys. As for America, Colorado is the perfect place to be for someone who loves rock climbing and mountains *per se*, as much as I do. There is no escape once you get the feel for "the Colorado Rocky Mountain High…"

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What´s up?

So here you are, in your first days of the first semester at University. All ready to study hard all day long, keen eyes and restless minds. It is a long journey from this day to the moment when you put on your white coat and sign with "Dr." in front of your name for the first time. And the journey's first obstacle lie right ahead of you. It is called Cellular Basis of Medicine!

In the month of October we enter the module called **Cellular Basis of Medicine**. The first course of the module will teach you all about the **cell structure**. From the perspective of histology you will learn about the methods of preparing a slide for light or electron microscopy in a way that's meaningful for learning about the particles or organelles you wish to learn about. Also, you will have the pleasure to meet every type of cells found in human body – and more, and we shall look in detail at the numerous electron micrographs and recognize the many cell organelles within a certain cell type. Later in the course we you will have get accustomed to all the types of epithelial tissues.

The module, as was mentioned before, is your first obstacle on your way to become medical doctors. **Do not underestimate** what may appear to some of you to be unnecessary theoretical teaching having little to do with clinical medicine. We believe that the main article in this Periodical about cilia will offer a better understanding that everything in the human body must be considered in coexistence, and what seem as a simple structure may actually be rather important and cause a lot of trouble when things go wrong there….

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Reminders

Let's to say it again; there is no better time to begin to study hard than right now! We will encourage you to do so during the practicals. Be aware of the fact that your knowledge will be evaluated as you go along. The results of the **short tests** will be taken into account for your credit examination at the end of each semester.

In your schedules, please register the time appointed as **individual learning**. During the hours given, the room no. 318 will be open and you can ask to borrow a set of slides. In your own time you can study the images, compare them, discuss either with a friend or a person – usually a senior student - present in the room and ready to assist and consult with you. Please, make sure you start taking advantage of the individual learning early enough. Later in the semester, the room gets crowded and often, there is less microscopes than students eager to study for their coming examinations. We cannot offer more chairs and microscopes so we strongly suggest you do not get behind!

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Cilia & Pancreas

What do you think is the purpose of cilia in pancreas? How do cilia influence the function of pancreas? What if something goes wrong with cilia; does it have anything to do with getting diseased with diabetes mellitus type II or even neurological diseases? A team

from the University of Massachusetts asked the same questions in their review article published in the Birth Defect Research in June 2014[1].

Introduction

In your lectures and practicals on epithelium you will learn that a cilium is an apical surface modification of cells. Cilia, in fact were described on the surface of nearly every eukaryotic cell. Hence cilia are common, evolutionarily conserved, antenna-like organelles. The function of cilia depends on their structure and the skills. Cilia consists of a set of microtubule duplets, either with or without the central duplet. Further, cilia either contain protein motors then capable of active movement or they do not.

Motile cilia

The cilia people know most about are the **motile cilia**. The function of motile cilia includes transporting secretions, proteins, foreign bodies or cells on their surface[2]. Motile cilia possess a typical 9x2+2 axonemal organization, motor proteins and are commonly found in the respiratory epithelium, ependymal tissue or ductus deference and uterine tube (let´s remember an interesting fact: cilia beat in a synchronous pattern - no random movements for cilia! They achieve an oriented and rhythmical motion of a frequency about 10-20 Hz[3]).

Primary ciliary dyskinesia (PCD) is a genetic disorder of motile – not primary – cilia. It is a rare disease, PCD has an estimated incidence of 1/15,000-1/30,000 live births, but this is probably an underestimate. Prevalence is difficult to determine.[4] The main consequence of impaired ciliary function in PCD is a reduced or absent mucus clearance from the lungs and therefore respiratory distress syndrome from early in childhood. Other common symptoms include: everyday cough, persistent runny nose and susceptibility to chronic recurrent respiratory infections resulting in bronchiectasis in early childhood, sinusitis, infections of the inner ears (otitis media), and later in age also infertility or subfertility due to absence of cilia or their improper function in the oviduct or ductus deference. About 50% of the patients can be diagnosed as early as in utero because they develop *situs inversus*. The combination of *situs inversus*, bronchiectasis and chronic sinusitis is called the **Kartagener syndrome.**

Primary cilia

Primary cilia are different from the motile cilia. Primary cilia are ubiquitous (the only cells that do not express cilia on their surfaces are hepatocytes, pancreatic acinar cells and differentiated cells of myeloid or lymphoid origin[1.]), they are capable of passive movement only and their axonema lacks the central pair of microtubules (the patterns is 9x2+0).

