Computer listing of the effects of drugs on laboratory data

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SYNOPSIS A listing of approximately 10000 effects of drugs on tests performed in clinical laboratories has been developed in a time-shared computer. The list contains a directory for matching proprietary and generic names of drugs and an explanation for the mode of action of the drug on each test. Each entry is supported by a bibliographical reference that contains the author's names, and the title of the article and journal. It is possible to search for specific 'character strings' (word or words, number, etc) to obtain all the effects of a particular drug, or all drugs that affect a particular test, or even to search for a specific explanation for an effect. The system is undergoing trial in the Department's own computer to permit of automatic correlation of the effects of drugs with laboratory data from patients in one hospital ward.

Modern medicine has been characterized both by an increase in the number of drugs administered to patients and also by an increase in the number of laboratory tests ordered. In this centre it is now quite common for a patient to receive as many as 10 different drugs at one time. Recently one patient received 43 different drugs during his hospital stay of three months. Twenty of these drugs were received during one critical phase of his illness. Nowadays 20 or more laboratory tests may be requested at the same time. Only recently have physicians considered the consequences of these trends on the interpretation of laboratory results.

It is now recognized that much effort is expended in hospitals in the treatment of iatrogenic disorders (Melmon, 1971). This increased economic burden on the patient and community may be attributable, in part, to unrecognized effects and toxicity of drugs. Although there is increasing evidence that many drugs affect laboratory tests (Garb, 1971; Hansten, 1971; Martin, 1971) leading to potential misinterpretations, Van Peenen and Files (1969) contend that the incidence of significant effects of drugs on laboratory tests is low. However, we have determined that day-to-day variation in the concentration of many blood constituents is small in normal subjects (Young, Harris, and Cotlove, 1971) and believe that many of the changes in concentration of blood constituents occurring in hospital patients may be due to the effect of drugs. With the increasing

precision of analyses now obtainable in clinical laboratories it should be possible to identify more incidents of drug-induced modifications of laboratory data.

Many physicians are uncertain how to interpret these small changes. Most physicians are familiar with the major effects on laboratory tests of drugs administered for specific purposes but many are unaware of the side effects of drugs on other biological functions. Few are aware of the analytical methods used to determine the constituents in blood serum or the influence of drugs on these procedures.

To facilitate the interpretation of alterations in laboratory tests, we have developed a central file of the effects of drugs on laboratory tests. This file is stored in a computer to permit rapid interrogation in response to telephone queries and to permit automatic correlation of tests requested with the drugs that are administered to different patients. This approach allows continual updating as new effects are reported or analytical methods are changed. In this preliminary report, we describe the structure of our computer listing of anticipated and unintended drug effects (Claude). Later reports will detail the role of the system in the automatic correlation of changes in laboratory tests with drugs administered to patients.

Structure of a File for Interrogation and Editing

The system for rapid retrieval of information from

our drug/test interaction file is based on the Wylbur computer program developed by the Stanford University Computation Center and adopted for use at the central computer facility of the National Institutes of Health. Wylbur was designed to provide a comprehensive editing facility with prompt responses through typewriter terminals without interfering with other jobs being processed by the central computer. The editing facility of Wylbur allows the user to create, modify, store, and retrieve text on a line-by-line basis so that no other lines in the data set are affected. An especially useful attribute of the system is its ability to search for a particular 'character string' (word or words, number, etc) and to print at the terminal all lines in the data set in which this character string appears. Our information retrieval system was designed to exploit this capability.

The maximum length of the line of text is 120 characters, and was determined by the limitations of the size of the carriage of the existing typewriter. Thus, if all the information concerning a particular drug/test interaction is stored in a single 120-character line, we can use the system's ability to search a particular character string to retrieve all entries that might include a specified drug, test, mechanism, etc. We therefore set up the information in our file as indicated in Table.

