PERSONAL VIEW

Is there a Need to Change the Basic Principles of Histology? Educational, Functional and Embryological Perspective

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Summary

Although it is not an easy task to classify cells into different types, or in turn cell types into tissue types, a clear, understandable, didactically and clinically relevant tissue classification is indispensable for undergraduate medical education, expert discussions in biomedical research as well as for clinical practice. From the earliest discovery of the light microscope on, tissue classification has been a dynamic process. Historically, it was not a rare occurrence that different textbooks offered different tissue classifications. Nowadays, classifications have almost become uniform – the most common is the histological classification into four basic tissue types (epithelial, connective, muscle, nervous), which is recognized by the majority of modern histology and pathology textbooks. The reason is that, with some exceptions, this classification seems to be the most relevant not only for educational purposes but also from an embryological perspective and clinical-histopathological practice. Recently, attempts have been made to abandon this established classification and replace it with a new one. Any new classification, which would improve the presently used is welcomed. However, if the proposed innovation does not satisfy the needs of modern education and clinical practice, it should be handled with great caution or reconsidered.

Keywords

Classification • Education • Four tissue types • Terminologia Histologica

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Everything should be made as simple as possible – but not simpler. (Albert Einstein)

The human body comprises of a finite number of recognizable cell types. Unfortunately, to distinguish a cell as an individual cell type is a demanding task. Even though a particular cell shares a similar morphology, function, and biochemical properties with a given (i.e., named, identified, recognized) cell type, it is not enough to be classified as such. The classification is complicated by many variables, which are rooted in the fact that cells are dynamic systems, which undergo continuous change. It is also difficult to determine an optimal method of cell type identification. Are the traditional morphological techniques sufficient, or is the implementation of modern approaches of molecular biology inevitable [1,2]? Although a mature human body can consist of as many as tens of trillions of cells, most histological textbooks suggest that there are only about 200 varieties of cells, however, many of these cells are at different stages of development [3]. On the other hand, other data suggest that neurons, glial cells, smooth muscle cells and fibroblasts may merely represent a broad category of innumerably diverse cell types. Based on these findings, Maclean and Hall [1] published a list of 411 cell types, which constitute the body of a normal, healthy (i.e., disease-free) human adult. Nonetheless, the definitive and exact number of cell types is far from concluded, what is best demonstrated by one of the largest international projects currently in progress – Human Cell Atlas. Its main aim is "to create

comprehensive reference maps of all human cells as a basis for both understanding human health and diagnosing, monitoring, and treating diseases" [4]. Despite an enormous advancement in the biomedical sciences, unravelling the precise quantity of cells in the human body has been a key challenge for more than 150 years.

In any case, for didactic or many other reasons, it is important to classify these 200 or more than 400 types of cells based on the properties they have in common, functions, embryonic origin or behavior under pathological conditions into several categories, known as tissues. Perhaps, the topic of this commentary many seem as "rediscovery of something widely known". We agree that the four-tissue-type classification is taught at every single university and high school and is described in all the modern histology and pathology textbooks. In spite of that, there have recently been several attempts to introduce a new classifications of tissue types, which undermine the four-tissue-type "doctrine". We are by no means against any refinement of existing tissue classification if it provides an added value, from the educational point of view or from the clinical perspective. Unfortunately, many of these new attempts to overhaul the long-established tissue classification hardly brings something progressive, innovative of useful; it is the other way around. They unnecessarily overcomplicate the classification. Moreover, these factitious new classifications have neither been based on embryonic origin nor on pathological practice, and finally yet importantly, they do not bring any contribution to the teaching of histology.

A historical perspective on human tissue classification

The discovery of cells and tissue types was necessarily predated by the emergence of microscopy as a technical field. From a historical perspective, the applicability of the knowledge of histology to clinical medicine was delineated by two key moments, which may also be seen as defining milestones. The first one was undisputedly the application of light microscopy to biomedical research in the 17th century, and later the electron microscope in the 20th century, which revealed the realm of "microcosmos" to the scientific community [5]. The second milestone in the development of clinically oriented histology is represented by the establishment of the cell theory (*"omnis cellula e cellula"*) in the 19th century, which is equally applicable to the pathological formation of neoplasms, as well as normal embryonic development. This contribution of Robert Virchow (1821-1902) have initiated a cell-focused perspective on the etiopathogenesis of countless diseases, which is prevalent to this day [6].

