

Histology's Nomenclature: Past, Present and Future

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Abstract

Histology's nomenclature has grown and changed since tissues were first conceived and identified grossly, sectioned, and observed microscopically. But this nomenclature has been dominated by static views of adult tissues and has not incorporated insights acquired through modern techniques for preparing and examining tissues and contemporary theories of tissue dynamics (e.g., stem cells). Hopefully, incorporating dynamics into tissue nomenclature will illuminate tissues' relationships to each other and their evolution, and alter concepts of tissues' mechanisms of development, maintenance, and pathology.

Keywords: Parenchyma; Histology; Anatomy; Stem cells

Histology's Past

Much like taxonomy and classification in biology generally, histology's nomenclature has been concerned with adults. Throughout most of histology's history, adult tissues have been identified with a static bias equated to the normal and serving as a basis for comparison to the developmental and pathological. This history falls into two periods, prior to and after the advent of the cell theory. The historic distinction is sharp, but contemporary usage of terms is not [1-3].

Prior to the cell theory: Morbid anatomy

Parenchyma (parenkhuma; Gk, para beside + enkhuma infusion, hence something poured in beside) is probably the oldest word in histology's contemporary lexicon. The Greek physician Erasistratus of Ceos (born 3 BCE) coined "parenchyma" for the soft parts of organs in the belief that blood poured into organs and coagulated there (The term was later adopted by botanists for soft, succulent parts of plants and fruit poured in by plant vessels in the pith, xylem, phloem, and bark).

Parenchyma became the general term for the major or distinctive material composing a tissue or comprising the bulk of an organ and was used in this context for the substance of lungs in 1578. Robert Hooke (1635-1703) then used parenchyma to designate the mucous jelly of a sponge in 1665, and later parenchyma appeared frequently in volumes of the Philosophical Transactions of the Royal Society to designate the normal or inflamed juicy or fatty parts of vertebrate organs (e.g., skin, liver, and spleen).

With the exception of Robert Hooke and the discovery of cells (or, more precisely, the walls surrounding minute holes in cork) coupled to his suggestion that living things were made of cells, the classic 17th century microscopists did little for histology. Their failure to solidify a discipline of histology or galvanize a study of tissue does not rest with the microscope, which was available commercially, but with the technical problem of preparing solid tissue for microscopic examination from suspensions or "infusions."

The alternative, adopted by morbid anatomists, for studying tissues and organs was to employ methods of chemistry. Parts of previously healthy or diseased cadavers were allowed to putrefy or dry and then placed in crucibles and boiled in acids, alkalis, and salts in order to discover their chemical properties.

Marie Francois Xavier Bichat (1771-1802) planted histology's roots firmly in morbid anatomy and the look-and-feel methods of observations made by surgeons and physicians on cadaveric organs. Without so much as touching a microscope for the study of tissues,

Bichat left his mark on special histology (the study of tissues in organs) where he introduced the concept of collaborative "membranes of organic economy" and gave special histology its mission, namely to understand relationships among tissues in organs. That accomplishment earned Bichat the title of histology's first parent [4].

Bichat is also remembered for coining the terms "mucus," "serous," and "fibrous" membranes in use today. In his own words (translated) [5]: We may distribute the simple membranes into three general classes; the first comprises the mucous membranes, so named from the fluid which habitually moistens their unconnected surface, and which line all the hollow organs which communicate exteriorly by different openings through the skin. In the second class are found the serous membranes, also characterized by the lymphatic fluid, which incessantly lubricates them. The third and last class comprehends the fibrous membranes; these, not moistened by any fluid, are thus named from their texture, composed of a white fibre. Each of the preceding simple membranes concurs, in different parts, to form the compound membranes.

Another long standing contribution of morbid anatomy is the distinction made between parenchyma as the most conspicuous or major part of organs and stroma or other parts of organs. After prolonged soaking in moving water, what remained after parenchyma was washed away was called stroma (Gk., bed covering). Stroma first appeared in the English literature in 1835 when Richard Owen (1804-1892) used the word to designate the fine fibrous tissue embedding eggs in the ovary, and, later, stroma became associated with pathology through benign fibrous tumors and malignant cancers. Today, stroma is equated with connective tissue, from dense regular and irregular (capsules, trabeculae) to loose fibrillar and reticular embedding parenchyma.

