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Organization and Development of a Computerized Drug-Drug Interaction File

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ORGANIZATION AND DEVELOPMENT OF A COMPUTERIZED DRUG-DRUG INTERACTION FILE

BY

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TITLE ABSTRACT

COMPUTERIZED DRUG-DRUG INTERACTION FILE

ABSTRACT

The project was designed to organize and develop a computerized drug-drug interaction file. The methodology for the organization, storage and retrieval of drug-drug interaction information is discussed. In order to accomplish this objective several requirements were met. They are as follows: (1) Selection and evaluation of clinically significant drug-drug interactions from the scientific literature, (2) Creation of a computerized data bank for drug-drug interactions, and (3) Design and development of a computerized printout which reports the information in concise summaries.

The file is designed to be compatible with existing computerized record keeping and drug information systems. In addition, the retrieval system has several unique characteristics. The reporting format is designed to provide practical drug-drug interaction information in a concise summary which can be easily understood and utilized by either a physician or pharmacist in a patient care environment. It will provide the clinical pharmacist with a invaluable reference to be utilized as a "key" to clinical involvement with the medical staff. The printout may be incorporated into a patient's cumulative medication profile or merely used as a reference source to screen for probable drug-drug interactions. Another unique feature of the system is that it reports important drug-drug interactions with each drug entity the patient is receiving. The system is not limited

to the reporting of specific interactions which may occur with the patient's current therapeutic regimen.

Several illustrations are presented using the file in conjunction with a computerized medication profile system. The applications of this system provide a rational approach towards determining the probability of drug-drug interactions resulting from the concurrent administration of drugs.

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I. INTRODUCTION

In the last several years there has been an increasing awareness of drug interactions in the medical and pharmaceutical literature. The recognition of drugs that interact with other drugs is of more than passing interest because of the potential consequences of unpredicted reactions.

The phrase "drug interactions" is now part of the common terminology used in medicine and pharmacy. The phenomenon of drug interactions includes the interaction of drugs with certain foods, laboratory tests, and various underlying pathological states. The scope of this project is restricted to drug-drug interactions.

Drug-drug interaction is a phenomenon which occurs when the effects of one drug are altered by the prior or concurrent administration of another (or the same) drug (s). It presents a complex and profound problem. The means by which drug interactions occur are varied and complex. They may arise either from alteration of the absorption, distribution, biotransformation or excretion of one drug by another, or from a combination of their actions or effects.

In order to have a general understanding of drug interactions one must have a basic knowledge of a number of mechanisms. The basic causes for these interactions are as follows:

1. Potentiation

   Drugs having similar pharmacological properties can

be expected to potentiate one or more of the pharmacological effects in patients taking these medications.

2. Antagonism

Drugs which have opposing pharmacological effects may produce a combined effect less than that of the active compound. The basic underlying mechanism of drug antagonism may be chemical, competitive, non-competitive or physiological.

3. Alteration of Gastrointestinal Absorption

Drugs may alter gastrointestinal absorption by complexation or be changing the pH of the gastric fluid. Since many drugs are weak acids or bases, the pH of the gastrointestinal tract will influence the extent of absorption and also the site at which absorption takes place. Drugs may form inactive or insoluble complexes with other drugs in the gastrointestinal tract. It is well known that tetracyclines can combine with di - and trivalent cations to form a complex which is poorly absorbed.

4. Stimulation of Metabolism

A number of drugs can increase the activity of liver microsomal enzymes. The enzyme stimulation results in a more rapid metabolism and excretion of other drugs

that are simultaneously administered.

5. Inhibition of Metabolism

Drugs that can inhibit the activity of liver enzymes indirectly may increase the activity of drugs which depend on this enzyme for their metabolism.

6. Displacement of Drugs from Protein Binding Sites

A competition will exist when two or more drugs are administered concurrently which are capable of binding to proteins. The drug that has the greater affinity for the binding site will displace the other from the plasma or tissue proteins.

7. Interactions at the Receptor Site

Some drugs combine with receptors to form complexes that elicit responses (agonists). Other drugs combine with receptors and elicit no responses (antagonists). In this type of interaction the degree of response will depend on the drug and its affinity for the receptor site.

8. Alteration of Electrolyte Levels

Changes in electrolyte levels may make certain physiological systems more sensitive to the effects of a particular drug.

