

## Unseen Battles Within Tissues Histopathological Insights Into Disease Progression and the Fight for Timely Diagnosis

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### Abstract

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The microscopic examination of tissue samples (the study of diseased tissues) is the foundation of many contemporary diagnostic fields. It provides fundamental insights into how diseases progress. Most diseases start silently at the cellular level long before clinical symptoms present, thereby making them extremely difficult to detect early. Abnormal findings detected by histopathology

include changes in tissue architecture, changes of cellular morphology, and changes of molecular compounds. All of these abnormal findings are directly associated with

inflammation, infection, degeneration to the tissue level, and the development of malignant (cancerous) tissue. Therefore, histopathology enables clinicians to identify diseases sooner (while they are still treatable) and intervene in an expeditious manner. Diseases such as cancer, autoimmune diseases and chronic inflammatory diseases arise from complex interactions of many different types of cells, tissues and molecular pathways. The use of histopathological analysis will provide insight into these changes and assist in determining the classification of the disease, the stage of the disease and the prognosis of the patient with the disease. Advanced technologies that utilize advanced methods (including immunohistochemistry, digital pathology, and artificial intelligence) have further enhanced both the accuracy and efficiency of diagnostic testing, therefore transforming pathology into more accurate and predictive science. Despite the advancements associated with histopathological testing, there are still many issues regarding the use of histopathological testing in practice. Some of those issues include: diagnostic variability, limited access to diagnostic testing in lower resource areas, and increased complexity of the diseases that require testing. Resolving these issues is critical to enhancing the clinical utility of testing. Altogether, histopathology serves as a bridge between clinical symptoms and the underlying biological processes, thereby contributing enormously to the: early detection of disease; early intervention and treatment of disease; and ultimately improving patient care.

**Keywords:** Histopathology, disease progression, early diagnosis, tissue pathology, cancer detection, inflammation, biopsy, diagnostic medicine, digital pathology, molecular pathology

### Introduction

The body operates through an array of complex cellular and biochemical processes, which require maintenance of their balance (Alzeer, et al 2024). Disease occurs when this balance is disrupted and as a result of many factors (internal as well as external). While clinical signs are usually indicative of a person's health status, disease ultimately begins at the cellular /microscopic level prior to any visible evidence of any illness in tissues; histopathology reveals these changes at this early stage in development and thus provides insight into disease processes and progression.

Histopathology's importance is in its ability to identify abnormalities in cellular structures, tissue organization and molecular make-up prior to any visible abnormalities. These changes exist prior to the individual having any clinical signs/symptoms of disease, therefore histopathological examinations provide an essential means of diagnosing or identifying early stages of disease for the purpose of early intervention/prevention (Eshkoo, et al 2015). A great example is the progression from normal cells to malignant cells, which occurs over time through a number of stages (each associated with a unique set of microscopic characteristics); identifying these stages before the clinical symptoms of illness appear can greatly enhance remedial treatment results and improve survival rates.

Histopathology has progressed significantly since its inception as a single-phase discipline, to a multidisciplinary field that combines traditional microscopy techniques and advancements in technology (like molecular diagnostics and AI). This progression has extended histopathology's ability to diagnose and treat patients in more precise ways, building upon the original goals of histopathology, which were to give diagnostic information about disease at the tissue level.

### **Histopathological Basis of Disease Progression**

The progression of a disease reflects physiological and/or pathological changes at the cellular and/or tissue levels. Changes in the body that affect the body's normal physiological function can be observed through histopathology (Virchow, et al 1863). In particular, a significant portion of the patients' injuries approximately 98% will present with some form of inflammation; inflammation is the body's first line of defence against injury. Inflammation is characterised by the rapid influx of immune cells, increased blood flow and permeability of small blood vessels. Acute inflammation, therefore, is to help the body expel foreign substances and help aid in the body's healing process. While acute inflammation is an appropriate response in the short term, if acute inflammation persists for an extended period of time (i.e. chronic inflammation), the result of that chronic inflammation will often lead to tissue damage and contribute to the onset of numerous diseases. Histopathology of inflamed tissues often shows evidence of leukemia or lymphocytic infiltration, as well as tissue distention/edema, which reflects the underlying pathology resulting from a patient's injury.

