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History and prospects of Pathology in Medicine

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ABSTRACT: To address the historical advance of Pathology and predict all its future development in a single article would be very pretentious, if not impossible. In the present article, we will present the key development points in the field of Pathology through the centuries, and particularly the reflex of such development at the Department of Pathology of University of Sao Paulo School of Medicine. Each of the later cited "ages" include pivotal stages of development of Pathology, new tools and Disease Development Theories in each period of time, as well as its relationship to the general history of medicine. We conclude pointing some interesting perspectives on molecular and digital pathology as well as on interdisciplinary integration.

Keywords: Pathology/trends.

RESUMO: Embora seja excessivamente pretensioso apresentar o histórico avanço da Patologia e prever todos os seus desdobramentos em um único artigo, tentaremos apresentar os pontos chave do desenvolvimento da área e, particularmente, seus efeitos no Departamento de Patologia da Faculdade de Medicina da USP. As aqui chamadas "eras" agrupam fases importantes do desenvolvimento da patologia, suas ferramentas e teorias de desenvolvimento das doenças, além de sua relação com a história da medicina como um todo. Concluímos com algumas perspectivas interessantes em termos de patologia digital e molecular, bem como de integração interdisciplinar.

Palavras-chave: Patologia/tendências.

The analysis of the different records in medicine history clearly shows the fascination of man not only with the cure of diseases, but primarily with the understanding of the process of development and manifestation of the various diseases. It is no wonder, therefore, that the history of Pathology blends, in many ways, with the history of Medicine itself.

The events that followed throughout the development of the area do not have clear boundaries, just as any historical evolution, but for didactic purposes we present the main developments separated by periods or "ages" characterized by their features in terms of tools used and disease development theories in force at the time.

The early days of Pathology - Descriptions and Humoral Theory

In the early days of pathology, unsystematic, general descriptions of the diseases are observed, accompanied by their manifestations and numerous theories related to the

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causes and development of these observed diseases. Still deprived from any technological tools, the physicians and thinkers of that time used empiricism and the observation of a few dissections to understand the disease process.

In this context, the first records of the presence and manifestation of diseases date back to the 16th and 17th centuries BC, in the Edwin Smith Papyrus, which depicts skin ulcerations in patients in the Valley of the Nile, still with no causal relationship or clear development mechanism. It was only in the 4th century BC, during the heyday of Greek civilization, that more detailed descriptions and the first theory of disease development, the Humoral theory, suggested by Empedocles and applied to Medicine by Hippocrates, arise. Moreover, Hippocrates was one of the first physicians to make clear descriptions of the inflammatory process and of tumors. These detailed and objective reports gave Cornelius Celsius the foundation to publish, more than 400 years later, his "De Re Medicina" presenting the four phlogistic signs of inflammation (heat, tumor, redness and pain), complemented a century later by Galen (loss of function)[1].

Another interesting description of this stage attributed to Galen refers to the "crab-shaped" aspect of tumor growth, a description that is the basis for the term used to this day for malignant neoplasms (cancer)[2].

The isolated descriptions of diseases or their groups and the strengthening of the humoral theory was the foundation for everything that is considered closest to "Pathology" for that time, until much of the Middle Ages.

The first age of Pathology - Autopsies and Macroscopy - Anatomical and organic bases of diseases

During much of the Middle Ages the dissection of corpses and, in many cases, even animals, was considered to be a very grave desecration, punishable with excommunication. Still, some thinkers and physicians of the time, with the desire to better understand the diseases, performed dissections and autopsies on their patients. One of these physicians was Antonio Benivieni (1443-1502) who published a book with more than 100 cases to which he had attended, 20 of them with the description of the autopsies. His "De abditis Nonnullis ac Mirandis Morborum et Sanationum Causius" (On the hidden causes of diseases) is the first publication in which pathological findings appear separately and in a systematic way.

This first age was also important in changing the understanding of the development of diseases. The works of dissection and detailed description of the circulatory system and of blood done by William Harvey (1578-1657) represented an undoubted strike on the humoral theory, which was hegemonic at that time, making room for the emergence of the first associations that would compose the anatomical basis of diseases. Harvey himself had an important contribution in this area describing left ventricular hypertrophy in patients with aortic valve insufficiency and already proposed a possible causal association between valve failure and hypertrophy[2].

With the advance of the Renaissance and a greater appreciation of science, the early 18th century was fruitful in setting the organic and anatomical basis of diseases, culminating in the works of Giovanni Morgagni (1682-1771) who published a book describing more than 600 autopsies with their respective clinical correlations and macroscopic findings[3].

