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A Study of Automated Information Processing Systems in Drug Reaction Surveillance and Reaction Prevention *

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This paper is a study of a set of automated information processing systems which transact with data about drugs, their use, and their adverse effects. Drug *reaction surveillance* systems are used in epidemiologic research to detect adverse effects occurring in the normal therapeutic use of drugs. Drug *reaction prevention* systems are used to prevent inappropriate prescribing of drugs known to cause adverse reactions. Specific systems designed for one or both purposes are described and compared in detail. Some proposed basic principles regarding the design of information processing systems for reaction detection and prevention also are presented.

INTRODUCTION

This paper is a study of automated information processing systems which transact with data about drugs, their use, and their adverse effects. The paper is a state-of-the-art survey which develops a framework for the classification and critical evaluation of drug reaction information systems, then applies that framework to analyze major existing programs in drug reaction surveillance and reaction prevention. It is a position paper which makes recommendations towards the future development of drug reaction information systems, and discusses methodological and research questions that require future consideration. It is also intended as a prototype for what hopefully will be an increasing application of the information processing viewpoint, and the insights and methods of computer science, to the critical analysis and improvement of the total pharmacological information system.

1. BACKGROUND

The increasing therapeutic use of powerful modern drugs, singly and in combination, has spawned a major new health hazard—the *adverse drug reaction* (ADR)

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(*1–5*). The World Health Organization has suggested the following definition of an adverse drug reaction: "one which is noxious, unintended, and occurs at doses used in man for prophylaxis, diagnosis, or therapy" (*6*). Gardner and Cluff have argued that, for operational purposes, only those reactions should be included "which require the physician to discontinue or reduce the dosage of a drug suspected of causing an unwanted effect" (*7*). In their recent review article, Gardner and Cluff also document the scope and seriousness of the problem by summarizing the findings of almost one dozen independent investigations:

> . . . the percentage of patients with untoward reactions to drugs in the hospital has ranged between 10 and 18% despite a wide variety of institutions and investigational methods. In addition, 4–7% of patients have a drug induced disease on admission to the hospital and of these approximately half required hospitalization because of this occurrence . . . In hospitalized patients experiencing a drug induced illness, the case-fatality rate has ranged from 0% to 12.9%, averaging 5.0% . . . (*7*).

These adverse drug reactions occur in the normal therapeutic use of drugs after they have been tested in laboratory animals and in clinical trials and found by the FDA to be both safe enough and effective enough to be marketed.

The need for continuing investigations of the effects of marketed drugs was recognized in the 1950s and resulted in the formation of *spontaneous reporting* systems by the FDA and the AMA (*2*). Physicians were encouraged to submit voluntary, anecdotal reports of suspected ADRs. By the mid 1960s, the FDA and the AMA had coordinated their activities into a single Hospital Reporting Program. Currently, 12 000 to 14 000 new reports are added each year to the existing file of 100 000 computerized entries (*8*). These are in turn submitted to the World Health Organization International Drug Monitoring Project, which maintains a data base representing contributions from 10 countries (*9–12*).

Spontaneous reporting systems have several advantages (*4*). Since the potential data base from which the reports are drawn consists of all persons consuming drugs, very rare reactions may be discovered. The cost of the resulting information is low. Since the system actively involves the medical profession, it serves an educational function which is likely to improve physician prescribing practices. There are, on the other hand, major disadvantages. Physicians do not always suspect the new and unexpected, so the system's sensitivity to previously unrecognized reactions is low. Spontaneous reports lack sufficient detail to allow reliable evaluation. They also cannot accurately establish the incidence of drug reactions.

In a pioneering 1964 paper, D. J. Finney then proposed a new approach, drug *monitoring*, which he defined as "any systematic collection and analysis of information from the normal therapeutic use of drugs, with the object of acquiring evidence on adverse effects or other phenomena associated with this use" (*13*). He suggested:

> . . . a panel of physicians (or of hospitals) . . . would undertake to report in detail all uses of specified drugs, together with information on the patients receiving each (sex, age,

> occupation and environment, health and medical history); they would also report every instance from a long, carefully prepared, list of untoward reactions and events among their patients, *without regard to whether or not they believed a particular instance to be consequential upon the drug regime*. Such reports would be continuously compiled and analyzed by one central computer with a view to picking up any hints of unexpected drug behavior (*13*).

Thus *intensive surveillance* systems based on Finney's model are used for epidemiological *research* on adverse effects occurring in the normal therapeutic use of drugs.

In parallel, a set of drug *reaction prevention* and *utilization review* systems have been developed to achieve goals in *patient care* and *hospital administration*. They seek to promote more effective utilization of existing pharmacological knowledge in preventing the prescription of excessive amounts of a single drug or the concurrent prescription of drugs known to react together adversely. They are also designed to accumulate data about physician prescribing practices and eliminate costly excessive prescribing and to make pharmacy operation more efficient and less costly. For years, hospitals and pharmacies have sought these goals by instituting new administrative procedures, for example, establishing information centers and equipping experts with reprint files, reference sheets, and wall charts (*14–17*). The development of automated reaction prevention systems is a natural outgrowth of these efforts.

2. Classification and Analysis of Drug Reaction Information Systems

A. Identification of project
   1. Name of project
   2. Type of project: reaction surveillance, reaction prevention
   3. Principal investigator(s)
   4. Location
   5. Time period active

B. Goals, methodology, and results
   1. Major stated goal(s)
   2. Observed population, inpatient or outpatient, how selected
   3. Information stored in computer system, its quantity (approximate number of bits per patient, per drug, or per ADR) and its quality (source, method of collection, method of accuracy verification)
      a. Basic drug data
      b. Drug warning data
      c. Prescription data
      d. Diagnosis data
      e. ADR data
      f. Clinical laboratory data
      g. Other patient history data
   4. Are there linkages from the data to a primary medical record of patient history? What kind of linkages? How is the primary record accessed?
   5. Software mechanisms, on-line and off-line, currently available for accessing, retrieving, and browsing among the data
   6. Research and statistical methodology currently employed for epidemiologic analysis

7. Use made of the drug warning data in patient care, to prevent inappropriate prescribing
8. Summary of major results published to date
9. What exists in the way of documentation and/or a precise description of the data base's contents, structure, and access mechanisms? What are the prospects for export or sharing of the system?

C. Implementation details
1. Hardware and storage media used
2. Software used
3. Method of data input and retrieval
4. Approximate running costs per patient, per drug, per ADR, or some other unit (once system development is complete)

The Boston Collaborative Drug Surveillance Program

A. Identification of project
1. Name
The Boston Collaborative Drug Surveillance Program (*18–39*)
2. Type
Reaction surveillance
3. Principal investigator(s)
Hershel Jick, M.D., and Dennis Slone, M.D.
4. Location
Tufts University School of Medicine, Clinical Pharmacology Unit, 400 Totten Pond Road, Waltham, MA 02154
5. Time
1966–ongoing

B. Goals, methodology, and results
1. Goals
Research
". . . an ideal drug-surveillance program records all drug exposures and all adverse events, regardless of whether or not these events are attributed to a drug. Such a system is largely independent of clinical judgment in establishing a connection between a drug and an adverse effect, and in addition to efficient detection, it permits quantification of drug effects, . . . evaluation of efficacy, . . . [and] assessment of drug interactions, as well as of the possible role of certain patient characteristics . . ." (*21*).
"The major goals of this study are to obtain the following types of information about specific drugs: (1) How often is there apparent benefit and how often apparent harm from each drug? How serious is the harm done? (2) What associations exist between specific drug effects and various subgroups in the medical population? (3) When do drugs interact to produce a clinical effect?" (*26*).
2. Observed population
Patients in specially selected wards of 11 hospitals in the United States, Canada, and Israel are under surveillance. From 1966 through 1971, records were collected on over 10 000 patients undergoing over 12 000 hospital admissions. These patients received over 175 000 drug orders. Currently, there are 12–15 highly-trained full-time nurse monitors, each responsible for collecting data on 1 ward of 20–30 patients.

