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Paul Langerhans (1847-1888): perceiving the unknown and describing it

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Summary
Paul Langerhans Jr. described under the microscope single cells and aggregates never seen before; he had broad interests and a non-ordinary biography. He died young from tuberculosis, but continued to study until the end, driven by curiosity and disregarding his fate. In him coexisted the genius of the discoverer and the diligence of the observer of nature.

Key words: Paul Langerhans Jr, pancreas, islet, neuroendocrine, discovery

Introduction

The first volume of the journal *Pathologica*, in the issue of October 15, 1909, contains an article of the endocrinologist Nicola Pende entitled *"Ancora sulla teoria insulare del diabete"* [1]. The text opens with the following statement: *"Based on the anatomo-pathological and experimental data we currently possess, it is not possible to affirm that the internal secretion of the pancreas, the so-called antidiabetic function, should be attributed exclusively to the islets of Langerhans and not also to the exocrine acinar tissue of the pancreas."* The author's skepticism was based on a presumed lack of evidence regarding the persistence of the islets alone, with normal blood glucose levels, after ligation of the Wirsung duct. Based on literature and on experimental data and histological studies conducted by the author (in an article without a clear subdivision among Materials and Methods, Results, and Discussion – as often seen in the scientific literature at that time), Pende conceded that *"it is possible that the islets of Langerhans participate in the antidiabetic function alongside the acinar tissue,"* but he still considered pivotal the role of the acinar component [1]. The following year, Sir Edward A. Sharpey-Schafer (or, according to some authors, Jean de Meyer in that same year, 1909) coined the term *insulin* to refer to the molecule, not yet isolated but believed to originate from the islets of Langerhans (Fig. 1, A, B) and responsible for blood glucose control [2]. Many studies, along with the dense capillary network surrounding the islets, suggested an endocrine function of the islets [3]. Moreover, some pathologists [4] described lesions in the islets of the pancreas removed at autopsy from diabetic patients (Fig. 1 C). At that time, however, the main challenge faced by scientists was the experimental separation of the islets from the rest of the exocrine pancreas. It was not until 1921 that the

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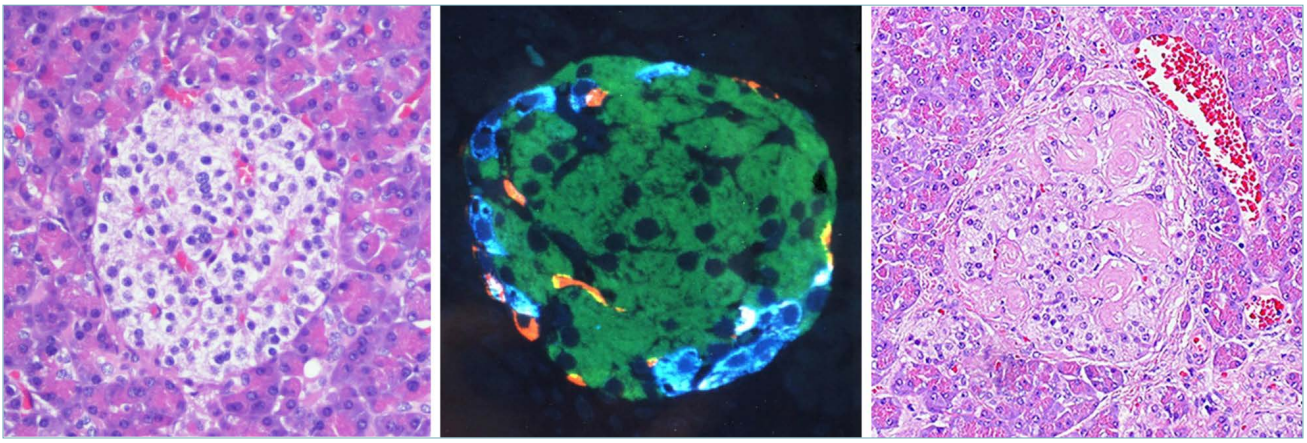

Figure 1. Normal human Langerhans islet (left) (A) and disrupted by amyloid deposits (right) (C); hematoxylin and eosin staining. In the center (B), mouse Langerhans islet showing insulin (green), glucagon (blue), and somatostatin (orange); immunofluorescence – a gift from Andrew B. Leiter, MD, PhD, *in memoriam*.