The second age of Pathology - Microscopy, tissues and the Cellular Basis of Diseases

The French Revolution is known to be a milestone in history due to the profound political and social changes it caused over the world. Its marks, however, go beyond these historical pillars. While heads rolled from the guillotines installed in the square of the Place de la Bastille, Marie François Xavier Bichat, a French surgeon, was allowed to dissect the freshly guillotined bodies[4]. One of the main strategies used by Bichat was to submit parts of the body to high temperatures (literally cooking them). Evaluating the consistency, color and other characteristics after the "treatment" he was able to identify 21 different types of tissue, without any use of microscopy techniques.

Despite the cutting-edge description, it was the microscope, created in 1590 by Zaccharias Jansenn and improved into the compound format in 1655 by Robert Hooke that definitely propelled Pathology in that age. Although it was created in the 17th century, it was only in the 19th century that its utilization for the study of diseases and tissue was popularized. At that time, when

the anatomical/organic bases of diseases were already well-known, the researchers began seeking more detailed explanations on the mechanisms involved. By that time, two lines were prominent[5]: (1) Carl von Rokitansky (1804-1878) defended that the advances in the understanding of diseases depended fundamentally on the study of the chemical aspects of the organs; (2) Rudolf Virchow (1821-1902), in turn, was betting on the study of the cell structure with a microscope for a better understanding of diseases. Because he disseminated the use of microscopy and wrote numerous descriptions of the microscopic characteristics of the diseases studied at autopsy, Virchow is deservedly known as the "Father of Modern Pathology". In 1858 Virchow already presented studies on different tissues, published in his work "Die Cellular pathologie" and was the postulant of the theory of the origin of the cell from the division of pre-existing cells (*omnis cellula e cellula*). In the 19th century the Cell Theory was born, and with it the study of cellular pathology and of the cellular bases of diseases[6].

In the last decades of the 19th century there has been a development of additional techniques that have improved the visualization of the tissues, such as fixation, embedment, microtomes to perform finer cuts and specific dyes for different tissues and components. The first articles with microscopic descriptions of various diseases began to emerge. Also by that time, Julius Cohnheim (1839-1884) was one of the pioneers in using histological sections of frozen material, nowadays widely disseminated in health services to ensure quick and conduct-defining intraoperative results.

Despite the differences between Rokitansky and Virchow and the resounding predominance of Virchow's line of thought during that period, history came to show that Rokitansky was also not wrong, just a little ahead of his time.

The third age of Pathology - Immunology and Molecular Biology at the service of the study of the physiopathological and molecular bases of diseases

The first half of the 20th century in Pathology has been developed through the study of microscopic structures and their relationship to diseases, such as the description of the reticuloendothelial system by Aschoff (1866-1942) and proposition of the role of cholesterol in the development and formation of atherosclerosis by Anitschkov[7]. Although these studies were still based solely on traditional microscopy and histochemical staining, they already pointed towards the new reality: the inclusion of concepts of chemistry, molecular biology, immunology and physiology in the understanding and characterization of diseases.

Throughout the 1900s we observed an exponential increase in knowledge in the areas of Biochemistry, Immunology, Physiology and Molecular Biology. The discovery of antibodies and the possibility of marking these antibodies with fluorescein[8,9] and, subsequently, the description and synthesizing of monoclonal antibodies[10] guaranteed the foundations of what would become Immunohistochemistry. This tool opened endless possibilities within Pathology, allowing the identification of specific proteins *in situ* enabling initially a better characterization of diseases and afterwards, with the knowledge obtained, the investigation of the origin of the tumors, the assessment of specific elements that could be therapeutic targets and definition of parameters to be followed and of prognostic indicators.

Progress, however, did not stop there. With the invention of the Polymerase Chain Reaction – PCR method[11], which granted the Nobel Prize in Chemistry in 1993 to Kary Mullis, it became possible to amplify genetic fragments even in reduced samples. The dissemination of laser dissection microscopes[12] from the year 2000 on also allowed significant advances, since now single cells or cell fragments and organelles can be separated for molecular analysis of proteins and nucleic acids.

Although simplified, we demarcate here some of the essential technological steps for the insertion of Pathology in the medical context, from the Humoral age to the molecular age. Research on gene mutations were increasingly included in the patient diagnostic, treatment and follow-up repertoire, in addition to preventive strategies for diseases transmitted within the family, of course.

In the current stage, the diseases are studied in their molecular details, through the knowledge of subcellular structures and of the interactions between the various biochemical and metabolic pathways of the cells,

their role in the tissue and consequently in the organs and systems. The concept of "organ restriction" of the disease is abandoned and the process is understood as an inseparable relationship between the causative agent, cell and tissue damage and the response of the organisms through their biochemical and immunological mechanisms.

Thus, nowadays, any center committed to developing high-level pathological activities, both for health care and for research, should feature not only a center of provision of samples (biopsies, surgical parts or autopsies) but also tissue processing, histochemical, immunohistochemical and molecular biology techniques.

