DEVELOPMENT OF A TOXICOLOGIC PATHOLOGY SYSTEM USING PERSONAL COMPUTER NETWORK

Hisako Fujii, Toshihiko Makinose, Hiroyuki Ogasawara, Akiko Murata, and Hidetoshi Takagi
Department of Pathology, Biological Research Laboratories, Lederle (Japan), Ltd.
Fumio Furukawa and Hiroshi Onodera
Division of Pathology, National Institute of Health Sciences
Toru Hoshiya
Safety Research Laboratories, Gotemba Research Division, Bozo Research Center

Abstract: An integrated toxicologic pathology system named “MacMic” has been developed and expanded for use in toxicological studies. By utilizing a personal computer Local Area Network (LAN), high user interface and easy data sharing were achieved at low cost. The studies covered by this system are all of the general toxicological studies including carcinogenicity studies. It was designed for the purpose of easy handling from the standpoint of pathologists, and it offers high usability. At histopathological examinations, screeners can refer to the data entered from other subsystems: body/organ weight measurement, urinalysis, hematology, and blood chemistry, and also those data summaries, which clarify the differences at a given rate from controls by different color. Entry of gross and histological findings is done by referring to the specialized dictionaries, which are maintained routinely, and the selection of the findings and copy from those entered before are easy. Movement to the next step is quick with function keys, and the proceeding status of histological examinations is obvious with a key for fixing and color distinction. There is a memo function for communication between screeners and exclusive control function to allow multiple access to the same study but not to the same organ at a time for protection of data. “MacMic” was originally the system using personal computer LAN for a certain laboratory, but it was found to be applicable to other laboratory/institute. (J Toxicol Pathol 9: 13-21, 1996)

Key words: Toxicologic pathology system, Personal computer, LAN, MacMic

Introduction

In toxicity studies with new chemicals and compounds, pathological assessment is the final key factor in toxicological evaluation, and the interpretation of pathological changes caused by chemicals greatly affects its risk assessment. Furthermore, in the development of new drugs, accurate and quick evaluation of pathological findings is required for early marketing.

In this situation, many laboratories have been introducing various types of computer systems for recording and processing pathological data1-5. Some of those systems in the market require great investment, and some are not easy to handle for pathologists in practice. When the system’s development work is asked to an outside softhouse, it sometimes becomes an insufficient system due to the lack of understanding between pathologists who don’t know computer and system engineers who don’t know safety assessment studies.

For the purposes of easy handling by pathologists and low cost, a new integrated toxicologic pathology system using the personal computer Local Area Network (LAN), “MacMic”, has been developed in collaboration with pathologists as users and a system engineer. After several upgrades, the system has now become applicable to all general toxicological studies, including carcinogenicity studies, regardless of whether they are GLP or non-GLP.
The present status and future potential of "MacMic" in toxicologic pathology are reported in detail in order to articulate the concept for introduction of the computer system.

Materials and Methods

Hardware

"MacMic" runs on the PC9801® series made by NEC (NEC Corp., Tokyo, Japan), and a hard disk and an extended memory are necessary. The reasons for selecting the PC9801® series are 1) the cost is not high, 2) there are many application software products for this series available on the market and usable for the purpose other than "MacMic", 3) there are many supporting tools for the system's development, and 4) competition among many computer shops will decrease the investment. The printers selected were the LASER SHOT® series made by Canon (Canon Inc., Tokyo, Japan) and the PC-PR201® made by NEC. These printers have a high market share.

Software

"MacMic" runs on the MS-DOS® (Microsoft® Corp., USA) operating system. The dBASE format, which is the most popular data base for personal computers in Japan, was used as the file format for the pathological dictionaries and data, which obviated a system engineer in developing a program for maintenance required by other systems using the original format, and reduced the workload. Since the dBASE format has the index function, data are processed quickly.

Network

It is possible to use "MacMic" with one personal computer. It is usual, however, for several pathologists to conduct microscopic examinations at the same time, and the personal computer LAN has been introduced. "MacMic" has the exclusive access control function for running on LAN, a data reference function, and the ability to share the pathology dictionary and data, and microscopic examinations in the same study. Data reference for hematology, clinical chemistry, and organ weights during microscopic examinations are possible, and great effectiveness which cannot be obtained with the stand-alone type has been achieved.

