

## HISTORICAL PERSPECTIVES

# Reminiscing about Jan Evangelista Purkinje: a pioneer of modern experimental physiology

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Submitted 16 May 2017; accepted in final form 5 September 2017

**Cavero I, Guillon JM, Holzgrefe HH.** Reminiscing about Jan Evangelista Purkinje: a pioneer of modern experimental physiology. *Adv Physiol Educ* 41: 528–538, 2017; doi:10.1152/advan.00068.2017.—This article reminisces about the life and key scientific achievements of Jan Evangelista Purkinje (1787–1869), a versatile 19th century Czech pioneer of modern experimental physiology. In 1804, after completing senior high school, Purkinje joined the Piarist monk order, but, after a 3-yr novitiate, he gave up the religious calling “to deal more freely with science.” In 1818, he earned a Medical Doctor degree from Prague University by defending a dissertation on intraocular phenomena observed in oneself. In 1823, Purkinje became a Physiology and Pathology professor at the Prussian Medical University in Breslau, where he innovated the traditional teaching methods of physiology. Purkinje’s contributions to physiology were manifold: accurate descriptions of various visual phenomena (e.g., Purkinje-Sanson images, Purkinje phenomenon), discovery of the terminal network of the cardiac conduction system (Purkinje fibers), identification of cerebellar neuronal bodies (Purkinje cells), formulation of the vertigo law (Purkinje’s law), discovery of criteria to classify human fingerprints, etc. In 1850, Purkinje accepted and held until his death the Physiology chair at Prague Medical Faculty. During this period, he succeeded in introducing the Czech idiom (in addition to long-established German and Latin) as a Medical Faculty teaching language. Additionally, as a zealous Czech patriot, he actively contributed to the naissance and consolidation of a national Czech identity conscience. Purkinje was a trend-setting scientist who, throughout his career, worked to pave the way for the renovation of physiology from a speculative discipline, ancilla of anatomy, into a factual, autonomous science committed to the discovery of mechanisms governing in-life functions.

Purkinje biography; Purkinje phenomenon; Purkinje-Sanson images; cardiac Purkinje fibers; Purkinje cerebellar cells

THIS REVIEW HONORS the memory of Jan (Johann or Johannes) Evangelista Purkinje (or Purkynje: spelling according to German pronunciation of the Czech Purkyně), an extraordinary 19th century scientist who contributed significantly to elevate physiology to a modern, independent biological science, exploring and characterizing the functions that differentiate living organisms from the inanimate world. Purkinje performed research in many interrelated biological disciplines, such as anatomy, pharmacology, embryology, and histology. His discoveries concerning the structure and function of the eye, touch, brain, heart, and reproduction system were seminal in paving the road of these cognate sciences into modernity. Purkinje also made significant contributions to humanistic

disciplines, such as language and literature. His active engagement as a Czech patriot contributed substantially to the development and establishment of a strong national Czech conscience, which ultimately led to the independence of the Czech nation at the end of the First World War (19, 26).

The name of Purkinje shines in biological and medical dictionaries, encyclopedias, and scientific accounts, as attested by his eponym, which has been assigned to many of his discoveries [Purkinje cells in the cerebellum, Purkinje cardiac fibers, Purkinje bone corpuscles, Purkinje granular layers (branched spaces in tooth enamel), Purkinje-Sanson images in the pupil, Purkinje tree (shadows of retinal vessels), Purkinje phenomenon, and the Purkinje axis-cylinder in nerve fibers] (61). This remarkable scientific recognition by the biological research community bears witness to the lasting value of Purkinje’s ground-breaking contributions to the biological sciences.

A chronological summary of Purkinje’s key life events is presented in Table 1.

### Biographical Highlights

The publications entitled *Jan Evangelista Purkyně, Czech Scientist and Patriot, 1797–1869* (24) and *Jan Evangelista Purkyně* (30) provided the material for this section.

Jan Evangelista Purkinje was born on December 18, 1787, to a peasant family in Libochovice, a small village in northern Bohemia, then a territory of the Austro-Hungarian Empire and now part of the Czech Republic. His father Joseph (manager of the Count Gundaker Dietrichstein estates) passed away when Jan was 6 yr old, leaving the family (2 male children and his wife) in a precarious economic condition.

Jan received a 4-yr primary education in the public school of his native village. At 10 yr of age, he was selected for the boys’ choir of the Piarist monastery of Mikulov (South Moravia), where he successfully completed 3 yr of grammar school (1798–1800), followed by 4 yr of senior high school (gymnasium). At that time, instruction in Austrian Catholic Piarist Brother schools (4, 27) was delivered in German and Latin. When Purkinje entered the Mikulov Piarist school, he spoke only Czech, but he had also a good knowledge of Latin, taught to him by his village parson.

In 1804, at the end of the gymnasium schooling, Purkinje joined the Piarist monk order, since joining a religious organization was then the only avenue for poor people to acquire advanced education. He started his novitiate (3-yr probation period) at the Stará Voda monastery (Moravia), where he was clothed with the uniform of the order and given the Piarist

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Table 1. *Chronology of key events in the personal and professional life of Purkinje (30)*

Date	Key Events
Dec. 17 or 18, 1787	Birth in Libochovice (Bohemia, Empire Austro-Hungarian, now in Czech Republic) from Joseph Purkinje and Rosalia Šafráková.
1793–1796	Primary school in Libochovice.
1798–1804	Choir boy at the Piarist Monastery in Mikulov (South Moravia), where Purkinje attended junior (3 yr) and senior (4 yr) high school.
1804	Entry as novice of the Piarist order at the Stará Voda monastery (Moravia), where Purkinje obtained the title of Professor in <i>Humanibus Litteris</i> .
1805	Professor of grammar at the gymnasium of the Strážnice Piarist College (Moravia).
1806	Student at the Piarist Philosophical Institute in Litomyšl (Eastern Bohemia), where Purkinje obtained the certificate for admission at University.
August 1807	Renouncing to become a monk of the Piarist order.
1807 (fall)–1809	Attended the Philosophical Institute of the Universitas Carolo-Ferdinandea in Prague, where he primarily attended physical science courses.
1809–1812	Worked as private tutor of Baron Hildprandt's son for financial need.
Nov. 1812	Initiation of Medical Doctor studies at Medical Faculty of the University of Prague.
Nov.–Dec. 1818	Defense of Medical Doctor dissertation, <i>Contributions to the Knowledge of Vision from the Subjective Point of View</i> , and graduation as a Medical Doctor.
1819–1822	Instructor in anatomy at Prague Medical Faculty.
1823–1850	Professor of Physiology and Pathology at the Medical Faculty of the Royal Prussian University of Breslau.
Dec. 1823	Defense of dissertation, <i>Commentary on the Physiological Examination of the Visual Organs and the Cutaneous System</i> , for teaching habilitation at Breslau University.
1827–1845	Elected four times Dean of Medical Faculty at the University of Breslau.
1827	Marriage with Julia Agnes (1800–1835), daughter of Karl Asmund Rudolphi, Professor of Physiology at Berlin University.
1829–1834	Birth of daughters Rosalia and Johanna (died of cholera in 1832) and sons Emanuel, future Professor of Botany, and Karel, a future distinguished Czech painter who died suddenly in 1868.
1835	Death of wife (typhoid infection).
1850–1869	Professor of Physiology at the Medical School of the University of Prague.
1853	Cofounder of the Czech science periodical <i>Živa (Alive)</i> .
1861	Cofounder of the Society of Czech Physicians and its Medical Journal ( <i>Časopis Lékařů Českých</i> ).
1861–1866	Elected deputy member of the Bohemian Provincial Diet.
1868	Honored with the Imperial Austrian Order of Leopold, conferred for merit and moral integrity.
July 28, 1869	Death after protracted illness.
July 31, 1869	Buried with honor at Prague Vyšehrad National Cemetery for distinguished Czech citizens.