Primary cilia in pancreas are not present on acinar cells although they appear in large numbers in the ductal cells and endocrine cells of the Langerhans islets.

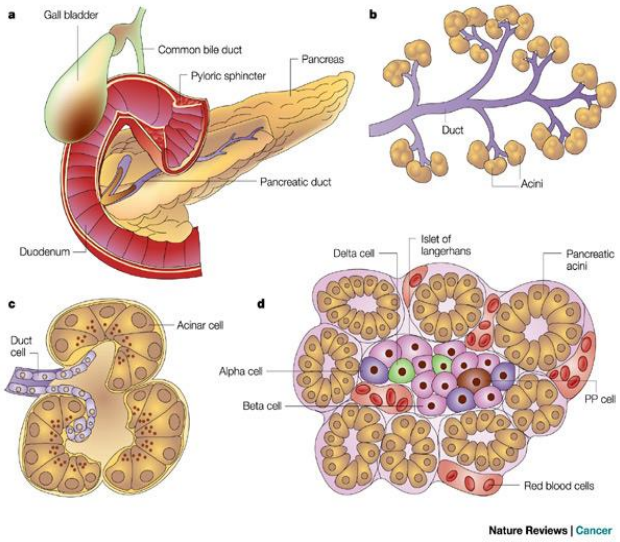

Figure 1. The pancreas is comprised of separate functional units that regulate two major physiological processes: digestion and glucose metabolism. The exocrine pancreas consists of acinar and duct cells. The acinar cells produce digestive enzymes and constitute the bulk of the pancreatic tissue. The duct then empty into the duodenum. The endocrine pancreas, consisting of four specialized cell types that are organized into compact islets embedded within acinar tissue, secretes hormones into the bloodstream. The α- and β-cells regulate the usage of glucose through the production of glucagon and insulin, respectively. Pancreatic polypeptide and somatostatin that are produced in the PP and δ-cells modulate the secretory properties of the other pancreatic cell types. **a** | Gross anatomy of the pancreas. **b** | The exocrine pancreas. **c** | A single acinus. **d** | A pancreatic islet embedded in exocrine tissue.[5]

Organogenesis of pancreas

*Early in the development, in the time of organogenesis, pancreas develops from two buds – **pancreatic buds** – of the **foregut**, the parenchyma of the pancreas is*

*therefore derived from the **endoderm**. Pancreatic acini begin to develop from cell clusters around the ends of the network of tubules from the pancreatic buds, and the pancreatic islets develop from groups of cells that separate from the tubules and come to lie between the acini*[6].

Cilia in Organization of Pancreas

In 2000, the team of professor Pazour from the University of Massachusetts published a seminal work describing the essential role of **intraflagellar transport** (IFT) in formation and maintenance of primary cilia[7]. The work was done on the algae *Chlamydomonas* however the particles transported via IFT in the algae are no different from those in nematode or vertebrates. Further, the team of prof. Pazour found out that the gene IFT88 at algae is identical with the human and mice gene Tg737, and discovered that mice with defect genes Tg737 die early after birth due to polycystic kidney disease. However, further works came up with results that mutant Tg737 have an impact even on the **organization of pancreatic tissue**. Mutation in IFN88/Polaris causes the cilia in pancreas to go absent or stunted. Under such circumstance, the mutant mice at the end of gestation show significantly reduced mass of acinar tissue (yes, paradoxically, it is the acinar tissue that lacks cilia), abundant connective tissue (fibrosis), cyst formation, and aberrant duct cell morphology.[1.] The loss of cilia after the critical period of formation of the pancreatic tissue (organogenesis) does not change the phenotype of the tissue. Making such a discovery in 2006 the team lead by Dr. Cano brings even more support for the hypothesis about the essential role of primary cilia in organogenesis.[8]

