Introduction

Human pathology is a science dealing with organs, tissue specimens or cells, all taken from patients through biopsy, surgery or autopsy. Undoubtedly, the fruits born by the studies of human pathology contribute greatly, not only to better diagnosis and therapy of diseases but to elucidation of their mechanism. In performing the study, pathologists resort predominantly to the analysis of biostructure and its form. While various knowledge and technique have been introduced to pathology from other fields like biochemistry, immunology or molecular biology, it is the science of form that has been and still remains the core of research in pathology. What are the principles underlying the normal structure of an organ? In diseases, what deviation from the norm do the organs undergo and how does it explain the abnormal organ function? And how can we better recognize the changes of structure and form, with which to improve the diagnosis of diseases? These are problems pathologists have been engaged in, all of which, if solvable at all, should be solved mainly by studies of form. What a pathologist encounters throughout life amounts to a vast accumulation of widely varying form. In a sense, human pathology is a treasury of forms and of problems about the form.

However, this does not mean that so far, pathology as a science of form has managed to establish a methodological basis of its own, and many problems of form are being left unsolved. Yet recently, the studies of form have attained a dramatic extension by the hand of non-biomedical scientists including image engineers, mathematicians and statisticians, giving us an impetus, influence and stimuli. In this book, I intend to compile the studies of my team and my own, which were mostly performed resorting to analysis of form. Particularly it seems essential to demonstrate, in what aspect of study we came to face a bar, and how we were assisted in overcoming it with new methodology, technology and way of thinking. Also, it will be shown how much our studies have been assisted by the recent advancement of computer technology. Listed below are the main problems to be discussed.

1. The quantification of form

Consider the diagnosis of cancer. There is no doubt that today, the final diagnosis of this disease is given mainly by pathologists. New methods like analysis of DNA from tumor cells or of specific molecules of patients' serum still remain as an auxiliary measure, while in the medical scene, decision-making about a patient mostly relies upon form-related information, including clinical images, macroscopic organ changes and microscopy of specimens. Yet strictly speaking, a form-based diagnosis made by pathologists cannot be exempted from having a streak of ambiguity. The microscopic diagnosis of cancer differs from biochemical analysis, in the latter of which the result is given in the form of titer for a specific molecule in the serum. In evaluating the form of tissue and cells, the examiner cannot but depend upon one's own experience, which brings about a limitation upon the reproducibility of diagnosis. Moreover, the object of pathological analysis mostly assume a shape that is irregular, variable, far from geometric, and seemingly least accessible to quantification. Still, it is imperative to introduce quantitative methods to this domain if we try to bring the morphological pathology closer to the level of science.

2. Three-D quantities and their estimation

Another difficulty awaiting us is the need to obtain quantitative information about the 3-D structure. On most occasions, what we can access is only 2-D section. Whether light or electron microscopic, the sections available are thin enough for disregarding their thickness. However, the real object of observation is always a 3-D parenchyma that continues behind the sectional plane. On account of this, the need often arises to know the 3-D structure and geometry. When the need is of such a nature as to be satisfied if 3-D quantities are provided, one might sometimes be able to resort to stereology. This is a generic term for the principles and technique with which one can estimate the quantities characterizing the 3-D structure through measurement or sampling upon small number of 2-D sections. As one may expect, principles of stereology are mostly deduced from statistics and geometric probability. Consider, for example, how the total surface area of alveolar septa was estimated for the human lung, the right and left combined together. This is a problem solved by Weibel (1963) who developed a new theorem of stereology to apply to this task. Also there are other problems in human pathology in which stereology can work as an effective tool, but unfortunately, we cannot say that the knowledge about stereology is being widely distributed among researchers working in pathology.

3. Problems that require 3-D reconstruction

Though stereology is a "bright" method of morphometry, its applicability to real problems is not free from limitation, as will be shown. When the problem one is facing has proved to be beyond the reach of stereology, there is no other way than to perform 3-D reconstruction from serial sections, i.e., to have direct access to the space by reproducing the 3-D structure. Problems that need reconstruction are found in every sector of pathology, and it is in these problems that my colleagues and I have been engaged for many years. After having consumed much time and energy in performing this, we recently managed to introduce computer-assist, which greatly helped expand the scope of 3-D analysis. Problems that require 3-D reconstruction are mostly those dealing with either the connectivity of structure or the spatial distribution of lesions. A series of such examples will be shown.

Sometimes the author performed what may be called 3-D measurement. When one needs to obtain at any cost 3-D quantities that apparently are not susceptible of stereological approach, direct 3-D measurement upon serial sections may be the last resort. Today, in this aspect too, we can expect computer assist in the form of computational geometry.

4. Topological problems in pathology

Not rarely we face lesions of such a character as to be studied from a structural connectivity point of view. How the structural components are connected in space is a problem of topology and therefore is beyond the scope of stereology. This is symbolized by the history of computer-aided 3-D reconstruction, which in the earliest stage of development was designed exclusively to visualize the connectivity of neuronal network (Capowski, 1977). To put it in other words, structural connectivity is a problem studied most effectively by applying topological parameters. Several examples will be shown in the following, in all of which, approach to the problems was guided along the topological way of thinking. Particularly, in studying the morphogenesis of various lesions, one never fails to find connectivity and its changes defining the way of development. An appropriate example may be found in the development of cirrhosis from chronic hepatitis, where the advancement of disease involves a series of radical transformation in the skeleton, which can be described only in topological terms.

The experience obtained through the study of cirrhogenesis helped characterize the structure of adenocarcinoma and adenoma with various grades of differentiation. It will be shown that the concept of differentiation, hitherto applied only to the individual cells, can also be extended to the structural aspect, allowing us to define "structural differentiation" or "structural atypism."

5. The adequate classification of form

Classification is a method widely applied in pathological research. However, no attempt has been made at examining whether the object under study is classifiable at all, or when it really is, how one can define the most adequate and therefore reproducible classification. These are questions accessible to the method called cluster analysis, an application of multivariate statistics. This is a way of thinking, for the application of which, one can find a fertile soil in the domain of pathology. In this book, several of our attempts will be presented: the classification of liver cirrhosis, and that of atypical cells found in carcinomas and pre-carcinomatous lesions.

In writing the manuscript, my attention has been focused on making this book accessible not only for researchers working in pathology but for those in other fields, including non-biomedical scientists. It is for this reason that for each of the studies introduced, efforts have been made to shed light on its biological background or clinical significance. To pathologists, sometimes such explanations might appear redundant, but if the readers could be kind enough to tolerate the boredom, I would be much grateful.