For our network system, NetWare® (Novell® Inc., USA) is used. As a server, an IBM compatible machine was employed, not the PC9801, for its cost performance. NetWare® has obtained the top market share in Japan and the U.S. because of its relatively high capability with a personal computer as a server, and not only the PC9801 but Macintosh® (Apple® Computer Corp., USA), which are preferred in many laboratories, can be connected with NetWare®. Many application software products for NetWare® are available and a virus check and backup software are employed in this system.

Dictionary

The dictionaries are composed of six parts: organ dictionaries, finding dictionaries, and qualifier dictionaries for both gross and microscopic findings. Each dictionary is duplicated for the master dictionary applicable and the temporary dictionary for the study in progress. The pathologist registers terms not included in the master dictionary in the temporary dictionary and continues working. On a regular basis, pathologists decide whether or not these terms should be registered in the master dictionary. Dictionaries consist of Japanese and English words and abbreviations for screen display. The pathologist can find necessary terminology by entering the first one or two letters of the English word at any operation of inputting findings or modifying the dictionaries.

In some of the pathology systems available in the market, organ, finding, and qualifier dictionaries are not separated, and the dictionaries are apt to expand easily and lack flexibility. As for "MacMic", the maintenance of dictionaries has become very easy because it has three separate dictionaries and also a temporary dictionary for each study in addition to the master dictionary. As a result, maintenance of dictionaries has become very easy and expansion of the master dictionary can be avoided.

Organ dictionary

The dictionary for organ includes the names of organs/tissues.
Finding dictionary

In the dictionary for gross findings, the terminology is grouped into findings by region in appearance such as the surface and cut surface, and size, color, and contents, and grading of the frequency in appearance of each finding is added for easy retrieval.

The dictionary for microscopic findings includes the findings with the names of organs/tissues with the findings and the frequency in appearance in three degrees, that is, frequent, rare, and medium. When the pathologist wants to select a finding from this dictionary, "MacMic" displays the findings only applicable to the organ/tissue under examination in order of the frequency of appearance.

Qualifier dictionary

In the qualifier dictionary for gross findings, the region of the organ/tissue, and quantitative qualifier of its size, color, etc. are included.

In the qualifier dictionary for microscopic findings, the region of the organ/tissue, extent or distribution of changes, etc. are included.

Entry of Protocol Information

To process gross findings and microscopic findings in a study with "MacMic", it is necessary to input protocol information, but entry can be made when necessary as the examination progresses (Fig. 1).

Study information

The study title, species and strain of the animal, number of the experimental group, test substance, etc. are entered.

Group information

The test substance, doses, and administration route are entered for each group. This system can also be used for co-administration studies and multiple information on compounds and doses are accepted. Furthermore, since the administration route is entered for each group, it is applicable to studies in which the routes are different for each group.

Animal numbers in each group

The beginning and final numbers of each group are entered. The animals are divided into five subgroups according to necropsy date; that is, the end of the dosing group, end of the recovery group for repeated toxicity study, end of the observation period group for acute toxicity study, and the end of two interim necropsy groups when necessary. Necropsy dates are entered automatically by the system's calculating function.

Organs/Tissues for gross examinations

There are two ways to process gross findings data. When the way to enter the findings directly into "MacMic" at necropsy is selected, the organs/tissues for gross examinations should be selected in advance. The findings can be selected from the master pattern for routinely tested organs/tissues, and they can be corrected at any time if necessary. The order of printing is that of the organs as entered. If some findings are recognized in the organs or tissues not entered in the protocol, they are recorded being entered.

Fig. 1. Protocol entry.
posterior to the organs/tissues entered in the protocol.

**Organs/Tissues for microscopic examinations**

The organs/tissues for microscopic examinations are selected and entered. The master pattern for the organs/tissues tested routinely can also be used. The selected organs/tissues can be corrected at any time and they can be corrected any time and the order of printing can be changed by indicating the order in advance, if necessary.

**Carcinogenicity examinations**

In the case of carcinogenicity studies using carcinogens, the number of the lesions is sometimes needed to be entered. In the case that “carcinogenicity study” is selected, a screen is displayed where the entry of the number of lesions (0-99) not the grade of the findings, can be made upon entering the findings.