Since the advent of the cell theory: Microscopic anatomy

At the approach of the 19th century, histology turned away from morbid anatomy and toward microscopic anatomy. Several technical advances in microscopy conspired to bring about the change. In

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particular, improved methods for visualizing cells led to explanations for phenomena only partially appreciated previously. Thus Casper Friedrich Wolff (1738–1794) described granules (probably nuclei) in membranes (i.e., germ layers) that created the chick embryo within an egg, and Lorenz Oken (born Okenfuss, 1779–1851) suggested that cells built organisms, but in 1839, Theodor Schwann (1810–1882), building on the work of Matthias Jakob Schleiden (1804–1881) epitomized these ideas in the “cell theory,” namely, that the growth (*Wachsthum*) of animals and plants depended on the same elementary parts. In his words [6]: Wir haben gesehen, dass alle Organismen aus wesentlich gleichen Theilen, nämlich aus Zell zusammengesetzt sind. (We have seen, that all organisms are assembled by essentially the same parts, namely by cells).

Understandably, microscopic technology at the time led to confusion, conspicuously about how cell populations grew. Indeed, cell division was mired in mystification arising from a combination of 19th century materialist ideas of life's chemistry and vitalist notions of spontaneous generation. The rudiments of a correct description only appeared in 1852 when Robert Remak (1815–1865) described cleavage in amphibian embryos, but controversy continued to reign regarding cell division as a mechanical process resembling separating links of sausage versus a precise process of separating cellular parts. Finally, in the 1870s, an essentially correct microscopic description of mitosis (the nuclear events accompanying cell division) was thrashed out preparing the way for Rudolf Virchow (1821–1902) to enunciate the second cell theory.

Virchow's view of organismic growth is epitomized by his adage “Where a cell arises, there a cell must have previously existed (*omnis cellular e cellula*)” or, “No developed tissues can be traced back either to any large or small simple element, unless it be unto a cell” [7]. Thus Virchow emerged as histology's second parent by introducing the modern cell into “developed tissues” where it has remained since.

Virchow proposed that cells produced four fundamentally different tissues: epithelia, connective, muscle, and nerve. His fifth, vascular tissue is easily redefined as blood cells and lymphocytes, and his sixth, germ tissue—egg and sperm and their antecedents is understood by adopting the distinction drawn by August Weismann's (1834–1914) between germ and soma [8].

Beyond fashioning general histology (the study of cells' characteristics in and contributions to tissues), Virchow launched general histology on its mission: understanding the role of tissues in anatomy, physiology, and pathology. But Virchow did not come to grips with tissue dynamics, and his interest in pathology did not spill over into an interest in mechanisms of tissue maintenance, aging, and morbidity.

Regrettably, Virchow was not concerned with an interface of adult tissues with evolution and development. Indeed, for most of his mature years, Virchow was not even on speaking terms with his erstwhile student, “the German Darwin,” Ernst Haeckel, [9] and Karl Ernst von Baer, the parent of embryology, is not even mentioned in Cellular Pathology. Consequently, without Virchow's endorsement, embryology, evolution, and histology failed to interact creatively at the time.

On the one hand, Virchow spared histology from the agony of teleological speculation over recapitulation and arguments that marred evolutionary and embryologic inquiry, but, on the other hand, he cast histology on a course bereft of a comparative tradition and lacking a developmental perspective. Histology also failed to incorporate the

dynamics that complement evolutionary and embryologic research. Consequently, histology became preoccupied with stasis. Development, aging, healing, and regeneration became marginal issues instead of fundamental features of histology. Tissue turnover was of secondary interest in histology, and, most unfortunately, stem cells were relegated to the role of cells playing a quotidian role in tissue maintenance and not central players in the games of determination and change.