9. Alteration of Urinary Excretion

Alteration of urinary excretion can be accomplished by

changing the urinary pH or by interfering with tubular excretion. The renal tubular reabsorption of a drug can therefore be increased or decreased by another agent.

The economic consequences of drug reactions are staggering. It has been reported that one seventh of all hospital days are devoted to the care of drug toxicity, at an estimated yearly cost of three billion dollars (1). Considerable attention has been focused on the increasing incidence of drug reactions. Approximately 18 to 30 percent of all hospitalized patients experience a drug reaction during their hospitalization (2). In addition, 3 to 5 percent of all admissions to hospitals are primarily due to an adverse drug reaction (2, 3).

It is a difficult and cumbersome task for a hospital pharmacist to accurately review all medication profiles on a routine basis for drug interactions. Hospital pharmacists in the past (4, 5, 6) have attempted to meet this challenge by developing charts and card files specifically designed for the rapid retrieval of drug interaction information. However, this is an extremely time consuming task. Often it is a retrospective review rather than a prospective analysis. This situation has created a growing interest as well as a potential need for more efficient electronic data processing (EDP) methods designed for the retrieval and utilization of documented drug-drug interactions.

Another factor creating an interest in the field of drug inter-

actions is the potential liability of the pharmacist and physician. The failure to avoid or notice a potentially harmful effect resulting from a drug-drug interaction can make either the physician or pharmacist a candidate for liability. If screening a patient's medication profile is a duty pharmacists accept in a particular locale, then this will undoubtedly become part of the standard of care for patients in that area (7). When such is the standard of practice the public will expect the pharmacist to perform this function carefully and prudently.

This project was undertaken to organize and develop a file of drug-drug interaction data suitable for computerization. In order to accomplish this objective several requirements were met. They are:

1. Selection and evaluation of clinically significant drug-drug interactions from the scientific literature.
2. Creation of a computerized data bank for drug-drug interactions.
3. Design and development of a computerized printout which reports the information in concise summaries.

The scientific literature is replete with relevant clinical studies (8, 9, 10, 11) and isolated case reports (12, 13, 14, 15) citing drug-drug interactions. The National Library of Medicine's computer-based Medical Literature Analysis and Retrieval System (MEDLARS) compiles and produces Toxicity Bibliography which covers the adverse and toxic effects of drugs reported in approxi-

mately 2,300 biomedical journals. This reference is similar to other indexing and abstracting services in that they are all designed to provide a means to access the scientific literature pertaining to chemical and biological interactions. Services such as this are an important contribution towards realization of a comprehensive toxicology information system; however, they only constitute the initial phase in developing a mechanism which provides the clinician with drug-drug interaction data in a practical "ready to use" format.

Multiple-drug administration is common to both hospitalized and ambulatory patients. It is extremely common for a patient to be suffering from more than one unrelated disorder which demands simultaneous treatment with two or more drugs. In such instances interactions are often unexpected. Melmon (1) reported that the average patient in a hospital receives six to ten drugs during his hospitalization. At this level of multiple-drug administration, the adverse reaction rate was reported to be 7 to 10 percent. Some patients receive more than 20 drugs simultaneously. Under such circumstances the patient has at least a 40 percent chance of having adverse reactions to one or more of the drugs. Multiple-drug therapy generally provides greater efficacy than can be achieved with full doses of single drugs, greater margin of safety, or more satisfactory onset or duration of effect. In addition to the administration of drugs concurrently for their independent and unrelated effects,

drugs are sometimes administered concurrently to make use of expected interactions. The phenothiazines markedly affect the actions of a number of other drugs. Phenothiazines are often prescribed for their ability to potentiate the effects of central nervous system depressants. It is common practice to administer a phenothiazine such as promethazine hydrochloride concurrently with a narcotic analgesic in order to reduce the dosage of the narcotic that would normally be required to produce the desired level of analgesia.

II. METHODOLOGY

The scientific literature, both primary and secondary reference sources, was reviewed and evaluated for clinical significant drug interactions. Only drug-drug interactions reported in humans are included in this compilation. Drug interactions occuring only in animals or only in vitro systems have been excluded.

