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Rudolf Virchow (1821-1902): Founder of Cellular Pathology and Pioneer of Oncology

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Summary

Rudolf Virchow, distinguished pathologist, physical anthropologist, and statesman, was probably the most distinguished German pathologist of his age, and is regarded as the founder of Cellular Pathology. He contributed greatly to the study of tumors, leukemia, hygiene, and sanitation.

Key words: cellular pathology, oncology, physical anthropology, Virchow

The rise of modern medicine and surgery is inextricably linked with the career of Rudolf Ludwig Carl Virchow, one of the greatest figures in the evolution of pathology and a dominant figure in European medicine during the second half of the 19th century.

Life and career

Virchow (Figure 1) was born on 13 October 1821 at Schivelbein, Pomerania, Germany; he died in Berlin on 5 September 1902. A landowners's son, he proved to have an enormous capacity for learning. Before starting medical studies at the renowned Kaiser Wilhelm Institute in Berlin, he had mastered French, English, Hebrew and Italian, as well as the classics and Arabic poetry! In Berlin he met two great teachers, the physiologist Johannes Müller (1801-1858) and the clinician who named the disease "hemophilia", Johann Schönlein (1793-1864). They persuaded him to enter research, and he graduated in 1843 with a dissertation on rheumatic illnesses [1].

Appointed to a minor post at the *Charité,* in 1845 he gave one of the two first independent de-

Figure 1. Portrait of Rudolf Virchow by Hugo Vogel. Berlin, Hospital Rudolf-Virchow.

Figure 2. Virchow (1900) attending an operation in Paris.

scriptions of "white blood" ("leukemia"). In 1846 he became assistant prosector in Pathological Anatomy at the *Charité* (Figure 2). In 1847 he became Privatdozent, and with Benno Reinhardt (1819-1852) he founded the *Archiv für Pathologische Anatomie*, which Virchow edited alone for 50 years [2].

In November 1849 the University of Würzburg appointed Virchow to the first chair of Pathological Anatomy in Germany. His seven years there were among the most fruitful in the history of Pathology because he did brilliant work concerning cells. Virchow was an outspoken personality who often found himself in personal difficulties because of his brashness. In 1856 he was appointed Professor of Pathology at the university of Berlin and concurrently assumed directorship of that city's Pathology Institute (Figure 3) [3].

He remained at Berlin till the end of his life. In 1859 Virchow was elected to the Berlin City Council, and he remained a member until his death. He was responsible for many of the social, sanitary and medical reforms carried out there. In 1861 he was elected to the Prussian Parliament. Bismarck became Prime Minister in 1862, and his policy was strenuously opposed by Virchow. In the wars of 1866 and 1870 Virchow equipped the first hospital trains and built military hospitals. He was a member of the Reichstag from 1880 to 1893 [4].

In 1869 Virchow founded the Berlin Society of Anthropology, Ethnology and Prehistory, of which he was President until his death. He was instrumental in founding the Berlin Ethnological Museum (1886) and the Folklore Museum (1888) (Figure 4). His lasting friendship with H. Schliemann (1822-1890), the archaeologist who excavated Troy, he owed initially to William Ewart Gladstone (1809-1898). Among Virchow's many honors was that of Foreign Membership of the Royal Society (1884), to which he delivered the Croonian Lecture in 1893 [2].

Figure 3. Virchow (1900) in his Institute of Pathology at the hospital *Charité* in Berlin.

Figure 4. Virchow (1900) examining a giant in his Institute of Pathology.

The fame of Virchow included his social initiatives. First he was sent to investigate a typhus epidemic in Silesia, and condemned the government for denying its poor Polish population the simplest sanitary and humanitarian facilities. This report made him unpopular, and two years later he took part in the unlucky revolution of 1848, thus losing his job. When he returned to Berlin as the country's best medical theoretician, he entered politics again and for a long time was a member of the Parliament. He was so progressive that he nearly had to fight a duel with Bismarck, the Iron Chancellor. In addition, he stimulated the study of anthropology and archaeology [5].