**Organ/Tissue weight**

There is no restriction for entering data, such as for each individual or for each organ/tissue. If there are “no-determined” or “re-determined” data, the sheet for stating the reason is produced automatically, which is completely applicable to GLP studies. The data measured can be analyzed using SAS® (SAS® Institute Inc., Japan).

**Gross Findings**

Gross findings are entered individually. There are two ways to process gross findings data. One is to record manually the gross findings observed on the data sheet printed from “MacMic” which has already been supplied with protocol information before necropsy (raw data). The form of raw data sheet can be changed at any time. In this case, the findings will be entered into “MacMic” after necropsy for reference in microscopic examinations and preparing tables and appendices. The other way is to enter the findings directly into “MacMic” at necropsy and produce a printed data sheet as raw data. In both cases, the printed data sheet is defined as raw data after signature by the persons conducting necropsy and recording and the principal investigator of that pathological examination.

**Entry of gross findings**

Entering gross findings is possible at necropsy or after necropsy. Selection from the organ, finding or qualifier dictionaries is possible by entering the first one or two letters. Three qualifiers can be selected for one finding. To reduce workload, a copying function from the findings of other animals and a selecting function from the listed findings already entered are added. In the case of direct entry at necropsy, the raw data sheet for gross findings is automatically printed upon registering the data.

**Editing of gross finding data**

“MacMic” permits pathologists to edit terminology from several descriptive findings in the same category. Pathologists can select from edited data or non-edited data while preparing tables and appendices.

**Microscopic Examinations**

Microscopic findings are entered for each group and for each organ/tissue. When microscopic examination of every organ and tissue of the individual animal is finished, pathologists press the key “registered.” Since the colors of “registered” data and non-entered data are different, the status of the examination progress can easily be identified (Fig. 2). If there is not-registered data even in one animal, the words “not registered” are shown in any of the output data sheets.

**Selection of animal and organ**

Pathologists select the individual and organ/tissue for entry of its microscopic findings. In this screen, the status “registered” for an individual, the start date for entry and the final revision date can be confirmed. If there are groups or organs/tissues unnecessary to be examined, pathologists can select all or one group or all or one organ/tissue and enter “Not Examined”.

**Entry of microscopic findings**

In the screen for entry of microscopic findings, ten animals are shown for each group and for each organ/tissue. The animal numbers already “registered” and “not registered” are shown in different
colors. The animal number whose gross findings have already been entered is shown in reverse. Movement to the next group and the next organ/tissue is very quick and requires only one key operation (Fig. 3). The letters for grading and the color can be customized easily by each laboratory. Carcinogenic findings are shown in a different color from other findings. In carcinogenicity studies, two-digit numbers of lesions can be input.

In entering findings, in addition to the method by selecting from dictionaries, pathologists can copy the findings of other groups such as high-dose groups and select and copy from a list of findings already entered (Fig. 3). Also, several findings can be combined and processed as one finding with grading. If correction of a finding already entered is necessary, other data of other groups are automatically searched and the system asks the pathologists whether or not these data should also be corrected.

Data reference

In the screen for entry of microscopic findings in "MacMic", gross findings and microscopic findings of the selected individual can be referred to at any time.
Also, organ weight, urinalysis, hematology, and blood chemistry data of the selected individual can be referred to for each animal or group. Controls can be selected at any time, and the individual data out of mean±2SD or mean±3SD are shown in different colors (Fig. 2).

*Memo for microscopic findings*

In “MacMic”, a memo can be entered for each group and printed out. There are two types of memos; that is, a general memo and a GLP memo where the column for the signature is printed out. The general memo is used for communication between pathologists or information for technicians for preparing specimens. The GLP memo is attached to the raw data after entering the comments to the findings observed.

*Printing of raw data for histological examinations*

Two types of raw data sheet for microscopic examinations can be printed out. One type is several sheets of the data of ten animals printed out for each organ/tissue. Another type is one sheet of the data for all organs/tissue of one animal printed out. Pathologists sign on them and file them as raw data. If there is a non-registered individual, a title with the words “not registered” is printed.