Another significant factor contributing to disease progression and seen throughout histopathology is cellular adaptation. As a result of stressors being applied to a cell, the cell will often adapt by either hypertrophy (increase in size), hyperplasia (an increase in number), atrophy (decrease in size), or metaplasia (a change in function) (Chen, et al 2024). Typically, cellular adaptations can be reversed; however, if a stressor is perpetual and continues to be present, irreversible damage to the cell will occur and progression to disease states will begin e.g. dysplasia and cancer.

Cell death can occur via either necrosis or apoptosis, both of which play an important role in the development of disease. Necrosis is frequently due to trauma and will result in inflammation and destruction of the affected tissue. Conversely, apoptosis is a regulated process and is required to maintain tissue homeostasis. Disruption of either of these mechanisms can lead to the development of pathologies, indicating that histopathological evaluation of tissue samples is critical to understanding the pathophysiology of disease processes.

### **Histopathology in Cancer Development and Progression**

Cancer is considered to be one of the most extensively studied diseases by pathologists and has a very complicated and important role in global health (Franceschi, et al 2013). The tumorigenesis of cancer occurs in multiple steps and involves the following elements: genetic change, unregulated (or uncontrolled) proliferation, invasive disease into surrounding tissues, and metastasis (the ability to spread to other sites in the body). In order to establish whether or not a patient has cancer, pathologists perform histological examinations on biopsy or tissue specimens from patients diagnosed with cancer to establish a pathology diagnosis of the patient's cancer type and to determine the stage and grade of the patient's cancer. This evaluation of histopathological specimens allows Pathologists to examine a variety of microscopic parameters that may influence a patient's diagnosis. The evaluation of these different parameters will help patients develop a personalised treatment plan; obtain prognostic estimates or recommendations (Kent, et al 2018).

The development of malignant tumours typically begins with the development of various pre-malignant stages (hyperplasia, dysplasia, and carcinoma in situ), which can be identified microscopically. Each of the tumor's precancerous stages contains specific

characteristics that can be visualised microscopically. Therefore, early identification of these precancerous changes is critical to prevent metastasis and to improve patient outcomes.

The use of new immunohistochemical techniques has greatly improved the potential for making histopathological diagnoses including the identification of specific protein expression (based on the type of tissue) during histopathological evaluations. The ability to use this technology to identify the source of the tumour and perform targeted therapy has provided a significant advantage to pathologists. The advent of molecular pathology and the ability to examine patients for genetic mutations has enabled heightened levels of customised treatment and has represented a true advancement in cancer treatment; therefore, the overall standard of care has improved with respect to cancers.

### **Role in Infectious and Inflammatory Diseases**

Histopathology is an important tool for determining whether someone has an infectious disease, as it allows observation of pathogens and how the immune system reacts to them in the affected tissue. The ability to envision these components, at a microscopic level, is one of the major advantages of histopathological testing and is very different from most other laboratory tests, which often identify infection indirectly (Gupta, et al 2009). Pathological findings frequently reveal structural evidence of the disease process within the infected tissue at the microscopic level. Biopsy or surgical samples can provide histologic findings that often demonstrate specific disease characteristics that can be used for diagnosis based upon specific patterns of morphology. One such pattern is the formation of granulomas, which consist of organized clusters of macrophages, lymphocytes and multinucleated giant cells, and are common in chronic infections such as TB and some fungal diseases. Necrotic tissue, often associated with neutrophilic infiltration, is also indicative of acute bacterial infections. Additionally, some histological techniques can be employed to selectively stain microorganisms directly in tissues, which enhances the diagnostic utility of histopathology.