Brother name of Silverius. In this monastery, his studies led to his receiving the title of Professor in *Humanibus Litteris* (philosophy, history, and literature). During the school year starting in 1805, Professor Silverius Purkinje taught grammar to a second-year gymnasium class of 17 pupils in the Strážnice (Moravia) Piarist College.

Clericus Silverius spent the last year of his novitiate (1806–1807) in the Piarist Philosophical Institute in Litomyšl (Eastern Bohemia) at the end of which he had to decide whether or not to take the four life-engaging vows of the Piarist order (poverty, chastity, obedience, and dedication to education of poor children). During this period, Purkinje successfully passed the examinations for admission to the Czech University faculties of theology, law, and medicine. Additionally, he had time to also familiarize himself with the Romantic movement pervading the European culture of his time. In particular, he nourished his soul with the poetry of contemporary German poets Novalis (Georg Friedrich Philipp Freiherr von Hardenberg 1772–1801), Friedrich Schiller (1759–1805), and Johann Wolfgang (von) Goethe (1749–1832), as well as with the philosophical writings of Friedrich Wilhelm Joseph (von) Schelling (1775–1854) and Johann Gottlieb Fichte (1762–1814). He was fascinated by Fichte's *Über die Bestimmung des Menschen zur Unbeschränkten Seelischen Freiheit (The Call of Men to an Unlimited Mental Freedom)* (14). In lecture IV of this work, Fichte outlines the human mission of each individual man, the society, and the scholar within the society: "The ultimate purpose of each individual man, as well as of all society, and consequently of all the labors of the Scholar in society, is the moral elevation of all men" (13). Throughout his career,

Purkinje conformed his life to the humanistic vision of the 19th century Romantic philosophy (Naturphilosophie) movement.

At the end of his novitiate in August 1807, upon duly obtaining a release from his superiors, Purkinje left the Piarist order, and, in the fall of this same year, he enrolled as a student at the Philosophical Institute of The Universitas Carolo-Ferdinandea in Prague, where he predominantly attended physics courses. However, due to financial difficulties, he interrupted these studies in 1809 to become the private tutor of Baron Hildprandt's son, a position that he kept for 3 yr. In November 1813, with the generous financial support of Baron Hildprandt, Purkinje registered as a Medical Doctor (M.D.) student at the Medical Faculty of the Universitas Carolo-Ferdinandea in Prague. During the 5-yr study course, he received an *emintenter* (excellent) grade in all of his examinations. This allowed him to garner free tuition and housing (24).

On November 30, 1818, at 32 yr of age, Purkinje defended his Doctor of Medicine (MD) dissertation, entitled *Beiträge zur Kenntnis des Sehens in Subjektiver Hinsicht (Contributions to the Knowledge of Vision from the Subjective Point of View)* (42), and, on December 9, 1818, the MD degree was bestowed upon him (30). His thesis was printed 1 yr after the defense at the expense of Baron Hildprandt, to whom it is dedicated (24, 42). The fundamental question Purkinje answered in his experimental work was that the subjective phenomena observed within one's own eyes (scientifically called entoptic phenomena) were the manifestations of inborn physiological mechanisms responsible for peripheral visual functions.

In the formulation of a color theory, the German poet (who was also a scientist) Goethe (1749–1832) proposed that the

colors of objects were mental elaborations rather than materializations of Newtonian physics principles. Goethe studied Purkinje's dissertation with great interest, as reported in his diary: "I turned to researches on nature and have to say that I was especially stimulated by Purkinje work on subjective vision." In a letter to Knebel, he noted:

I am sure that you too were highly interested in Purkinje. It seems remarkable how he escaped the papists by his own strength and how he developed and educated himself in an autodidactic manner when he started out on his own (24).

From 1819 to early 1823, Purkinje worked in the Faculty of Medicine of The Universitas Carolino-Ferdinanda as a prosecutor (instructor in charge of dissecting human cadavers for anatomy lectures) (33). During this period, Purkinje unsuccessfully applied for professorship vacancies (anatomy, materia medica, physiology, and pathology) at universities within the Habsburg Empire (Prague, Budapest, Graz, Ljubljana) of which he was a citizen. However, in the summer of 1821, Johann Nepomuk Rust (1775–1840), Professor of Physiology at Berlin University, informed Purkinje (known to Rust as a brilliant student of the Medical Faculty of Prague) that the professorship chair of Physiology and Pathology at the Royal Prussian University of Breslau had become vacant. Following an endorsement letter by the Professor of Anatomy and Physiology Karl Asmund Rudolphi (1771–1832) of the University of Berlin, the Prussian Education Minister Freiherr von Altenstein (1770–1840) invited Purkinje to Berlin for an interview, and, on January 25, 1823, Purkinje received the appointment for the vacant professorship chair of Breslau University by King Friedrich Wilhelm III of Prussia. The Medical Faculty of Breslau protested with the minister against this nomination, since Purkinje was a foreigner and did not have the German title of Dozent (university teacher). However, with time, Professor Purkinje gained the respect and friendship of his colleagues and became an appreciated teacher and researcher of the university (24, 30).

In 1827, Purkinje married Julia Agnes, the daughter of Professor Rudolphi, who gave him two daughters (who died of cholera in early age) and two sons (Emanuel, who became a Professor of Botany in Vienna, and Karel, who became a distinguished Czech painter). Julia succumbed during an 1835 outbreak of typhus, leaving Purkinje a widower for the rest of his life (26, 33).