3. Information stored
a. Basic drug data
The system contains names and code numbers for over 1200 drug categories.

b. Drug warning data
None.

c. Prescription data
All drug starting orders are written by the attending physician on a routine drug order sheet. The name of the drug, date started, dosage, frequency, and instructions are all noted. The nurse-monitor interviews the physician, obtains the indication (medical justification) for starting the drug, and classifies it into one or more of 68 broad categories. The nurse-monitors transcribe all data onto specially coded data sheets and check it for accuracy. A data item of 260 bytes is kept for each drug given a patient during a hospital visit. This includes the ADR data described below. Thus approximately 175 000 drug orders × 260 bytes = 45 000 000 bytes of drug and reaction data are currently on file.

d. Diagnosis data
The data base includes admission diagnoses, diagnostic indications that were used to justify drug start orders, diagnoses of adverse drug reactions (see below), and diagnoses made upon discharge of the patient.

e. ADR data
"All alleged adverse drug reactions recognized by the attending physician are reported to the nurse-monitor and through her to a member of the clinical pharmacology unit as soon as possible after a reaction is suspected. One of the physicians in the clinical pharmacology unit then determines whether the reaction should be investigated, and, if so, he begins a comprehensive work-up (usually within 24 hours). The investigation usually includes an interview and examination of the patient, interview of the doctor and ward nurse, review of the record of the patient, and follow-up when indicated. The following descriptive categories related to the alleged reactions are evaluated, estimated, and recorded in the data base: (1) speed of onset: (2) severity and morbidity; (3) causative factors (e.g., hypersensitivity, intolerance, drug interaction); (4) site; (5) duration; (6) whether the reaction was life-threatening; (7) whether length of hospitalization was increased due to the reaction; (8) final impression of the attending physician concerning whether the drug implicated really caused a reaction; (9) impression of the clinical pharmacologist concerning whether the drug implicated really caused a reaction; and (10) outcome of the case.
"Two specific questions are asked for each drug on each patient in order to obtain a complete recording of all recognized adverse reactions. The first question is the specific reason for discontinuing a drug, and one of the categories for discontinuing is 'side effects.' If the drug is stopped for any other reason, another question is asked, namely, 'Has any adverse reaction occurred with this drug?' This question documents all recognized reactions which were not serious enough to cause discontinuation of the drug" (*19*).

f. Clinical laboratory data
Upon admission of the patient, the nurse-monitor takes samples from which are performed routine blood and urine studies and typings for a group of genetic markers. Tests performed include Agglutinogen systems, ABO and other subgroups, Rh and other subgroups, Kell, Lewis, MN, Ss, Duffy, Kidd, Xg, Secretor status, Serum protein systems, Haptoglobin phenotype, Haptoglobin titer, Total serum protein, Serum albumin, Color blindness, and Ability to taste phenyl-thiourea. The result is a genetic profile of the patient. This procedure is being discontinued due to its expense and the unreliability of the data obtained.

g. Other patient history data
Upon admission of the patient, the nurse-monitor gathers such vital statistics as sex, race, birth date and location, religion, marital status, national origin of parents, allergies, previous drug reactions, use of tobacco and alcohol, and medication history within 3

months prior to admission. At the time of patient discharge the nurse-monitor again interviews the doctor to obtain information on instances of (currently) 20 adverse events such as fever, infection, bleeding, and sudden death, and whether or not any of these have been attributed to a drug. Each patient's history data (including laboratory tests and diagnoses) is organized into that which is invariant from one admission to the next, a total of 152 bytes, and that which is taken anew at each admission, a total of 448 bytes. Thus approximately 7 000 000 bytes of vital statistics data are now on file.

4. Linkages to a primary medical record
   The primary medical record for the purposes of the project is the set of coded data sheets prepared by the nurse-monitor. There is a Vital Statistics sheet, a Medical History sheet, a Drug Starting–Drug Stopping sheet, a set of Adverse Reaction sheets, a Discharge sheet, a Genetic Blood Profile sheet, and a Genetic Code sheet. Print-outs obtained from the screening and analysis programs include patient identification numbers by which the original data sheets can be retrieved from a manual file. No use is made of the traditional medical record which remains back at the hospital.
5. Software mechanisms for retrieving and browsing
   Two major files are kept, a vital statistics file, and a drug file. About once a month, new data is input, validated extensively and purged of data containing errors, and then added via standard update programs to the master files. Almost all of the ensuing analytical processing is performed via batch processing. Routine screening programs include a Patient Profile Program, which neatly tabulates key data on each individual patient, and a Drug Screening Program, which tabulates for each drug a profile that includes dosage, efficacy, starting and stopping reasons, number of exposures, and number and nature of side effects. Standard epidemiologic comparisons are made in the Drug Screening Program as well as in a Diagnosis Screening Program and in a Drug Event Analysis Program (see below). There are approximately 14 commonly used profile and screening programs.
   There also exist several hundred special-purpose programs which have been used to prepare spin-off files for detailed specific investigations. Continual development of such programs is a major task. The resulting spin-off files are then analyzed with the University of Chicago National Opinion Research Center's Statistical Program for the Social Sciences, or when unavoidable a tailor-made program.
   Finally, the APL time-sharing system is used for multivariate statistical analysis on highly aggregated data that is derived from the other work.
6. Research methodology
   In the Drug Screening Program a series of epidemiologic comparisons are made and tested for significance. People receiving "drug X" are divided into two groups—those incurring an adverse reaction to "drug X" and those not. The two groups are compared along such variables as sex, race, survival, ABO blood group, weight, and various genetic blood markers. The Diagnosis Screen is similar, however the two groups compared are those with and without each hospital discharge diagnosis. In the Drug Event Analysis Program, for a given side effect "Y", the population is divided into those having the side effect and those without. All drugs received by each group are tabulated. For each drug a chi-square is computed, comparing the numbers of people receiving the drug in each group to the total in each group. Drugs which are significantly associated with specific adverse reactions or with any adverse reaction are identified. Other standard epidemiologic screening tests are used. More detailed analyses suggested by these screens are specially programmed.
   Also, the system allows for the introduction of controlled drug trials, using techniques such as randomization and double-blind comparisons of various drugs and/or placebos.
7. Use of drug warning data in patient care
   None.

8. Major results
   The project has published a series of (currently, sixteen) papers, presenting both standard epidemiologic analyses of their data and the results of randomized, double-blind, controlled trials (*23–28*). The papers demonstrate the tremendous value of the project's data base for epidemiologic research on drug effects and drug interactions.
9. Documentation, export, sharing
   The system continues to grow slowly with the addition of new hospitals. Researchers from several countries have spent varying periods of time in residence with the group, either to learn the methodology, or to carry out specific investigations. The project is also willing to carry out investigations for others. The basic computer programs have stabilized, and, if better documented, could be exported to others. The project feels, however, that the high cost of operating the system will discourage anyone else from asking for it.

C. Implementation details
1. Hardware and storage media
   An IBM 370/155 is used for processing. The data files are kept on magnetic tape. Currently, about 3 tapes are needed.
2. Software
   Most programs are written in Fortran or Cobol, and run in batch processing under OS-370.
3. Method of data input and retrieval
   The nurse-monitors prepare the data on specially-designed coded forms, from which cards are punched and then input in batch. Most output is obtained from batch print-outs.
4. Approximate running costs
   Currently, the system is maintained by 3 programmers, a clerical assistant, 2 biostatisticians, 2 research pharmacists, 2 nursing administrators, a dozen nurse-monitors, and a half dozen research investigators. Computer costs are approximately $75 000–100 000 per year.

The Kaiser-Permanente Drug Reaction Monitoring System

A. Identification of project
1. Name
   The Kaiser-Permanente Drug Reaction Monitoring System (*40–48*)
2. Type
   Reaction surveillance
3. Principal investigator(s)
   Gary D. Friedman, M.D., and Morris F. Collen, M.D.
4. Location
   The Department of Medical Methods Research, Permanente Medical Group, 3779 Piedmont Avenue, Oakland, CA 94611
5. Time
   1968–ongoing

B. Goals, methodology, and results
1. Goals
   Research
   "What is greatly needed is objective quantitative information about drug reaction risk in the clinical setting—information that the physician can use to weigh the risks versus the benefits of a particular drug for his patient" (*44*).
   The goal of the Drug Reaction Monitoring System (DRMS) is "the quantitative measurement of risk of disease entailed by predisposing factors . . . [and it] is also expected to uncover previously unsuspected reactions" (*44*).