His works

Virchow showed that blood clots were due to changes in the blood's flow, composition and vessel walls – known as "Virchow's triad". He took almost a decade to publish the results, which are still valid today.

Virchow's scrutiny of the body's microcosmos led him into the science, which we now call Microbiology. His special interests were fungi and trichinosis. On the other hand, he was sceptical of bacteriology, which celebrated many triumphs in the late 19th century. Sometimes his attitude created scandals e.g. by breaking off a discussion with prominent research-

ers. He missed the mark badly on at least one occasion, Koch's epoch-making presentations in 1882 of the causes of tuberculosis [1].

His work on Cellular Pathology had far reaching consequences; it contributed enormously to the progress in Medicine and Surgery, and it showed the way to modern chemotherapy.

In the pathological field Virchow demolished the then current role of phlebitis (1846), and he introduced the concepts of embolism and of pyemia. He revolutionized the concept of inflammation. Relative to the role of the cell, Virchow wrote in 1854 that "There is no life but through direct succession". In 1858 Virchow gave a series of lectures on this subject to Berlin practitioners, and later in the year he published them as a book with the title *Die Zellularpathologie* [6]. Although others, e.g. John Goodsir (1814-1867), Professor of Anatomy in London, had claimed that cells arise only from cells, he was the first to apply this doctrine to pathological material, with immediate revolutionary effects in Pathology and Medicine. Virchow also worked intensively with tumors, and he published a large treatise on this subject which became one of the most important medical books ever written [7]. Among his numerous original contributions to Pathology is his work on the animal parasites of man, e.g. trichinella spiralis. Virchow was on the whole antagonistic to the role of bacteria in disease, and he rightly pointed out that the discovery of an organism in a certain disease did not explain how the organism caused the disease. He suggested the production of toxins before their existence was discovered. Virchow's publication in 1875 of his method of conducting post-mortem examinations had important consequences for the study of Pathologic Anatomy. Apart from his numerous original works, Virchow participated in a treatise of special pathology in 6 volumes, *Handbuch der speziellen Pathologie und Therapie* (1854-1865). He was also an anthropologist, interested in the problems of cranial development (1857). Of his many publications on anthropology and archaeology, we mention only his *Contributions to the Topography of Troy* (1879) and his *Ancient Trojan Graves and Skulls* (1882) [8].

Virchow and the rise of Cellular Pathology

Much of the information that led to the understanding and elaboration of the cell theory depended on technical advances in microscopes. It was not until the 1830s when Giovanni Amici (1786-1863) and Chevalier produced the achromatic lens so that the finer structure of cells could be examined [9].

Although it had been previously known that parts of plants were cellular, Mathias Jacob Schleiden (1804-1881) was the first to state explicitly that each plant was a community of cells with each cell having a separate existence. Theodor Schwann (1810-1882), generalized Schleiden's conclusions to all life-animal and plant. His model was reductionistic: cells, he believed, were the fundamental units of zoological and botanical activity. Incorporating a nucleus and an outer membrane, they could be formed out of a formless organic matrix that he called the blastema [3].

At first the model proposed by Schleiden and Schwann was embraced by many outstanding scientists, including Karl Rokitansky (1804-1878), but the concept of Virchow finally gained full acceptance. His microscopical work carried profound biological significance. In his *Zellularpathologie* [5], he disputed Schwann's notion of the blastema, and in his journal he published an article on Cellular Pathology, which contains the famous phrase "omnis cellula a cellula" (every cell is derived from a preexisting cell). This explained the growth of tumors and raised the possibility of stopping cancer [10]. If François Bichat's Traité *des Membranes* (1800) put tissues on the map, Virchow's treatise did the same for cells: it established a new, productive unit for making inferences about function and disease. Virchow's hypothesis had special pertinence for biological events such as fertilization, and for pathophysiological ones such as the source of the pus cell in inflammation. Diseases arise (he argued) from abnormal changes within cells; such abnormal cells multiply through division. Virchow thus regarded the study of cells as basic to the understanding of cancer where he invested much time, and, among other things, he described leukemia for the first time. His view of disease was essentially an internal one, and he was distrustful of the bacteriology of Louis Pasteur (1822-1895), which he regarded as rather shallow [11].