*Making Tables and Appendices*

“MacMic” has an output function of a text file
instead of a print function of tables and appendices for the pathology or final report. To print tables and appendices, the pathologist uses the spread sheet software or the word processor software on the market. It is necessary that the software has the function to read the text file. The output from “MacMic” is very effective considering the operation by the marketed software products. Pathologists can make the following selections while outputting data.

a) Edited data or non-edited data on qualifier (gross findings)
b) Separate output of all animals, scheduled sacrificed animals, and animals found dead
c) English or Japanese
d) Output of the animals in the selected necropsy period

The merit of the use of application software on the market is that it can answer any demand for preparing tables and appendices and continue receiving the merits of both a regular version improvement of software on the market and major new product. A disadvantage is the possibility of data changing by accident or intentionally. To avoid this, therefore, it is necessary to establish a firm procedure for checking and assuring accuracy of figures in the printed table and appendices against the raw data.

Others

Study summaries

“MacMic” shows the frequency of occurrence of gross and microscopic findings in a group on the screen. A summary of microscopic findings can be printed out, and pathologists use this summary for group discussion (Fig. 4). Organ weight, hematology, and clinical chemistry data include the mean and standard deviation for each group and the results of statistical analysis between a selected group and another group, showing the mean and standard deviation for each group. Gross findings, microscopic findings, organ weight, urinalysis, hematology, and blood chemistry data can be shown also for each individual animal. If necessary, a “Karte” for each animal can be printed and this is often used for dog studies and others (Fig. 5).

Supporting function for final pathology report

Through “MacMic”, the textfile for preparing pathology reports using marketed word-processing software can be printed out. The data of the experimental design, organ weight, gross findings, and microscopic findings are added to the textfile in which the format that can be customized by each laboratory is already entered, and the textfile is printed out. Pathologists obtain these data using a marketed wordprocessing software and finalize their reports.

Discussion

“MacMic”, a personal computer network system for toxicologic pathology, has been developed through the collaboration of pathologists and a system engineer. The concept of this system is to estab-
Fig. 5. “Karte” for each animal.

lish integrated data management system using a network and easy handing for end-users. In addition, the expansion to a bigger safety assessment system, this system being as a sub-system, was considered. The characteristics of this system at the first step were as follows: 1) easy handling of actual entering of microscopic findings, 2) high quality of data sheets and flexibility by utilizing the application software available on the market, 3) good cost performance, 4) expansion with no effect on the total system, as it is the development of a subsystem, and 5) compatibility with the marketed data base format dBASE. Later, several systems such as those for body weight, organ weight, urinalysis, hematology, and blood chemistry were developed and used. All of these data (data summary) can be refereed to at microscopic examinations through each terminal machine. Furthermore, there are some convenient functions such as a memo function for communication between screeners, a message board to the system engineer for requests, an exclusive control function to allow multiple access to the same study of different organs at one time for protection of data, a supporting function for report writing, and several other convenient functions to decrease the workload for input. Since “MacMic” users utilize the same dictionaries, the qualifier of findings could be standardized in facilities.

“MacMic” is now used in three laboratories. In one of them this system is used for all studies, both GLP and non-GLP, and in another laboratory this system is used together with its in-house system, not...
the marketed application netware used to print tables and appendices. In the other laboratory, this system is used for carcinogenicity studies. Various usages are made in these laboratories but the workload for customizing the system was very low. A version for each user was not necessary. Concerning easy handling, no manual for users is necessary even at the beginning and it did not take much time to educate users. Concerning cost performance, the investment was made on the purchase of personal computers, networking, and marketed application software, and the personal computers can also be used for office work such as word processing, etc. The cost performance, therefore, was very high.

The next step for "MacMic" will be the introduction of Microsoft Windows™, next generation of basic software after MS-DOS®, which will solve the problem of the shortage of software memory in "MacMic". In addition, image data can be used easily, and it will become possible to input findings with its standard image. We would like to revise and expand "MacMic" with the various ideas of many pathologists and hope that many pathologists will utilize "MacMic" for their daily work.

References
2. Abe, M, Hirouchi, Y, and Enomoto, M: Pathology data processing including both findings and diagnosis—Computer system used in animal toxicological experiments—. Pathol Clin Med 2: 574-581, 1983.