Drug Monitoring System*

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A description is given of the Bureau of Medicine, Food and Drug Administration, collection of drug data and of the system for evaluating, analyzing, and communicating the data. The collection, already very large, grows by several thousand documents per month.

The purpose of our Drug Information System is to develop an "early warning" alert for detecting previously unknown adverse effects of drugs or the incidence of adverse effects which were greater or less than our previous experience with a limited number of patients had led us to believe. It is a well-accepted fact of life to us in the Food and Drug Administration that surveillance of a drug during its first two years of marketing experience can provide us, under close supervision, with new knowledge of its adverse effects that are undetected during its developmental phase. The reason for this is, of course, the wider dissemination of the drug, the use in more diverse populations, the use by many more practitioners of medicine, and the greater opportunity for interaction with other drugs in patients with varying health problems.

A well-developed drug reaction system will enable us to develop an incidence of drug reactions and follow through to its ultimate conclusion, and will bring a knowledge of benefit-to-risk ratios to give the physician confidence in selecting which of a class of drugs would be best suited for his patient. It will also make us aware of hitherto unknown drug interaction, drug contamination, and drug labeling mix-up problems.

The drug reaction system, which we in the Bureau of Medicine are currently developing, has access to the largest collection of drug data available anywhere in the world. The effectiveness of the system is dependent upon the quality of the data collected and its intelligent manipulation, factors which we have taken great pains to evaluate to ensure that committing this information to computer memory banks and analyzing it will provide more complete information than has been available.

The data available to us and which we are utilizing are:

A. The Hospital Program of the Adverse Reaction Branch, Bureau of Medicine, operating within the Division of Medical Information of the Bureau of Medicine, arose in response to the definite necessity to make the scientific community aware of the drugs in current use. Basically, the program is an isolated case report surveillance system whereby physicians, dentists, and other professional medical personnel routinely check collection facilities within participating hospitals for reactions, possibly caused by drugs, and report this information at periodic intervals to the Food and Drug Administration. At the present time there are approximately 140 teaching hospitals participating in this program. All cases of adverse reactions to drugs, regardless of their severity or whether a definite cause-effect relationship is established in the mind of the physician, should be recorded. We have defined an "adverse reaction" as one which is noxious, unintended, and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. This information is received on a drug reaction report which has been designed to record some of the following parameters of information:

1. Patient's initials
2. Sex
3. Weight
4. Date of birth
5. Occupation
6. Date of hospital admission
7. Date of hospital discharge
8. Race
9. Sources of report
10. Adverse reactions
11. Date of onset
12. Date of diagnosis
13. Type of onset
14. Relevant laboratory studies
15. All drugs taken by patient
16. Total daily dose
17. Route of administration
18. Duration of therapy
19. Disorder for which drug is used
20. Concurrent diagnosis
21. History of previous exposure
22. Potentially toxic agents to which patient has been exposed
23. Reaction factors
24. Source of drugs
25. Outcome of case

Detailed instructions as to the type of drugs and reactions which we wish to have reported are supplied to the reporting physician in a detailed instruction booklet, and we maintain a close contact with our reporting physician in the field *via* telephone, written instructions, and personal visits.

B. We have available to us this same type of information on the drug reaction report form from Veterans Administration, Public Health Service, and the Military Service. In recent meetings with surgeon generals of these groups, we have been and are attempting to step up this program in the federal hospitals.

C. Another source is information derived from private physicians solicited and received primarily through the AMA with whom we have agreed to accept and exchange this basic data on drug reactions.

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D. Federal regulations require that the pharmaceutical manufacturers who produce or distribute drugs for which an approval is in effect submit reports of adverse effects, for their drugs and related drugs, which come to their attention. This information is submitted to the Bureau of Medicine and provides another extremely valuable source of drug data which are unavailable from any other source. The above information which is described represents the largest collection of unpublished drug information in existence.

E. The published world literature on drug toxicity is another source of drug data, and the Medical Literature Branch of the Bureau of Medicine itself scans 275 major journals in collaboration with the National Library of Medicine.