Cilia orientation & function of pancreas

There is another issue in formation of cilia and that is their orientation, and that seem to be the role of protein Lkb1. During the first eight weeks in development Lkb1 is present in both, acinar cells and the cells of future Langerhans islets. Defected Lkb1 causes an impaired polarity of the target cells. Hypothetically, defective orientation of cilia could result in overall dilution of sensed insulin by interconnected beta cells. This may promote conditions for insulin hypersecretion.[1]

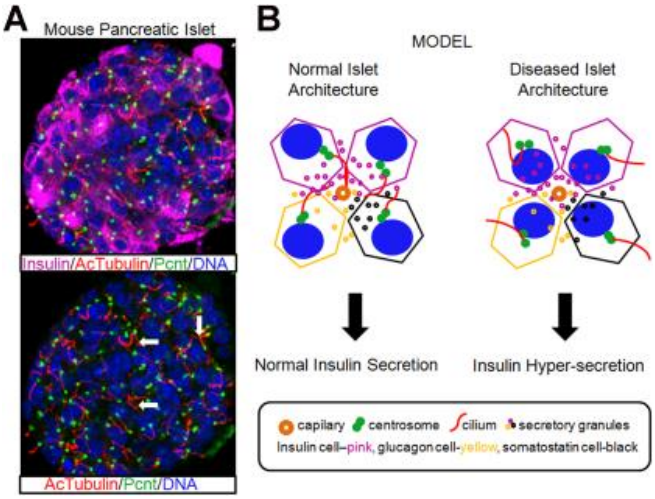

Figure 2. Primary cilia in mouse pancreatic islets. (**A**) Immunofluorescence images of primary cilia in mouse pancreatic islets show overlay with insulin (top), and long cilia (Acetylated Tubulin stained) positioned in the interstitial space between islet cells (bottom, white arrows). Centrosomes are stained with pericentrin. (**B**) Schematic illustration showing cilia on islet cells: insulin expressing β-cells, glucagon expressing α-cells, and somatostatin expressing δ-cells, nuclei in blue. In the normal state (left), the cilia face the interstitial space between islet cells where granule secretion of endocrine hormones first occurs, followed by diffusion into the capillaries. In the diseased state (right), the cilia are mispositioned away from the interstitial space and the nuclei (blue) are clustered toward the capillaries. Without the proper signaling crosstalk that is mediated by receptors on the cilia, insulin secretion is dysregulated.[1]

Primary cilia in cellular responses

Primary cilia play roles as modulators of signal transduction to shape cellular responses to environmental cues to maintain proper tissue development and homeostasis in adulthood.[1] In pancreas primary cilia are considered as **hubs for signaling pathways**. E.g. the hedgehog signaling is crucial for transfer of information to embryonic cells and depends on functioning primary cilia, as Noch and Wnt signaling do.

Cilia as receptors

Somatostatin is a hormone produced in pancreas and it regulates endocrine and cerebral function. The secretion of somatostatin depends on primary cilia because they carry a somatostatin receptor 3 (SSTR3) on their surface. There is an unbalanced secretion of somatostatin in type I diabetes and increased number of somatostatin producing cells in type II diabetes. That

points to the importance of somatostatin and its' receptors for normal glucose homeostasis. [1]

Primary cilia in human disease

In humans, dysfunctional primary cilia cause disease classified as "ciliopathies". The review written at the University of Massachusetts includes a comprehensive table of association between neurologic disorders, cilium phenotype and manifestation of human type II diabetes however the ciliopathies that exhibit the highest risk of diabetes include two syndromes:

Alström syndrome is a rare disorder with a defect gene ALMS1 characterized by impaired vision in infancy, deafness, obesity, progressive kidney failure and type II diabetes in 70% of patients before they reach 20. Patients with a wrong gene ALMS1 have reduced number and stunted cilia.