EVALUATION PROCEDURE:

In the assessment of drug interactions for this compilation a selected number of original references were reviewed and evaluated. Secondary references (eg. review articles, drug interaction tables, manuals, etc.) generally do not provide sufficient information on which to make an evaluation. Secondary references are useful in cross-indexing closely related drugs but not, of the same group mentioned in the primary reference source. This is an extremely complex problem since for every basic drug class (eg. barbiturates, corticosteroids, sulfonamides) there are many similar generic drugs which closely resemble the parent compound. In order for a drug interaction compilation to be of any practical value the structure activity relationships of these various compounds have to be taken into consideration. Secondary reference sources were first evaluated on the content of the discussion and the references they provided the user before any decision was made concerning the validity of a particular drug-drug interaction listed in the text.

The initial undertaking was to review a number of abstracting and indexing services, which included, Toxicity Bibliography, International Pharmaceutical Abstracts, Clin-Alert, and FDA: Clinical Experience Abstracts.

In the evaluation of the primary literature for reports of drug interactions the following journals were consulted whenever possible:

1. American Journal of Psychiatry
2. Annals of Internal Medicine
3. Clinical Pharmacology and Therapeutics
4. British Journal of Anesthesia
5. British Medical Journal
6. Anesthesia and Analgesia
7. New England Journal of Medicine
8. Lancet
9. Neurology
10. Journal of Pediatrics

Isolated case reports were only considered if there was some conclusive documentation cited in the literature. Generally speaking, it is extremely difficult if not impossible, to differentiate a case report of a suspected drug interaction from a idiosyncratic or hypersensitive reaction attributable to one of the active components in the multi-drug therapy. What further complicates a literature search for drug interactions is that there are few accepted scientific

studies. The well-controlled clinical experiment is virtually non-existant for obvious reasons. It is difficult for a practitioner to justify re-challenging a patient to a drug when a drug interaction is suspected. Especially if there are other drugs or therapeutic measures available to treat the condition. When there was a choice of references a number of criteria were used to evaluate the study. The general requirements for an adequately controlled study are an objective and practical (sensitivity) method of evaluation, an adequate number of subjects, lack of bias, concurrent comparison of the drug regimen in question with a reference standard, dosage variance, and appropriate statistical validation.

EVALUATION CRITERIA:

There are many factors which may modify the effects of drugs. Some of these result in qualitative differences in the effects of a drug while others produce only quantitative changes in the effects of the drug which are dose dependent. It is extremely important to evaluate a number of specific patient factors before an adverse response is attributed to a drug-drug interaction. The physiological, pathological and genetic factors which are well known to alter response to drugs and which were taken into consideration are age (infant and elderly), sex, race, body weight (nutritional state), tolerance, pathological state, metabolic differences and organ function. The specific mechanisms for these physiological states altering drug response

are well documented in the literature (16, 17).

Another area of paramount importance is the variables associated with drug dosage and route and method of administration. Specifically these factors can be categorized as dosage, route of administration, dosage form, frequency of administration and duration of therapy.

In any defined population, response to a drug generally follows a normal distribution. That is, a few patients will be hypersensitive and will respond to a small dose while a large majority will respond best in the therapeutic range. On the other hand, a few will be relatively resistant to the effects of the drug. This kind of response curve applies to both therapeutic effects and adverse responses which may include drug-drug interactions.

There are a number of parameters which proved helpful in determining the clinical importance of reported drug interactions. They are: occurrence (animal or human, in vivo vs. in vitro), incidence, etiology, structural activity relationships, severity of reported interaction, clinical manifestations, clinical course, prognosis and treatment.

FORMAT AND INDEXING:

This computerized drug interaction file is designed to be compatible with a number of existing computerized record keeping and drug information systems. The information in the file provides a

concise pharmacological summary in a reporting format suitable for actual clinical use in the patient care environment.

The specific drug entities are cross-indexed to a message code. The message code was assigned from a listing of valid numbers calculated by (5A + 4B + 3C + 2D + E/11 = Y x 11). The source document (reference document) which consists of the message codes, arranged sequentially, and the appropriate drug interaction summary was then compiled. In the source document the interactions enumerated in the summary or message are coded to one or more specific references. This particular coding system offers the user a means to obtain the specific references on which the information in the message is based.