Rokitansky, who worked in Vienna at the Institute of Pathology, was the most outstanding morphological pathologist in the world. Together with his assistants he performed almost 60,000 autopsies in less than 50 years. His classifications of the changes in organs produced by disease set standards acclaimed by all. However, Rokitansky's reliance on humoral theories (he tried to reconcile the ancient concepts with modern anatomical knowledge) led to devastating criticisms by the young Virchow, which shook his standing, but he remained an honored pathological anatomist throughout his life [9].

By reducing all vital phenomena into cellular phenomena, Virchow canceled all those theories attributing an active role to the magma or the lymph liquid for the generation of cells. Those derive from a division of the mother cells.

Like Joseph Broussais (1772-1838), Virchow revealed the role of local irritating agents in the development of cancer; he created the "irritative theory", which Louis Lumière (1864-1948) defended till his death. For the explanation of metastases, however, the liquid theory again took primacy. Virchow considered propagation through transport of tissue parcels at distant sites improbable, and believed that the liquid action of the tumor's juices was the most important element. "The juices coming out of the tumor, he declares, exert an action analogous to that of a seed on some elements". The notion of cancer heredity preoccupied him: "The hereditary transmission of cancer may be congenital, like the naevi (birth-marks), but it comes mostly out of predisposition…It is the predisposition and not the malady that we inherit; because if it was the malady we ought to have already recognized something earlier" [11].

In the 19th century the cellular structure of normal or pathological tissues was documented and Müller showed the cellular nature of neoplasms in his work *Über den feineren Bau und die Formen der krankhaftern Geschwülste*, published in Berlin in 1838. His pupil Jacob Henle (1809-1880) established the modern classification of tissues. However, it was Virchow who showed how the cellular theory enriched Pathological Anatomy and allowed many errors of the past to be rejected.

He was one of the first to observe the leucocytosis, which appeared in some cases of leukemia and understood the role of lymph nodes or the spleen in those conditions. He studied the microscopic aspects of inflammatory lesions, understood how the lesions of tuberculosis formed and, despite the primitive microscopes which he had at his disposal with no specific coloration, and the rudimentary methods of tissue preparation, he made many discoveries which are famous even today: his work on the supporting cells of the central nervous tissue (to which he gave the name "neuroglia"), the role of the lymph nodes in the extension of cancer, the importance of the intercellular substances in the conjunctive tissue [10].

Virchow's Cellular Pathology is based on the cellular theory, formulated by the adage "Omnis cellula a cellula", which opposed completely the notion of "blastema" or the formation of cells without preexisting cells. This idea, which is the basis of all biology, may seem elementary today because we know the significance of the cell and its genetic code. It is not without interest, in order to appreciate Virchow's work, to note here what Professor Pierre Picard said in the preface of the french translation of *Pathologie Cellulaire* in 1861: "Humoral pathology sees blood, vessels, perspiration everywhere and nothing else… Practice…tends to explain, continues Picard, the morbid facts through hypotheses on the action of nerves... That's the reason, concludes Picard, for the contradictions science is full of, and for the obscurities which discourage an exact and positive mind, but 20 years of persistent work, conscientious research and incessant labor have permitted Mr. Virchow to create Cellular Pathology" [11].

In the domain of oncology, the discovery of the cellular theory was to open the way for impressive progress. Looking through the microscope most of the animal and plant tissues, normal or pathological, being composed of elementary cells, we believed for a second that we were at the point of piercing the Sphinx's enigma.

François Raspail (1794-1878) can be considered the founder of this science of cells, which later will take the name of Cytology. Studying the adipose cells, he believed that he could affirm that all cells are born from other cells, thus forming new tissues. The work of Raspail was completed by the research of Antoine Royer-Collard (1768-1825) [12].

