A.M.A. Registry on Adverse Reactions*

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The American Medical Association established a registry for the reporting of drug-induced blood dyscrasias in 1953. Later, to supplement the direct reports received from physicians and hospitals, a review of the world literature available to the registry was undertaken. In 1960 the registry was expanded to an over-all registry on Adverse Reactions. Advisory panels were established in the fields of allergy, dermatology, gastroenterology, hematology, nephrology, neurology and psychiatry, pediatrics, and household and economic chemicals. In 1967 the emphasis was shifted to the study of drug utilization. Since the primary objective of the A.M.A. is continuing medical education, exhibits at meetings, tabulations of direct reports, brochures, and articles dealing with drug-induced reactions have been developed. The proposed effort at computerization of these data is described.

The late Dr. Torald Sollman, in 1953, said, "It is necessary still to emphasize that the administration of potent drugs involves a 'calculated risk' where the presumptive benefit is balanced against the possibility of toxic effects and idiosyncracies; but to calculate wisely it is necessary to know, as accurately as possible, what the risk may be in kind, degree and frequency; and the special conditions which may increase or decrease the chance of injury."

"With the older drugs, considerable data are generally available; but when a new drug is introduced they can often be learned only be experience. If the incidence is small, the injury may not become apparent for some time; or one of the earlier cases may happen to be one of the exceptions, and so bring a valuable drug into disrepute, perhaps depriving the public of an exceptionally valuable remedy, . . . Full information will serve to protect in both ways: against the risk of unjustified fear as well as against the risk of rashness."[1]

The majority of drugs used in medicine today are the result of the tremendous advances made in chemical and pharmaceutical research during the past 25 years. Many of these therapeutic agents are extremely potent, and physicians must understand their physiological, pharmacological, and toxicological actions. Physicians must always be on the alert for the appearance of unusual reactions caused by "old drugs," "new drugs" administered alone or in combination, and the interaction from drugs or dietary constituents administered concomitantly.[2]

The constitution of the American Medical Association states that the Association's purpose is ". . .to promote the art and science of medicine and the betterment of public health."[3] The Council on Drugs of the American Medical Association, formerly the Council on Pharmacy and Chemistry, has recognized the importance of informing physicians about drug-induced reactions and as a result has published statements periodically dealing with the problem. As new data have become available, the Council has revised its monographs on drugs to incorporate such information.

HISTORICAL BACKGROUND

In 1953 following the appearance of a number of papers dealing with the hematopoietic toxicity of chloramphenicol, the Council on Drugs decided to investigate the problem of iatrogenic blood dyscrasias. A meeting of hematologists and representatives of the pharmaceutical industry was convened after which the Council directed its former Committee on Research to establish a Subcommittee on Blood Dyscrasias charged with the responsibility of creating a Registry on Blood Dyscrasias. The mission of the Registry was to assemble information on drug-induced hematopoietic reactions, and alert the profession to the potential for hematopoietic toxicity of drugs and chemicals at the earliest possible moment. Medical schools, medical societies, governmental agencies, and hematology groups were contacted to encourage them to report to the A.M.A. Registry. After several years, the routine review of the literature available to us on drug-induced hematopoietic toxicity was added as a regular feature of the Registry operation.

In 1959, the Council on Drugs reviewed the results of the activities of the Registry and concluded that it was a valuable mechanism for the acquisition of information. In 1960, the Council recommended to the Board of Trustees of the American Medical Association that the Registry be expanded to an over-all Registry of

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Adverse Reactions whose purpose would be to assemble information on drug reactions; evaluate the accumulated data; and disseminate the information so gathered.[4] The Board of Trustees approved this recommendation in May 1961 and the Registry on Adverse Reactions came into being. Groups of experts were consulted and the A.M.A. was advised: that there was a need for a central registry of national scope; that only a small percentage of drug reactions are reported in the literature and thus physicians are not too well informed in this area; that organizations such as pharmaceutical manufacturers and governmental agencies were collecting information on untoward effects of drugs with little of such information reaching the practicing physician; that physicians would be less reluctant to report their suspicions to the A.M.A. rather than to a drug manufacturer or a regulatory agency; and that the American Medical Association was well suited to maintain a registry since it could provide the necessary impartial expert evaluation of data and possessed adequate facilities for the dissemination of such information through its publications.