The articles in 2,600 journals scanned monthly by the National Library for drug toxicity are received by the Food and Drug Administration in the form of "MEDLARS" printout. This branch creates a literature abstract of important toxicology articles and publishes a collection of these abstracts weekly, mostly for the use of our medical officers and also for those who have an interest or need for drug toxicology literature. A major step which is currently contemplated by the Food and Drug Administration is to associate the published toxicology literature to the drug reaction system currently being developed for the unpublished literature.

Reports of drug reactions that are received by the Food and Drug Administration are reviewed by members of the professional staff for possible significance. This evaluation is an important part of the over-all decision and an integral part of a drug reaction system. The development of such a system presupposes a lack of language barriers and the technology available to handle large volumes of data. This language barrier unfortunately existed and required a major effort by government, industry, and the scientific community to overcome it. This impetus was provided by the Food and Drug Administration.

In the evaluation of Drug Reaction Reports in the Bureau of Medicine, we have constantly been aware of two major problems in vocabulary control. One is the fact that both in the literature and direct reporting of Drug Reactions there is a distinct problem because of the use of uncontrolled vocabulary by the clinician or researcher. There is wide variety of medical terms. The effect of synonyms, various shadings of meaning which are not precisely synonymous, and the differences between signs, symptoms, and diseases as well as geographical preferences for medical terms present a great interpretative problem. This problem is further compounded by the fact that this material is interpreted at many sources and many levels of training, namely, librarians, medical records personnel, journal editors, academicians, researchers, and government personnel, for many diverse uses.

This vocabulary problem has long been recognized by industry, government, and other interested scientific groups and was recognized as one of the greatest stumbling blocks in the creation of a meaningful Drug Reaction System.

In October 1964, a workshop to discuss the drug reaction vocabulary problem was sponsored by the American Medical Association in response to the need for the Food and Drug Administration, the drug industry, and the scientific community to work out this problem. The original workshop was followed by another meeting in January 1965 and the creation of a subcommittee of the workshop which has been working to resolve the problem of vocabulary control. Certain concepts arose from the discussions at the workshop and by an intensive review of the problems that were presented to the workshop by Food and Drug Administration. They have provided the guide for our Drug Reaction System and are:

1. The need for an adverse reaction vocabulary was agreed upon as a necessity for coding and exchanging scientific information of this nature.
2. The users of this vocabulary go beyond FDA and the pharmaceutical industry, who have a statutory as well as scientific need for this type of vocabulary, and extends to those groups which also have a scientific need such as the American Medical Association, *Chemical Abstracts*, National Library of Medicine, clinical investigators, scientific journals, and others.
3. This dictionary or vocabulary must be designed for retrieval systems which have diverse goals.
4. This vocabulary must be designed to describe defects in humans in other than drug areas, for example, hazardous substances and pesticides.
5. It must be designed for use for either manual or automatic retrieval equipment.
6. In its design for retrieval it must include provisions for synonyms and genus and species relationships as well as recognize the fact that retrieval of these relationships must be of a controlled nature. At the same time we must recognize the fact that for the present the input at the scientific source is essentially uncontrolled and should not be subject to interpretation at a different scientific level either above or below that of the source, dependent upon who is using the system.
7. The next logical step will then be to establish a controlled aspect of the vocabulary by establishing preferred terms. The basis for this should be widely accepted medical usage.
8. The following step would then be to establish a system which can take into account generic, species, or synonym retrieval.
9. Following this, there remains setting up the facilities to publish and constantly update an edition to this open-ended vocabulary and publish its results.

Following the above concepts, a group of frequently submitted adverse effects were collected from the literature and physician reports. These were then evaluated for the meaning of the terms in any context and poor descriptive terms were eliminated from the vocabulary. Many of the terms became preferred because of wide medical usage or prominent mention in accepted medical text. Other terms were classified as synonyms.