During the 27-yr period spent at the University of Breslau, Purkinje made his best known scientific discoveries in a variety of fields (see *Principal Experimental Discoveries of Purkinje* below). Because his 1831 request for the establishment of an independent Physiology Institute within Breslau University was rejected, he founded it in his Breslau home. In a letter to Professor R. Wagner he wrote: "I have been afflicted by many unfortunate bereavements, my living quarters, thus, became half empty, but physiology entered to glorify these empty rooms" (24). This was one of the first Physiology Institutes in the world (26). Purkinje's request for an academic institute of physiology was renewed and again refused in 1835, but was finally accepted in 1839 and successively implemented by the construction of a small building that, however, was inadequate for the purpose. Purkinje was elected dean of the Medical Faculty of the Royal Prussian University in Breslau four times in a row (Table 1) (16).

In 1850, Purkinje accepted the nomination of Professor of Physiology at the Faculty of Medicine of Charles University in Prague where he graduated as an MD in 1818. During the 19-yr period spent in this position, he built a very modern Physiology Institute, which delivered advanced physiology education to many Professors of Physiology of his time. Additionally, he devoted himself to resolving serious contemporary educational issues and to promote the emergence and the consolidation of a patriotic Czech national conscience. In this context, a very important achievement was his success in obtaining the adoption of Czech as a teaching and examination language (along with German and Latin) in the Faculty of Medicine. It took several years of difficult discussions with the Medical Faculty Board before Czech medical students were accorded the right to be taught and examined in their native language, as previously established by the Austrian-Hungarian Emperor.

In 1853, Purkinje founded the Czech science journal *Živa* (*Alive*; still published today) and many years earlier (1823) was among the founders of *Krok*, the first popular scientific Czech periodical in which Purkinje published several scientific and cultural essays. Purkinje also collaborated in the establishment of the Society of Czech Physicians and its Medical Journal (*Časopis Lékařů Českých*), the first issue of which appeared in 1862 and is still currently published and indexed by PubMed (Table 1).

In 1868, Professor Purkinje was honored with the prestigious distinction of Imperial Austrian of the Order of Leopold, conferred for merit and moral integrity (*Integritate et Merito*) (Table 1).

Jan Evangelista Purkinje (Fig. 1) died on July 28, 1869, at noon. The announcement of Purkinje's death in the Prague



Fig. 1. Jan Evangelista Purkyně (1787–1869). Drawing by J. Vilímek, in *Zlatá Praha* 4: 581, 1887. [Retrieved from Institute for Czech Literature website (<http://archiv.ucl.cas.cz/index.php?path=ZlataPrahaII/4.1886-1887/37/581.png>); public domain.]

daily newspapers was signed by his surviving son Dr. Emanuel Purkyně, his two daughters-in-law (Marie and Emilie), and five grandchildren (Jan, Cyril, Růžena, Julie, and Otokar). The day before the funeral, the body of Professor Purkinje was taken to the Physiological Institute for public viewing (24). Purkinje rests in the Prague Vyšehrad National Cemetery of distinguished Czech citizens (16).

### *Scientific Domains of Physiology in Early 19th Century*

The word “physiology” was used for the first time in 1853 by the French scientist Jean Frenel to denote the corpus of knowledge concerning life processes in healthy humans and animals. In contrast, the word “pathology” was introduced to designate a discipline concerned with disease processes. Albrecht von Haller (1708–1777), a Swiss anatomist, physiologist, naturalist, and poet, defined physiology “*anatomia animalium*,” i.e., living anatomy. He was the author of the first known treatise of physiology (29).

In German universities of the first half of the 19th century, the scientific domain of physiology was restricted to the description of certain body phenomena without any reference to the medical practice. Purkinje, throughout his entire career, rejected the traditional discursive and romantic vision of physiology, the investigational domain of which was limited to the identification of general laws of life believed to be deductible and understandable from speculation. He strived, throughout his professional life, to render physiology a factual, experimental, medical science soliciting “nature to answer our questions and certify the correctness of our findings” (24). Purkinje considered vital phenomena as not essentially different from those of the inorganic world and thus interpretable according to the laws governing the physical and chemical worlds. Hence, physiological work had to address the discovery of physical and chemical processes that account for in-life functions.

As a Professor of Physiology and Pathology at the University of Breslau, Purkinje never taught physiology as an abstract discipline. He valued the emerging research approach of the French School lead by François Magendie (1783–1855), who performed animal vivisection (in that time anesthesia was not available) experimentation to characterize in-life phenomena. In 1816, Magendie published the *Precis Élémentaire de Physiologie (Elementary Treatise of Physiology)* (32), the first two-volume modern physiology textbook. For Magendie, “To express an opinion, to believe, is nothing else than to be ignorant” (11).

The research of Magendie and contemporaneous physiologists can be better appreciated by recalling that, in the early 19th century, vital phenomena were explained by two essentially opposing theories, vitalism and materialism. For vitalists, life was the manifestation of extraphysical, creative forces, whereas, for materialists, life was the outcome of common chemical and physical laws governing natural phenomena. Purkinje’s definition of physiology was strongly influenced by the vitalist beliefs of his Catholic faith and the romantic culture. For him, physiology was an experimental science:

To learn to know man as an embodied spirit placed above all the creatures on earth, endowed with excellent bodily and spiritual strength, in order to investigate all of nature, to recognize its sublimity, and its Godly origin and to learn to govern it wisely by conscious and unconscious earthly powers

as far as God wills it. This is the task of physiology, in general, and the physiology of man, in particular (24).

In Breslau, students were very appreciative of the teaching skills of Purkinje. Indeed, he revolutionized the teaching methods of physiology by complementing orally delivered lectures with practical experimental laboratory demonstrations. For this innovative teaching approach, Purkinje merits recognition as the initiator of modern pedagogical methods in scientific disciplines. When he introduced practical laboratory work as an integral part of his physiology course, the Medical Faculty Board of Breslau University sent a complaint to the Education Ministry, suggesting that Purkinje should be placed under the coaching of an experienced lecturer and be forced to adopt a textbook. The Ministry of Education rejected this demand and commended Purkinje’s teaching approaches (23, 24). Purkinje teaching methods are still applied today, although in vitro and in vivo animal experimentation, which were applied in physiology and pharmacology classes during the last century, have now been largely replaced by computer simulations.