At the same time the Council established a Committee on Adverse Reactions within its organizational structure and charged it with the supervision of the Registry on Adverse Reactions. To provide consultative service to the Registry in the various branches of medicine the following panels were established: allergy, dermatology, gastroenterology, hematology, nephrology, neurology and psychiatry, pediatrics, and household and economic chemicals. A separate panel of consultants-at-large was formed to handle problems which did not fall into specific categories.

A report form incorporating information considered essential to an understanding of a case was devised with the help of the panels. The panels reviewed the reports received by the A.M.A. Registry to determine: the adequacy of the diagnosis on the basis of the clinical history and laboratory information; and the possible casual relationship between the development of the reaction and the use of drugs. Screening of reports was performed by one or more panels having an interest in the particular problem. For example, a report of a skin reaction in a child would be reviewed by the dermatology and pediatric panels.

To promote the Registry, hospitals accredited for internship and residency training and medical societies were contacted by letters outlining the objectives and activities of the Registry. Presidents of all state and larger local medical societies and the editors of their journals were contacted in the hope of enlisting their help in promoting the Registry. Notices were carried in a number of specialty publications calling attention to the existence of the Registry and recommended that members report their observations to the A.M.A. By 1965, we were receiving direct reports at the rate of approximately 200 a month. During 1967, the Registry received 852 reports without any effort at solicitation. We received a total of 8200 reports from 1953 through 1967, of which 2900 were reports of blood dyscrasias received during the 10-year period from 1953 to 1963.

Education Program: The major objective of the A.M.A. Registry is the development of an educational program. This has been accomplished through the distribution of tabulations of the direct reports received; the publication

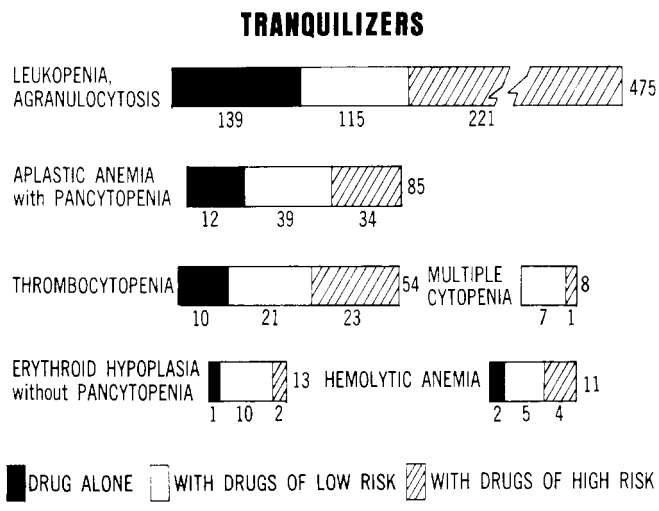


Figure 1. Bar graph of reports of blood dyscrasias associated with the use of tranquilizers

of articles discussing various aspects of the drug reaction problem; the development of audio-visual material such as exhibits and slides to be used with the exhibits; talks to medical societies and specialty groups; the sponsorship of symposia on adverse reactions; the exchange of information with governmental agencies and pharmaceutical manufacturers; and the providing of information to physicians concerning drugs or reactions.

Between 1957 and 1964 semi-annual hand-generated tabulations of the direct and literature reports of blood dyscrasias were prepared and distributed to a mailing list of about 3000 hospitals and individuals. During 1964 and 1965 the Committee sponsored a series of 27 articles on aspects of the problem and in 1966 republished them under one cover. Three exhibits for use at medical meetings have been developed. One of these exhibits is equipped for projecting colored slides showing examples of reactions. Booth attendance at medical meetings annually has run between 5200 and 6900 and has resulted in the filling of between 3400 to 4500 requests for reprints each year. Talks have been given to a variety of specialty groups and a number of state medical societies. A symposium was held at the 1965 annual A.M.A. meeting in New York City where eight formal papers were presented along with a panel discussion. A second symposium was held on June 19, 1968, at the annual A.M.A. meeting in San Francisco, where the following papers were presented: "Ocular Complications to Drugs," "Gastrointestinal Reactions to Drugs," "Drug Interactions," "Photosensitivity to Drugs and Chemicals," "Hepatotoxicity to Drugs," and "Reactions to Household and Economic Chemicals."