With regard to inflammatory diseases, histopathology provides a wealth of information regarding how tissues are injured and how the underlying disease will progress (i.e., advance). Chronic inflammatory diseases, particularly autoimmune

diseases, are characterized by the continued activation of the immune system, whereby the body produces antibodies against one's own tissues (Pisetsky, et al 2023). With this process, continued immune activation results in the deterioration of the tissue and in significant changes in the structure of the tissue. Through histopathological evaluation, pathologists can observe different patterns of inflammatory cell infiltration based upon the cellular component of the immune response. For example, many autoimmune diseases will demonstrate marked lymphocytic, plasma cell, or macrophage infiltration depending on whether the autoimmune disease is primarily due to the actions of B-cells, T-cells, or monocytes, respectively. However, additional features of tissue damage (e.g., fibrosis, vascular changes, and alteration of the usual tissue architecture) provide valuable information regarding the chronicity and severity of tissue damage due to inflammation. For instance, long-term inflammation usually causes excessive fibrotic connective tissue formation that leads to the formation of a scar and impairs normal organ function. The histopathological findings not only contribute to the diagnosis of a specific inflammatory disease, but they also aid clinicians in evaluating the activity of the inflammatory disease, as well as in planning appropriate therapeutic interventions.

The ability of histopathology to identify whether the inflammation is from an infectious or non-infectious source is another significant aspect of determining how to manage the disease (Hofman, et al 2017). The treatment plan for managing these types of inflammation is vastly different. Treatment for infectious forms of inflammation generally involves the use of antimicrobial therapies directed at the infective agent, whereas treatment for non-infectious (e.g. autoimmune) forms of inflammation is usually accomplished through the use of immunosuppressive or anti-inflammatory drugs. The evaluation of histopathological data aids in the determination of infectious versus non-infectious origins of inflammation by examining the types and distribution of inflammatory cells, the presence or absence of identifiable pathogens, and the distribution pattern of the tissue damage. For example, the presence of either microorganisms or a very distinct pattern of tissue damage would raise a suspicion of an infectious inflammatory process, while an evenly distributed (diffuse) tissue damage that showed no evidence of an identifiable pathogen would suggest the inflammatory source was non-infectious.

## Technological Advancements in Histopathology

The histopathology field has experienced drastic changes since the addition of new technology; it has transitioned from relying heavily on the microscope to being a high-tech, data-driven discipline (Dalton, et al 2024). Histologists have traditionally relied on two techniques when processing histology slides: manually preparing them and then viewing them microscopically. Modern digital pathology has transformed the nature of histology by providing numerous innovative ways to improve the speed, quality, accuracy, and availability of diagnoses. For example, record glass slides have been converted to high-quality digital images that can be displayed, analyzed, and shared electronically (digitally). Furthermore, digital pathology assists pathologists in consulting with physicians and obtaining second opinions from specialists anywhere in the world, making it possible for pathologists to obtain a second opinion from anywhere.

To accurately capture tissue structures down to their finest detail, digital pathology utilizes superior imaging technologies which provide the ability to zoom in and out, annotate, and analyze digital pathology samples with fantastic clarity. Additionally, digital pathology provides software-based automated image analysis tools that can be used to quantify variables (for example, cell numbers, stain intensity, and tissue architecture) which, due to the absence of human error, would provide far better accuracy, consistency, and reproducibility than pathology performed solely by humans. In addition to helping improve laboratory workflow, automated image analysis systems would promote more uniform diagnoses, especially for patients with lacks of common characteristics (e.g., cancers), since these complex cases frequently present pathologists with diagnostic challenges.

AI technology has advanced rapidly recently and is being applied to histopathology. Machine learning and deep learning are two AI technologies used to enable machines to learn how to identify certain types of patterns that may be difficult for humans to see in histological images (Sultan, et al 2020). Applications of AI include automating tasks such as recognizing tumors (detecting, classifying, and grading) and predicting disease progression based on the morphological characteristics of tumors. By rapidly processing large quantities of tissue samples and providing a list of potential findings for pathologist interpretation, AI can dramatically reduce the time it takes to

analyze tissues, as well as the risk of missed diagnoses. Pathologists will not be replaced by AI; rather, AI is being developed to supplement the skills of pathologists, thereby enabling them to enhance the accuracy and efficiency of their diagnoses.

In addition to imaging, advances in the field of molecular techniques (genomics/proteomics) represent significant changes to the traditional histopathology workflow. These techniques will provide much more comprehensive information about the genetic and molecular characteristics of a disease, beyond what can be seen under a microscope. The approaches used for detecting specific genetic mutations, patterns of gene expression, and the presence or absence of particular protein markers related to different types of disease are known as polymerase chain reaction (PCR), next generation sequencing (NGS) and fluorescence in situ hybridisation (FISH). The molecular results can be correlated with the histological characteristics of tissues, leading to a more comprehensive diagnosis.