2. Observed population
   Outpatients at the Kaiser-Permanente Medical Center in San Francisco
3. Information stored
   a. Basic drug data
      Name of drug (usually trade name), form, strength, and usage instructions to patient
   b. Drug warning data
      None.
   c. Prescription data
      The pharmacist enters each patient prescription into the computer. This includes a prescription number, the name of the drug (usually trade name), the form, strength, usage instructions to the patient, the amount dispensed, and the refill instructions. The physician in the clinic records additional medications that are injected into or supplied directly to the patient.
   d. Diagnosis data
      The physician in the clinic records each patient's diagnosis or diagnoses for entry into the computer. The physician also indicates whether each is a new or recurrent event, a continuing preexisting condition, or a worsening condition.
   e. ADR data
      The physician records suspected ADRs.
   f. Clinical laboratory data
      Results of tests performed in the hematology, urinalysis, and chemistry laboratories are to be added to the monitoring system. The intent is to detect common reactions to drugs, such as, hyperglycemia, hyperuricemia, anemia, leukopenia, and albuminuria.
   g. Other patient history data
      Northern California Kaiser-Permanente patients have a variable-length, variable-format, computer-stored medical record. The tree-structured file contains identification, administrative, and medical data. The medical section is divided into chronologically ordered patient visits which are subdivided into parts containing medical history, examination findings (including multiphasic screening exams), diagnoses, prognoses, and laboratory and X-ray reports.
4. Linkages to a primary medical record
   The Patient Computer Medical Record (PCMR) described above includes all medical data thought by Kaiser-Permanente to be required for both medical care and medical research purposes.
5. Software mechanisms for retrieving and browsing
   There is extensive software for maintaining and massaging the Patient Computer Medical Record, including mechanisms for retrieval of data on an individual prescription, on an individual patient's visits, and on his total medical history. The patient visit summary data is a chronological list of date, time, visit location (pharmacy or clinic), drug prescribed at the pharmacy, and diagnosis made at the clinic.
6. Research methodology
   Large-scale search attempts are made to detect statistically significant associations between drugs and subsequent untoward events and to provide a measure of the magnitude of the association. Only the patient visit summary data on date, time, prescription, and diagnosis is used. Any occurrence of a "new" or "worse" diagnosis is considered an untoward event and possible ADR. Several statistical techniques are in use and others are under development. One new technique is a formalization of the common notion that information on the timing of drug administration and event appearance can be used as a basis on which to judge the relevance of event appearance "after drug." (*45*) It uses a measure of the relative excess of the observed rate of "after-drug" event occurrence over the rate expected under the

hypothesis of "no effect." Standard statistical techniques used include comparisons of users of the drug to nonusers, and comparisons of users before and after receiving the drug. Both relative risks and attributable risks are calculated. In addition to these large-scale monitoring and screening efforts, ad hoc in-depth studies are planned. These will be "applied to individual drug-event associations to determine the likelihood that the drug actually causes the event and to define better the patient and drug characteristics and other circumstances that foster the adverse reaction." (*47*)

7. Use of drug warning data in patient care
   None.
8. Major results
   Data derived from approximately 220 000 clinic and pharmacy visits by about 75 000 patients during the period, July to December 1969, has been analyzed. Both positive epidemiologic results, stating the discovery of statistically significant associations between drugs and effects, and negative results, stating the discovery of no association, have been published (*44*).
9. Documentation, export, sharing
   There is extensive documentation, particularly about the Medical Function Control System, the Patient Computer Medical Record, and the research and statistical methodology used in the epidemiologic analyses. The PCMR is logically structured in such a way that should facilitate its use by other investigators and their computer programs.

C. Implementation details
   1. Hardware and storage media
      The central computer facility in Oakland consists of an IBM 370/155 with a variety of input, storage, and output devices. The hospital data subsystem in the San Francisco Medical Center consists of a Honeywell DDP 516 and 416 with 40K core memory, 5 000 000 bytes of disk storage, and 24 Sanders Associates character display terminals.
   2. Software
      The central computer operates under the Medical Function Control System (MFCS) which runs under OS/MVT. MFCS consists of five groups of programs: medical record manipulation routines, encoding and translations routines, medical language routines, medical function routines, and a medical function control program. All satellite system and application programs have been written in a "JOSS"-type re-entrant interpretive compiler language.
   3. Method of data input and retrieval
      The pharmacist types the prescription information directly into the computer from a character display terminal. Physician diagnoses are similarly entered by clerks.
   4. Approximate running costs
      ??

The LA-USC Drug Utilization Review System

A. Identification of project
   1. Name
      Responsive Prescription Processing to Study Computer-Based Drug Utilization Review Methods (*49–52*)
   2. Type
      Utilization review
   3. Principal investigator(s)
      Robert Maronde, M.D.
   4. Location
      Los Angeles County/University of Southern California Medical Center, 1200 North State Street, Los Angeles, CA 90033

5. Time
   1965–ongoing

B. Goals, methodology, and results

1. Goals
   "Our overall aim is directed towards achieving a more rational use of drugs and consequently improving patient care through the development of a computerized center for drug utilization review" (*52*).

   Hospital Administration
   "This procedure was implemented to obtain information about prescribing practices and to develop methods for storage, analysis, and retrieval of drug usage data" (*50*).

   Patient Care
   ". . . it would appear that some degree of control might well be instituted—in part to reduce the unjustifiable expenditure of funds, and in part to limit the risk of accidental or deliberate poisoning or the amount of these drugs moving into illicit channels" (*51*).

2. Observed population
   The project's major focus is outpatient prescription processing. 900 physicians write over 700 000 prescriptions annually to over 200 000 outpatients. Additionally, a "model ward" of 110 beds, with its own chemical laboratory, administrative area, patient record files, social service, and pharmacy is being developed. It will utilize the hospital EDP system and will serve patients coming from a select small geographic area of the Los Angeles community.

3. Information stored
   a. Basic drug data
      The "Generic File" tabulates strength, route of administration, packaging and dispensing information, limitations and warnings for use, total quantity used, and the cost and number of prescriptions written. There are 2000 generic drug items, in 2000 records of 101 bytes each. The "Combined File" is an index to the Generic File, containing the drug code and generic name for every item in the Generic File, as well as commonly used brand names and synonym names. There are 2500 synonym and brand names, giving a total of 4500 records of 63 bytes each. The drug data files are based on the Medical Center's formulary which is supervised and maintained by the Therapeutic Committee made up of physicians, pharmacists, pharmacologists, and nurses.

   b. Drug warning data
      The Hospital Advisory Committee of five physicians and two pharmacists, working for a year and a half in frequent consultation with medical specialists, adopted definitions of inappropriate prescribing activities. These definitions were based on the judgment and experience of the committee and took into account such factors as the type of drug, its potential for abuse, the need for physician supervision and observation, the possibility of serious side effects, and considerations of the hospital's environment, namely, the crowded clinics, the heavy patient load, the patients the hospital serves, and the accepted practices of the community. Three general categories of inappropriate prescriptions were defined:
      1. Inappropriate drug quantities by single prescription.
      2. Inappropriate amounts of individual drugs in patient's possession as the result of multiple prescriptions.
      3. Inappropriate concurrent prescriptions.
      Prescriptions that are inappropriate for specific disease entities or therapeutic indications are being developed.

   c. Prescription data
      The intent is to maintain the patient's complete drug history by having the pharmacist

store, modify, delete, discontinue, and refill drug orders on-line. A drug order consists of a drug name and quantity, instructions for usage including route of administration and therapeutic indication, and any other pertinent special instructions. There are approximately 50 bytes per prescription. Currently, the system allows random access on-line analyses of at least six months of data, 350 000 prescriptions each consisting of 50 bytes.

d. Diagnosis data
The pharmacist enters the physician's diagnosis concurrently with the prescription information. SNOP 2 byte codes are used for more than 96% of all diagnoses and therapeutic indications. The others are entered as text without coding.

e. ADR data
None.

f. Clinical laboratory data
None.

g. Other patient history data
None.

4. Linkages to a primary medical record
None.

5. Software mechanisms for retrieving and browsing
On-line capabilities allow the retrieval of basic data on a specific drug as well as a individual patient's prescription history. Off-line capabilities include the retrieval of data on excessive prescribing, keyed to an individual patient, an individual doctor, or a specific drug.