Also, during this same period information has been exchanged with pharmaceutical manufacturers, FDA, USPHS, and the Registry of Tissue Reactions to Drugs of the Armed Forces Institute of Pathology. An average of several hundred inquiries for information from physicians are answered annually.

In connection with the talks given to medical societies and specialty groups, Figure 1 is an example of the type of information which can be gleaned from the reports received by the Registry. Figure 1 represents the reports

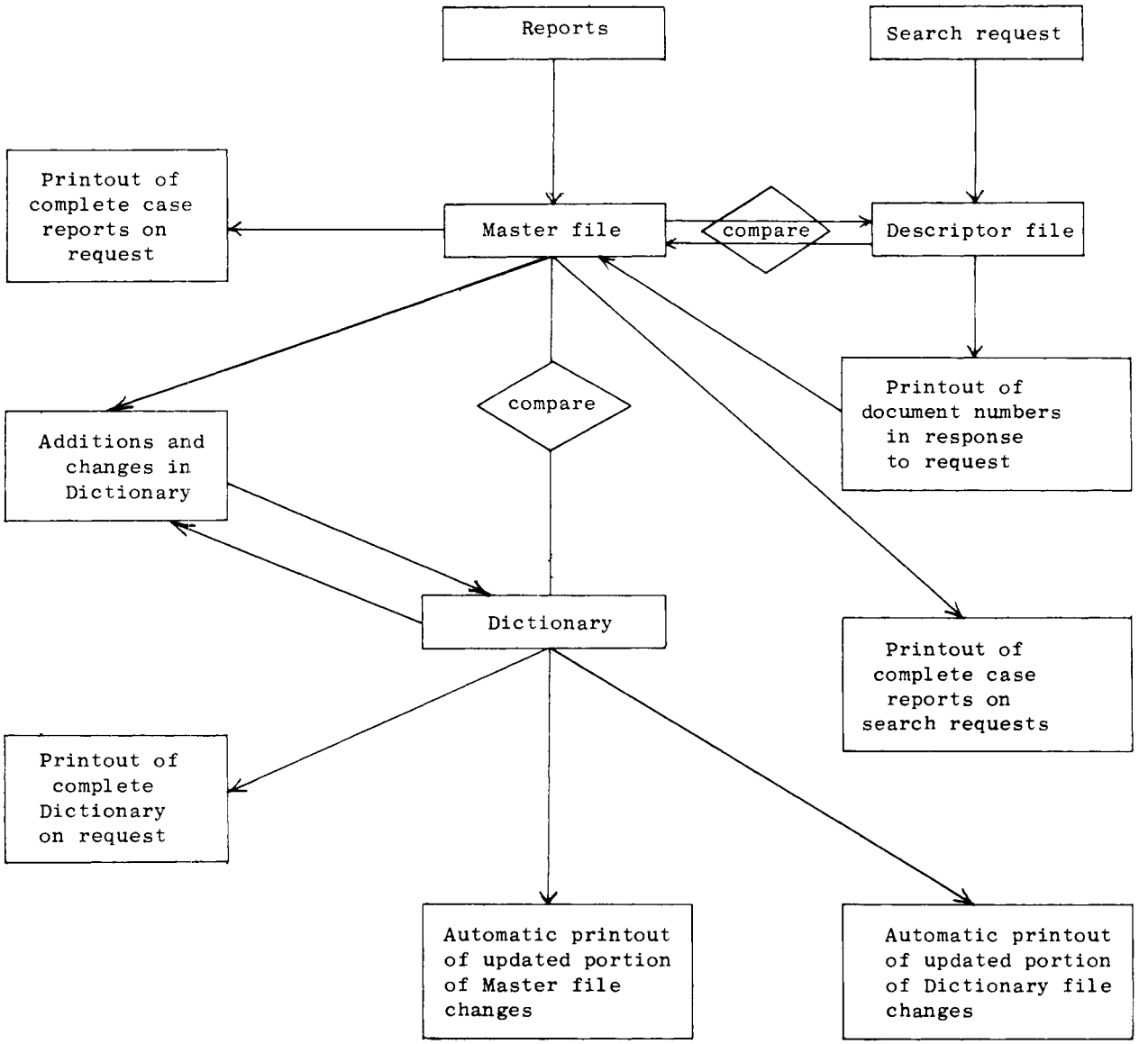


Figure 2. Diagramatic flow sheet of the proposed AMA Information Storage and Retrieval Program for Adverse Reaction Reports