Characters	Subject
1-19	Drug name
20	Code for sample type
	B = whole blood
	S = serum
	P = plasma
	U = urine
	C = cerebrospinal fluid
	O = other fluids
21-22	Blanks
23-49	Test affected and effect
	Inc = increased
	Dec = decreased
	Z = no effect
50	Code for type of interactions
	V = physiological or pharmacological
	M = methodological
	N = if method in use at NIH affected
51-54	Blanks
55-107	Mechanism of interaction
108-111	Number of article describing this interaction in reference file
112-116	Blanks
117-120	Number code for test at NIH

Table Line structure

If one of the laboratory staff or a clinician wishes to know the effects of acetophenetidin on laboratory tests he types the character string 'Acetophenetidin' into the computer at one of the terminals and all lines containing this word, ie, all the effects of the drug, are printed. Similarly the character string that

is entered could be a test, eg, sodium, a test on a particular type of sample, eg, U sodium (for urinary sodium), an effect on a particular test, eg, U sodium inc' (for increased excretion of urinary sodium) or a particular analytical method. If Folin-Ciocalteu is entered all methodological interferences involving the use of the Folin-Ciocalteu reagent are listed. Part of this listing is illustrated in Figure 1. By entering the name of a drug and a description of a laboratory test in a defined manner it is possible to determine if an interaction exists as the line containing the combination will be printed. Physiological or pharmacological side effects of drugs may be listed by entering key words such as 'cholestatic' or 'nephrotoxic', in which case all lines listing drugs which produce such effects are printed. All the effects cited in a single reference may be listed by entering the appropriate reference number, eg, R332. In each of the above examples all lines containing the entered character string, and therefore all drug/test interactions involved will be printed at the user's terminal.

Subfile Structure

This ability to search for character strings has been used to set up a cross correlation subfile of proprietary and generic names of drugs. All effects of drugs are entered according to the generic name of the drug. In one of the subfiles the generic name of the drug is followed by the common proprietary names. For several common over-the-counter preparations containing more than one generic compound the trade name is listed after each of the appropriate generic names. Thus 'empirin' is contained in the entries for acetophenetidin, acetylsalicylic acid, and caffeine. If a user requests a search on the basis of a proprietary name, the system responds with the line containing the generic name as the first entry with all the proprietary names appended. The user can then request a second search based on the generic name. When many drugs of similar pharmacological action are present in the file another entry is included in which the class of compound, eg, diuretic, is followed by all the appropriate generic names of the drugs in this class. Common effects of diuretics may then be listed by entering DIURETICS as the character string.

The search attribute has also been incorporated into a reference subfile. Each drug/test interaction in our system has been documented by a three-line reference entry. The first line contains the authors' names, the second the title of the article, and the third the journal, volume, and initial page numbers and the year of publication. Each line is preceded by the code number for that reference. Thus when the user requests a search for that reference code number