6. Statistical methodology
Simple tabulation and calculation of percentages.

7. Use of drug warning data in patient care
None yet, but the prevention of inappropriate prescribing is one of the eventual goals of the project. Plans have not been published.

8. Major results
"Of 52 733 consecutive prescriptions for the 78 drug products most frequently dispensed to outpatients, representing more than four fifths of all outpatient prescriptions, 13% represented excessive-quantity prescriptions . . . Only 1.7% of all prescriptions were judged to involve too frequent prescribing of a drug. . . . Numerous examples were found of concurrent prescriptions of two different drug products which could result in serious drug interaction or potentiation . . ." (*51*).

9. Documentation, export, sharing
There are nine volumes of documentation, including flow charts of programs.

C. Implementation details

1. Hardware and storage media
The hardware configuration consists of an IBM 360/50 with 131K bytes of core, 1 million bytes of bulk core, 233 million bytes of disk storage, and many 2260 character display terminals.

2. Software
Running under OS/360, MVT, is the PLEXSYS executive system, written in-house in PL/1. The drug utilization application programs are written in PL/1.

3. Method of data input and retrieval
The pharmacists works at the 2260 character display terminal.

4. Approximate running costs

The Stanford Drug Interaction Detection and Prevention System

A. Identification of project
   1. Name
      A Computer-based System for Prospective Detection and Prevention of Drug Interactions (*53–54*)
   2. Type
      Reaction prevention, reaction surveillance
   3. Principal investigator(s)
      Stanley N. Cohen, M.D.
   4. Location
      Division of Clinical Pharmacology, Stanford University Medical Center, Stanford, CA 94305
   5. Time
      1969–ongoing

B. Goals, methodology, and results
   1. Goals
      "The needs of the biomedical community require both an accurate and rigorously documented data base of drug interaction information, and a technology for dissemination of this information in a clinically relevant way" (*53*).
      Patient Care
      "We have developed . . . a computer-based on-line system for the prevention of drug interactions having clinically significant undesirable consequences. The system utilizes the central hospital distribution point for drugs (i.e., the pharmacy), an extensive data file of the drug interactions compiled by the Division of Clinical Pharmacology at Stanford, and a highly interactive computer program to provide rapid notification to pharmacists, nursing staff, and physicians when a potentially interacting drug combination is prescribed" (*53*).
      Research
      An additional goal is "to provide a framework for prospective clinical evaluation of the consequences of administering therapeutic agents which have been reported to interact, and, in addition, to facilitate documentation of the clinical significance of such interactions" (*53*).
   2. Observed population
      Inpatients at Stanford University Medical Center.
   3. Information stored
      a. Basic drug data
         Drug names, both brand and generic, abbreviation codes, strength, pre-packaged quantity, usual dosage regimen.
      b. Drug warning data
         "During the past two years the Division of Clinical Pharmacology has been accumulating a large drug-interaction data base by utilizing various bibliographic indices and search procedures to locate primary references containing information about possible drug interactions, and reviewing and evaluating this literature" (*53*). Thus far, 8–10 man-years have been invested in the effort. Reported interactions whose supporting evidence is judged to scientifically substantiate them are entered into the computer data base, which now contains 11 000 individual interactions. Information entered includes "the pharmacological effects of each interaction, the mechanism for each effect, the clinical symptoms expected, the clinical relevance of the interaction, possible remedial measures which might counterbalance the effects of administering the interacting drug combination, and appropriate literature references documenting each point covered in the interaction record . . . Each

drug interaction is then assigned an 'alert' class designation, depending upon the immediacy and severity of its effects, and/or its clinical significance . . .:
Class 1: Interactions which are both well documented and potentially life threatening, although not necessarily frequent.
Class 2: Interactions which result in less threatening and/or less immediate, but nonetheless serious potential clinical effects.
Class 3: Interactions which ordinarily do not produce clinically relevant effects until the interacting drug combination has been administered for some time.
Class 4: Interactions which . . . are not sufficiently well documented to warrant sending out drug interaction reports from the pharmacy.
Class 5: Interactions concerning combinations of drugs having pharmacologic toxicity which is potentially cumulative" (*53*).

c. Prescription data
The patient's entire prescription history is recorded. This includes what is prescribed when and in what quantity, orders to refill or discontinue a prescription, and details of any medication that is dispensed from the nursing unit floor stock of drugs rather than from the pharmacy.

d. Diagnosis data
None.

e. ADR data
None yet.

f. Clinical laboratory data
Links to the Clinical Chemistry and Clinical Microbiology Laboratories are planned.

g. Other patient history data
None.

4. Linkages to a primary medical record
None.

5. Software mechanisms for retrieving and browsing
On-line capabilities include the retrieval of the patient's medication history, the massaging of the drug interaction bibliography containing titles and summaries, the massaging of the drug interaction data base, and the retrieval of the interaction potential of any single drug or class of drugs, and the data profile on any interaction.

6. Research methodology
This has not yet been published.

7. Use of drug warning data in patient care
Alerts are handled as follows:
Class 1: The nurse is required to contact the patient's physician before administering the first dose of the drug.
Class 2: The first dose of the drug is administered, but the physician must be contacted before the drug is continued.
Class 3: The drug is not withheld, although dosage adjustments may be made. Information about the interaction is placed in a conspicuous location on the patient's chart for use by the medical and nursing staff.
Class 4: Alerts are not sent to the nursing unit, but rather to the offices of the Division of Clinical Pharmacology for further study.
Class 5: A daily "cumulative toxicity report" is produced on a high-speed printer and sent to the medical staff via the standard hospital mail system.

8. Major results
Thus far, the most tangible result is the scientifically scrutinized drug interaction data base, currently in computerized form, and soon also to be published in book form. Baseline

"control" data on the frequency of drug interactions of various types, on the consequences of drug interactions, and on drug usage patterns is being accumulated. Interaction alerts are being generated and debugged, and will be used in practice beginning in January of 1973.

9. Documentation, export, sharing
   Very little documentation has been published. The interaction data base, however, appears to be cleanly and logically organized, which should facilitate its use by others. The minicomputer implementation will encourage its adoption by other groups.

C. Implementation details
   1. Hardware and storage media
      The system was originally implemented on an IBM 360/50 with Beehive character display terminals. A new implementation runs on a DEC PDP-11 minicomputer.
   2. Software
      The ACME (Advanced Computer for Medical Research) time-sharing system, developed in-house at Stanford Medical Center, was used for the 360/50 implementation. The PDP-11 version is written in MUMPS, the Massachusetts General Hospital Utility Multi-Programming System.
   3. Method of data input and retrieval
      The pharmacist works at the Beehive terminal. Prescription labels and alerts are produced on a GE Terminet printer.
   4. Approximate running costs
      ??

Other Projects

The programs of LA-USC and Stanford are prototype drug reaction prevention systems, designed to use existing pharmacological knowledge to prevent inappropriate and possibly dangerous prescribing practices. The programs of the Boston Collaborative Project and Kaiser-Permanente are prototype drug reaction surveillance systems designed to augment pharmacological knowledge through accurate data collection on drug effects, and epidemiologic research based on this data. (The Stanford system will eventually also function as a reaction surveillance system.) These systems have been described in detail because they have been the most heavily supported by public funds, and are the most thoroughly documented. The interest in automated drug reaction information systems is widespread and increasing, however, and other systems are under development. For example, there are currently projects at Duquesne University, at the University of Dundee in Scotland, and at the University of Florida.

Duquesne University's Computerized System for Drug Interactions and Interferences seeks to assist the pharmacist in recognizing potential drug interactions or drug-induced modifications of laboratory test values (*55*). Approximately 6000 specific interferences and 8000 drug–drug interactions have been collected from the literature and recorded in a computer file. When reviewing a patient's chart, the pharmacist can request that the list of drugs and laboratory tests ordered for that patient be compared to the contents of the file. These comparisons are batch processed overnight. He receives in the morning a drug-laboratory test profile which he

uses as a screening tool. He studies the patient's chart for evidences of interactions or abnormal laboratory findings, and weighs the evidence in the light of such factors as dose relationships, duration of therapy, prior drug therapy, predisposing factors in the patient and concomitant therapy. When appropriate, he communicates information and advice to the physician. Preliminary results indicate that the system furnishes a cheap method of reaction prevention within a traditional physician–pharmacist–medical record–patient relationship.