of blood dyscrasias associated with the use of tranquilizers. It will be noted that there were 475 reports of leukopenia, agranulocytosis, of which 139 were reports in which the tranquilizer was the only drug allegedly used, 115 reports of tranquilizers used with drugs of low risk, 221 reports of the use of tranquilizers with drugs of high risk; of the 85 reports of the aplastic anemia with pancytopenia, 12 reports were received in which the tranquilizer was the only drug mentioned, 39 reports of a tranquilizer used with drugs of low risk, and 34 reports of the use of tranquilizers with drugs of high risk; of the 54 reports of thrombocytopenia 10 were reports in which the tranquilizer was the only drug mentioned, 25 in which the tranquilizer was used with drugs of low risk, and 23 reports in which the tranquilizer was used with drugs of high risk. The same applies to the reports of erythroid hypoplasia without pancytopenia, hemolytic anemia, and cytopenia. In the case of the tranquilizers used with drugs of low risk one might suspect that the tranquilizer might have been responsible for the blood dyscrasia, whereas, in the reports in which the tranquilizer was used with drugs of high risk there is less suspicion that the tranquilizer may have been responsible for the reaction.

Hospitals interested in the educational aspect of the program are advised that: the identification of a reaction should be made by the attending physician; findings should be made a matter of record through a system of notification with the appropriate committee of the medical staff; and the Pharmacy and Therapeutics Committee should periodically review all reports of drug reactions occurring in the hospital, investigate the possible cause of the reactions, and make recommendations to the staff for improvement in the use of drugs and other therapeutic measures. It is felt that an awareness of the problem through the media of conferences, staff meetings, bulletins, etc., could improve the prescribing habits of the doctors of the hospital and house staff.

While the A.M.A. Registry was evolving, the Food and

For AMA use only

REGISTRY ON ADVERSE REACTIONS—COUNCIL ON DRUGS

AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Illinois 60610

See Guide For Reporting for special instructions and glossary to aid you in completing this form. If you wish to add any material, please enclose a separate sheet.

1. a. Patient's Initials____ b. Sex____ c. Weight____

d. Date of Birth____ (Mo./Day/Yr.) e. Occupation____

f. 1. ☐ Cauc. 2. ☐ Negro 3. ☐ Oriental 4. ☐ Amer. Indian 5. ☐ Other

2. a. Dr.____

b. Street____

City____ State____ Zip Code____

c. Date____

3. Adverse Reaction(s) (Describe)

4. a. Date of Onset____ b. Date of Diagnosis____ c. Was onset of reaction { 1. ☐ acute explosive 2. ☐ slowly developing

5. a. Result of Relevant Diagnostic Studies (Clinical Laboratory, Endoscopy, Biopsy, Autopsy, X-Ray, etc.):

b. Pathologist____ Hospital____ Tissue available? yes ☐ no ☐

6. List all drugs patient has received in the 6 months prior to onset of adverse reaction. Include biologicals, diagnostic agents, and transfusions. Give manufacturer's name and lot or code number, if available. Indicate date of first and last dose of drug for each course of therapy, and indicate route of administration.

NAME OF DRUG (Trade Name)	TOTAL DAILY DOSE	ROUTE (p.o., im, iv, etc.)	DURATION OF THERAPY (Days)	DATES OF ADMINISTRATION Date started	Date ended	DISORDER OR REASON FOR USE OF DRUG
(suspected drug)						

7. List all potentially toxic agents to which patient has been exposed, and describe circumstances of exposure. Give any information available on dose or exposure. (Include radiation, household products, industrial and agricultural chemicals, cosmetics, etc.)

