A STUDY OF THE AUTOMATION OF CYTODIAGNOSIS*

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Abstract—Clinical cytology is an important diagnostic procedure in the early detection of cancer. However, both the scarcity of cytologists and the time-consuming nature of the examination are hindering its application to mass survey. To alleviate this situation, a prototype apparatus was constructed so that the determination of malignancy could be made automatically. A spot of light is thrown upon a specimen. Scanning is performed over 10,000 cell nuclei. Optical density modulated by the nucleus is fed into a computer, which recognizes an individual nucleus as a single nucleus, classifies it into five area-levels, and totals the number of nuclei in each class. All the steps including the mechanical operation are completely automated. Preliminary tests revealed satisfactory results on the preparation made from Ehrlich’s ascitic cell tumour. Because the installed computer has other several potentialities for yielding available criteria, the decision-making procedure should finally be worked out by a composite criteria.

INTRODUCTION
Clinical cytology has been increasing in its importance for early detection of cancer. In the case of uterine cancer, only clinical cytology can detect exfoliated malignant cells in the vaginal smears. In the case of lung cancer, a report pronounced that the cancer detection rate increased 1.5 with the combined use of X-ray and cytological examination of phlegm compared with the use of chest X-ray only (LILIENFELD, 1966).

Both the scarcity of cytologists and the time-consuming nature of examinations are hindering its application to mass survey. To alleviate this situation, a method using instrumentation has been designed for the automation of cytodiagnostic procedures.

CYTODIAGNOSTIC PROCEDURE AND CRITERIA
The full diagnostic procedure is demonstrated in Fig. 1. The development of instrumentation for cytodiagnosis consists of a number of steps, each of which brings its own problems.

Step 1. Sampling of materials: simplification and unification of methods,
Step 2. Preparing of materials: unification and automation of methods,
Step 3. Screening of preparations: automation of the image processing (quantitative evaluation of diagnostic criteria and statistical judgment of malignancy), and
Step 4. Final diagnosis by cytologists: This step is not to be automated. The final diagnosis rests with a doctor.

Step 3 is the most elaborate and time-consuming task at present, and it was decided to automate this first.

From the standpoint of clinical cytology, about twenty morphological characteristics are believed to indicate cancer cells, (Fig. 2), but no items are exclusively specific to cancer cells. Therefore, in order to determine malignancy, it is necessary to use a statistical process with quantitative parameters. The essential features of these diagnostic criteria are attributed to the optical density and geometry of the microscopical images. First of all, the area of the cell nucleus was selected for investigation. In order to obtain the fundamental knowledge, the area of the nucleus was measured on the microscopical pictures.

* Received 21 September 1968.
Staining series

Simplification and unification of method

Unification and automation of method

Automation of method

Judgement by cytologist

Prevalent procedure

Sampling

Judgement by cytologist

Expected future procedure

Sampling

Staining series

cytological analyzer

Judgement by cytologist

Fig. 1. The proposed system for automation of cytdiagnosis.

(A) INTERRELATIONSHIPS OF CELLS
1. Grouping and crowding of cells
2. Anisocytosis
3. Anisokaryosis
4. Irregularity of cluster of cells
5. Engulfment of one cell by another.

(B) CYTOPLASMIC CHANGES
1. Atypical vacuolation
2. Cytoplasmic inclusion
3. Tadpole cell formation.

(C) NUCLEAR CHANGES
1. Increase of N/C ratio
2. Hyperchromasia
3. Thickening of nuclear membrane
4. Furrowing
5. Lobulation
6. Budding
7. Multinucleation
8. Irregularity in outline
9. Mitotic figure
10. Enlargement of nucleoli
11. Degeneration.

Fig. 2. Morphological characteristics of malignant cells in clinical cytology.

by a planimeter. For the investigation, 245 nuclei from preparations of 15 cases of uterine cancer and 359 nuclei from preparations of 14 normal subjects were selected. The frequency distributions of the area of nuclei are shown in Fig. 3. Both normal and malignant nuclei had complicated distributions. The equivalent diameter of the nucleus, being defined by the postulation that every nucleus has a circular shape, was calculated by the following formula:

\[ \phi = \sqrt{4A/\pi} \]

\( \phi \) = equivalent diameter of nucleus,

\( A \) = measured area of nucleus.

The frequency distributions of the equivalent diameter of the nuclei were plotted on a Gaussian distribution sheet (Fig. 4), the normal and the malignant nuclei each showed characteristic distributions. Therefore, it is believed that the equivalent diameter of the nucleus is significant as a statistical parameter.

INSTRUMENTATION

(1) General description

A prototype apparatus, named ‘Automatic Cytoscreener’, was constructed, which measured the area of the nucleus, and processed its data so that the determination of malignancy could be made automatically. Figure 5 shows a general view of the Automatic Cytoscreener, the left half of which is the electrical processing unit and the right half the mechanical processing unit. Figure 6 shows the block diagram of this apparatus. Luminous flux radiated from a flying spot