The Dundee Drug Monitoring Project is used for epidemiologic research on drug reactions experienced by patients in the Aberdeen General Hospitals Group (*56–60*). The computer file contains a "drug index" which records all "unit numbers" of patients receiving certain drugs. These provide linkages to conventional medical records such as medical admission notes, medical progress notes, discharge letters (summaries), nursing notes, and out-patient letters. The computer system is used to identify patients who have received a particular drug. Then the records are searched manually and retrospectively to identify adverse reactions and other specific medical characteristics. The system is also used in studies which follow-up "at risk" patients at predetermined intervals and on a prospective basis from the time of hospital treatment.

The University of Florida Drug Monitoring Project is similar to the Boston Collaborative Project, but seeks to include both inpatients and outpatients in their analyses (*61–62*). Its operation involves the coordinated activities of drug study clerks, ADR pharmacists, and physician epidemiologists. As one phase of its work, the project is carrying out the first large-scale epidemiologic study of ADR's in a pediatric population.

3. The Design of Drug Reaction Information Systems

A. Relationships between Reaction Detection and Prevention

Both reaction detection and prevention systems can ideally be characterized along the three dimensions of goals, methodology, and cost. One system design viewpoint is to choose a set of goals, then develop an appropriate methodology and embody it in a working system at minimum cost. Alternatively, one can seek a methodology that satisfies the greatest number of relevant goals per unit cost. In other words, by expanding the scope of a project, or coupling it to another related activity, greater cost-effectiveness may be achieved. To discuss drug reaction information systems in these terms, we must first dissect them into their structural components.

We begin with a definition. A patient's *medical record* is the collection of his prescription history, diagnosis history, adverse drug reaction history, laboratory test data, and other medical history data included in a drug monitoring system. Medical records may minimally consist of little more than basic vital statistics and prescription history, as in the LA-USC system, or they may be detailed and inclusive, as in the Boston Collaborative system. They may also be multilevel, or hierarchic,

as in the Kaiser-Permanente system, where large-scale screening tests are performed on a record consisting of prescriptions and diagnoses only, and more detailed intensive studies may be carried out on a very inclusive and highly structured Patient Computer Medical Record.

The function of a drug surveillance system is to collect data items of the following form: adverse drug reaction R is observed when drug D is administered to a patient with medical record M. From this data, statistical analyses are used to extract reaction statements of the form: If drug D is given to patients with medical characteristics $C_1, \ldots, C_n$, the result will be adverse drug reaction R with probability between $P - p$ and $P + p$. In practice, these statements vary widely in the complexity of the set of medical characteristics. One important case consists of a characteristic that is the prior administration of another drug, in other words, a drug–drug interaction.

Such facts, and other similar observations obtained from basic and clinical pharmacology, may eventually be incorporated as part of a drug reaction prevention system. This is done by choosing a set of reaction statements whose reactions are judged severe enough or whose probabilities are judged great enough to warrant detection and withholding of the drug. In other words, the drug warning data consists of a set of statements of the form: If a patient has medical characteristics $C_1, \ldots, C_n$, withhold (or reconsider) drug D. In practice there is wide variation in the complexity of the set of medical characteristics. One of the simplest is the prior administration of another drug.

Thus, there is a duality between the two kinds of systems. In each case, the drugs administered to patients along with a set of medical history characteristics are recorded. In the reaction surveillance case, adverse drug reactions are recorded and their likelihood predicted; in the reaction prevention case, likely adverse reactions are used to suggest the withholding of a drug and hence prevent the reaction.

One implication of this duality is that reaction detection systems and reaction prevention systems require very similar information-gathering and information-handling tools. More specifically, both require a medical record consisting of at least a complete prescription history, usually all diagnoses and major observed effects (including adverse reactions), and sometimes laboratory tests and other patient history. Reaction surveillance systems require in addition access to a library of statistical and other analysis techniques. Reaction prevention systems require in addition access to a library of drug warning imperatives—in case of characteristics $C_1, \ldots, C_n$, withhold drug D.

We now recall the argument that systems be designed to satisfy the greatest number of relevant goals per unit cost. Because of the similarity in tools required for reaction detection and prevention, we conclude that any system planned for one purpose should also be designed so that it can be used for the other. Unfortunately, the only existing system so designed is the Stanford system, and Stanford's surveillance methodology is yet to be published.

One can also adopt a slightly different point of view to argue the case for including

reaction detection and prevention functions in a single system. At any instant of time, as a function of the set of medical history-taking and -recording tools, a patient may be described by some set of medical characteristics, roughly speaking, his medical record. With respect to a proposed drug administration, and with respect to each subset of his medical characteristics, there exists a likelihood of an adverse reaction. Each such likelihood is either large, small, or unknown. (We assume for simplicity a probability threshold which determines whether the reaction is "likely

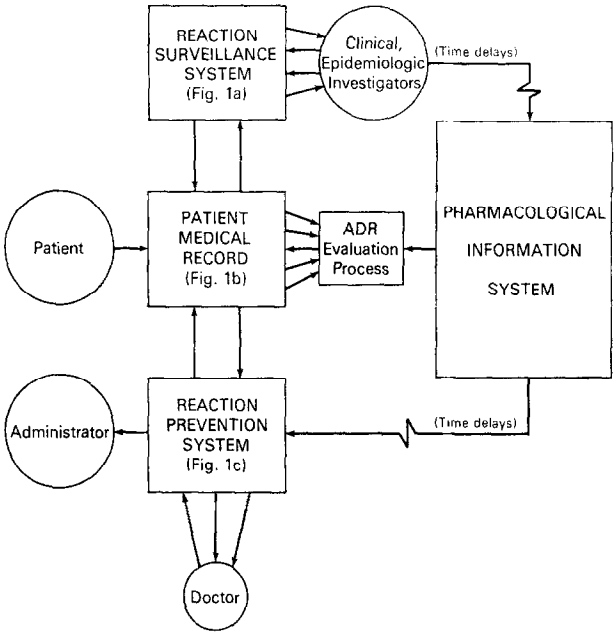

FIG. 1. A comprehensive drug reaction information system.

enough" to warrant issuing an alert.) Most of these likelihoods are unknown, for example, the probability with respect to his unique medical record. A few will be known, such as, for example, the cumulative probability of an adverse reaction to that drug for all individuals. Thus the information system can and should always play the dual role—issuing warnings where appropriate, and continually gathering more data from which these warnings can be made increasingly precise.

In conclusion, we present in Fig. 1 a model of a comprehensive drug reaction information system, a diagram which we shall elaborate in the remainder of the discussion.

B. Adverse Drug Reactions and the Patient Medical Record

The patient medical record, and particularly the record of a (presumed) adverse drug reaction, plays a central role in a reaction detection or prevention system. On the content and validity of the medical record rests the ability of epidemiologic

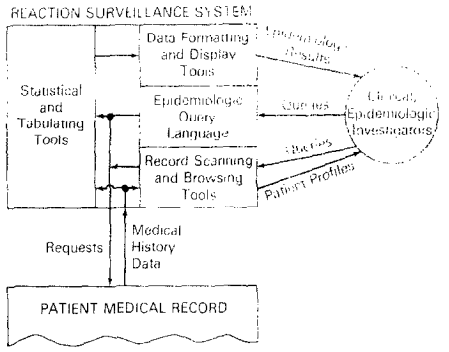

FIG. 1a. Reaction surveillance system.

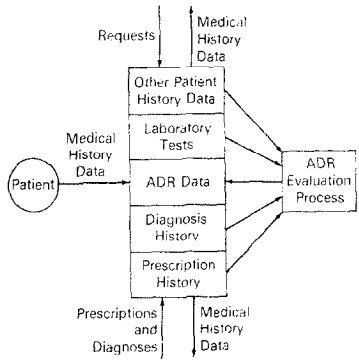

FIG. 1b. Patient medical record.