Histology's Present

Tissue dynamics, the missing dimension

Tissue dynamics were not originally included among criteria for identifying tissues, their varieties, and pathological alterations. The omission of tissue dynamics is not difficult to understand: In practice, mitotic figures (dividing cells) and pycnotic nuclei (dying cells) were ambiguously defined and elusive. Furthermore, quantitative methods were complicated by section thickness and cell size. The “stem cell,” nowadays the heart of cell dynamic theory, was (and is) not identifiable by routine histological methods. Consequently, confusion reigned (and reigns) about the dynamic qualities of turnover, repair, and regeneration in tissues, and even about the identity of dividing cells generally and stem cells in particular.

Which is not to say that some hearty souls did not persevere and lay the foundation for dynamic histology. Of course, Julian Huxley (1887–1975) contributed with Problems of Relative Growth [10] and D'Arcy Wentworth Thompson (1860–1948), anticipated allometric equations in On Growth and Form [11], but growth of the organism and its parts did not rest on dynamic histology.

The search for growth in tissues only began in earnest following World War II and the use of autoradiography to follow the incorporation of radioactive phosphorus and tritiated thymidine into genetic material. Thus Charles Phillip Leblond (1910–2007), exploring tissue dynamics discovered that mitosis was not destiny: asymmetric division occurred and both cells produced by mitosis did not necessarily follow the same fate in normal epithelia [12].

Adult cell populations with three different dynamics were finally identified after considerable juggling of nomenclature [13,14]. Static or decaying cell populations contained stored cells, generally incapable of cell division (or with limited proliferative capacity), or cells that were lost over a lifetime; steady state cell populations maintained themselves via self-renewing cell division by stem cells with division rates tuned to the replacement of normally lost cells; expanding cell populations consisted of differentiated cells all of which retained the ability to undergo cell division, although cell division may be rare and only conspicuous in response to trauma. An intermediate fourth type of cell population contained reserve cells (RCs) that were more or less quiescent cells supporting re-growth of otherwise static cell populations in the event of traumatic cell loss (e.g., the satellite cells of skeletal muscle) [2].

Steady state cell populations and self-renewing stem cells initially garnered the most attention if only because the methods of autoradiography made their dynamics the most accessible. Self-renewing stem cells were proposed as the source of cells for growth and maintenance in adult epithelia, blood, and pathological tissue [15–17].

A great impetus to study dynamics in tissues, however, came with the discovery of the Philadelphia chromosome formed by a translocation between chromosomes 22 and 9. Tracing the chromosome in bone marrow aspirates and peripheral blood, Laszlo G. Lajtha detected a slight overproduction of myeloid cells and their early release into

peripheral circulation in cases of chronic myelogenous leukemia [14]. Indeed, tumors led to a new stem cell concept.

Stem cells muddled history

The term, "stem cells" was introduced into zoology in 1892 when Valentin Hacker used it for the germ cells of a crustacean embryo [18]. E. B. Wilson then used the term in his historic *The Cell*, for fertilized eggs of the crustacean *Cyclops*, the round worm *Ascaris*, several dipterans and higher invertebrates [19]. For several years thereafter, stem cells were equated to germ cells capable of giving rise to the entire organism [20]. Hence, stem cells were first epitomized by their pluripotency, the ability of cells to differentiate into representatives of the three primary germ layers of embryos (endoderm, ectoderm, and mesoderm).

The notion of pluripotency carried over to embryonic cells [21] and to the celebrated embryonic stem cell (ESC) of tissue culture fame. Ultimately, the notion of potential came to dominate thinking about stem cells derived from vertebrate embryos generally (despite differences in morphology and potential). Indeed, today, bounding hope and glowing promises "to transform regenerative medicine" [22] rest on the attribution of natural pluripotency of ESCs to the induced pluripotency of somatic cells (iPSCs) [23,24].

Of course, with the exception of animals capable of regenerating entirely from stem cells (e.g., famously *Hydra* but also some sponges and planarians), somatic tissue does not normally contain pluripotential stem cells. Indeed, the loss of broad potency (multi-potent > oligo-potent > mono [or uni]-potent) generally accompanies development and differentiation in a fertilized egg's cellular progeny. In fact, the self-renewing stem cells of adult tissues typically have limited potency and give rise to cells with even more limited ranges of potency.