Although the first classification of human tissues was proposed in "*Anatomie générale*" in 1802 by a French anatomist and pathologist Xavier Bichat (1771-1802), the available references regarding the work of Bichat indicate that he had not used microscopy as a method to describe his 21 types of tissues [7, 8]. Neumann and Neumann [9] provided a thorough historical overview of tissue classification by several authors from the 19th century. In addition, we summarize the general tissue classification of some 19th and early 20th century original textbooks in Table 1.

Present situation

The vast majority of modern histology textbooks recognizes four types of tissues – epithelial, connective, muscle and nervous [17 - 22]. The tissue classification presented in the first edition of *Terminologia Histologica* in 2008 [23] introduced two novelties. The term "connective tissues" was replaced by the term "connective and supporting tissues". This term including connective tissue proper (including loose, dense and adipose connective tissue), cartilage and bone has been routinely used for decades in, e.g., German ("Binde- und Stützgewebe"), in Slavic languages (in Czech as "podpůrná a pojivová tkáň"), but also in Hungarian ("kötő- és támasztószövet"). Therefore, we consider this as a foray of "European tissue classification" into English terminology. Moreover, the union of connective and supporting tissue is not arbitrary given they have the same embryonic origin (from mesenchyme). Most importantly, they have the same histological characteristics (cells embedded in well-developed extracellular matrix, which consists of protein fibers and ground substance) and they give rise to the same types of tumors (sarcomas).

The second novelty in *Terminologia Histologica* was the decision to put "Haemolymphoid tissue" in an individual category. This is surprising because blood can

Table 1. Tissue classifications of selected 19th and early 20th century histology textbooks and Nomina Histologica nomenclature

Author	Textbook	Original terminology	Translation
Leydig, 1857 [10]	Lehrbuch der Histologie	Bindesubstanzgewebe	Connective tissue
		Gewebegruppe der	Tissue of cells that
		Muskelgewebe	Muscle tissue
		Nervengewebe	Nervous tissue
Orth, 1878 [11]	Normale Histologie	Zellen- oder Epithelgewebe	Cellular or epithelial
		Bindesubstanzen	Connective substance
		Blut und Lymphe	Blood and lymph
		Muskelgewebe	Muscle tissue
		Nervengewebe	Nervous tissue
Schaffer, 1933 [12]	Lehrbuch der Histologie und Histogenese	Blut	Blood
		Epithelgewebe	Epithelial tissue
		Binde- und Stützsubstanzen	Connective and
		Muskelgewebe	Muscle tissue
		Nervengewebe	Nervous tissue
Levi, 1935 [13]	Trattato di Istologia	Tessuto epitheliale	Epithelial tissue
		Tessuto ghiandolare	Glandular tissue
		Tessuto a funzione meccanica	Tissue with mechanical
		Tessuto a funzioni trofiche e	Tissue with trophic and
		Tessuto musculare	Muscle tissue
		Tessuto nervoso	Nervous tissue
		Umori circolanti	Circulating fluids
Patzelt, 1945, 1948 [14, 15]	Histologie	Epithelgewebe	Epithelial tissue
		Zwischengewebe	Intermediate tissue
		Muskelgewebe	Muscle tissue
		Nervengewebe	Nervous tissue
Eliseev, 1965 [16]	Nomina Histologica	Textus epithelialis	Epithelial tissue
		Mesenchyma	Mesenchyme
		Sanguis (Haema)	Blood
		Lympha	Lymph
		Textus conjunctivus	Connective tissue
		Textus musculares	Muscle tissue
		Textus nervosus	Nervous tissue

also be considered as connective tissue after all "by circulating in the bloodstream it connects all the organs of our bodies". Not only that, blood elements have also the same embryonic origin as the cells of cartilage or bone, the only difference is that the extracellular matrix (blood plasma) is a fluid without protein fibers typical for other "connective and supporting tissues".

The future of tissue classification?

In 2021, Neumann and Neumann [9] made attempt to establish a new classification of tissues which should consists of 11 basic tissue types and 30 second-order tissue types (Table 2).