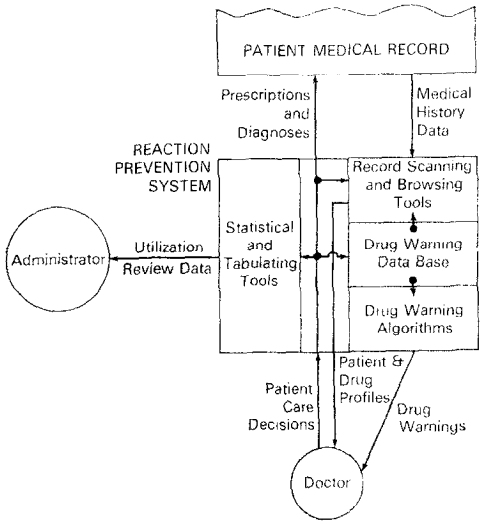

FIG. 1c. Reaction prevention system.

investigators to uncover statistical associations between adverse drug reactions and patient characteristics. When such data on ADRs is later used by a physician in clinical decision-making, its implications are re-evaluated in the context of that individual patient's medical record.

1. The medical record in reaction surveillance. Three different approaches to the role of the medical record have been adopted in reaction surveillance systems. The Boston Collaborative Project, acknowledging the inadequacy of the traditional medical record, has instituted a new, computer-based record designed specifically for drug reaction studies, and a thorough methodology in which specially trained nurse-monitors gather the data. Kaiser-Permanente has instituted simple and straightforward methods for recording prescriptions and diagnoses, and a large-scale screening methodology designed to uncover suspicious associations between drug administrations and untoward events. More detailed epidemiologic investigations will utilize existing computer-based medical history-taking and -recording mechanisms such as the Automated Multiphasic Screening Project and the Patient Computer Medical Record. The Aberdeen–Dundee project has instituted a standardized computer-based drug prescribing and recording system which is used to provide automatic linkages to the traditional medical records of those patients who received a particular drug.

The Boston Collaborative Project has given careful thought to the design of a patient medical record for drug reaction studies. Their data collection and accuracy validation procedure includes laudable standards of quality control. Thus it would be helpful if they would publish a more detailed description of the structure of the data base, and a retrospective evaluation of its strengths and weaknesses based on five years experience. However, there are serious inefficiencies and extra costs inherent in keeping a dual medical record—traditional plus computer-based. The nurse-monitors, an expensive addition to the health care team if used only for drug reaction studies, must obtain their data from order books, charts, patients, and doctors, in other words, from elements of the traditional medical record system. This suggests the importance of attempts, such as Kaiser-Permanente's, to integrate drug reaction studies with modern, sophisticated attempts to restructure the entire process of medical data-collection and record-keeping. Such attempts do not always succeed (*63*). Yet, because of the relative ease with which drug reaction information can be manipulated with the aid of good computer-based medical record systems, any new project in computerized medical records could realistically consider reaction surveillance, and also reaction prevention, as possible additional design goals (*64–65*).

2. Imprecise medical records and the consequences. Despite the care with which the Boston Collaborative Program has designed a data-collection methodology, published controversies have arisen over the validity and interpretation of several of their results. We shall comment only upon the issues in information-handling methodology raised by these controversies.

In a 1969 issue of the JAMA, the Boston Collaborative Program reported a new association between intravenously given ethacrynic acid and gastrointestinal bleeding (*27*). A trio of other investigators then reviewed the hospital records of the 32 patients whose gastrointestinal bleeding had been associated with intravenously given ethacrynic acid. Among other criticisms, they claimed in a letter to the JAMA that:

> . . . [Of the] . . . patients' records examined, there were 12 patients in whom bleeding occurred prior to ethacrynic acid administration. Three of these patients were admitted because of hemorrhage, and in nine, hemorrhage occurred during hospitalization, before ethacrynic acid administration. One patient had no record of ever receiving ethacrynic acid, and in one patient there was no indication in the chart of bleeding at any time (*66*).

The Boston Collaborative Program responded with a letter in the same issue:

> . . . the review by Wilkinson et al was subject to substantial biases of interpretation. For example, they consider it reasonable to state that there were 12 patients in whom bleeding occurred prior to the administration of ethacrynic acid. Yet, on reviewing copies provided to us of the abstracts which they prepared from the clinical records of these 12 patients, we find the sequence often to be ambiguous, to say the least . . . In an instance like this we find it difficult to accept their categorical statement on the sequence of drug administration and bleeding. There were several other cases in which we had similar reservations . . . (*67*).

A further controversy arose in response to the Boston Collaborative Program's 1972 JAMA article reporting a strong association between tetracycline and "clinically-significant," drug-attributed rises in blood urea nitrogen (*34*). A subsequent exchange of letters debated the meaning of the term "clinically-significant," and the adequacy of the original report's definition of its use of that term (*68–69*). Also, there was again controversy over the timing of the treatment and the observation of the adverse reaction.

The significance of these controversies can be drawn in both a narrow and a broad sense. The narrow interpretation is that because the Boston Collaborative Program data coding sheets record event times only to the day, and not with finer resolution to the hour, temporal relations may remain ambiguous. The credibility of the data and the resulting conclusions can therefore be questioned. As Weed has stated in proposing a problem-oriented medical record to facilitate the collection, organization, interpretation, use, and review of a patient's medical history:

> . . . Data involving physical findings, vital signs, laboratory values, medications, intakes and outputs can lead to sound interpretations and decisions only if they are organized (by means of a 'flow sheet') to reveal clearly temporal relations . . . Flow sheets can be used to facilitate the comprehension and interpretation of multiple interrelated and changing variables . . . (*70*).

3. The recognition and characterization of drug reactions. The broader significance of these controversies is that of all the data in the medical record, the identification, description, and recording of "untoward reactions and events" is most central to

drug surveillance methodology, and most critical to the validity of its findings. Finney's original definition of drug monitoring stated that there would be reported "every instance from a long, carefully prepared, list of untoward reactions and events among their patients, without regard to whether or not they believed a particular instance to be consequential upon the drug regime" (*13*). Jick et al. argue that the detection of previously unsuspected drug effects or influencing factors is aided by the "uniform recording and routine collection of data on all drug exposures and their indications, all alleged side effects and other adverse events, efficacy ratings, patient characteristics, etc . . ." (*21*). They cite the discovery of the previously unsuspected association between intravenously given ethacrynic acid and gastrointestinal bleeding as a case in point, since in no instance was the bleeding attributed to that drug.

However, though the recording of data on untoward events is said to be "uniform and routine," a detailed investigation by a physician in the clinical pharmacology unit is immediately undertaken when a drug reaction is suspected. This includes a review of the record, interviews with the doctor, nurse, and patient, and an attempt to categorize the reaction along such descriptive categories as speed, severity, site, duration, and causative factors. In other words, the attempt to recognize and characterize the drug reaction is a difficult exercise in clinical decision-making.

How are such clinical evaluations made? How does the pharmacologist synthesize his knowledge and the patient's medical description into a clinically significant judgment? How does he proceed in the face of incomplete or ambiguous data? How does he augment and refine the data upon which to base his judgment?

That such decisions are made in reaction surveillance programs offers medical science an opportunity to improve its understanding of clinical decision-making in general, and adverse drug reaction detection in particular. For the judgments made by the clinical pharmacologist is a case of clinical decision-making that occurs in a highly structured research environment, one where medical history and other data are well documented. This is an excellent environment for clinical pharmacologists and information scientists to study the ADR identification process, to develop explicit descriptions of decision processes that are now only implicit and intuitive. This work could profitably proceed in the spirit of Newell and Simon, who have shown us how to observe a "subject," and how to analyze his actions and the audio protocols which reflect his thought processes, in order to develop information processing models of problem-solving, decision-making, and other cognitive tasks (*71–73*). These information processing theories are expressed as computer programs.

For example, we might begin by developing a description of the following form: In the case of a suspected untoward event E, patient characteristics $C_1, \ldots, C_n$ appear "abnormal." Normal values for an individual of that sex, age, race, and medical condition would be $C_{1'}, \ldots, C_{n'}$. The *a priori* likelihood of someone having these characteristics by chance lies between $P - p$ and $P + p$ at confidence level L. Additional characteristics $D_1, \ldots, D_m$: are now measured. Finally, after considering facts

$F_1, \ldots, F_l$, and deducing facts $G_1, \ldots, G_k$, a decision is made that an "adverse reaction" has occurred. It is summarized by the set of characteristics $E_1, \ldots, E_j$.