The greatest problem arose in the area of those terms which were not quite synonyms but required reference to other terms. In order not to lose meaning, cross indexing might involve as many as 10 or 20 descriptors, and therefore, it was decided that only full and imaginative use of a computer could enable one to retrieve information about these terms in a multifaceted manner.

Computer technology using adequate information storage and retrieval programs can solve the problems

which heretofore have been unsolvable, that is, using a multifaceted system for cross indexing the hierarchical relationships of signs, symptoms, and diseases. This permits the scientists to use natural languages without intermediary interpretation which tends to subvert the means of information.

THE SYSTEM

Input data are extracted from the drug reaction report forms which are created at many different sources either by hospitals under contract or reporting voluntarily to FDA, private physicians, the drug industry, the American Medical Association, or the professional staff of the Bureau of Medicine. This information is further evaluated by the Bureau of Medicine professional staff prior to input. In some instances baseline data programs and adverse reaction programs are submitted to the Bureau of Medicine in the form of drug reaction reports already transferred to magnetic tape.

The items of information are key punched on cards, entered directly onto magnetic tape into the input formats. A drug reaction report and its medical evaluation generate from 12 to 40, 80-column card images; the average is 30 cards.

The method of coding selected is that in which a professional person transcribes the information from a drug reaction report onto coding sheets, in a prescribed format in English language, just as the physician has worded it. The assignments of preferred names, synonyms, and index terms have been predetermined in a dictionary file, and these assignments are made by the computer. Therefore, the computer not only edits misspellings and language usage but also makes the decisions of preferred terminology and body systems and body topography relationships.

In this system, information is stored in three files: Master File, Descriptor File, and Dictionary File. The Master File is a serial file consisting of individual file records representing each element of data in a drug reaction report, descriptors (searchable items), and nonsearchable textual data. The Descriptor File serves as an index to the Master File. It consists of an alphabetic list of all descriptors (index terms) which have been used in the Master File.

The Dictionary File contains a list of allowable descriptors which may be used on the Drug Reaction Report. Some of the entries in this file are preferred terms and others are synonyms. Before updating the Master and the Descriptor Files, each descriptor in the input data is compared with the Dictionary files, thereby maintaining vocabulary control. Invalid or new descriptors are printed out for professional action. Since hierarchical relationships exist in the fields of medicine and drugs, most descriptors are automatically expanded to one or more additional descriptors during the pass of the input against the Dictionary File. This function is essential when the descriptor is the name of a disease; expansion causes indexing to the appropriate body system, etiology, etc.; proprietary drug names are expanded to drug classes and generic names, chemical names, etc.

Searches are performed by first extracting from the Descriptor File the list of drug reaction report numbers for a selected descriptor in the search request. This reduces the number of possible responses to the request—from the entire Master File to a limited item list. The entries in this list are then examined in the Master File with detailed comparison with the complete request. If all of the criteria are met, the Master File record is retrieved. Thus the actual search is performed on the Master File; the Descriptor File is only a means for reducing the scope of the search.

A search request contains several descriptors. One of these descriptors is selected to retrieve the list of adverse reaction report numbers associated with that descriptor in the Descriptor File to obtain a short list of potential hits. A pass of the Master File against this list, with detailed comparisons in terms of the complete request on the potential hits, concludes the search.

The system accommodates three types of requests:

(a) Document. Specified records are retrieved from the Master File.
(b) Boolean. Records are retrieved from the Master File which satisy the logical relationships of the descriptors in a request. Three logical operations are used: ADD, AND NOT, OR (AND/OR). Six arithmetic relations are also included.
(c) Mixed. This request retrieves a specified list of records if they satisfy a Boolean expression.

The Search Run. The search run begins with the batching of up to 99 search requests and ends with a printout of the retrieved records. The system is designed to provide many types of informational searches usually falling into one of three categories.