The integration of molecular information into histopathology has greatly enhanced the discipline, especially in the area of oncology (Shmatko, et al 2022). Molecular data has allowed for the identification of numerous specific biomarkers related to the diagnosis of a particular cancer type that can then be utilized to select an appropriate therapy for each patient based upon their unique disease characteristics. Personalized or precision medicine represents a significant departure from traditional therapy modalities that are based upon a general classification of disease type. In addition, the integration of molecular diagnostics with digital pathology and artificial intelligence has led to the establishment of integrated diagnostic platforms. Integrated diagnostic platforms utilize the combined information gathered from morphological, clinical, and molecular sources to provide a complete picture of disease that allows greater accuracy in diagnosing patients and making more complex clinical decisions (Korf, et al 2013). As these technologies progress, they will continue to improve the efficiencies, accuracy and accessibility of histopathology.

Even though there are advances being made, adopting new technology comes with challenges such as needing specialized training, having high implementation costs, and having uncertainty around data management. Continued research and technology

innovation will probably resolve all of these problems. Histopathology will remain a key area of modern medicine.

### Challenges in Histopathology

Although histopathology has developed a significant amount through advances in technology and still plays a key role in modern-day healthcare, there remain many barriers that limit the efficacy of histopathology as it applies to patient care. One of the greatest sources of variability in histopathology is the fact that there is a high level of subjectivity associated with the evaluation of histological specimens and samples. Unlike most laboratory (clinical) tests, histopathological testing does not usually produce numeric or automated results, but instead depends on the pathologist's level of expertise and judgment. Different observers may have very different interpretations of subtle differences between cells, tissues or staining patterns; therefore, inter-observer variability is common in histopathology (Dunn, et al 2025). Even experienced pathologists often disagree on how to categorize borderline lesions (e.g., whether a lesion represents a reactive change versus an early form of malignancy). Variability can influence diagnosis, treatment decisions and patient outcomes. To address this issue, there are ongoing initiatives to create standard criteria for diagnosing a given type of specimen by creating guidelines and classifying systems, and to use digital methods and artificial intelligence methods to create more objective/reproducible diagnostics.

A second large challenge faced by the field of histopathology today is that many parts of the world, especially resource-limited or low-income regions, do not have direct access to the services and resources provided by histopathology. Such regions typically do not have laboratory infrastructure, modern lab equipment or trained personnel experienced in conducting and interpreting tissue analyses. Diagnostic delays may occur when laboratories either take a long time to respond to test results, or when the specimen has to be shipped to distant laboratories. This is especially problematic in the case of cancer, when diagnosing early is imperative for having the best chance of treatment success. Additionally, establishing and operating histopathology labs requires both substantial initial and ongoing capital investments (equipment, reagents, trained staff), which can be out of reach for many communities (Wilson, et al 2018). Practical solutions to these problems must include investments in health-care infrastructure,

education of pathologists and histotechnicians, and utilizing low-cost, technology-based options (e.g., telepathology) that can facilitate remote diagnoses and consultations.

The increasing complexity of disease will also further complicate and challenge the histopathology diagnostic process. Emerging infectious organisms, evolving antimicrobial resistance patterns, and increased recognition of genetic and molecular disorders have all led to dramatic increases in the number of diseases that require histopathological evaluation. Furthermore, several conditions have similar or atypical histological characteristics that will make their diagnosis more difficult. Modern classification systems, particularly in the area of cancer, increasingly use genetic and molecular factors as a basis for disease classification instead of morphological factors. Consequently, pathologists will need more than traditional skills associated with microscopy; they will need extensive knowledge of molecular biology and the many new diagnostic procedures that arise from it.