At the same time that potency is reduced, the phenomenon of self-renewal (replacing a stem cell with another stem cell as a function of asymmetric division) [25] remains the distinguishing characteristic of adult stem cells (ASCs). Thus, Samuel Butler's quip "A hen is only an egg's way of making another egg" is 180° out of phase: eggs are hardly self-renewing. In fact, intercellular bridges that uniquely bind self-renewing oocytes and spermatocytes are not renewed once broken. Moreover, fertilized eggs are not self-renewing, since they require a sexual process before recurrence (i.e., fertilization or parthenogenesis followed by development and maturation).

Regrettably, the definition(s) of stem cells remain ambiguous and usage continues to vacillate. Indeed, "[v]arious definitions for a 'stem cell' have been adopted by different authors" [26]. Moreover, some criteria are impossible to reconcile. For example, "[d]efining a population of cells *in vitro* as stem cells presents inherent problems, including, most importantly, the demonstration that the cells retain the capacity to fully develop into all of the mature fates of the cells for which the putative stem cell is supposed to be a precursor" [27].

The "confusion looks set to continue" [28], because fundamental issues are not resolved: What is the relationship of ESCs with virtually unlimited potential to ASCs with limited potential? Do ESCs mature into ASCs or are ASCs "reinvented" stem cells in adult tissues? And what is the role of ASCs in generating a tissue. Indeed, ASCs "may not be the first cells that are present embryonically in a specific tissue to create that tissue, but rather appear later in development where they can replenish adult tissue populations ... [Furthermore, introducing an evolutionary perspective, the] shift from a large number of more restricted progenitors capable of tissue formation to a later-emerging

population of multipotent lifetime self-renewing stem cells participating in repopulation suggests that these stem cells may be differentiated for a specific adult task necessary for the organism's survival" [29].

These problems with defining stem cells were crystallized in the late 1970s when Christopher Potten admitted that, "What fraction of the proliferative pool of cells in epithelial tissues functions as stem cells ... [is still] uncertain [. Indeed,] stem cells cannot be reliably morphologically identified and their study is restricted to various functional tests" [30]. Refining the problem, Marcus Loeffler joined Potten to proclaim the "stem cell uncertainty principle" according to which "answer[ing] the question whether a cell is a stem cell ... alter[s] its circumstances and in doing so inevitably [distorts] the original cell" [31].

The fraction of cells legitimately considered stem cells, thus, remains "uncertain" today when "hundreds of different human cell lines from embryonic, fetal and adult sources have been called stem cells, even though they range from pluripotent cells to adult stem cell lines" [32]. Indeed, the stem-cell enigma will only be solved when potency and dynamics are reconciled, and a strategy is accepted for differentiating and classifying various types of stem cells.

Histology's Future: Inserting Parameters of Tissue Dynamics

In amending histology's nomenclature, care must be taken to accommodate both the fixity and flexibility of tissues revealed by their cell dynamics. Are these dynamics (a) a one-way street (i.e., flow-through dynamics as in some surface epithelia and germ tissue)? Do they play (b) hide-and-seek (i.e., cryptic) dynamics of division in which differentiated cells reproduce themselves surreptitiously as in some glandular epithelia? Or are they (c) the stop and go or reactive dynamics that follow mobilization of dormant cells in the wake of trauma or stress as in skeletal muscle and germ-line tissue? In addition, attention should be drawn to (d) cell durability in potentially dividing cells as opposed to stasis in non-dividing cells; (e) to cellular mobilization of local cells in contrast to recruitment via circulation (of blood cells or blood-borne mesenchymal cells); and (f) whether mobilized and recruited cells contribute to maintenance and regeneration or only wound healing and repair [33, 34].

Furthermore, the suspension of division in differentiated cells is a common feature of some epithelia, cellular muscle, and connective tissue. Cell division may then resume in different tissues under particular circumstances. For example, the cells of glandular epithelia (liver, pancreas, salivary glands, pituitary, urinary system, accessory sex glands and their ducts), and connective tissue cells in a state of suspended proliferation may resume division following trauma.