A. Routine Searches and Reports. This is defined as those reports provided to those physicians who have a need for various parameters of information in our system without request: (1) periodic cumulative and current report of adverse reactions by drugs within pharmacologic class; (2) report by drugs of adverse reactions based on user profile of scientific interest or medical speciality; (3) administrative report by hospital and physician evaluation for quality control of the program; and (4) creation of Adverse Reaction Branch Bulletin for dissemination of information.

B. Alerting System. This segment of the system is based on the utilization of physician evaluation reports, edited routines to scan for duplication, and establishment of limits of significance for automatic reporting. Using statistical analysis programs, some of the following reports would be produced: (1) analysis of adverse reaction types and/or disease incidence; (2) analysis of adverse reactions by drug; (3) analysis of adverse reaction types by chemical and/or pharmacologic relationship; (4) analysis of adverse reaction types by geographical relationships; (5) analysis of adverse reaction types by patient demography; and (6) trends in time.

C. Demand Inquiry. This is defined as those inquiries requested, based on previous cumulative reports supplied or information derived from the alerting system or for special studies. The types of these reports are limited only by the parameters of the information in the system, the availability of easily used and adequate information, and retrieval programs. Permuting the parameters of information in the system creates an almost limitless variety of analyses.

The volume of adverse reaction reports currently

pouring into the Bureau of Medicine is of the magnitude of several thousand reports per month. This data currently represents the largest collection of safety, efficacy, and manufacturing about pharmaceuticals that exist in the world today. Together with the system necessary to evaluate and analyze this information, we have created a scientific tool for the measurement of drug effects, which is only the first of a series of giant strides the Food and Drug Administration is contemplating in the near future.

Information Needed for Clinical Trials of New Drugs*

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The kinds of information a physician needs before he prescribes a drug for the first time and the importance of proper animal and clinical testing are discussed.

Although I am a member of the Advisory Committee on Investigational Drugs to the Food and Drug Administration, this paper does not necessarily reflect the views and opinions of the Committee nor of the FDA.

This paper discusses in general terms the kind of information a physician should have before he introduces a drug into a human for the first time. Other papers in this symposium indicate some methods that have been used or proposed to handle this information so as to derive the maximum benefit for the investigator and the minimum risk to the patients he studies. There is obviously a great need to supplement and improve the methods and systems now available. Dr. Kelsey has spent the major part of his time during the past two years in seeking a forward looking far-reaching solution to this problem. It is by the ready availability and interchange of information available about drugs that we can best carry forward the progress made in developing new and potent agents for use in the conquest of disease. Time, properly trained people, and facilities are too short in supply for us to squander them in nonproductive endeavors and in repeating useless experiments. We must look to the entire globe as the boundaries from which and to which this information must flow. The thalidomide incident demonstrates the importance of easy access and interchange of information on drugs across national boundaries and language barriers.

One of the factors that calls forth strong emotional reaction to a discussion of the information that should be in hand before a drug is administered to a human comes from man's innate hostility towards the formal regulations established in any area which limit his freedom of action. The fact that they come from the government produces a synergistic effect. This reaction is not peculiar to the field of drugs and by its very nature and scope does not lend itself to any productive discussion in the setting and time available here. However, the pragmatist realizes, I think, that more and not less regulation must be expected in a society increasing in complexity as rapidly as ours. Certainly, any reasonable extrapolation of the immediate past into the future gives credence to this prediction. It is then for us, especially those with special knowledge and training, to try and make whatever regulations are imposed work to the maximum benefit and minimum hindrance of progress and to make strenuous efforts to modify these regulations when cold, hard facts can be marshalled to support such changes. I am increasingly convinced that the FDA is committed and dedicated to such a course of action in the field of drugs.

Before deciding to study a drug in humans, the proper answers to the following questions should be at hand. (1) What is the need and importance of a new drug for treatment of a given disease? (2) Is there evidence from preclinical studies that the drug might be expected to be effective in the disease? (3) Has sufficient data been obtained to permit estimation of the human dose that would be effective? (4) Is there enough information about the possible hazards and discomfort of the drug to the patient?

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