The revolutionary upheaval of 1830 stopped the development of histogenesis in France. Leaving biology, Raspail and Royer-Collard made a career in politics. But the flambeau of early Cytology would pass to the hands of German savants. They with the French shared from then on an almost exclusive monopoly on oncological conceptions of the 19th century. Schleiden, Schwann and Müller continued the work of Raspail and Royer-Collard. But bringing accidental cell production back to the cellular unity, they proved incapable of classifying them [4].

In 1843, Adolphe Hannover (1814-1849) discovered that the cancer cells show characteristics of epithelial cells and, for the first time, he coins the term "epithelioma" [5].

At that time, we must admit, Cytology was the exclusive work of microscopists, and oncology would have possibly been lost in the mist if they had never taken the trouble to observe the patients and if clinical doctors hadn't stopped glowering at the microscope.

It was Hermann Lebert (1813-1878) who, for the first time, made a synthesis of clinical and microscopic observations. In his *Traité des maladies cancéreuses* and the *Traité d'Anatomie pathologique générale et spéciale* (1855-1861), he concluded that cancer is a local disease which is characterized by a substitution of a "new material" or "neoplasm" in the normal tissues. This material is composed of multinuclear cells with hypertrophic nuclei. For having established the specifics of the cancer cell, Lebert may be considered the father of the cellular theories of cancer [12].

However, those discoveries were not enough for a definite triumph of the cause of Pathological Anatomy. That a cancer can suddenly attack any cell without the existence of any reason, was something that created scepticism. Lebert was thus opposed by Alfred Velpeau (1795-1867) who, since 1854, had supported his unified conception of cancer.

At this time, the existence of cancer cells was accepted. But no one yet knew whether this modification was the result of a local phenomenon, spontaneously generated, that no one was then in a position to explain, or the result of a deeper alteration of the organism.

As long as microscopy was limited to the field of speculation, surgeons accepted it with curiosity. But when they were asked to submit to the dictatorship of the microscope, when they were confronted with new forms of tumors coming from the microcosmos and which they should be able to distinguish at the patient's bed, when their diagnosis was canceled by the absence of multinuclear cells which they didn't know how to handle, then a wind of revolt was roused.

They initially challenged the exactitude of the microscopic observations. They proclaimed that the microscope was an unreliable, if not hallucinatory, instrument and that microscopists were mythomaniacs with their head filled with ghosts.

An immediate change of language was needed and a removal of all accusations of mythomania from the microscopists. But the surgeons did not consent to acknowledging the exactitude of the microscopic observations and added that those observations were worthless anyway. What mattered was the study of the tissues with the naked eye, not their molecular structure. The truth was going to emerge from a synthesis of those two attitudes, but for the time being, the debate seemed to be going to last forever.

The discussions between unitarians, organicists and surgeons was still ongoing when Virchow published his ideas.

Virchow and the cellular division

Published since 1859 in the *Pathologie Cellulaire*, Virchow's theory is revolutionary and, as with all revolutionary things, it makes judgments without concession. Paul Broca (1824-1880) himself didn't hide his admiration for his "German master". However, he paid him an equivocal homage: "Mr. Virchow has a lot of talent. He skillfully uses a language, which purposely makes clear or obscures the idea he exposes, according to necessity. Passionate worker supported by an imagination full of resources, he excels in forcing the approximations made by his predecessors, lighting the unknown by the unknown, and simplifying everything by transcendent generalizations" [10].

That was the opinion formulated by Broca of his colleague from the other side of the Rhine, although he had no knowledge yet of the definitive content of his doctrine. When he at last did, he made the following comment: "Today, having in front of me the French translation of *Pathologie Cellulaire* by Mr. Virchow, twice revised and corrected by the author, I must accept the evidence and reconcile with my German master. What seemed to me obscure hasn't become more clear and what annoyed me continues still to annoy me". But what was this doctrine? It was a cellular and oncological conception, named "continuous development" which, sweeping away the neo-humoral theories emerging from Pathological Anatomy, overthrew in a defiant way all conceptions of the 19th century minds in the domain of cell generation.