ACETOPHENETIDIN	C	PROTEIN INC	N	REACTS AS IF PHENOL WITH FOLIN-CIOCALTEU REAGENT
ACETYLGLUCOSAMINE	T	PROTEIN INC	M	SLIGHT REACTION WITH FOLIN-CIOCALTEU REAGENT
ACETYLGLUCOSAMINE	C	PROTEIN INC	N	FALSE POSITIVE WITH FOLIN-CIOCALTEU REAGENT
AMINOSALICYLIC AC	C	PROTEIN INC	N	REACTS AS PHENOL IF FOLIN-CIOCALTEU REAGENT USED
ASCORBIC ACID	C	PROTEIN Z	N	NO EFFECT ON FOLIN-CIOCALTEU PROCEDURE
ASCORBIC ACID	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY PROCEDURE
CHLORPROMAZINE	C	PROTEIN INC	N	REACTS AS IF PHENOL WITH FOLIN-CIOCALTEU REAGENT
CYSTEINE	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY PROCEDURE
DITHIOTHREITOL	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY PROCEDURE
EPINEPHRINE	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY PROCEDURE
ERYTHROMYCIN	C	PROTEIN Z	N	NO EFFECT ON FOLIN-CIOCALTEU PROCEDURE
GALACTOSAMINE	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY METHOD
GLUCOSAMINE	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY METHOD
GLUTATHIONE	T	PROTEIN INC	M	REDUCED FORM REACTS WITH FOLIN-CIOCALTEU REAGENT
GUANINE	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY METHOD
INDOLE	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY METHOD
LIDOCAINE	C	PROTEIN INC	N	REACTS WITH FOLIN-CIOCALTEU REAGENT
MORPHINE	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY METHOD
NALORPHINE	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY METHOD
OXYTETRACYCLINE	C	PROTEIN INC	N	REACTS AS IF PHENOL WITH FOLIN-CIOCALTEU PROCEDURE
PENICILLIN	C	PROTEIN INC	N	REACTS AS IF PHENOL WITH FOLIN-CIOCALTEU PROCEDURE
PHENOTHIAZINES	C	PROTEIN INC	N	FALSE POSITIVE WITH FOLIN-CIOCALTEU REAGENT
PHENYLTHIOUREA	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY METHOD
PROCAINE	C	PROTEIN INC	N	INTERFERES WITH FOLIN-CIOCALTEU REAGENT
SODIUM BISULFITE	T	PROTEIN INC	M	AT CONC HIGHER THAN 0.01 % AFFECTS FOLIN-CIOCALTEU
STREPTOMYCIN	C	PROTEIN INC	N	REACTS AS PHENOL IF FOLIN-CIOCALTEU REACTION USED
SULFADIAZINE	C	PROTEIN INC	N	REACTS AS IF PHENOL WITH FOLIN-CIOCALTEU PROCEDURE
SULFAGUANIDINE	C	PROTEIN INC	N	REACTS AS IF PHENOL WITH FOLIN-CIOCALTEU PROCEDURE
SULFAMERAZINE	C	PROTEIN INC	N	REACTS AS IF PHENOL WITH FOLIN-CIOCALTEU PROCEDURE
SULFANILAMIDE	C	PROTEIN INC	N	REACTS AS IF PHENOL WITH FOLIN-CIOCALTEU PROCEDURE
SULFONAMIDES	C	PROTEIN INC	N	REACTS AS PHENOL WITH FOLIN-CIOCALTEU REAGENT
TETRACAINE	C	PROTEIN INC	N	INTERFERES WITH FOLIN-CIOCALTEU REAGENT
TETRACYCLINE	C	PROTEIN INC	N	REACTS AS IF PHENOL WITH FOLIN-CIOCALTEU PROCEDURE
THIAMYL SODIUM	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY METHOD
THIOUREA	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY METHOD
TRYPTOPHAN	C	PROTEIN INC	N	INTERFERES WITH FOLIN-CIOCALTEU REAGENT
TYROSINE	C	PROTEIN INC	N	REACTS AS IF PHENOL WITH FOLIN-CIOCALTEU PROCEDURE
URIC ACID	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY METHOD
XANTHINE	T	PROTEIN INC	M	REACTS WITH FOLIN-CIOCALTEU OF LOWRY METHOD

Fig. 1 Retrieval based on Folin-Ciocalteu. 'T' in the sample-type column indicates that test conditions have been used to study the effect of a compound on the Lowry procedure. The results are not necessarily applicable to physiological samples.

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Fig. 2 Entries from reference file. Each entry contains the common number for author, title of article, and journal so that all three items will be listed when the one reference number is entered.

the three appropriate lines are returned. Examples of reference entries are illustrated in Figure 2. As it has been necessary to make some entries in code form and to abbreviate some test descriptions, another subfile of short forms has been created so that users unfamiliar with the abbreviations may obtain complete information.

Operation of the System

This system currently functions on the NIH time-shared IBM 360/65 computer with a capacity of over 100 simultaneous users. It requires 13 seconds of computer time to search the entire 10000 line drug/test interaction file for a particular test string. If the character subfile to be searched is specified, the search time can be markedly reduced. Access to the system is gained through the use of a set of authorized initials to designate the operator of a terminal and then by using an appropriate keyword. At that point the file description must also be entered to define whether the main file is to be used or the reference or short-form files.

New entries may be added to the existing files at any time. The entries do not have to be alphabetized although the search time is reduced when all entries related to one drug are together. Existing entries may be overwritten to update or correct the original information as more complete information becomes available. Theoretically any user can update, or add to, the file from his own terminal. However, we have restricted access to the system to ensure that the existing files are not altered and that no inappropriate information is entered.