Name and Type of Agent	Type & Description of Exposure	Amount, Dosage and Duration

8. a. Has patient been exposed to suspected drug or agent before? ☐ Yes ☐ No

b. Was suspect drug or agent used according to directions? ☐ Yes ☐ No Explain____

9. Other Disorders Which Existed Prior to Onset of Adverse Reaction or Are Now Present:

10. Factors Contributing to Reaction (check all applicable boxes):

a. 1 ☐ self medication by patient
2 ☐ accidental exposure
3 ☐ occupational exposure
Comments:

b. 1 ☐ drug mislabeled
2 ☐ decomposition of drug
3 ☐ contamination of drug
4 ☐ drug outdated
5 ☐ interaction of two or more drugs

11. Outcome of Case

1 ☐ Recovered
2 ☐ Alive with sequelae
Explain____
3 ☐ Still under Treatment
4 ☐ Died____ (date and cause of death)
5 ☐ Autopsy (Describe in item 5)

12. Sources of Suspected Drug:

1 ☐ from physician
2 ☐ physician's sample
3 ☐ hospital
4 ☐ pharmacy
5 ☐ other retail source
6 ☐ mail order
7 ☐ door-to-door salesman

13. a. Has this case been reported to any other group or agency?
☐ FDA ☐ Mfr. ☐ Poison Control Center ☐ Other (specify)

