

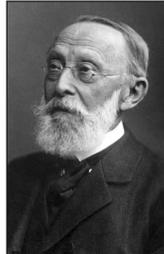
# Cell Theory and Neoplasia

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## MILESTONES

### "*Omnis cellula e cellula*"

Virchow and Remak on Cell Theory and Neoplasia



Rudolf Virchow

The critical reader of the scientific literature knows it is the rare big idea that derives from the work of a single scientist. And yet many pathologists growing up in the second half of the 20th century, I among them, were willing to forego their skepticism and accept Virchow as largely, if not exclusively, responsible for the theory that

all cells derive from pre-existing cells and do so by cell division.

A more realistic story begins with the promulgation of Theodor Schwann's cell-theory. Although the facts supporting the generalization that all biological structures are comprised of cells did not originate with him alone, it was Schwann<sup>1</sup> who convinced most of his peers that nuclei-containing cells were the universal, essential units of life. Schwann's cell-theory also included his claim that the increase in number of most animal cells depended on the formation of new nuclei by a process akin to crystallization around nucleoli in an extracellular stuff he termed the Cytoblastem. Together with the rest of Schwann's argument, his proposal for cell formation was widely adopted in spite of the lack of convincing, supportive microscopic evidence and reliable reports of cell division in protists and filamentous algae. In fairness to Schwann, the difficulties he faced as a microscopist in the late 1830s should not be underestimated. The compound microscope had come of age with the partial correction of chromatic aberration in achromatic objectives, but fixatives were limited, and neither embeddings, microtomes nor differential stains were available. In any case, Virchow, like most others at the time, adopted Schwann's story of animal cell creation wholeheartedly.

It was left to Robert Remak, following the lead of the botanists, to provide the initial evidence that binary division was responsible for animal cell replication rather than cell generation in a dubious extracellular slime. His initial observations were made on embryonic

erythrocytes of the chick embryo<sup>2</sup>. These studies were followed by investigations of developing muscle in the frog embryo<sup>3</sup>, and in both he found cell forms that were consistent with binary cell division. Nowhere did he observe the extracellular, free nuclei demanded by Schwann's cell-theory. Remak's extensive embryological studies of chicken and dog published between 1851 and 1855<sup>4</sup>, added to the evidence that cell division was the principal if not the sole means of new cell formation from the beginning of development in the fertilized ovum.

Remak, like Schwann and Virchow, trained in Johannes Müller's laboratory at the University in Berlin. After earning his medical degree in 1838, he worked as an assistant to Müller and later Schönlein at the Charité Hospital, but, failing to be appointed to the position of prosector at the Charité, he found it necessary to support his family as a clinical neurologist, carrying out his embryological research and giving courses in microscopy in his apartment. An unconscionable delay in receiving an academic appointment in Berlin was the consequence of his unwillingness to forsake his Jewish religion, even as a formality. When his appointment at the University was finally approved, it carried with it neither salary nor laboratory<sup>5</sup>.

The trajectory of Rudolph Virchow's early career<sup>6</sup> was in stark contrast to that of Remak. Virchow received his medical degree in 1843, and three years later was appointed prosector at the Charité, the position Remak had sought. Although six years Remak's junior, the two were appointed to the faculty in Berlin in the same year, 1847. Suspended in 1849 from his University appointment for his political activity, Virchow was appointed professor at Würzburg. He returned to Berlin seven years later, again the victor in a competition with Remak, this time for the coveted appointment to a new professorship of pathology. Remak was not a strong contender for several reasons, not least among them his religion, but Virchow<sup>7</sup> took no chances in pursuing the appointment, writing his father-in-law with advice for neutralizing Remak's primary if not sole supporter,

Alexander von Humboldt, "As for Humboldt, he may perhaps be persuaded to change his mind. I do not know him personally, but Uncle Emil could certainly speak to him. Do you know any member of the Mendelssohn family? Since he (Humboldt) supports the Jews, one must use Jews to get the better of him." This proposal speaks more to Virchow's "Realpolitiken" and some ambivalence towards the Jews rather than any overt antisemitism. Years later as rector of the University, Virchow<sup>8</sup> would strongly oppose the antisemitism of the student organization and chide the faculty, "(Our age) still stands at a loss before the riddle of anti-Semitism....Until now no one has asked for a professorship of anti-Semitism, but it is said that there are already anti-Semitic professors". He obviously did not consider himself one.

Remak summarized his early work on cell generation in an 1852 paper<sup>9</sup> in which he reviewed the literature and summarized his own contributions, "Since the publication of the cell-theory, it has seemed to me that the extracellular creation of animal cells is as unlikely as the generation aequivoca (spontaneous generation). These doubts have led to my observations on the multiplication of blood cells by division in bird and mammalian embryos ..... and the division of muscle bundles in frog larvae; then finally in the spring of 1851, I succeeded in finding that all embryonic cells multiply by division." He concluded, "These results are just as closely related to pathology as they are to physiology.....I venture to suggest that pathological tissues are, like normal ones, formed not in an extracellular cytoblastem but are the descendants or products of normal tissues of the organism." At the time, Virchow was still laboring under a slow conversion from an unquestioning acceptance of Schwann's cytoblastem to a less committed view. Remak, following his own advice that further investigation of cell division in pathologic changes was warranted, examined two dermal tumors for evidence of the mode of cell generation, reporting his findings in 1854<sup>10</sup>. "One of the tumors appears to have been a sebaceous nevus, the other a sweat gland tumor." Apologetic for the limited number of examples, Remak still considered his findings together with the evidence in the literature sufficient to draw conclusions: "In general I find nuclei everywhere within cells and appearances which I consider to indicate an increase of the cells through division according to the mode I have described for normal tissues... I therefore now believe that the thesis can be formulated quite precisely that tumors are not new tissue entities but represent the transformation of normal tissues with growth by continued division in which either the structure and composition of the normal tissues persists (homology) or the structure and composition are modified through degenerative changes (heterology). Virchow<sup>11</sup>, reviewing the years' progress, reported on Remak's paper but was non-committal, acknowledging but neither rejecting nor accepting Remak's conclusion on cell formation in tumors.