Bardet-Biedl syndrome is also a ciliopathic genetic disorder that affects many body systems. It is characterized by obesity polydactyly, retinitis pigmentosa (degeneration of the retina – rods and cones are interconnected via primary cilia), mental retardation and renal failure in some cases, and manifestation of type II diabetes in about 50% of patients. Cilia in Bardet-Biedl syndrome have reduced markers ACIII, Gg13 and SLP3. [1]

There is much more to discover with the future research however, the fact is that we cannot consider primary cilium an „evolutionary vestige" any more. Primary cilia are very active organelles and their structure and function matter from conception to the very last breathe.

*

Birth Defect Research Journal is available at the Secretariat of the Department of Histology and Embryology. Please, ask Michal Skala for a photocopy if you wish to read the entire article *Role of Cilia in Normal Pancreas Function and in Diseased States*.

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We are aware that the review above is still probably beyond your current knowledge and ability to fully comprehend. However, there are reasons to present the article anyway: 1. It makes you realize that histology is not a theoretical subject per se, quite the opposite. The knowledge gained during the module Cellular Basis of Medicine not only builds foundation for your further years at the Faculty but also, for your everyday life as a medical professional. 2. It reinforces that human health is very complex. Although we will teach you about individual organs and disorders, never forget that a patient is a large mosaic of conditions and aspects that you, as a doctor, must unveil and try to understand. 3. keep the text in mind and open it again later, after several lectures on biology, biochemistry, genetics, histology…you will be surprised, and maybe proud of yourself, how much more you get now!

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Maybe you know… maybe you don't

Situs viscerum inversus is a congenital condition in which the major visceral organs are reversed from their normal position. For the cause search the nodal cilia. The nodal cilia in development move to create flow, which moves extracellular fluid containing soluble signaling factors from the right to the left. When nodal cilia were disrupted, general loss of left-right asymmetry occurred.[9]

Bronchiectasis refers to a permanent, irreversible dilatation affecting small and medium size bronchi.

Intraflagellar transport (IFT) is a rapid movement of multi-subunit protein particles along flagellar microtubules and is required for assembly and maintenance of eukaryotic flagella. [7]

Ependymal cells are cells that form epithelial-like lining of the ventricles of the brain and spinal cord. Unlike typical epithelium they lack an external lamina. The apical surface of the cell possesses **cilia** and **microvilli** – the latter are involved in absorbing cerebrospinal fluid.[2]

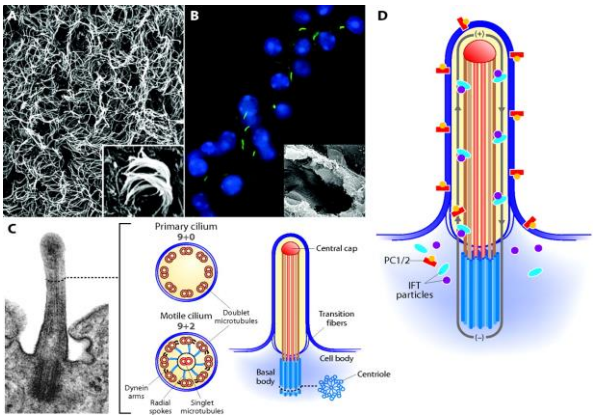

Figure 4 A) Scanning electron micrograph of motile cilia located on the ependymal cells that line the brain ventricles. Insert shows higher magnification of motile cilia. (B) Immunofluorescence micrograph of primary cilia (green) located on isolated renal tubule. Nuclei are shown in blue. Insert is a scanning electron micrograph looking into a renal tubule. (C) Architecture of cilia (primary and motile) and the basal body. (D) Intraflagellar flagella (ciliary) transport along the axoneme. Anterograde movement of the intraflagellar transport (IFT) particle is mediated by a kinesin complex, whereas retrograde transport is mediated by a cytoplasmic dynein. [10]

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Repetitio mater studiorum…

… cilia

Q: So what is the definition of a cilium? And how does cilia differ from microvilli?