b. Has or will this case appear in the literature?
☐ Yes ☐ No. Journal Ref.____

AR6-65

Figure 3. Copy of the AMA form for reporting of adverse reactions

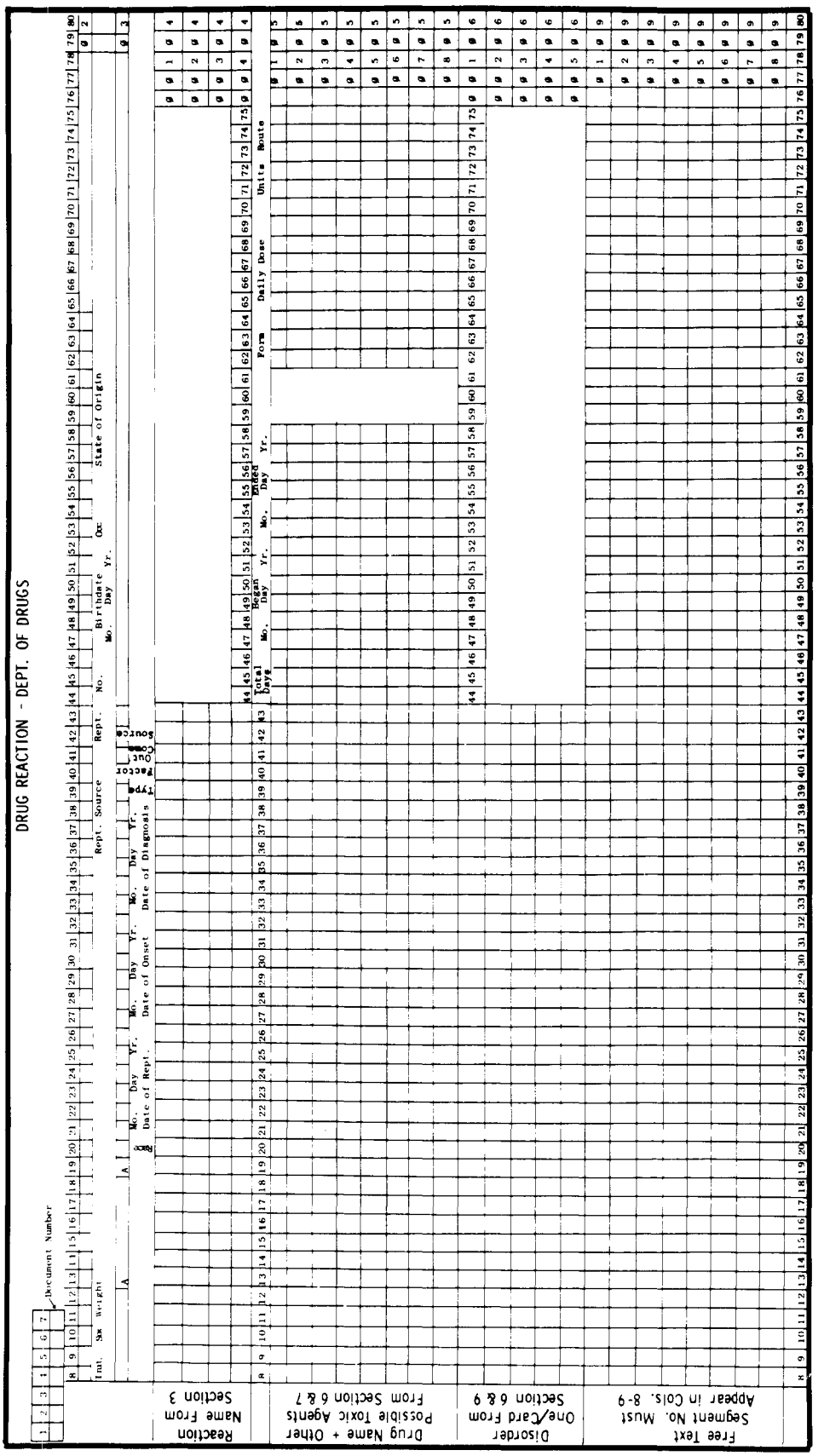
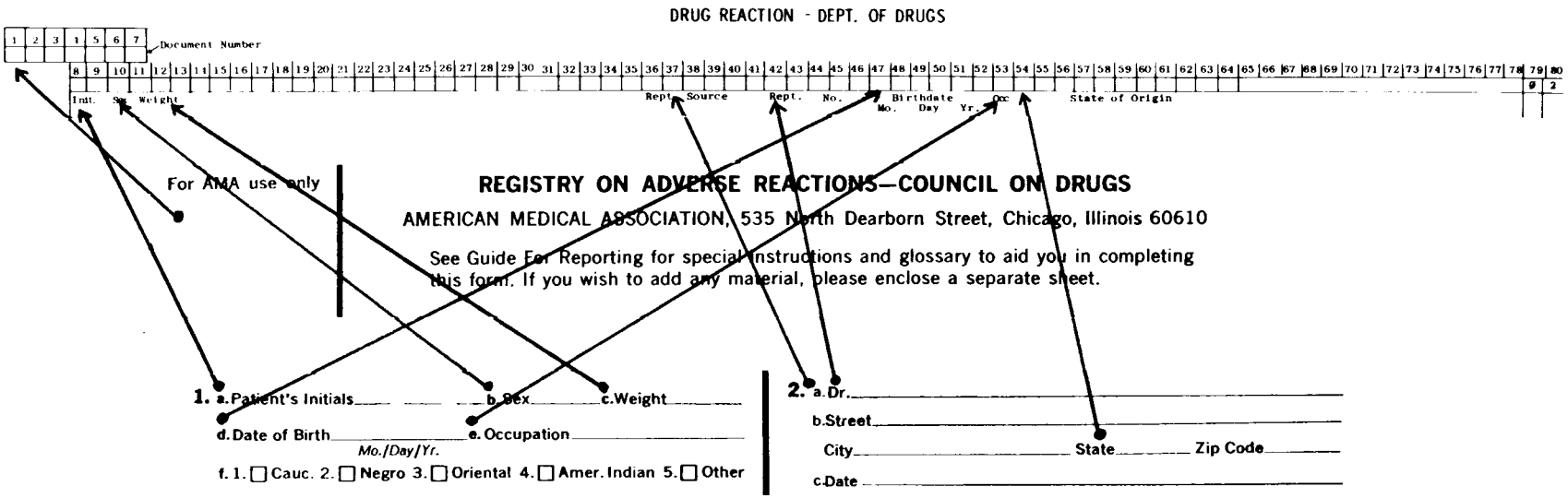


Figure 4. Copy of proposed work sheet for the Information Storage and Retrieval Program



CARD Ø2 corresponds to sections 1 and 2 of the report form.