In the same year in the first volume of the *Handbuch of Speziellen Pathologie and Therapie*<sup>12</sup>, Virchow offered his agreement with Remak that the formation of cells from free extracellular nuclei did not occur, but he was still unready to accept cell division as the exclusive mechanism of cell increase and listed four possible forms of cell replication: 1) the division of pre-existing cells, 2) cell budding 3) a modified form of Schleidin's proposed cell formation from intracellular particles, and 4) organization of an exudate or blood. Less than a year later, Virchow, in a bombastic editorial<sup>13</sup> adopted the aphorism, *omnis cellula a cellula*, applying it to

pathological changes including tumors. In the editorial, Virchow did not explicitly embrace cell division as the exclusive means of cell generation and provided no consideration of the mechanism; nor did he credit the work of Remak or anyone else for his modified position. Remak<sup>14</sup> took grave offense at what he perceived as Virchow's failure to acknowledge his contributions, writing in a letter to Virchow, "In the first issue of the 8th volume of your archives the phrase: *omnis cellula e cellula* appears as your own without any mention of my name. That you make yourself ridiculous thereby in the eyes of the knowledgeable, since you have no evident embryological expertise, neither I nor anyone else can undo. If however you wish to avoid a public discussion of this matter, I would ask you to immediately acknowledge my contribution when and where you choose. It goes without saying that I reserve the right to judge if your clarification is sufficient in form and content."

Two years later in his published lectures, *Cellularpathologie*<sup>15</sup>, Virchow notes Remak's studies on erythroblasts and comments on his embryologic observations, "... if what has been most rigidly maintained by Remak is correct, namely that the cleavage of the yolk also is due to a visible division of cells, ...we are not dealing with a free organizing impulse working within the yolk but with progressive divisions of an originally single cell." Even then Virchow was not ready to accept Remak's concept of neoplasms arising from the various specific tissues of the body by progressive cell division, turning instead to the connective tissue as the principle, common source of tumors, an idea he would never fully give up. With the passage of time, Virchow's renown has obscured the historical details and largely deprived Remak of the credit due him. In Henry Harris<sup>16</sup> cogent metaphor, Remak was the discoverer whose voice was almost drowned in the publicity unleashed by Virchow, the colonizer.

#### References:

1. Schwann T: Mikroskopische Untersuchungen der Übereinstimmung in der Struktur und dem Wachstum der Thiere und Pflanzen. G. Reimer, Berlin, 839.transl. by H. Smith. Sydenham Society, London, 1847.
2. Remak R: *Med Ztg* 1841, Ver. Heilk. Pr. 10:127,
3. Remak R: *Froriep's Neue Notizen* 35:305-308, 1845
4. Remak R: *Untersuchungen über die Entwicklung der Wirbelthiere*. G. Reimer, Berlin, 1855
5. Kisch B, *Trans. Am. Philos. Soc. New Ser.* 44:227-296, 1954 Schmiedebach, H-P, Robert Remak. G. Fischer, Stuttgart, 1995
6. Ackerknecht, EH, *Rudolph Virchow*. Arno Press, New York, 1981
7. Virchow R, Letters to his parents, 1839-1864, ed. Marie Rable. transl. L.J. Rather, Science History Publications, Canton, MA, 1990
8. Kampe N. *Leo Baeck Inst. Yearbook* 31:43, 1987
9. Remak R, *Arch. Anat. Physiol. wiss. Med.* pp47-52, 1852
10. Remak R, *Deutsche Klinik* 6:170-174, 1854
11. Virchow R, *Canstatt's Jahresber. Ges. Med.* 2:11, 1854
12. Virchow R, *Handbuch der speziellen Pathologie und Therapie*. 1:329-330, 1854
13. Virchow R., *Arch. Pathol. Anat. u. Physiol. u. klin. Med.* 8:3, 1855. transl. by L.J. Rather in *Diseases, Life, and Man*. Stanford U. Press, Stanford, 1958.
14. Letter from R. Remak. in the archives of the Staatsbibliothek Preussischer Kulturbesitz Berlin quoted by Schmiedebach (5)
15. Virchow R. *Die Cellularpathologie*. A. Hirschwald, Berlin, 1859. 2nd ed. transl. by F. Chance, J.B. Lippincott, Philadelphia 1863. reprinted by Dover Publ., New York, 1971.
16. Harris H, *The Birth of the Cell*, Yale Univ. Press, New Haven, 1999