The program of the “General Physiology” course taught by Professor Purkinje in Breslau (known from his personal lecture notes and 1831–1839 memoranda to the Education Ministry) covered multiple domains: anthropology as an introduction, anatomy, histology, embryology, phenomenology of life, physiological mechanisms, physiological chemistry, physiological dynamics, physiological psychology, general physiology, or philosophy of nature (Naturphilosophie), experimental physiology, and applied physiology. This multifaceted program covered most of the disciplines that comprise the modern definition of biology. However, it is clear that the study of Naturphilosophie is separate from the purely physiological domains. As such, it was not included in Purkinje’s physiology program in Prague, which encompassed general (notions on the phenomena of life) and special physiology topics [e.g., physiological physics (acoustics and optics), chemistry (composition of organs and tissues, digestion, respiration, etc.), dynamics (nervous and psychic functions), and psychology anthropology] (28).

### *Principal Experimental Discoveries of Purkinje*

The research interests of Professor Purkinje were many-fold. They encompassed anatomy, histology, embryology, pharmacology, physiology, microscopic investigations, and humanistic science issues (language studies and literature). His remarkable scientific achievements were the fruit of personal talent, hard work, excellent organization, and innovative technical instrumentation, which was often conceived and realized in the physiology laboratories (10).

The Opera Omnia of Purkinje consists of 13 volumes (each of ~180–500 pages) that were published from 1918 to 1985 (8, 30). None of Purkinje’s publications was written in English. The languages he used to present his scientific research included German, Latin, Czech, and Polish.

*Purkinje’s physiological investigations on vision.* Purkinje’s physiological investigations and discoveries on vision were performed mostly during the period he spent at the University of Prague as a medical student and instructor. These studies laid the foundation for ophthalmoscopy (method for the examination of the inner eye structure) and optometry (see below) developments. Additionally, they persuaded Purkinje that vi-

sual system functions were mediated by both peripheral and central nervous structures. Purkinje should also be considered one of the founding fathers of psychology, a discipline concerned with the study and understanding of the relationships between cognitive functions manifested by perceptions and physical realities. Experimental data supporting these claims can be found in the two booklets published by Purkinje during the first 2 yr after his arrival at Breslau University. The first, a novel (written in Latin) version of his MD dissertation (submitted in German) (42), is a 58-page masterwork published in 1823, which established him as a Dozent (lecturer) at Breslau University. Its title is *Commentatio de Examine Physiologico Organi Visus et Systematis Cutanei (Commentary on the Physiological Examination of the Visual Organs and the Cutaneous System)* (44). In 1825, Purkinje published a follow-up booklet entitled, *Neue Beiträge zur Kenntnis des Sehens in Subjektiver Hinsicht (New Contributions to the Knowledge of Vision from the Subjective Point of View)* (47).

These two publications describe numerous, predominantly entoptic, phenomena, which concern visual, intraocular images visible only to oneself, since they are shadow projections upon the retina of within-the-eye structures or images. These entoptic images are generated from physiological or pathological processes within the eye. They differ from optical illusions, which are also entoptic phenomena resulting from the cerebral elaboration of sensory stimuli. A feature common to entoptic images, optical illusions, and hallucinations is that they cannot be experienced by other people, since they are within ones' eyes or brain (3).

Purkinje considered peripheral subjective sensory phenomena as manifestations of inborn deterministic physiological laws mediating the functions of the eyes: "As physiologists, we search for the manifestations and laws of life in all their forms; subjective experience is just part of our heuristic (learning and discovering) apparatus" (50). The notion that there is an intimate relation between structure and function was innovative and revolutionary for physiologists of the 1820s. Purkinje also acknowledged that illusions of sensory origin were products of the laws of nature and, as such, were a potential matter of scientific enquiries. Indeed, according to Purkinje, "Life has entered inorganic nature to live in it in accordance with its laws and not to disturb them" (50).

Purkinje's research on vision was initially inspired by the *Zur Farbenlehre (Theory of Colors)* published in 1810 by Goethe (15), who considered colors as admixtures of light and shadow and, furthermore, held that any sensory experience, even visual illusions, was phenomena informing about worldly realities (64). Although Purkinje avoided citing Goethe's work, he acknowledged his debt to Goethe in the dedication of the *Neue Beiträge* (47), where he describes novel visual phenomena, such as afterimages, perception of the retinal blood vessels (Purkinje tree), and visual distortions, such as concentric circles seen while viewing geometrically periodic patterns. This visual motion after-effect was very clearly portrayed by Purkinje:

One time I observed a cavalry parade for more than an hour, and, then, when the parade had passed, the houses directly opposite appeared to me to move in the reversed direction to the parade (43).

The *Neue Beiträge* suggests principles and methods that were subsequently used in the establishment of optometry and retinoscopy. For instance, Purkinje recommended that the interior of the eye should be examined by directing a light beam exiting from a concave lens into the eye. This approach, exploited in 1851 by Hermann von Helmholtz (1821–1894) for the construction of the ophthalmoscope, is still in use by today ophthalmologists.

**PURKINJE PHENOMENON OR SHIFT.** The Purkinje phenomenon (known also as Purkinje shift or dark adaptation) is described in the MD dissertation of 1819 (42), in the 1823 *Commentatio* dissertation (44), and in the 1825 *Neue Beiträge* (43), where it is formulated in these simple words: "The intensity of illumination has a marked effect on the brightness of perceived colors." For example, under daylight conditions, green-blue colored objects under low-light environments are seen brighter than red ones of the same (under daylight) color intensity. The Purkinje dark-adaptation phenomenon may also be formulated in the following terms: as light intensity decreases, the brightness of red objects fades faster than that of green-blue objects, and vice versa. Purkinje explained this observation by proposing that the human eye has two detection systems for distinguishing colors, one under bright conditions and another under reduced light situations. The changes in the apparent relative luminosity of differently colored objects under dissimilar light conditions are now explained by the different adaptation rate of the human eye to light and darkness. This adaptation is carried out by two distinct types of photoreceptors within the retina: rods, which have a maximal detection sensitivity at 505-nm wavelength and mediate predominantly night or scotopic vision, and cones, which have a maximal sensitivity at 555-nm wavelength and operate in daylight or photopic color vision. As cone vision gradually switches over to rod vision throughout the dark-adaptation process (e.g., at dusk), daylight visual sensitivity shifts toward shorter wavelengths, such that green-blue objects appear relatively brighter than reds. Hence, the physiological mechanism of the Purkinje phenomenon is due to the differential spectral light sensitivities of human retinal photoreceptors (5, 62).