The new nomenclature must accommodate the proliferation of differences discovered among cell types and not allow notions of sameness to camouflage ignorance. For example, differences represented by inter-cellular bridges in germ-line tissue and rhizomatic growth of skeletal muscle (i.e., the fusion of products of proliferative satellite cells) may seem trivial compared to the vast sameness among cells, but these oddities may illuminate the function of cell fusion following metastasis of CSCs that heretofore has escaped explanation.

At the far end of cell dynamics, in adult mammalian tissues, cell loss either follows differentiation (e.g., sloughing of epidermis and intestinal villus epithelium) or occurs as part of differentiation as demonstrated by nuclear fall off, known as apoptosis, and phagocytosis (i.e., engulfment) by circulating monocytes and mobile tissue macrophages. Previously dismissed as pycnosis (the thickening of nuclei; Gk. thick

or dense), apoptosis is now routinely equated with programmed cell death, although an important part of the so-called program is the recruitment of monocytes and macrophages by chemokines as simple as free nucleotides [35] or as complex as complement and other elements of the immune system. A useful nomenclature could hardly overlook these differences.

A recently proposed nomenclature (1, 2, 3) incorporating tissue dynamics may avoid some of these problems and overcome some of these objections. This nomenclature incorporates the suggestion that two primordial tissues arose from originally independent epithelial-like and ameba-like ancestors that became integrated symbiotically in a primitive organism(s) and evolved by competition within the organism(s) into present tissues. In general, epithelia, muscles, nerves, and the germ line are derived primarily from the epithelial-like ancestor, while blood and connective tissues are derived primarily from the ameba-like ancestor. Epithelial-like tissues exhibit direct intercellular connections (gap junctions) and are coupled by external coats (e.g., basement and peripheral lamellae) otherwise absent in ameba-like blood and connective tissues. In contrast, extracellular material is abundant in ameba-like tissue, and intercellular connections rare.

Of course, consequent to the merging of the primordial tissues' genomes epithelial-like and ameba-like tissues in Phanerozoic organisms have some degree of mixed traits. For example, epithelial-like junctions are found between osteoblasts and osteocytes in compact bone, and epithelial collagen IV may reside beyond epithelial borders.

Surprisingly, ASCs of epithelial-like and ameba-like tissues seem radically different and not readily comparable. Epithelial ASCs and their derived clones of transit amplifying cells (TACs) support simple and stratified epithelia covering surfaces (epidermis, intestinal epithelium including intestinal glands known as crypts) and some epidermal derivatives (pilo-sebaceous systems, mammary glands, and parts of sex ducts), as well as some carcinomas. Interestingly and provocatively, research has yet to determine if cancer stem cells (CSCs) or cancer initiating cells (CICs) are genealogically linked to ESCs and/or ASCs [36], and if these cancer progenitors gain ascendance over ASCs or ESCs stochastically or through a cascade of mutations [37,38], i.e., the evolutionary theory of cancer.

Adding to the confusion about tissue dynamics are results *in vivo* on the alleged transmutation of hematopoietic stem cells (HSCs) to nerve and other nonhematopoietic tissues and of mammary cells to a spermatogenic cell fate in contrast to the much narrower transformation of stromal stem cells from marrow into osteoblasts, chondrocytes, adipocytes and possibly myoblasts [39]. The plasticity or potency of the HSCs may, however, have been exaggerated as a consequence of cell fusion [40]. Nevertheless, the potential of epithelial ASCs may be vastly limited compared to the potential of HSCs, and the two types of stem cells may be more unrelated than the name "stem cell" suggests.

Hopefully, histology will move into the 21st century by adapting its nomenclature, language, vocabulary, and usage to histology's many applications. But, changing a well-known system of nomenclature is fraught with dangers. Above all, uncertainty as well as advances in knowledge about tissue dynamics must be brought cautiously into histology's nomenclature. While histology's nomenclature has been revised in the past in response to and in order to solve biology's problems with respect to development and pathology, today the task is enormously more complex: revisions must now accommodate tissue dynamics, provide an evolutionary perspective of tissues' relationships, and suggest theories of disease. Indeed, progress in research on cancers and aging may well hang in the balance.

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