Table 2. Newly proposed classification of tissues according to Neumann and Neumann [9]

Basic tissue type	Second-order type class
Surface tissues	Epithelial surface tissue
	Non-epithelial surface tissue
Glandular tissues	Epithelial glandular tissue
	Neurosecretory tissue
Sensory epithelial tissues	Sensory epithelial tissues of internal ear, olfactory epithelium and taste bud
Germinal tissues	Tissue of lobule of testis
	Cortex of ovary
Connective tissues	Loose connective tissue
	Dense connective tissue
	Mucoid tissue
Cartilaginous tissues	Hyaline cartilage
	Elastic cartilage
	Fibrocartilage
	Chondroid tissue
Hard tissues	Bone tissue
	Cementum tissue
	Dentin tissue
	Enamel tissue
Adipose tissues	Yellow fat tissue
	Brown fat tissue
Hematolymphoid tissues	Hematopoietic tissue
	Lymphoid tissue
Muscular tissues	Smooth muscle tissue
	Cardiac striated muscle tissue
	Non-cardiac striated muscle tissue
Nervous tissues	Peripheral nerve tissue
	Ganglionic tissue
	Gray matter
	White matter
	Reticular formation

This attempt for a new classification seems even more complicated than the first tissue classification introduced by Bichat (1802) that recognized 21 tissue types[7]. Neumann and Neumann [9] argued that the current four-tissue-type classification contains instances where different types of tissues mix together. For instance, lymphocytes and antigen-presenting cells are connective tissue cells, but can be found also within the epithelial linings. Some neurons as well as adipose tissue cells can produce hormones, even though "the classical and established definition" reserves this as a typical feature of "glandular epithelium". Similar examples can be also found in the newly proposed classification, after all the nervous tissue (mentioned as grey matter or white matter) contains microglia, which now should belong to the category of "connective tissue" based on their function and embryonic origin. The fact that every rule has its exceptions is especially true and valid in medicine (including human anatomy), which seems a valid point from our perspective. For example, epithelial tissue is

typically avascular, however this is untrue for the stria vascularis of the internal ear [24]; skeletal muscles are typically controlled voluntarily, however, this is only partly correct for skeletal muscles in the esophagus; in general, muscles are of mesodermal origin, but sphincter pupillae and dilator pupillae muscles are of neuroectodermal origin [25], and the list goes on.

Pros and cons of the new tissue classification for histology education

We do understand that blind and obstinate clinging on to something only for the sake of tradition which is no longer useful in modern medicine is unscientific, as science is best defined by development and change. However, we hold the opinion that it is unnecessary to change well established and justified definitions and classifications into four basic types of tissues, and it is so for multiple reasons:

1) Histology is taught at the very beginning of biomedical graduate study programs including general medicine and dentistry [26-28]. Therefore, the goal should be to make the tissue classification simple to teach and easy to remember, so not to overcomplicate it.
2) We would not insist on simplifying if a new classification would provide some tangible improvement or contribution, e.g., to align with clinical pathology, or if it would bring new insights into diagnostics and disease classification. Unfortunately, the newly proposed tissue classification introduced by Neumann and Neumann [9] seems to have no benefit with regards to pathology, e.g., that it would improve the understanding of cancer genesis, so it seems to add little from this practical perspective. We teach our students to become (mainly) clinically oriented physicians. Therefore, it seems more logical to teach our students that sarcomas originate from connective and supporting tissues, compared to what one would have to teach according to a new classification, that sarcomas can originate from connective tissue, cartilaginous tissue, hard tissues but also adipose tissue. Even though this newly proposed classification considers them as four different groups, however, all these sarcomas display a number of common biological features. Students would be only confused, without any additional utility for their later life as practicing doctors. Contemporary developments in curriculum development strongly underpin how important clinically applicable and relevant knowledge should be. Another practical example: currently, as we make an introduction to histopathology, we teach students about common origin of carcinomas and adenocarcinomas from the epithelial tissue. It is concise and short. If one accepted such new classification according to Neumann and Neumann [9], one would then have to teach the following: “Carcinomas originate from some surface tissues, especially from epithelial surface tissue. The second category of non-epithelial surface tissue may be a source of some sarcomas and some neuroglial tumors. Adenocarcinomas originate from some glandular tissue, especially from epithelial glandular tissue, but not from neurosecretory tissue.”
3) Some of the newly proposed tissue types are literally confusing and would cause a complete mayhem in the teaching of pathology. If someone said that the tissue of the testicular lobule is a “germinal tissue”, a pathologist would think of “germinal cell tumors”. But a lobule of the testis contains not only “germ cells”, but also interstitial endocrine cells (of Leydig) and nurse or supporting cells (of Sertoli), both of which may be a source of sex cord-stromal tumors, often called non-germ cell tumors [29]. In result, students learning pathology or later surgery and urology would likely be confused – why forms germinal tissue a source of both germ cell as well as non-germ cell tumors?
4) The newly proposed nomenclature is not grounded in embryology. The new tissue categories make attempt to combine cells with diametrically distinct embryonic origin. For example, “non-epithelial surface tissue” merges cells of mesodermal origin (synovial intima) with neuroectodermal cells (ependyma). Again, cells of different origin have diametrically different biological and pathological properties/behavior.
5) The newly proposed classification is not universal. Exceptions in biology and medicine have always existed and will continue to do so. Even in the “classical” classification, and in the new one, there may be even more. Here are several examples for illustration. Every individual cell of the stomach lining produces mucus, so should it be classified according to the “new classification” as epithelial surface tissue or epithelial glandular tissue? How