The term "Purkinje phenomenon" was proposed by the French physicists, Jules Macé de Lepinay (1851–1904) and William Nicati (1851–1931) in 1882. However, the observation that the relative brightness of the colors of the light spectrum was affected by lighting conditions was described by the ancient Greek philosopher Aristotle (384–322 BC) in the *Meteorologica* (51) and in *De Coloribus* (52) treatises. Leonardo da Vinci (1452–1519) refers to the shift phenomenon in these clear terms, "Green and blue are invariably accentuated in the half shadow, yellow and red and white in the light parts" (8, 60).

**PURKINJE-SANSON IMAGES.** In the *Neue Beiträge* (47), Purkinje describes a phenomenon, now known as Purkinje-Sanson images: in dark conditions, within the eye of a person staring at a light source, it is possible to see four (Purkinje indicated three) specularly reflected images referred to as P<sub>I</sub>, P<sub>II</sub>, P<sub>III</sub>, and P<sub>IV</sub> (Fig. 2). These images are mirrored by the anterior and posterior ocular optical system interfaces. P<sub>I</sub>, the brightest and the simplest of the four images to locate, is created by a reflection of the light source (catoptric image) from the convex anterior surface of the cornea. P<sub>II</sub>, P<sub>III</sub>, and P<sub>IV</sub> are both reflection and refraction (catadioptric) phenomena,

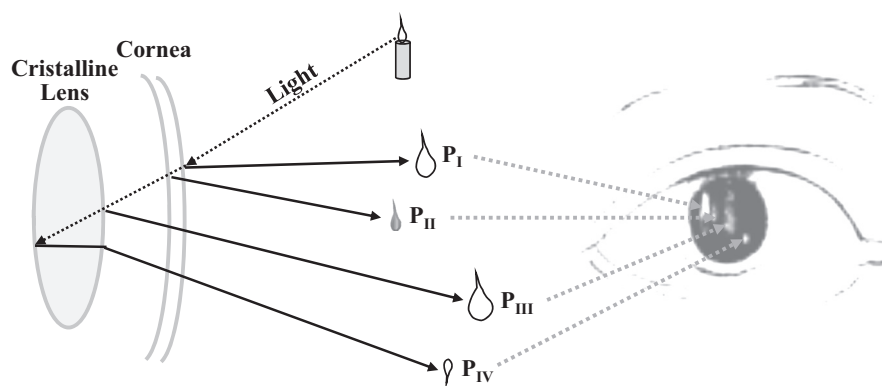


Fig. 2. Purkinje-Sanson images.

which may be of rather difficult location.  $P_{II}$ , the image generated by the light source impinging on the cornea posterior surface, was not described by Purkinje or Sanson, probably because it is the dimmest and the hardest to be seen due to some overlapping with  $P_I$  (25).  $P_{III}$  is formed by the anterior convex surface of the crystalline lens and is rather bright and the largest of the four images.  $P_{IV}$  (inverted image), generated by the posterior surface of the crystalline lens, is the smallest and the only real image.  $P_{III}$  and  $P_{IV}$  images can also become visible to the individual from within one's own eye (entoptic images) since they are refracted away from ocular lens surfaces onto the retina.

The eponym Purkinje-Sanson images is justified since, although Purkinje was the first to describe the phenomenon, it was the French ophthalmologist Louis Joseph Sanson (1790–1841) who, in 1838, provided an anatomical explanation (reflection/refraction of a light source by the outer and inner surfaces of the eye lens) of Purkinje's observations and proposed an ophthalmological diagnostic use of the images:

When a visual problem exists in the presence of one or two ocular images, this may be due to a cataract whereas when three ocular images are visible and the patient claims blindness, this signals an amaurose [blindness not resulting from defective ocular lens] condition (53).

The Purkinje-Sanson images have engendered numerous scientific applications, particularly in the optometry domain. For example, they can be used to measure corneal thickness, curvature, and the position, data necessary for correct intraocular lens implantation (25), to perform diagnostic tests of strabismus (eye misalignments), to determine exophthalmos degree (bulging of the eye out of the orbit), to locate axes and associated angles of the eye, and to design instrumentation (infrared  $P_I$ – $P_{IV}$  eye trackers) for monitoring eye position and movements (6, 20). The cornea-reflected  $P$  images used by eye trackers are known as glint (small flash of light, as reflected from a shiny surface).

**PURKINJE TREE.** In his MD dissertation (42) and again in the *Neue Beiträge* (47), Purkinje described how the movement of a candle across the visual field allows an individual to view the shadow of a tree on the inner surface of one's eye. This maneuver produces an entoptic perception referred to as the Purkinje tree, which is invisible under ordinary circumstances, because the shadows of the blood vessels on the retina are stabilized images.

A fine network of vessels delivers blood to the inner retina. These vessels become thinner as they approach the fovea

(small area within the macula region of the retina providing the clearest human vision). Since they lie in front of the photoreceptive cones within the fovea, they receive unobstructed incident light, which projects their shadow onto the retina (56). Under appropriate experimental conditions, a person with good macular function can see a uniform orange-red field occupied by the Purkinje tree (50). Visualization of the vasculature using kinetic techniques to displace the shadow of blood vessels facing the fovea was used by Johannes Peter Müller (1801–1858), Professor of Physiology at the University of Berlin, to localize the retinal photoreceptive layer and has been used for a variety of clinical applications (56). Recently, a selective stimulation of fovea L and M, but not S, cones (three types of cones classified according to wavelength necessary for their activation) (38), allowed a clear view of the retinal vascular network (56). The Purkinje Vascular Entoptic Test is a simple and reliable assay for assessing retinal function and the presence of mature cataracts (3, 58).

**PURKINJE BLUE ARCS.** The retinal blue arcs phenomenon is the most beautiful perceptible entoptic event. In the *Neue Beiträge* (47), Purkinje saw these arcs for the first time arising from glowing kindling while lighting a fire in the dark, but could not understand their significance (34). In a dark room, an observer (preferably with one eye closed) looking briefly at a patch of light (preferably red), in addition to the light source (the primary stimulus), will notice two curved bands arching from where the light hits the eye and cross the visual field toward the blind region (39). Regardless of the stimulating light color, the entoptic arcs always appear as varying shades of blue. Their blueness is enhanced in the dark-adapted eye by increasing the inducing stimulus intensity. However, the brilliant blue observed after 2–3 min of dark adaptation fades to gray and white with longer periods of dark adaptation. The blue color of the arcs is probably due to the activation of the blue-yellow opponency cone photoreceptor system (22, 38). The shape of the arcs conforms to the individual anatomical topology of the retinal ganglion cell axon bundle, which sends signals from where a spot of light is focused onto the retinal area close to the fovea (31). The inability to perceive these arcs may underlie pathological conditions. For example, they appear to be correlated with certain structural and functional features of glaucoma (39).