The developments in these areas require that pathologists have to continue their education/training/and adaptability to keep up with the pace of change in the way we conduct research, how we interpret results, and the new technologies available to us in order to provide an accurate diagnosis. Professional development opportunities can be difficult to find when resources and other opportunities are limited (Wynants, et al 2018). In addition to these challenges, there are many other challenges: workload burden, increased demand for diagnostic services, and the need for quality assurance create an additional layer of complexity to the practice of pathology. The incidence of non-communicable diseases such as cancer is on the rise globally, and so is the need for histopathological examination as a result. As a consequence, there is an increased burden placed on already strained healthcare systems which will have significant implications for the timeliness and accuracy of diagnosis. Furthermore, in order to achieve the maximum benefit from histopathology in diagnosing and treating disease, histopathology must meet several challenges that currently exist. The future of histopathology will depend on standardisation, advancing technology, increasing access and providing ongoing professional development.

### Importance of Timely Diagnosis

A key aspect of clinical management of disease is prompt recognition of disease as it relates to how well a patient responds to treatment, how long they can expect to live, and their overall health-related quality of life (Gilbert, et al 2015). For many diseases, particularly chronic and life-threatening illnesses, the disease process tends to take place slowly over time and may not be detected as the individual will not develop any notable symptoms during the early phases of the disease process. However, even during the early phases of the disease, the cellular and tissue structures within the body will have undergone substantial changes. Histopathology is a valuable tool in identifying these early cellular and tissue changes through the microscopic evaluation of tissue architecture (structure) and cell integrity. By examining tissues obtained from biopsies and other surgical specimens, pathologists can identify cellular and tissue changes associated with neoplasia, dysplastic changes in cells, or subtle inflammatory processes long before they are manifested on physical examination. For cancers and other diseases with a highly aggressive course of progression, it is critical that the disease be diagnosed at the earliest possible timeframe. This allows the patient to experience a higher survival rate as well as experience fewer side effects from severe treatments and have better long-term prognoses.

Having the correct diagnosis of a disease at the right stage is vital to the patient. If a patient does not receive a proper diagnosis of their disease and receives treatment at a later time in their disease's course, they may have permanent damage to their tissues and organs (Dörr, et al 2018). Since late diagnosis of cancers is generally associated with either metastatic disease and/or the availability of fewer options for treatment as well as poorer survival rates; the same can occur with a late diagnosis of chronic bacterial and/or viral infection if undetected in that these diseases can result in complications such as total organ failure, multi-systems affected or debilitating conditions. In addition to increased financial (health care) burden by delayed diagnosis due to longer periods of hospitalization, more complex and prolonged treatment regimens as well as intensive care, histopathology will help to resolve all of these issues through precise and direct positive identification of disease allowing for accurate diagnosis, staging and treatment planning. In addition, histopathological findings are

important not only for an initial diagnosis but for the evaluation of the status of a disease over time by comparing histological specimens from an initial time to subsequent times in order to identify whether the disease has improved, remained stable, or worsened allowing for appropriate therapy to be adjusted in a timely manner. This outlines how vital a role histopathology plays in managing patient care both during the acute and long term stages. A comprehensive approach is needed for diagnostic success, through public awareness, organized screening, and improved access to diagnostic services. Public awareness will help patients understand the necessity of visiting a physician sooner rather than later and will encourage patients to seek regular medical check-ups (Maulana, et al 2018). Through histopathological analysis, cervical, breast and colorectal cancers can be screened for pre-invasive and early malignant changes, as well as provide quality assurances that screening programs could significantly decrease the prevalence and mortality rate associated with these three cancers when implemented appropriately. Quality health care delivery systems must be developed to ensure that patients have sufficient access, affordability, and an efficient level of histopathologic services. In many regions of the world, delays in diagnoses are related to a lack of laboratory facilities and trained personnel and other logistical barriers associated with processing tissue samples. Expanding access to state-of-the-art diagnostic technology, such as digital pathology and telepathology, would help to address the barriers to timely information, allowing remote evaluation of tissue samples and speeding turnaround times.

Overall, histopathology is a very important means of linking clinical suspicion (presenting signs and symptoms) to the laboratory-confirmed diagnosis (histopathology). Histopathology takes vague signs and symptoms and precursory exam findings and converts them into clear, accurate, evidence-based conclusions to direct further clinical interventions (Stern, et al 2010). Histopathology supports a reduction in both the length of time to discover disease and clinically unpredictable outcomes from delay to clinically predictable outcomes; therefore, histopathology plays a significant role in improving the health outcomes of patients and in improving the overall effectiveness of health care systems.