Canadian surgeon Frederick Banting and the medical student Charles Best succeeded in isolating insulin for the first time. Two years later Banting and the laboratory director J.J. Richard MacLeod won the Nobel Prize for this achievement, and they are thereafter recognized as the real and sole discoverers of insulin – though with reservation by some medical historians [2].

Thus, the speculations made by the then 29-year-old Nicola Pende – who, 30 years later, would be guilty of far graver assertions as a supporter of the so-called scientific basis of the Italian and fascist racial laws [5] – do not appear so reckless, given the confusion still partially persisting in 1909. Moreover, they are difficult to contest given the lack of a clear methodological exposition in his study. However, they stand in stark contrast to what Paul Langerhans had written with exemplary honesty 40 years earlier regarding the function of the islets he just discovered: *"I admit frankly I have no possible explanation"* [6].

Paul Langerhans Jr (1847-1888)

In the "Scientific News" section of the November 1888 issue of *The American Naturalist* [7], the first news item reads: *Dr. Paul Langerhans, formerly professor in Freiburg i. B., died in Funchal, Madeira, July 20th, 1888, aged 41 years.* Why did the announcement of Langerhans' death appear in the obituaries of an American natural sciences journal? And why did he perish so prematurely and in an island of the Atlantic Ocean?

Paul Langerhans Jr (Berlin, 1847) was born in a bourgeois family and in a culturally stimulating and liberal environment (Fig. 2). His father, Paul Sr., was a physician involved in politics and a frontline advocate for mandatory vaccinations [8]. He was a friend of Rudolf Virchow, who, as is well known, was highly active both politically and socially [9]. A step-brother of Paul Jr. was Virchow's assistant and became professor of pathological anatomy in Berlin in 1896. Paul Jr.'s mother, who also came from a well-off family, died of tubercu-

Figure 2. Paul Langerhans Jr.

losis when he was only 6 years old [10]. Paul Jr received a first-class university education, initially in Jena under Ernst Haeckel, a famous zoologist and fervent defender of Darwin's theories, and then in Berlin with Rudolf Virchow.

Even before graduating, at the age of 21, Paul made his first original discovery, destined to leave a permanent sign on medicine. He was the first to identify intraepidermal dendritic cells using *the gold chloride staining technique* [11]. Initially, he interpreted these cells as intraepidermal receptors of nervous origin, and later he corrected this interpretation, although it would take more than a hundred years to uncover their actual immunological role [12]. Nevertheless, it is truly remarkable how precisely he managed to describe dendritic cells, given the optical instruments of his time (Fig. 3). His description was soon recognized for its originality. One of the first eponymous associations with Langerhans was made by Enrico Sertoli (1842-1910), who described the cells as *'corpuscoli di Langerhans'* [13].

However, in 1869, at the age of 22, Langerhans defended his thesis in a different field – the pancreas – under Virchow's supervision. The title of his thesis was *Beiträge zur mikroskopischen Anatomie der Bauchspeicheldröse* (*Contributions to the Microscopic Anatomy of the Pancreas*) [14]. In the 19th century, the pancreas was still considered as *"a gland salivaire abdominale"* despite the eminent physiologist Claude Bernard having already described its complex digestive function in his *"Mémoire sur le pancréas"* [15]. In the thesis, based on his study of the rabbit pancreas, Langerhans provided a meticulous description of pancreatic histology and its vascular and nervous support, without the aid of microtomy or hematoxylin-eosin staining. Using Muller's fluid, he hardened the gland and then carefully macerated it. The histology was differently highlighted with various stains, such as gold chloride, carmine, and solutions of osmic acid.

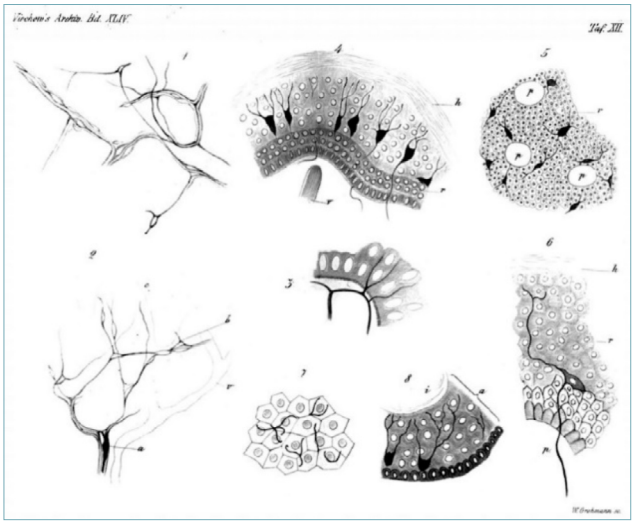

Figure 3. Langerhans cells of the skin in the original drawing of Paul Langerhans (Cohnheim's gold chloride technique).