**Classification criteria for human fingerprints.** Fingerprints are now routinely used as a personal identification tool, in particular, for forensic purposes. Purkinje, in 1823, devised a method for a systematic classification of fingerprints: "After

innumerable observations, I have found nine important varieties of pattern of rugae and sulci serving for touch on the palmar surface of the terminal phalanges of the fingers” (44). He categorized fingertip furrows into nine geometric types: arch, tented arch, ulna loop, radial loop, peacock’s eye/compound, spiral whorl, elliptical whorl, circular whorl, and double loop/composite. Purkinje recommended further research in the field without providing any hint on the potential application of its classification.

The short section dedicated to the finger cutaneous system describing fingerprints in the *Commentatio de Examine Physiologico Organi Visus et Systematis Cutanei* (44) remained virtually unknown for many years, probably due to its publication in Latin. Nevertheless, it provides the founding principles of the science of the study of fingerprints (dermatoglyphics), which was subsequently refined by various investigators and, in particular, by Sir Francis Galton (1822–1911) who, from a careful analysis of 8,000 individual fingerprints, proposed a classification method (simpler than that of Purkinje) based only on spirals, loops, and arches (17). Seventy years after its initial publication, Galton translated the pages of the Purkinje *Commentatio* on fingerprints by remarking “The *Commentatio* of Purkene [sic] has the great merit of having first drawn attention to the patterns of skin ridges and attempted to clarify them” (40). Scotland Yard established the first Fingerprint Bureau in 1902. This was followed 1 yr later by the British judiciary and, in 1903, by American police departments. These public institutions adopted fingerprints as means for individual identification in criminal investigations (17).

*Histology discoveries.* Purkinje was among the first users of an improved version of the compound achromatic microscope, which the University of Breslau acquired in 1832 from the Austrian optical instrument manufacturer Georg Simon Plössl (1794–1868) (10). This instrument, one of the best microscopes of its time, could bring simultaneously two colors into focus. Its use opened a novel, unexploited field in Purkinje’s physiological investigations from 1832 to 1845. Purkinje very enthusiastically wrote:

With the acquisition of the Plössl microscope in the summer of 1832, a new epoch in my physiological activity began. . . . With inevitable wolf hunger, I have investigated all types of tissues, animal and plants. . . . (24).

Purkinje also developed new laboratory methods for processing, sectioning, and embedding biological tissue preparations. He was the first investigator to use a forerunner of the modern microtome, which was constructed by his assistant Adolph Oschatz (1812–1857) (10, 40) for automatically cutting histological sections for microscopic examinations. Purkinje used ethanol, glacial acetic acid, and potassium dichromate to fix tissue slices and introduced the glass slide mount embedded with Canada balsam, amber, or copal varnishes to render tissue slices suitable for microscopic scrutiny (23). These histology technological improvements allowed systematic analysis of the microscopic structure of numerous human and animal body tissues (sweat glands, skin, cartilage, blood vessels).

*Purkinje cells in the cerebellum.* *Über Neuesten Untersuchungen aus der Nerven- und Hirn-Anatomie (New Investigations on Nerves and Brain)* (49), a paper dealing with the

histology of the central nervous system, presented by Purkinje in Prague in 1837, describes cerebellar cells later designated as Purkinje cells. This discovery was made possible by examining alcohol-fixed slices of sheep cerebellum. In the late 19th century, Camillo Golgi (1843–1926), at the University of Pavia (Italy), stained these cells with silver nitrate. The black reaction (name given to this fixation procedure) revealed the full cerebellar neurons, i.e., cell body with multipolar peripheral processes (37). Santiago Ramón y Cajal (1852–1934), working at the University of Barcelona (Spain), after refining the black reaction, discovered that Purkinje cells (eponym proposed by him) have dendritic spines (small, knob-like protrusions on dendrites). Golgi and Ramón y Cajal were honored with the 1906 Nobel Prize in Physiology and Medicine for their central nervous system researches and discoveries.

*Purkinje, a drug self-experimenter.* During his third year of medical training, Purkinje assiduously frequented the Golden Crown pharmacy in Prague, where the owner permitted him to become familiarized with tasting, touching, smelling, and collecting samples of pharmacy available drugs.

Purkinje was dissatisfied with the therapeutic claims and practices of his time and with the manner of university teaching of *materia medica* (term used in the 19th century to designate pharmacology), which dealt with the mere description of the organoleptic (taste, color, odor, and feel) properties of drugs (mostly of vegetal origin) and their therapeutic indications, generally derived from crude tests in animals. *Materia medica* lectures did not provide information on the effects of drugs on various body organs.

Purkinje considered that the small doses of drugs present in homeopathic preparations (very popular at his time) were not sufficient to unveil the intrinsic therapeutic potential of a treatment. He defined this approach as “nothing but mysticism.” Purkinje was particularly interested, in addition to the generally sought systemic effects of a drug, in determining also the sensory and mental effects of drugs.

In the 1829 publication *Einige Beiträge zur Physiologischen Pharmacologie (A Contribution to Physiological Pharmacology)* (45). Purkinje reports self-experimentation observations with several drugs and stresses the need of adopting experimental physiological principles to profile drug effects in humans. This strategy was later implemented by Rudolph Buchheim (1820–1879), the founder of experimental pharmacology who, in 1869, established a Pharmacology Institute in Giesen (Germany), where he developed methodologies (bioassays) for determining the pharmacological action and the potency of drugs. His student, Oswald Schmiedeberg (1838–1921), should be regarded as the Father of Modern Pharmacology for his drug-structure-activity relationship studies performed during his 46 yr as a pharmacology professor at the University of Strasbourg, France.

Purkinje did not consider it very appropriate to evaluate drugs for human use primarily in animals in accordance to the old dictum *fiat experiment in corpore vili* (do the experiment in the animal body), since this approach cannot reveal the effects of a drug on all body systems and, in particular, on sensory organs. Meaningful “pharmacological” experiments require studies *in corpore nobili* (in the human body) (59).

Purkinje investigated on himself belladonna, aqueous extracts of digitalis leaves, water and alcoholic extracts of ipecacuanha (ipecac or ipecac), emetine (the emetic component

of ipecacuanha), camphor, water extract of stramonium seeds, opium, and turpentine (59). In testing a belladonna aqueous extract, he experienced typical autonomic nervous system effects (mediated, as we now know, by the blockade of muscarinic receptors by atropine, the belladonna active principle), namely, dry nose and mouth, oppression of the precordial region, heart rate disturbances, and urinary bladder contractions. He also suffered anxiety, hypochondria, and visual disturbances due to pronounced pupil dilatation (mydriasis) (19). Purkinje also tested an alcoholic extract of stramonium seeds, the effects of which (also due to muscarinic receptor blockade) were found to resemble those of belladonna (18, 19, 59).