To summarize, a suspected drug reaction should be documented with a description of the signs, symptoms, observations, and logic that form the judgment. The logic of the decision process should be represented as a program in an appropriate "drug reaction description language." These descriptions will constitute an evolving yet explicit and testable theory of the clinical recognition and characterization of ADRs. The theory will be of increasing value to physicians and pharmacologists faced with practical decisions of terminating, modifying, or continuing a particular drug administration after initial signs of a possible adverse reaction.

C. Reaction Surveillance Systems and Pharmacological Research

1. Facilitating the testing of epidemiologic hypotheses. The major function of a reaction monitoring system is to enable the application of statistical analyses to masses of data describing patients, drugs, and the effects of drugs on patients. Computational techniques of epidemiologic statistics have existed for many years. The Boston Collaborative Program has provided its investigators a powerful collection of such tools. Their work is pragmatic, and the result is effective but appears ad hoc. Future developments, hopefully, will integrate reaction surveillance software into a coherent *system*.

Such a system should be as powerful and as reponsive as that described in Finney's original paradigm:

> . . . A general computer programme can automatically up-date standard tabulations, print them out on request, and signal to the operator whenever any one of many specified indicators of suspicious drug associations (such as trends, differences between comparable series of figures, and so on) exceeds a stated threshold. As soon as such a signal is given, the operator can ask for additional analyses and tabulations bearing on the situation, after which he can decide whether or not a request for further checks by follow-up cases or for other special investigations is justified. Programmes can be provided that enable the whole record store to be searched and interrogated in respect of many different lines of inquiry (*74*).

To encourage and facilitate direct access to this system by nonprogramming pharmacologists and epidemiologists, an epidemiologic query language should be designed and implemented. This language would allow the expression of inquires in terms of drug administrations, medical history events, control variables, standard epidemiologic indicators, thresholds, and the maximum computer costs and response times that can be allowed for each inquiry.

The system embodying the epidemiologic query language should be made as independent of computer, auxiliary memory, file structure, and medical record format as possible. Such generality is costly, but results in more elegant systems which are easier to modify and easier to transfer. It is important that future systems as rich in research potential as the Boston Collaborative Project be disseminated and used

by others. Yet auxiliary storage hierarchies, file structures, and medical record formats vary widely, and it is unlikely that they will be standardized in the near future. Thus systems might sensibly be written to facilitate easy "recompilation" for different environments. For example, search requests would be expressed in terms of a few basic primitives that can be supplied anew for each machine, storage hierarchy, and file structure. A data description language and processor for drug reaction data could be developed to allow an easy description of file content and format and its automatic mapping into an appropriate set of accessing functions.

The issues of effective, convenient, and economic use of time-sharing and batch processing, and of multilayered hierarchic storage must also be investigated. Because of the vast amounts of data that are collected, economy and efficiency must be considered in system design. Two aspects are central to this concern. One is that of operating system, and the provision of a coherent and economical mix of interactive computing and long off-line file massaging. Investigators probably will find it satisfactory to state and refine their queries with a highly interactive, intelligent processor, then submit the result for a long batch run. The other issue is that of file management, particularly the effective shuttling of subsets of data into and out of expensive memory when needed, and the choice of storage hierarchy and design of file structures suited to this task. The design of an intelligent, adaptive memory management system for drug reaction data is one of the most challenging computer science tasks that lies ahead.

2. *Record scanning and epidemiologic hypothesis formation.* There is a secondary function of reaction surveillance systems which has achieved far less attention and work than analytic processing, and this is the facilitation of record scanning, file perusal, and browsing. Browsing among, perusing, or scanning large data files is an exercise in serendipity, the trained observer seeking, more or less systematically, observations, patterns, and glimmers of insight that can perhaps be later formalized, tested, and accepted or rejected.

Finney discusses the significance of this process:

> In all this, the role of formal statistical tests of significance and estimation is small. Values of Chi-square or of regression coefficients may be useful summaries of numerical evidence, but the biases inherent in the collection of data will almost always forbid probabilistic interpretation. When faced with 50 records, the trained human brain can remarkably effectively survey the information and detect interesting patterns or associations. Possibly one man can still deal with 500 records, by rapid reading and subjective sorting. But 5000 or 50 000 is too great for storage by the human mind, at least in any form that permits rapid access to all facets of the information. We require to study carefully how the trained man operates in scanning 50 or 500 records, and then to formalize as many aspects as possible of this so that the same procedures can be applied to 50 000 records. Inevitably something is lost, but the very process of analysis of his own method of working that this formalization demands of the human expert should increase understanding of the problem. Of course the human component must be maintained and even increased, but medical and statistical skill is better employed in devising new critical investigations to be made when suspicions are aroused than in routine sorting and tabulating.

> Statistical practice to-day provides excellent methods for testing quantitiative hypotheses and for estimating parameters. We statisticians are far less competent in the examination of large bodies of information with a view to scientific detection and the formulation of hypotheses for further study. Drug monitoring needs this kind of skill, yet practically no principles or theory exist . . . (*74*).

His goal, therefore, is the formalization of aspects of the process of record scanning, pattern detection, and hypothesis formation so that it may eventually be automated. This is an ambitious goal. There are two ways in which an automated aid for scanning and browsing may speed the achievement of this goal.

First, we believe that a properly designed computer-mediated system for medical record perusal will facilitate the process of serendipity and hypothesis formation described above. Epidemiologic investigators trying to comprehend 5000 or 50 000 records will be aided by a tool for describing and immediately accessing various subsets of 50 or 500 records. How best to employ computer and information display technologies in designing such a system is beyond the scope of this paper.

Secondly, the design and use of a computer system to aid record scanning and browsing will aid the scientific study of the process itself, the task suggested by Finney. Again in the spirit of Newell and Simon, analyses of traces of system requests and audio protocols reflecting user thought processes can provide a framework for the design of information-processing models of epidemiologic hypothesis formation. This may in turn yield the ability to build better tools to aid the perusal process, or even to the automation of aspects of the hypothesis formation process.

3. Administrative issues in reaction surveillance. Having focused on the individual reaction surveillance system, we now enlarge our scope to consider how individual systems fit into the larger picture of epidemiologic pharmacology. The human and monetary resources available for drug monitoring are severely limited. Hence it would be most desirable if individual programs were effectively and economically integrated into a nationwide or worldwide system of drug reaction data collectors.

Reaction surveillance now appears to be "in." In addition to the major projects we survey in this paper, numerous other smaller studies have been undertaken (*75–79*). Hospital pharmacists particularly are interested in contributing their skills to such efforts (*62, 80–82*). All studies, however, are not cost-effective. There is little need for further studies of the over all frequency of adverse reactions. There is little need for further studies of the frequency of reactions associated with different classes of drugs. There is little need for studies which collect data on several hundred patients and then stop for lack of funding or interest. Such results are now a waste of effort and money. What is needed most are large-scale, carefully-designed, continuing efforts which will accumulate validated data bases, substantial enough to allow the discovery of relatively rare reactions, and to allow the establishment of associations between reactions and more detailed sets of medical characteristics.

More thought must be given to the relative cost-effectiveness of cheap versus expensive designs for reaction surveillance. Kaiser-Permanente's statistical analysis

of the temporal sequence of drug administrations and diagnoses is an example of a cheap methodology that could be implemented with a very simple data collection and medical record-keeping capability. The Boston Collaborative Program's extensive data collection and validation procedure is an example of an expensive methodology. Although the latter program is clearly a more sophisticated research tool, the former is adequate for generating preliminary warnings linking drug to effect. What mix of research strategies and systems embodying them will be most cost-effective on a nationwide or worldwide basis?

This leads naturally to the concept of the distribution and sharing of resources. Although the growth of the Boston Collaborative Program to encompass new countries and hospitals is encouraging, it is disappointing that the system cannot expand more rapidly or be transplanted in toto into other environments. Of even greater potential, however, are the data bases being established by their program, Kaiser-Permanente, and others. These are rich resources which should be "published" and made available to other investigators for browsing, study, and analysis. Recent technological advances, specifically, the stabilization of several widely-used high-level programming languages, the sharp drop in the cost of and rise in the power of minicomputers, such as the DEC PDP-11 used in the Stanford project, and the establishment of computer communication networks all expand our ability to distribute and share computer resources (*83*). What is needed is a plan for applying these tools to facilitate drug reaction information handling.

