THE APPLICATION OF COMPUTERIZED HIGH RESOLUTION SCANNING TECHNIQUES TO THE IDENTIFICATION OF HUMAN CELLS AND TISSUES

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Supported in part by Grant No. 5-R26-CA-15803
of the National Cancer Institute through the National Bladder Cancer Project, Worcester, Massachusetts 01604

ABSTRACT

The purpose of this paper is to summarize the basic information on cell morphology useful in the microscopic diagnosis of human disease with special emphasis on morphologic identification of cancer cells. The rationale for computerized analysis of digitized cell images and the principal targets of this approach, namely, cytology of the uterine cervix, urine and sputum have been discussed. The technical and legal problems of sample preparation and the problems of sample interpretation have been outlined. A summary of present and future research trends concludes this paper.

1. INTRODUCTION

The introduction of the microscope to the study of tissue and cell samples of human origin during the latter part of the 18th and mainly during the 19th century has led to the current concepts of human disease. It has been firmly established that disease processes are the result of an altered state of cells or their components and products, and consequently of tissues which are best defined as aggregates of cells sharing common purpose. Many of the common disease processes cause changes in microscopic configuration of tissues and cells which may be quantitative or qualitative. The quantitative changes may be the result either of an increase or a decrease in the number of cells composing a tissue or an organ. The qualitative changes pertain to the microscopic or submicroscopic modifications in the structure or in the function of cells (1).

In 1866 Paul Broca, the great French surgeon and cancerologist, said this about the microscopic study (2): "Les recherches microscopiques sont minutieuses et fatiguantes; elles exigent une patience à toute épreuve une persévérance prolongée, et les premiers observateurs auraient été bientôt découragés s’ils n’eussent été soutenus dans cette étude ingrate et difficile par l’appât puissant d’une brillante théorie." (The microscopic research is very precise and demanding; it calls for endless patience and perseverance. The early observers would have been rapidly discouraged in this thankless and difficult task were it not for the powerful appeal of a brilliant theory). Broca was referring to Virchow's concept of cell pathology with which he incidentally disagreed, much to the detriment of future developments in French pathology.

Nonetheless, the basic truth of Broca's words is still valid today and many of the common diagnostic procedures based on microscopic study are difficult, tedious, repetitious and time-consuming. Furthermore, the interpretation of the findings often depends on the experience, skill, and talent of the observer.

It is evident, therefore, that new approaches to the study of cells that may induce diagnostic objectivity in the identification of disease and relieve the tedium of microscopy would be of great benefit to the society. Image analytical techniques offer considerable promise in this regard.
It is beyond the scope of this summary to indicate the enormous variety of microscopic images that may be encountered in the study of human disease. Furthermore, these images vary significantly from organ to organ and even from tissue to tissue, thus preventing the establishment of general and simple classification rules that could have universal applicability. Therefore, image analysis techniques must seek specific and selective targets that would provide optimal cost:benefit ratio.

It is, of course, conceivable that the analysis of objective computer-based information could yield new data on the biologic nature of the disease studied and, in the case of cancer, data on sequence of cellular events, and even data of prognostic nature. The creation of appropriate computer algorithms coupled with simple and practical technical approaches, may prove to be a highly beneficial commodity that could be made available to the entire human race at a moderate cost, thus raising the level of microscopic diagnosis throughout the world without the need for extensive and time-consuming training of personnel. While this may be an utopic concept at this time, I am personally convinced that given adequate resources the target is achievable within the available technology.

2. CELL MORPHOLOGY

The obvious primary target of image processing are cells rather than tissues. The task is facilitated by the relatively small size of the cell and the relative ease with which it can be reduced to a digital form. With the exception of mature red blood cells and some epithelial cells which are composed of a cytoplasmic matrix alone, all other human cells display the 2 essential components: the nucleus and the cytoplasm. The nucleus is the site of the reproductive apparatus of the cells and contains deoxyribonucleic acid (DNA), whereas the cytoplasm is the site of metabolic events which are expressed morphologically and may provide the observer with information regarding cell function and destiny (1).

2.1. Resting cells

In the resting cell, the nucleus generally has a spherical configuration. The nuclear DNA and associated proteins, or the so-called nuclear chromatin, are hydrated, hence not visible except for granules of the so called heterochromatin which remain in condensed state throughout the resting phase. In duplicating cells, i.e., cells undergoing mitotic division, the amount of DNA will double during the synthetic or S-phase of the cell cycle with resulting nuclear enlargement. During mitosis the DNA condenses in the form of chromosomes. The chromosome complement and morphology is characteristic of each species. The chromosomes can be classified according to their size, configuration, and internal structural differences, expressed as alternating darker and lighter bands which can be brought out and classified by special techniques (3).

An important component of the normal nucleus is the nucleolus which is the center of formation of ribonucleic acid (RNA), the messenger substance that provides the communication between the nucleus and the cytoplasm. The number and the size of the nucleoli may vary according to the level of cell activity and other factors.

With a very few exceptions of highly specialized cells such as polymorphonuclear leukocytes, the configuration and the texture of the nuclei are not specific for normal cells and thus their images cannot be utilized for cell classification. On the other hand, the cytoplasm of the normal cells mirrors their origin and activity. Thus, a great variety of cytoplasmic images may occur which serve to classify many normal cell types. The size, texture, content and activity of the cytoplasm can be readily analyzed.

2.2. Reactions of cells to injury

Under abnormal or pathologic circumstances, the cells may undergo morphologic modifications which may be reflected either in the nucleus, or the cytoplasm, or both. In general, the reactions of the cells to injury, regardless of its nature, may take 3 pathways:

1. The cells die.