Pathology at the USP Faculty of Medicine

The teaching of Pathology is part of the USP Faculty of Medicine since its second year of undergraduate course in 191, with the General Pathology course. At that time, the teaching strategy followed the Flexner report model, which had been recently released, merged with European traditions brought by foreign Professors such as Alessandro Donati (1877-1949) and Walter Haberfeld (1885-1960).

In addition to educational activities, the Department of Pathology of the then called São Paulo Faculty of Medicine and Surgery began performing, from 1931 on, an important healthcare activity by conducting the Pathologic Anatomy section of the Bacteriological Institute, nowadays by the name of Adolfo Lutz, and Division of Postmortem Inspection Service of the Capital (Serviço de Verificação de Óbitos da Capital - SVOC). In addition to care, these bindings have enabled the expansion of the teaching and research strategies with practical demonstrations in histopathological preparations and macroscopic specimens obtained from necropsies[13]. In 1945, shortly after the inauguration of the Clinical Hospital, the Pathological Anatomy Division of the CH-FMUSP was created to meet the diagnostic and scientific demands of the hospital. These care activities were performed exclusively by professors of FMUSP's Department of Pathology. Over time, all the CH-FMUSP Divisions began having their own medical staff, but in all versions of the CH -FMUSP's regulations, they must always act under the supervision and guidance of the Department's professors. In 1955 the country's first Medical Residency in Pathological Anatomy was created. It was, however, short-lived, since it was closed in 1957. It was definitively reactivated from 1968 on. In 1975, the Post-Graduation Program in Pathology began, initially restricted to pathologists. The advance of pathology in its relationship with basic areas led to the inclusion of graduate students from these areas as well, resulting in the creation, in 1988, of the Experimental Pathophysiology Graduation Program, which enabled greater interdisciplinarity in an institutionalized manner, based on Pathology's successful integrated performance which has always occurred in a less formal way. From 1979 on, several LIMs, Medical Research Laboratories, have been installed in the Department, expanding even further the interaction of the Department with basic and translational research[13].

In addition to teaching, research and care activities directly linked to the pathology practice, the Department of Pathology had also an important institutional participation in other activities such as in the creation of the Faculty of Medicine Foundation and of the Medical Informatics and Telemedicine Courses[14].

The Department of Pathology proactively seeks to monitor the technical and didactic evolution of Pathology, acting nationally and internationally as a leader. Recent examples of this leadership include the Experimental Air Pollution Laboratory, the development of Molecular Pathology strategies applied to care in ICESP, the installation of modern structures for digitalizing slides and the recent deployment of the Image Platform in the Autopsy Room enabling for a unique environment for teaching and research in the area of interaction between Radiology and Pathology. Regarding teaching, the Department has been leading the development and use of teaching technologies, use of learning objects and interactive platforms for classroom and distance learning. In this sense, it is also worth noticing the creation of the Telepathology Project, which enables the holding of anatomical and clinical distance meetings with numerous institutions, allowing the spread of Autopsy use strategy in undergraduate education*.

* Minutes of the Board of the Department of Pathology FMUSP.

Prospects

Considering the current pace of the technological and scientific advance, accurately predicting the advances of this century in Pathology is purely an exercise in futurology. Still, some of the current outcomes allow, with a good deal of realism, tracing a possible future that may or may not be ratified by the 200 years issue of this journal.

In an era of cloud computing, high speed Internet connection and increasingly powerful equipment for photographing and digitalizing slides, Pathology services will increasingly use the high resolution images obtained from scanned slides for diagnosis, prognostic assessment, therapy selection and for analysis of morphological and quantitative experiments, allowing pathologists to dynamically and quickly analyze specimens, facilitating the collaboration between professionals, enabling a greater specialization and saving time and resources.

The increase in the resolution of imaging examinations and the growing scientific development in the area of radiological - pathological interaction should, in the future, reduce the number of invasive procedures and open spaces for minimally invasive autopsies in a considerable percentage of cases, although it is clear to us that a total replacement should not occur since it also has some limitations. The pathological and radiological knowledges combined should, in a not too distant future, be a decisive part of the professional training in these two areas, which are increasingly convergent.

The research on molecular markers of diseases should be expanded exponentially, tests that currently seek specific mutations should be replaced by tools for complete gene and protein analyzes, enabling the development of individualized therapies or more efficient strategies for tracing and preventing diseases.

Research in the Pathology area should increasingly have a multidisciplinary nature, involving details from all the underlying basic areas that make it possible to understand pathologic processes, to guide the selection of therapy strategies and to provide reliable information about prognosis and monitoring of patients.

From an objective point of view, what is done nowadays in Pathology around the world and inside the USP Faculty of Medicine, it is impossible to say how far we will get but one thing is already clear: In FMUSP, the Future has just arrived!

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