Alongside the exocrine part, Langerhans described for the first time those peculiar cell aggregates *(*"zellhaufen"*),* highlighted as *"rounded spots stained intensely yellow (…), small irregular polygonal structures with perfectly brilliant cytoplasm free of granules, distinct round nuclei of moderate size".* For the 19th-century pathologists, these cells were either invisible or merely different functional modifications of the exocrine pancreas [3]. Conversely, Langerhans described these aggregates as morphologically well-characterized and distinct entities from the rest of the gland. It is a pity that he did not include drawings in his thesis, as was common at that time. According to his thesis, these aggregates were present throughout the parenchyma and had no connection with the ductular-acinar branching he identified using Berlin blue combined with glycerin and other stains. He concluded his thesis by honestly admitting that he could not attribute any function to these cellular aggregates, and he proposed no name for these cells. However, his statement that *"these isolated observations suggest a much more complicated structure of the pancreas than hitherto accepted"* [14] paved the way for further studies.

Only 25 years later, the French histopathologist Edouard Laguesse identified these cell groups again (*"dans le pancréas d'un homme adulte je retrouve ces îlots très nombreux et volumineux"*) [16], calling them "ilots de Langerhans" and hypothesized that they might be the sites of internal secretion. In truth, as early as in 1854 Virchow himself had postulated that the pancreas might have an endocrine function [17]. However, B.M. Hausen attributes to Virchow's resignation on the meaning of this finding the fact that Langerhans did not further investigate the islands he had described in his thesis [18]. This seems rather surprising and may be better explained by the eclectic nature of Paul Jr.'s interests. Indeed, after another year in Virchow's laboratory, during which he conducted studies that anticipated research on the reticuloendothelial system, Langerhans made a sudden change at the age of 23: he embarked on a medical expedition to Syria, Jordan, and Palestine.

The events of this journey and details of Langerhans' biography are thoroughly documented in a series of four fascinating articles by B.H. Hausen [10,18-20]. We

simply mention here that during this journey, Langerhans deepened his knowledge of the pathological anatomy of leprosy [21] (two precious skulls for his studies were stolen in Istanbul along with a collection of arthropods) [19]. More importantly, he broadened his horizons by engaging in anthropological and anthropometric studies on the skulls of local populations, following the scientific trends of the time. In the *Journal of the Anthropological Institute of Great Britain and Ireland* of 1899, traces of his investigations from nearly 30 years earlier can still be found [22].

He was called back to his homeland by the Franco-Prussian War, during which he served in France as a physician in the army's mobile units. In 1871, he returned to his work as a pathologist and became an assistant professor in Freiburg, combining teaching and research. However, he did not give up his other interests and repeatedly took part in marine zoology expeditions to Sweden and Norway, sometimes alongside the well-known anatomist Karl von Kupffer [23]. During these trips his main investigation focus was on histology studies of lampreys tissues, which resulted in an illustrated volume [24]. Curiously, the young Sigmund Freud, who had a training in comparative anatomy and physiology, mentioned Langerhans and his technique for isolating the ganglion cells of lampreys [25].

At the age of 27, he became a full professor, but just a few weeks later, he discovered that he was affected by renal and pulmonary tuberculosis. The disease forced him to abandon his medical work and leave Germany in search of sunnier climate. Initially, he sought therapy in Switzerland, in Davos and Silvaplana, but the treatments were ineffective. It is worth noting that, in 1874, the Swiss sanatorium facilities were still in their infancy; the boom of high-altitude treatments and care would only occur in the following years and decades [26]. Even the identification of the *Mycobacterium tuberculosis* by Robert Koch came later (1882). In this regard, a letter Langerhans wrote to Waldeyer in 1880 is impressive: *"It is astonishing how many persons have become phthisical, particularly among the rising anatomical generation"* [20]. One wonders what kind of precautions the young doctors used to take in their anatomic theaters.