Genius observer, Virchow had seen and understood that the cells are not born from an amorphous blastema. Obeying the general laws of reproduction, all cells are born from other cells. Already, a few years before, the German biologist Remak had maintained the position of an endogenous generation of the cells. But in his mind, all cells were born from a mother cell through viviparity, something which led him to express an aphorism which had its time of glory. In Virchow's schema, the cells obey this principle, with the difference that they are not reproduced by viviparity but by division or scissiparity [12]. The phenomenon which scholars would one day call "mitosis" had been discovered. Eighty-five years would pass before cytology could accomplish progress with the discovery of the DNA.

The impact of Virchow's ideas was considerable because they gave an exciting image of the living material's unity. The cells, wrote Virchow, are also "living units carrying each in itself the complete characteristics of life" [6]. Normal or pathological, they behave like individuals. They are born from pre-existing cells as the animals are born from pre-existing animals. Like all beings, they originate in a straight line from an original being perpetuated by generation, in the same way every cell originates from mother to daughter, through a phenomenon of continuous generation, from the ancestral cell.

And cancer? For Virchow, it exists initially in the cancer cell which, like its homologous from the normal tissues, may be born from any cell: "During the first steps of my career, I was obliged to strive against the

error which circulated; today we know that no real specific elements of tumors exist that don't have an analogy with normal tissues. It suffices not to forget that the tumor, even if it is a parasite, is always a part of the body that it comes from, and that it doesn't develop in isolation, depending on some liquid essence, in some place of the body, by the inherent force of this producer-liquid. The tumor does not develop in the body like an individual entity, it is part of the body, it originates from it and submits to its rules. The laws of the body also govern the tumor" [6]. Thus, in the same way that the normal cell gives birth to new ones by proliferation or division, the cancer cell gives birth to other cancer cells under the influence of determined pathological states.

As for the cause of these pathological states, it resides in a chronic irritation, which provoked the formation of a "tissue of granulation", a bit similar to the embryonic tissues, degenerating gradually into a tumor. The phenomenon of germination would form preferably in a conjunctive tissue, giving thus birth to epithelial (epithelioma) or conjunctive (sarcoma) neoplasia [13].

Discussion

Combining genius with status, Virchow could be arrogant and spiteful. A famous debater, he was considered capable of demolishing opponents without even raising his voice. As an examiner he spread terror, but also affection – as it is often the case – and he gladly drank a beer with his students after lectures. Perhaps the "little doctor", as he was called, showed his true personality in caring for patients, with warmth that brought him esteem. And when his heart failed in 1902, he was given a state funeral in Berlin, a honor granted to very few German physicians. The historian George Bender has summed him up well: "Although he had many good points, his stubbornness could often impede promising projects. But his positive achievements were much greater than his errors. His courage, energy, diversity, humanity and scientific results made him unique and unforgettable" [12].

Virchow's book "*Cellular Pathology"* shines even today in the area of Pathological Anatomy, equal to Morgagni's work "*De sedibus morborum"*, with a light that hasn't faded at all through the years. It brings, on the basis of the cellular theory, a new scientific vision of facts observed in Pathology and considered under the most general and objective angle. The modern era of Pathological Anatomy is introduced through those 20 lessons, and the hesitations of the author himself, concerning for example the nature of cancer metastases, show his profound honesty and his concern never to escape from objective observances. The microscope thus becomes, also in these lessons, an indispensable instrument. The majority of wood engraved illustrations refer to documents observed with the microscope.

Conclusion

Virchow strove to integrate Clinical Medicine, Pathologic Anatomy, and Physiology. As the founder of Cellular Pathology, Virchow stressed the concepts that all cells came from other cells and that disease is an alteration of the normal structure and function of these cells. With Virchow oncology made a giant step.

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