## Data and Evidence

The central importance of histopathology in today's health care system is supported by an enormous amount of both clinical evidence and research. A huge number of medical decisions, from making an initial diagnosis to planning treatment and providing prognoses, depend on laboratory tests, especially for histopathology, which has a unique and vital role among laboratory tests. Unlike many other diagnostic modalities, histopathology provides direct visual evidence of the biological effects of disease at the cellular and/or tissue levels and so is one of the most reliable and definitive forms of diagnosis (Gurcan, et al 2009).

In cancer care, histopathology is the standard for diagnosing cancer and has a critical role in determining how to manage that cancer. It not only confirms the diagnosis of a malignancy but also provides important information about tumor type, grade, stage, and margin that are essential to determining the most appropriate therapy for a given cancer. Without histopathological confirmation of malignancy, cancer can not be managed effectively.

Large population-based epidemiological studies and clinical studies illustrate that histopathology has a significant impact on improving survival and quality of life for patients affected by disease. For example, many screening programs that include histopathological assessment have been able to reduce the burden of disease on populations. Cervical cancer screening is an example where established practices such as the Pap test have been followed by the confirmation of abnormal findings through histopathological examination, leading to a significant decrease in both incidence and death rates for cervical cancer in many countries. Breast and colon screenings have demonstrated similar outcomes whereby detecting pre-malignant or early-stage cancer allows for intervening at an earlier point in time and improving patient survival rates (Garcea, et al 2003). The above describes how both histopathology assists physicians in diagnosing patients, as well as how histopathology helps prevent the development of certain malignancies by detecting them at an earlier and more treatable stage.

In addition to its current-day use in the clinical setting, advances within the field of pathology through technology have further highlighted the importance of histopathology. For example, digital pathology has enabled high-quality imaging of

pathological slides, as well as off-site consulting capabilities, and more efficient ways to store and retrieve medical records. These advancements have resulted in efficiencies in diagnostics and expanded access to diagnostic services. This has been particularly valuable for allowing collaboration between specialists and allowing for faster diagnosis in places where there may be limited access to a pathologist or no access to one at all.

The introduction of artificial intelligence (AI) and machine learning has created a new dimension to histopathology. The ability of such technologies to interpret large image sets; to find complex patterns; and to recognize small abnormalities accurately has been demonstrated through studies showing that diagnostic systems using artificial intelligence can perform equally well as, and in certain instances better than, human beings at the same tasks such as identifying and classifying tumours. Artificial intelligence's capacity to decrease both the variation in diagnosis and the ability to reproduce diagnoses provide means by which it can greatly enhance the quality of histopathological evaluation through its continued incorporation into standardised digitised diagnostic workflows (Kiran, et al 2023).

The incorporation of AI-based digital workflows seamlessly into the diagnostic process provides for the ability to provide for the same high-volume diagnostic processes to be performed without requiring as much of the pathologist's attention on lower-complexity diagnoses so they can devote the majority of their time and attention to high-complexity cases. As this evolution continues, AI-based diagnostic tools and processes are anticipated to play a much more significant role in both clinical practice and research than presently.

### Conclusion

Understanding disease requires having a substantial knowledge of the tissue because complex tissue interactions at the cellular and molecular level are responsible for both the maintenance of health and the genesis of disease. Whereas histopathological analyses provide insight into the hidden processes occurring in tissues, the physician can use the results to develop a better understanding of the disease process in order to make educated clinical decisions.

Histopathology assists with all facets of modern medicine, including early detection, proper diagnoses, creation of an appropriate treatment plan and monitoring of the

patient's response to the treatment. Advancing technologies will continue to enhance the role histopathology has in providing accurate and personalized healthcare, and the opportunities for developing personalized and accurate approaches to care are limitless. Overcoming barriers of access, standardization and disease complexity is necessary if we wish to maximize the full potential of histopathology. Histopathology enhances our ability to relate the clinical signs and symptoms of disease with the corresponding pathological abnormality, thereby playing an essential role in improving patient outcomes and improving the future of medical science.

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