Columns:	01-07	DOCUMENT NUMBER (Prefix with ØØØ).
	08-09	PATIENT'S INITIALS (Numeric X (-) if not given).
	10	SEX (M or F, if not given Ø).
	11-13	WEIGHT IN POUNDS (ØØØ if not given).
	14-36	BLANK
	37-41	HOSPITAL NUMBER (Prefix with Ø).
	42-46	HOSPITAL REPORT NUMBER (Prefix with Ø's).
	47-52	DATE OF BIRTH (Mo.-Day-Yr.). (A in col. 52 if date of birth not given).
	53	OCCUPATION (1-9 from the Dept. of Labor Dictionary) (Ø if occupation is not given) (- if unemployed) (& if retired)
	54-76	ADDRESS (State only).
	77-78	BLANK
	79-80	CARD Ø2 IDENTIFICATION NUMBER

Figure 5. Composite of a specific section of the report form with instructions for transfer to the applicable portion of the work sheet

Drug Administration was developing its own hospital reporting program. By 1963, the A.M.A. recognized that some arrangement should be made with the Food and Drug Administration to avoid duplication of reporting and eliminate the confusion on the part of hospitals and the medical profession concerning where to send reports. Consequently, after a number of preliminary discussions, a meeting was held in May 1964 for the purpose of defining the areas of FDA and A.M.A. operations. It was agreed that the A.M.A. would assume the responsibility for developing information coming from the medical profession and those hospitals not reporting in the FDA program, and would distribute the resultant data to the medical profession, the FDA, and drug manufacturers. FDA agreed to restrict its reporting program to university affiliated institutions and teaching hospitals approved for internship and residency training with a bed capacity of 300 or more. It was mutually agreed that information would be exchanged on a coded basis so that FDA and A.M.A. would benefit and the confidentiality of the records could still be maintained.

It was recognized early that information received by the Registry might be either a trickle or a torrent. Consequently, it was decided to move toward computerization of the data contained in the reports. A program for storage and retrieval of information was developed.[5] The format for storage was based on the concept of coordinate indexing implemented by a "serial file" and an "inverted file." The serial or "master file" contained the complete record of each case while the inverted or "descriptor file" consisted of an alphabetic listing of all descriptors used, along with the accession number of each report in which the descriptor appeared. A third file, the "dictionary file," contained a list of allowable descriptors found in the reports along with preferred terms or synonyms. The "master" and "descriptor" files were intended primarily for search and retrieval while the "dictionary" file was intended to assure the accuracy and integrity of the "master" and "descriptor" files. A search for a specific reaction could be performed by first extracting from the "descriptor" file a list of accession numbers of the reports in which the name of the reaction appeared. A printout would be requested from the "master" file of all reports with accession numbers meeting the criteria.

It was intended that the "master," the "descriptor," and the "dictionary" files would be used in file maintenance. The updating and maintenance of the "descriptor" file would be an automatic byproduct of the "master" file maintenance program and would accurately reflect the content of the "master" file, and since each descriptor would be compared with the "dictionary" file, vocabulary control would be maintained (Figure 2).

A work sheet for the transfer of information from the report was devised which carried the information in natural language (Figures 3 and 4). Figure 5 shows how information from a specific section of the report form is applied to the appropriate portion of the work sheet, and the instructions for such transfer. The program for storage and retrieval of information has now been placed in abeyance since the Council on Drugs recommended that the operation be expanded from a Registry on Adverse Reactions to a drug utilization study.

I believe we must recognize that the ultimate success of any Registry operation is dependent upon the desire of every physician to bring all such information to the attention of the profession as a whole rather than withholding it for whatever reason he may have, *viz:* medical (incorrect use or misuse of a drug) or legal (fear of a malpractice suit). We have been advised that an "error of omission" is more damaging than an "error of commission" in regard to the recording of reactions in the patient's record. In the last analysis, a chain is as strong as its weakest link and the weakest link in the Registry chain probably is the individual physician. A solution may be found through certain changes in the legal aspects of the problem plus a greater degree of understanding and cooperation among all the parties involved—namely, the medical profession, the pharmaceutical industry, and governmental agencies.

Hippocrates said in his Aphorisms: "Life is short, the art long: opportunity fleeting, experience treacherous, judgment difficult."[6] This, I believe, describes the situation as it applies to the reporting of drug reactions to a Registry, and the use of these data as an educational tool for the benefit of the profession.

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(5) De Nosaquo, Norman, "The Use of Computers for Storage and Retrieval of Adverse Drug Reaction Information," Fourth Pan American Symposium on Pharmacology and Therapy, Mexico City, August 24-26, 1967.
(6) Hippocrates "Aphorisms," Sec. 1, No. 1.