Discussion

There are several ways in which drugs may affect laboratory tests. Physiological processes may be modified thereby altering the concentration of constituents in body fluids. A pathophysiological process, occurring secondary to a particular disease, may be modified by therapy. Diseases may alter the metabolism of drugs so that effects produced in normal individuals occur with increased magnitude and/or new effects may occur. Drugs or their metabolites may be measured as analytes by various chemical methods or interfere with the analytical method.

More than nine drug/test combinations are possible according to our system of entries. A drug may have a 'physiological' or 'pathophysiological' effect that increases or decreases the concentration of a test constituent, or it may have no effect on the concentration of the constituent. Drugs may increase or decrease the apparent concentration of

a constituent as determined by the analytical method in use in our laboratory, or by methods in use in other laboratories. Separate entries are made for our routine methods and those in use elsewhere. For those methods which are not known to be influenced by particular drugs specific separate entries are also made.

We have included in the file apparently contradictory information when the information has been substantiated by publication, although we have not confirmed the effects ourselves. We prefer to think of the file as a mechanism to alert clinicians and clinical pathologists to possible complications rather than a literal explanation of what happens when a drug is given to a patient. The file includes both the effects anticipated when a drug is given to a patient as well as the untoward effects to which a physician should be alerted to modify or stop treatment. At present we have not tried to delineate the quantitative effects of most drugs on laboratory tests, partly because little of this information has been recorded, but also because of the great variation in response to the same dose exhibited by different individuals.

The file includes several tests, such as flocculation tests, that are no longer performed in most large laboratories, but we have included them to provide as broad a base of information as possible. We have also included many tests that cannot yet be considered routine in hospital laboratories. Several entries have also been made of conditions that may affect tests that should be considered when hospital patients or outpatients are studied. In this category we include the heading of intramuscular injections, haemolysis of samples, foods, and exercise. We intend to add the effects of diurnal variation, pregnancy, altitude, seasonal variation, age and sex differences.

The majority of the effects listed (more than 80%) are concerned with *in-vivo* effects and less than 20% are concerned with analytical methods. Under the category of analytical influences, we include the effects of organic iodides on PBI measurements and any unusual colour of urine due to drugs or their metabolites. With the introduction of mechanized analytical methods specific for constituents such as glucose and uric acid that are measured frequently in the clinical laboratory the number of chemical interferences will be reduced further. The uricase procedure for uric acid is much less influenced by drugs than the more commonly used methods in which reducing substances are measured (Gochman and Schmitz, 1971).

The computer file has been used extensively by the staff of the Clinical Pathology Department to assist in the interpretation of, in most cases, unexpected changes in test values without a corresponding

change in the clinical condition of patients. It has assisted physicians in planning study procedures so that these may be performed at a time when interactions between drugs and tests would not arise. We have avoided considering the effect of drugs upon the action of other drugs in the present system except in so far as they may influence the action of anti-coagulants on the prothrombin time.

The file has been modified so that it also exists in the departmental CDC-3200 computer where it is being used on a pilot basis to provide automatic interpretation of data from one nursing unit. Both information on drugs and on tests requested is entered into the computer which generates an interpretative report on each patient. An analysis of this experiment will be published at a later date.

Although several publications concerning drug/test interactions have appeared recently, only a computer-based file of the type described here permits the rapid identification of those tests which are affected by a drug as well as listing those drugs that affect a particular test. The critical differentiation between physiological and analytical effects has not been made in several publications. Our laboratory-orientated file allows clinical pathologists another avenue for increased participation in

improving the care of patients. Widespread use of such a system should reduce the incidence of mis-interpretation of laboratory results, especially when the appropriate modification of entries is made to reflect the different analytical procedures in use in clinical laboratories.

We intend to publish the information contained in the files and to update the files as new effects are identified. We would be pleased to receive reports of drug/test interactions observed by physicians to maintain our files up to date, and to assist in the dissemination of such information.

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