Adolf Martin Pleischl (1787–1867), a pharmaceutical chemistry professor at the Prague Medical Faculty, asked his student Purkinje to test on himself the effects of several extracts of the root of ipecacuanha and of a preparation of emetine (still used as an emetic drug). Purkinje performed six experiments within a 3-wk period and reported nausea, vomiting, salivation, cramps, and diarrhea. At the end of the experimentation, he developed a peculiar conditioned reflex, “for every sight of brown color resembling that of emetine evoked in me the sensation of strong aversion (nausea)” (1, 59).

The effects of ground nutmeg (*nux muscata*: seeds of *Myristica fragans* tree) suspended in a glass of wine, reported by Purkinje, were headaches, nausea, euphoria, hallucinations lasting days, dry mouth, nausea, tachycardia, cutaneous flashing, paresthesia, hypotension, and dyspnea. We now know that the main pharmacologically active principle of *nux muscata* is the alkaloid myristicin, a precursor of MMDA (3-methoxy-4,5-methylenedioxyamphetamine; 3-methoxy-MDA; MMDA), which belongs to the amphetamine pharmacological class and possesses psychedelic properties (55).

Probably the most famous and dangerous drug self-experiment that Purkinje performed was with high doses of digitalis (used since the 17th century to treat heart disorders) to investigate effects on vision. Here is a brief excerpt of Purkinje’s account (1):

At about 8 o’clock in the morning, and one hour after a full breakfast, I took a concentrated decoction of the leaves of digitalis purpurea. . . . Toward 10 o’clock I became nauseated, and my pulse, whose ordinary rate was between 60 and 70, had slowed down to 54, missing beats many times, and I felt a sensation of oppression with each beat. . . . (19).

Overall, Purkinje performed at least 35 self-experiments (none after his marriage for respect to his family), often suffering rather serious drug reactions (59).

*Purkinje fibers in the heart.* The main components of the cardiac conduction system are the sinoatrial node, the atrioventricular node, the His or atrioventricular bundle, the right and left bundle branches, left posterior bundle, and an extensive terminal network structure discovered by Purkinje in 1839 (2). This fibrous structure of specialized myocytes conveys sinoatrial pacemaker generated stimuli to ventricular contractile myocytes. Its discovery was described in the last 2 of a 15-page article published in 1845 (46) with these words:

Directly under the serous membrane (skin) on the interior walls of the sheep heart I observed firstly a network net of grey, flat and gelatinous fibers that partly spreads to the papillary muscles and to other neighboring fibrous trabecular and that partly bridges trough of the heart walls. . . . It is currently more

likely to me to consider this tissue an independent locomotive apparatus.

In 1852, Professor Rudolf Albert Köliker (1815–1905), a Swiss anatomist, elucidated the conducting role of the fibers, which he named “Purkinje fibers” (12). These fibers are cardiomyocytes specialized for electrical signal conduction from the His bundle to the ventricular contractile myocytes around which they anastomose. The excitation wave delivered by the Purkinje fibers causes the myocytes to contract, thereby generating mechanical forces ejecting blood from the right and left ventricles, respectively, into pulmonary and the systemic circulation.

*Purkinje law of vertigo.* During the period 1820–1827, Purkinje carried out systematic investigations on vertigo and physiological phenomena related to body posture and equilibrium maintenance. The Purkinje law of vertigo states that, when one stops after rotating around the body axis, the apparent motion of the surroundings changes from horizontal to vertical if the head is inclined toward the feet. Although this observation was previously made by Erasmus Darwin (1732–1802), who is the grandfather of Charles Darwin (1809–1882), and Sir Francis Galton, who was mentioned in *Classification criteria for human fingerprints*, above, Purkinje refined it by noting that the subjective perception of the direction of motion on post-revolving vertigo depends on the position of the head during the rotation with respect to the feet. He proposed that direct mechanical effects on certain brain structures (chiefly the cerebellum) were responsible for vertigo. However, it is now known that the information for vertigo sensations are relayed to specific brain structures by the vestibular system within the inner ear.

Based on the law of vertigo, pilots receive special training to be aware that, in the absence of free external references, head down or lateral movements of the head can be followed by uncontrollable vertigo.

*Purkinje vesicle and introduction of protoplasm and plasma as scientific terms.* During the period 1825–1839, Purkinje studied the early development of avian eggs in the female body. These investigations led to the discovery of the germinal follicle (Purkinje vesicle later identified as egg cell nucleus) on the spot of the yolk from where the bird embryo starts to develop. These findings were presented at the Congress of German Naturalists and Physicians held in Dresden in 1825 and published in 1829 (48).

In 1839, Purkinje coined the term, protoplasm, to designate the colloid substance (cytosol) within the cell outer membrane where the information for life development is stored. This concept contributed to the elaboration of the most important biological discovery of the 19th century, namely, that all living systems are aggregates of different cell types and living organisms, which result from the coordinated and integrated functions of tissues made by different cell types. In 1839, Theodore Schwann (1810–1872), in a book coauthored by the botanist Matthias Schleiden (1804–1881), published in German and 8 yr later in English (54), theorized that cells are the fundamental units forming all terrestrial living organisms and containing all needed information for any vital processes to take place (9). This sounded the death knell of vitalism, which, from Aristotle on, held that some special energy was necessary for initiating each vital processes (35, 36, 63).



In the congress of German Naturalists and Physicians held in Prague in 1837, Purkinje suggested that “granules,” i.e., cells, which contain small grains (nuclei), appeared to him to be the constant basic structural units of animal tissues. Hence, the Granule Theory of Purkinje would appear to be one of the first formulations of the more general cell doctrine proposed by Schwann and Schleiden (54) 2 yr later.

*Other Purkinje contributions to science.* Purkinje, together with his student Gabriel Gustav Valentin (1810–1883) [who also worked as his research assistant before moving, as Physiology Professor, to Berne University (Switzerland)], in 1836, discovered the presence of incessantly vibrating cilia on genital and respiratory epithelia of mammals, birds, and amphibians, the function of which was proposed to be the extrusion of foreign substances from the epithelial tissue floor (29).