4. Relationships among epidemiologic, clinical, and basic pharmacology. One of the reasons for publishing the data bases of epidemiologic pharmacology is to stimulate the interactions among it and clinical and basic pharmacology. That these fields be mutually enriching is important, for each provides a different point of view towards understanding the effects, and the underlying mechanisms, of the action of drugs on humans. The epidemiologic approach focuses on the discovery of significant associations between drug administrations and effects; the clinical approach focuses on the description and elaboration of drug effects in the context of a detailed medical history of the patient; and, the basic approach focuses on a search, usually in abstracted laboratory situations, for fundamental biochemical explanations of the structure, functions, and effects of drugs.

Ideally, the "clinical" investigation and the "epidemiologic" investigation proceed hand in hand. As we have described above, the ability to search and browse through a set of clinical histories, and locate and study "interesting" patients, aids the formation of hypotheses which can then be confirmed by statistical methods. Basic and clinical knowledge must also be used to rule out spurious statistical associations that arise in surveillance systems, although, as Friedman observes, "rigid adherence to textbook pharmacology will stifle the possibility that epidemiologic data may provide clues to pharmacologic mechanisms" (*48*). Correspondingly, after identifying "interesting" individuals by epidemiologic methods, it should be possible to examine their complete clinical record. Thus, the usefulness of the drug monitoring system

for clinical investigation depends upon the quality and completeness of the underlying medical record.

One of the challenges for the future lies in integrating the theories of basic pharmacology with drug effects observed at the clinical and epidemiologic levels. Can theories of drug action and their underlying mechanisms expressed in terms of basic biochemistry and physiology (the "microscopic" level) be used to predict the drug interactions observed in patients (the "macroscopic" level)? Computer aids for biomedical theory formation are currently being developed in a variety of contexts, from pharmacological effects on neuromuscular control to disease processes of glaucoma, from the general pharmokinetics of drug therapy to the specific modeling of leukemia chemotherapy (*84–87*). Hopefully, groups of investigators in centers of good epidemiologic, clinical, and basic research will identify and explore in a carefully selected domain of drug effects the formation and testing of a unified theory which explains and integrates phenomena observed at all three levels, and whose component subtheories are mutually synergistic and enriching.

D. Pharmacological Knowledge, Drug Warning Data, and Adverse Reaction Prevention

Finally, we turn to the reaction prevention component of automated drug information systems, and to the structure, delivery, interpretation, and use of drug reaction warnings. The drug warning data base and the algorithms which utilize it to emit drug warnings constitute a predictive theory of drug reactions in the clinical setting. Effective drug utilization depends critically upon the implicit partner of drug alerts, the pharmacological information system through which the physician accesses relevant data to aid his judgment of the significance of the alert, and how to act upon it. If we can better characterize and understand this decision process, we can design better drug information systems, and eventually improve the decision process and the resulting patient care.

A drug warning alert is a statement that prescribes the withholding of a drug upon the discovery of a set of patient characteristics. Of particular interest is the case where one characteristic is the previous or concurrent administration of another drug, in other words, a potential drug interaction. Since the consequences of drug interactions range from mild discomfort to death, and since some reactions are well established while others are only suspected, the Stanford group has established a set of drug alert levels and corresponding procedures for responding that range from making a note in the medical record to the immediate withholding of the drug.

The drug alert program is most elegantly viewed as a drug warning algorithm driven by a drug warning data base. The data base consists of a collection of statements describing "serious enough" potential drug reactions. The algorithm, expressed in a suitable drug reaction description language, is a precise statement of a pharmacological theory—a predictive theory of drug reactions. Currently, that theory is very primitive, consisting mostly of statements of the form: Beware of

drug A together with drug B. The theory will eventually progress to a more sophisticated set of alerting functions which involve vital statistics, medical history, and laboratory tests. Attempts to state this theory are valuable, for they make explicit and hence more amenable to discussion and improvement our understanding of effective drug reaction prevention in the clinical setting.

After an alert is issued, there usually remains the substantive problem of interpreting the danger to that patient at that time and then acting upon that interpretation. Although the issuing of the alert is the only automated part of the decision process, it is desirable to provide the physician with assistance in making his decision. Access to the total pharmacological information system is then required. The drug warning system should serve as a window on the drug information system, a selective, goal-directed magnifying window which helps him zoom in on that portion of the store of pharmacological data which will most aid his decision in that context. Thus, a drug reaction warning should consist of a recommendation for further study as well as for action, and mechanisms to assist in this task. Ideally, this would include a computer-based interrogation and browsing facility through which the physician could access complete information profiles on the particular patient and drug(s). One great advantage of a computer-based system for this purpose is the ability to keep the data base current. If economics preclude the use of an on-line computer system, the data for inclusion in a manual system is best stored, organized, and kept current on a computer publishing system, or purchased from an organization that maintains the information base in this manner (*53*, *88–90*).

The use of an on-line computer system that issues drug alerts and provides clinically relevant drug data upon demand will yield another by-product, a laboratory for the study of clinical decision-making. The problem is to characterize the decision process whereby a drug reaction alert, patient medical characteristics and history, and drug data profiles are utilized by the physician in determining how to act on the alert. The methods almost certainly would include the Newell–Simon techniques of computer trace analysis and protocol analysis mentioned above. Again the goal is to describe explicitly the logic of the decision process. Such work will increase our understanding of what information to provide the physician in the decision-making process. It will increase the literacy with which we can communicate this process to the learning physician. Finally, it will help us refine the predictive theory of drug reactions discussed above.

4. Summary and Conclusions

A. Towards Cost-Effective System Design

This paper suggests a number of methods, technical and administrative, for increasing the cost-effectiveness of drug reaction information systems: (1) Design and build integrated systems for reaction detection and prevention (3.A). (2) Include a drug reaction information component in new computerized medical record projects

(3.B.1). (3) Aid the task of the epidemiologic investigator by designing for him an integrated system with a powerful and flexible query language and a record scanning and browsing capability (3.C.1, 3.C.2). (4) Establish administrative procedures that effectively and economically integrate individual reaction surveillance systems into a nationwide or worldwide system of drug reaction data collectors (3.C.3).

B. Drug Reaction Information Systems and Data Bases as Resources

Drug reaction information systems and data bases are public resources. Effective distribution and sharing of these resources is essential to achieving the greatest increase in health care for a given level of public expenditures to combat ADRs (3.C.3).

C. Drug Reactions, Clinical Decision-Making, and Theory Formation

Modern research tools of artificial intelligence, particularly the cognitive information processing viewpoint, should be applied towards building formal testable models of clinical decision-making and theory formation in the characterization of drug reactions. At least four specific questions should be investigated: (1) How does a clinical pharmacologist decide that an ADR has occurred (3.B.3)? (2) How does an epidemiologist form hypotheses about the causes of drug reactions (3.C.2)? (3) How can we explain observed drug reactions in terms of basic pharmacology, biochemistry, and physiology (3.C.4)? (4) How does a physician utilize drug reaction warnings in choosing a course of action with respect to a suspected drug reaction (3.D)? The answers to these questions will in turn enable us to design and build better drug reaction information systems.

D. A Broader Point of View: Pharmacological Information Systejs

The functions of drug reaction detection and prevention are both elements of the *pharmacological information system*, the combination of the knowledge and data base of pharmacology and the processes by which this information is collected, interpreted, integrated, disseminated, and applied. This information system is very complex. It includes the research and publication processes of basic, clinical, and epidemiologic pharmacology, and the communication processes of drug therapy with both prescription and nonprescription drugs to both inpatients and outpatients (*91–96*). Reaction surveillance programs are data-collectors whose interpreted results are added to the information base of drug effects, adverse reactions, and drug interactions. Reaction prevention programs mediate the practical application of this data in patient care. Drug reaction detection and prevention are only two components of the pharmacological information system. To be effective, they must be harmoniously integrated with the other components. This suggests the need for a detailed study of all pharmacological information-handling projects and resources, and critical analyses of other components of the information system. We hope that the methodology and spirit of our analysis will stimulate and aid such efforts in the future.

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