Milestones... in Investigative Pathology

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Proving Virchow's "Omnis cellula e cellula" ("All cells derive from other cells")

Flemming W., **Contributions to the knowledge of the cell and its vital processes**, part 2. Arch Mikr Anat 18:151, 1880 (English transl. at *J Cell Biol* 25: 3–69, 1965).

Rudolph Carl Virchow
1821 - 1902

As you count mitotic figures per 10 high-power fields, your activity presumes knowledge that the gross tumor seen on PET/CT scan was due to the accumulation of neoplastic cells, and that the basis for this accumulation was a net difference in cell birth and cell death rates. You know that the cell birth rate is a function of the cell cycle time and the percentage of the population in the cell division cycle, and that cell birth is due to division of a parent cell into two similar daughter cells. You know that the daughter cells have features similar to the parent cell because of the similarities of their template DNA, and that the daughter cells are similar to each other in large part because of the semi-conservative replication of the parent cell's template DNA. You bother to count mitoses to define grade because statisticians have correlated neoplastic cellular kinetic parameters in certain neoplasms with natural history (think untreated Burkitt's lymphoma and follicular lymphoma) and response to chemotherapy.

It wasn't always so. In the first half of the 19th century, one of the scholarly debates in microscopic anatomy and pathology was how cells in the various tissues came into existence. Schools of thought ranged from spontaneous generation (Aristotle on), to physicochemical crystallization within pre-existing cells (Schleiden, Schwann), to origin of new cells from pre-existing cells (Remak, Virchow). Pasteur's goose-neck experiments of the 1850 served to disprove the 2,000-year-old concept of spontaneous generation.

It was left to Walther Flemming (English translation at *J Cell Biol* 25: 3–69, 1965) to use histochemical stains on acid-fixed fire salamander epithelia to observe and describe the phases of mitosis and cytokinesis. The studied cells were large and flat, allowing finely detailed observations with available optics. He noted that duplication of nuclei requires an intermediate step during which there is a "metamorphosis of the nuclear mass into threads" that align and separate, i.e. mitosis. He referred to this as "indirect nuclear division," and commented that he never observed "direct" nuclear division (without mitotic progression) in the plants or animals that he studied. He coined the term "chromatin" for the stained nuclear material, and the term "mitosis," combining the Greek term mit (thread) with –osis (accumulation) to describe the process of nuclear dissolution and duplication. Flemming described the phases of mitosis, drawing the compaction, alignment, and subsequent segregation of sister chromatids into daughter cells, with reversal of the compaction process in the newly formed daughter nuclei. He noted a standard progression in the mother cell nucleus from "skein" (early prophase) to "star" (metaphase) to "equatorial plate" (anaphase). He noted that this metamorphosis into threads (mitosis) is a standardized sequence of nuclear events across multiple tissue types and across multiple species, with the end result that a mononuclear cell divides into 2, and only 2, daughter cells. He concluded that mitosis is the usual process for nuclear (and cellular) division of a mother cell into two daughter cells, commenting: "The most significant result at this point to me, consists in having retained the possibility of reducing the division process everywhere to phenomena which are fundamentally and in principle alike, and are produced by the same forces." His documentation of division of eukaryotic mother cells into two similar daughter cells supported Remak's and Virchow's theory that all cells are derived from other cells *("Omnis cellula e cellula").*

We now know that chromatid segregation is the last step in a cell division cycle that begins with fast, coordinated replication of the entire chromosome complement using multiple origins of replication, with centromeric cohesion of sister chromatids until microtubule tensions are balanced at metaphase (Blow, EMBO Rep 6:1028, 2005). Mother cell DNA replication leads to sister chromatid segregation into daughter cell neo-nuclei via the stepwise process of Flemming's mitosis. Repeat as able, until your telomeres wear out. Distort the process by running through your cell division cycle checkpoints and ignoring the DNA damage, and you can end up with daughter cells showing non-diploid chromosomal numbers and translocations, all now detectable once Flemming's stars and equatorial plates could be dissected and catalogued into unique numbers and types of chromosomes for each species. In this sense, Flemming was the father of modern Cytogenetics. Once you can put numbers on human chromosomes, you can recognize by G banding that some cases of chronic myelogenous leukemia (CML) and acute lymphocytic leukemia (ALL) show reciprocal translocations between chromosomes 9 and 22. Once you recognize this physical (9;22) translocation, you can figure out that the translocation juxtaposes portions of the *BCR* and *ABL* genes into a *BCR-ABL* fusion gene, and you can design drugs that normalize the excessive Abl tyrosine kinase activity of its fusion protein. No Flemming, no t(9:22), no *BCR-ABL* fusion gene, no hyperactive Abl, no Gleevec.

The challenge for us is to preserve and protect that evolutionarily conserved stepwise cell division cycle of DNA replication and chromatid segregation from cellular mutagens that can distort the delicate cellular equilibria of P53, RB, E2F, cyclins, CDKs, CDKIs, replication origin licenses, spindle microtubules, and cohesins. We should aim for the pristine anaphases of Flemming's fire salamanders for our own cells, and we should aim for the scientific instinct to recognize "phenomena which are fundamentally and in principle alike." ***Omnis cellula e cellula.***