A: Both, cilia and microvilli (and stereocilia) are common apical modification in eukaryotic cells. Cilia are hair like extensions of the apical plasma membrane containing axoneme. Describing cilia, don´t forget the protein motors in the motile cilia. There are no motors or microtubules in microvilli, only a bunch of actin filament anchored again in a network of actin filaments near the apical surface of the cell.

Q: So what is an **axoneme**?

A: Axoneme is the microtubule-based internal structure of cilia. The structure is anchored in the basal body (see Figure 4)

Q: Now you know enough to summarize all four types of cilia…

A

1. Motile cilia, 9x2+2 pattern of microtubules
2. Primary cilia, 9x2+0 pattern of microtubules
3. Non-motile with 9x2+2 pattern e.g. hair cells in the inner ear
4. Nodal cilia (motile, 9x2+0 pattern of microtubules, essential in developing left-right asymmetry of internal organs)

Q: Primary cilia were discovered in

a. 1898

b. 1926

c. 1969

A: a. is correct. Primary, non-motile, cilia were first discovered in 1898 however, for nearly one hundred years scientists ignored them. *Although ubiquitous, the primary cilium was considered – with a few exceptions – to be largely useless evolutionary vestige, destined to go the way of the tailbone and the wisdom tooth.*[11] How wrong that view was you can read above…

Q: What type of cilia is the longest? What is the longest cilia in human body?

A: The longest type of cilia are the motile cilia typically from 5-10μm of length. Flagella in sperm cells are in fact long motile cilia, however their length is exceptional; 50-100μm.

Q: What type of cilia is disrupted in the disease called primary ciliary dyskinesis?

A: If you don't know the answer, search for it in the article above…

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Websites worth checking…

What makes you laugh and then think?

Have you ever pondered the physics of slipping on a banana peel? Have you ever seen Jesus on a piece of toast? Ever wondered if defecating dogs are sensitive to changes in the Earth´s magnetic field? The Ig Nobel Prize 2014 recipients give answers to these question and many more that seem laughable first but there is a serious research behind. If interested, check the website **http://www.improbable.com/ig/winners/** Btw, the 2014 recipients include two Czech research teams!

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Eponyms

Camillo Golgi (1843-1926)

Camillo Golgi is a well-remembered man. He gave his name to **Golgi apparatus** inside the eukaryotic cells, **Golgi tendon organ** and **Golgi tendon reflex**. There are two types or Golgi cells in the cerebellum; **Golgi I** with a long axon and **Golgi II** bearing a short or no axon. And there is Golgi reaction, or "reazione nera" as he called it, a histological method to contrast cells of the nerve tissue with fixing silver chromate particles to the neurilemma (the membrane of neurons). As a result the nerve cells as whole will stand out against a yellow background. Last but not least, the fellow citizens of Camillo Golgi renamed their Alpine town of Corteno in Lombardy after the eminent native making **it Corteno Golgi.**

Camillo Golgi' father was a physician and district medical officer. Young Golgi, too, studied at a Faculty of Medicine to become a medical doctor. He chose the University of Pavia. Interestingly, the University of Pavia, a prime educational center in the northern Italy, was founded by **Charles IV,** the Holy Roman Emperor and the King of Bohemia, in **1361**. It was thirteen years after he brought into existence the University in his beloved Prague, Charles University.

Later in his life, Golgi studied the life cycle of *Plasmodium*, a genus of parasitic protozoa whom four species cause malaria. Several years later, it was a pupil of Golgi, **Adelchi Negri** (yes, Negri bodies in the Purkinje cells of the cerebellum!) who lead the malaria eradication efforts in Lombardy.

Camillo Golgi, together with **Santiago Ramón y Cajal**, received the Nobel Prize in Physiology or Medicine in 1906 for his studies of the structure of the nervous system.

Born into the turmoil of the second half of the 19th century in the Austrian Empire, Camillo Golgi died as a greatly renowned Italian, in Pavia in 1926.

Figure 5 and the text inspired by[12]

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