He spent some time in Capri and Naples (where he learned to speak Italian) before moving to Madeira, the small Portuguese Atlantic archipelago. The disease did not prevent him from continuing to pursue his interest in marine zoology. After three years of relative well-being, he temporarily returned to Germany, but his condition worsened rapidly to the point that he had to resign from the University of Freiburg. He therefore moved southbound again, first to the Canary Islands and then back to Madeira, where he regained a certain degree of well-being. His repeated attempts to return to Germany were unsuccessful; the cold and damp Central European climate always forced him back to the south.

The final years of his life were very active. He married and resumed practicing medicine, treating many European patients who, like him, moved to the archipelago for tuberculosis treatment, to which he also dedicated his last scientific works. Notably, in one of his last scientific papers, he discussed the possible hereditary predisposition to tuberculosis [27], the disease that claimed his mother, afflicted his brother Robert, and was consuming him as well. He even found the strength to write a travel guide of Madeira, published in Berlin in 1885, which remains one of the most comprehensive guides to the small archipelago [28].

What is particularly interesting is that, during this final Atlantic period of his short life, he studied and described 153 species of marine invertebrates, including new species of annelids, which he collected from the nets of Portuguese fishermen in Madeira's ports. These were meticulous morphological studies accompanied by drawings, some of which considered original by specialists and cited decades later in journals such as *The American Naturalist* [29]. Once again, his name became inextricably linked to an entity –though this time, it was a marine creature: *Verrillopsis langerhans*, a name officially designated by the French zoologist P.L. Favel in 1905. Additionally, following his studies on annelids, he took the initiative to name a new species after his mentor: *Acicularia virchowii* [18,30].

These scientific traces are the legacy of a man who waged a long battle with tuberculosis and never lost his curiosity, even while describing himself as a *"half-invalid man."* Langerhans continued to study the surrounding nature and practice medicine until his death in Madeira in 1888, at the age of 41.

Conclusions

In the daily practice, the importance of a clear, detailed, and reproducible description of simple microscopic observations cannot be underestimated. Even today, the introduction of a new immunohistochemical marker in pathology – just like the discovery of a new gene fusion –requires an initial wide description of its expression in hundreds of tumor tissues before its diagnostic and research significance can be understood. However, if it involves seeing details never noticed before, the challenge becomes even greater. The almost philosophical statement that "one only sees what one knows" is well-suited to pathologists engaged in diagnostics and serves as an incentive to

enrich their knowledge and experience. Whether identifying a micrometastasis or an uncommon histotype, seeing is fundamentally seeing again.

Yet, the mind of a scientist transcends this rule. A talented researcher is able to *see the unknown*, as Langerhans did with the epidermal dendritic cells and the pancreatic islets, and describe them so well that others can rediscover them, placing them in the realm of established knowledge.

Paul Langerhans Jr. identified the endocrine islets while still an undergraduate student, and in this, there is an underlying connection with another undergraduate student, Charles Best, who, 50 years later, made a fundamental contribution to the discovery of insulin. Best, however, was excluded from the Nobel Prize, and only later on did the Nobel Foundation acknowledge that he should have been awarded as well. These are not the only cases in history where young researchers made significant discoveries; in this journal, we also discussed the case of Enrico Sertoli, whose findings were ignored for decades [31]. In Langerhans' case, having a mentor like Rudolf Virchow and writing in German language was certainly advantageous. However, it is undeniable that certain original observations can be best made by young, sharp minds, free from biases and light.

Finally, the breadth of Paul Langerhans' interests should not be too surprising, as it was typical of an era when physicians were somehow naturalists too. Langerhans simply expanded his field of interest more than others, ranging from anthropology to marine biology. What is most striking, however, is the perseverance with which he continued to engage in science, undeterred by the illness that was gradually overcoming him and driven by a curiosity that is perhaps the only force capable of winning such obstacles.

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Conflict of interest statement

GR declares competing interests (Boheringer Ingelheim GmBH; IPSEN Pharma SAS).

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Authors contribution

CP and GR for ideation, CP for writing, all authors for critical discussion of the manuscript

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