### Discussion

The numerous topics covered in this report each would merit dedicated commentary and supplementary elaboration. However, only a few of them will be taken into consideration in this discussion section due to spatial constraints. Wherever possible, we have followed the advice of Johann Wolfgang von Goethe: “. . . should you fail to understand, let Purkinje give you a hand!” (65). For this, we delved into the writings that Purkinje has left to us.

A first remark concerns the surprising maturity displayed by the 20-yr-old Purkinje at the end of his monk novitiate when he had to decide whether or not to embrace the life of the Catholic *Fratres Piarum Scholarum* (Brothers of Pious Schools) by pronouncing four life-engaging vows (4). Then, Purkinje opted for “another possible and happier calling to achieve something significant in natural sciences” by honestly recognizing “the longing for a higher-grade education took me into the monastery and the same longing took me out of the monastery” (21). Additionally, in his autobiography, Purkinje adamantly refuted popular reasons advanced to account for the renouncement of young people to certain constraints of monastic life:

I had no revulsion towards poverty, to which I would have been bound as a monk *pauperum scholarum piarum*. I did not know poverty for I did not know wealth. I did not know celibacy since I did not know sexual love (24).

However, the education and teaching experience that Purkinje acquired during the years he spent as a novice in the Piarist monasteries contributed substantially to the formation of his personality and his conduct as a university teacher, researcher, and student advisor.

The German Romantic Naturphilosophie movement, born at the end of the 18th century, believed that the laws governing natural phenomena could be understood and unveiled by speculative (metaphysical) labor and knowledge of work of past famous men. In contrast to these beliefs, Purkinje, as a conscientious experimental scientist, acknowledged that nature had to be investigated as it manifests itself, from a materialistic, and not an idealistic, standpoint. His Catholic education and the pervasive Naturphilosophie culture of his time influenced his proposed assignments for physiology which were “to investigate all of nature, to recognize its sublimity, and its godly origin.” Nevertheless, although Purkinje could not entirely renounce the cultural values of his epoch, from his entry into the scientific realm, he considered that biological struc-

tures, such as sensory systems, functioned in accordance to inborn laws. For him, “the sensory organs are the finest indicators and analyzers for exploring the pertinent qualities and material relations making the world.” “Physiology is a science of facts, its investigations cannot wander in remote misty skies, it must stand on empirical basis. It needs to observe, to grasp the rules of organizing nature.” “Life entered into the world of inorganic things in order to follow Nature’s laws not to disturb them” (29). These physiological laws (mechanisms) accounting for experimental data obtained during human and/or animal investigations had to comply with the experimentalist research principles that Purkinje outlined in his MD dissertation (44). The following 1827 remark places Purkinje definitively in the modernity of experimental biological sciences: “. . . there are physiological and pathological functions. . . the latter appear in the foreground only in unusual conditions but for that are not less orderly manifestation of the same principles,” which are the “eternal laws of nature” (28).

The scientist can discover and understand such laws only through accurate and conscientiously performed studies by applying appropriate experimental methods.

Although some visual phenomena reported by Purkinje were also observed by his predecessors (see PURKINJE PHENOMENON OR SHIFT above), Purkinje’s approach to report and interpret them was not simply descriptive, but, whenever possible, he proposed potential mechanisms for his observations. Thus the following remark by the French writer Marcel Proust fully applies to Purkinje’s sensorial investigations:

The only true voyage of discovery, the only fountain of Eternal Youth, would be not to visit strange lands but to possess other eyes, to behold the universe through the eyes of another, of a hundred others, to behold the hundred universes that each of them beholds, that each of them is (41).

This citation can be complemented by the following consideration of the Hungarian biochemist Albert Szent-Gyorgyi, 1937 Nobel Prize for Medicine: “Discovery consists in seeing what everyone else has seen and thinking what no one else has thought” (57).

Purkinje’s conduct concerning scientific discoveries was in full compliance with the laudable and humanistic mission that the Romanticism envisaged for the scholar. Theophile Eiselt, a pupil of Purkinje, remarked about his mentor:

To pursue a single discovery before it is completely exhausted—a path to glory for so many researchers—Purkyně simply did not care for such a thing. . . . In addition, this noble mind possessed two uncommon features: he showed a deep respect for young investigators and he was determined not to speak about himself (*de nobis ipsis silemus*; let’s not talk about ourselves) (26).

It was a firm belief of Professor Purkinje that:

Science is not about names but discoveries, that knowledge is not a value in itself nor for the author and that it is not to serve the author’s pleasures nor benefits: it is to serve universality as it is the property of the nation and humanity (17).

The Purkinje’s vision of the mission of a physician, outlined in the initial paragraph of the *Commentatio de Examine Physiologico Organi Visus et Systematis Cutanei* (44) deserves citation.

When I think about the problem of a practicing physician, the most important appears to me not to be his effort to renew

a life already shattered, or to sustain a life a bit longer, but his efforts should be directed towards the support of life which is continuously evolving; to protect it from harm; finally, to bring it to the peak of perfection and beauty. It appears to me that the present goal of endeavor should be to preserve such untarnished life at all costs as ideal. The physician who assumes this task may be called an artist. Otherwise he merely performs the task of a repairman.

Purkinje was also a scientist with prophetic ideas, as indicated by this 1836 statement concerning the mission of physiological physics which was part of the physiology teaching program of Purkinje:

When anatomy has revealed organs of different functions and their mechanisms, these will be raised to a true theory only when we shall have succeeded in constructing corresponding physical devices and transpose mechanical processes of the body in mathematical formulas (29).

The current efforts of physiological disciplines, such as Systems Biology, to develop in silico models of biological processes and organ functions address Purkinje's proposal of transcribing life processes into immaterial mathematical formulas. The new disciplines dedicated to the development of computational modeling borrow ideas and principles from mathematical, physical, and engineering sciences (7).

As a conclusion of this paper, we wish to quote what Purkinje said on New Year's day of 1869, 7 mo before his death:

I have indeed discovered various things, but, as for the immortality of my name, this should not be taken literally. A hundred years hence perhaps only a few will know who Purkinje was. But that makes no difference. For, indeed, we do not know who discovered the plow, and yet it serves all humanity. The cause remains the same, but not the name and that is the important thing (18).

## ACKNOWLEDGMENTS

The authors thank Drs. Najah Abi-Gerges, Nicolas Couvreur, and Peter Siegel for critically reviewing the manuscript.

## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

I.C., J.-M.G., and H.H. conceived and designed research; I.C., J.-M.G., and H.H. prepared figures; I.C., J.-M.G., and H.H. drafted manuscript; I.C., J.-M.G., and H.H. edited and revised manuscript; I.C., J.-M.G., and H.H. approved final version of manuscript.

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