endothelium and mesothelium should be classified? Are they "epithelial surface tissues", despite the fact that they are of mesenchymal origin like other connective tissues? Should they be classified regardless of their connective tissue-like biological features under pathological conditions? Why then has adipose tissue not been classified as "glandular tissue" considering its massive endocrine activity [30] or as "hematolymphoid tissue" due its important immunological function and its role in low grade chronic inflammation [31]? Similarly, the cardiac striated muscle tissue cells have mixed muscle-secretory phenotype and produce the natriuretic peptide family [32, 33]. Nevertheless, no one doubts that it is a "real" muscle tissue and not a glandular tissue. Which category should the thymic reticular epithelium belong to? It is neither "surface epithelial tissue" nor "epithelial glandular tissue", in spite of its hormone production [34]. Classifying it into "hematolymphoid tissue" would not make any sense from the pathological perspective, because its cells are epithelial cells (arranged as reticular epithelium) and can give rise to thymomas and thymic carcinomas [35], i.e., tumors which are completely different compared to tumors originating from the cells of hematolymphoid tissue. A last example of such inaccuracies is the description of the synovial intima according to Neumann and Neumann [9] classification: „Synovial intima is not a connective tissue in sensu stricto, and the absence of a significant amount of extracellular matrix argues against classification as a connective tissue". The extracellular matrix of fibroblast-derived synovialocytes is the synovial fluid. Synovialocytes with phagocytic activity are truly typical monocyte-derived macrophages, what is confirmed by their CD 68 positivity. Synovial intima can also appear in extra-articular locations. It can originate directly from the connective tissue proper, as confirmed by our own study [36]. Therefore, the view that the synovial intima is a typical "connective and supporting tissue" is supported by its embryonic origin, composition and immunohistochemical characteristics. If the authors´ definition was to be applied strictly, one would have to make an extra class also for anterior limiting layer of the iris, since its surface also contains flattened fibroblasts and melanocytes and not epithelial tissue [37].

Conclusions

Classification of tissues into four (or five) basic types may not be considered being optimal, unchangeable and flawless, however, nothing superior has been proposed to date. The classification based on four-basic types is logical from the educational standpoint, it is also useful for histopathology teaching and primarily it respects (as much as possible) the embryonic origin of cells. The newly proposed classification provides only superficial categorization of cells based on some of their common morphological or functional features, but neglects their embryonic origin which is vital for the understanding of pathological processes. When proposing a new classification, it is necessary to bear in mind that histology forms the basis for histopathology. Any classification must be justified and applicable to current pathological practice. We think that future scientific discussion will definitely deepen our knowledge and our view on this rather academic problem and we hope that the final solution will be agreed upon to fully satisfy terminologists, histologists, embryologists, pathologists and educators alike.

Conflict of Interest

The first / corresponding author is currently the coordinator of Histology working group under the Federative International Programme of Anatomical Terminologies (FIPAT). This article is only his own viewpoint which may not be the same as the opinion of other experts of the International Federation of Associations of Anatomists (IFAA).

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