Combination products in the top two-hundred prescribed drugs are included if one or more of the active ingredients was implicated in a drug interaction. For example, Desbutal-15 Gradumet which contains methamphetamine hydrochloride 15 mg. and pentobarbital sodium 90 mg. is assigned two different messages. The messages for barbiturates and amphetamines will be reported when the file is searched for possible drug-drug interactions involving this combination product.

III. RESULTS AND DISCUSSION

The system is designed to provide the physician with important drug information on selected drug-drug interactions. In addition, and equally as important, it will provide the clinical pharmacist on the Patient Care Unit with a valuable reference to be utilized as a "key" to clinical involvement with the medical staff. The basic objective of the system is to provide the physician and clinical pharmacist with a reference source enabling him to rapidly screen a medication profile for possible drug-drug interactions. When a probable drug-drug interaction is noted, and it is definitely determined the patient is receiving both medications concurrently the clinical pharmacist may then elect to contact the physician. In certain instances it may be only necessary for him to inform the nurse of the possible interaction. For example, if a patient is receiving both an antacid preparation and bisacodyl tablets, an enteric coated laxative, the pharmacist should advise the nurse not to administer both medications simultaneously, but rather as far apart as possible.

A source document (reference document) was the first document compiled (Appendix I). A five character numeric code was assigned to each message. The specific drug entities which were coded in the source document were compiled and cross-indexed to the respective message code (Appendix II). A second index (Appendix III) was compiled listing the message codes in sequence and the par-

ticular drugs to which the summary applies. This index is useful to the user when it is necessary to determine the complete list of drugs which have been indexed to any one particular message. The source document codes the specific interaction enumerated in the summary to one or more specific references thereby offering the user a means to obtain the references on which the information is based. A list of the selected references utilized is included (Appendix IV).

A printout of the messages exactly as they were retrieved from storage is included for illustrative purposes (Appendix V). The printout included in this document represents a xeroxed copy of a computer printout which was photoreduced by twenty percent.

The following message represents an example of a summary as it was printed from the data bank:

> Salicylates elevate the anticoagulant response to oral anticoagulants, increase plasma levels of unbound penicillin G and derivatives and potentiate methotrexate and sulfonylureas. Salicylate plasma levels may be decreased by corticosteroids. They may decrease serum levels of indomethacin (Indocin) and inhibit uricosuric activity of sulfinpyrazone (Anturane) and probenecid (Benemid).

If the information is of interest to the physician hopefully he will be stimulated to seek the references and request a "consultation" from the Pharmacy for further evaluation. A pharmacy consultation would consist of a pharmacist reviewing a patient's medical record in light of the drug-drug interaction information reported for a particular patient. The pharmacist would determine if the drug-drug

interaction information is significant in that patient and whether the patient's physician should be informed of the findings. In order to accomplish efficient retrieval of the specific references which were applicable to the message, a source document (reference document) was created (Appendix I). Ideally it would be advantagious to create a file containing the hard copy of the references most frequently requested. As the number of references increase the original copy can be microfilmed and placed in a microfiche to reduce storage requirements. The previous example appears in the source document as:

04383 Salicylates

Salicylates elevate the anticoagulant response to oral anticoagulants (13), increase plasma levels of unbound penicillin G and derivatives (14) and potentiate methotrexate (16) and sulfonylureas (17). Salicylate plasma levels may be decreased by corticosteroids (15). They may decrease serum levels of indomethacin (Indocin) (53) and inhibit uricosuric activity of sulfinpyrazone (Anturane) (18) and probenecid (Benemid) (19).

Generally speaking, the reference selected for the list (Appendix IV) represents the most scientific and significant literature citation reviewed for that particular interaction. In certain instances two or more references are cited for a specific interaction. When more than one mechanism has been postulated in the literature a cross sample of references are included. For example, salicylates have been shown to displace methotrexate from plasma protein binding, thereby elevating plasma levels of free methotrexate. However,

salicylates may also block the renal excretion of methotrexate. Therefore the increased activity of methotrexate, usually manifested by increased toxicity, is attributable to both of these mechanisms.

REPORTING FORMAT:

The reporting format is designed to provide practical information in a concise summary which can be easily understood and utilized in a patient care environment. The printout may be incorporated into a patient's cumulative medication profile or used strictly as a reference source to screen for drug-drug interactions.

A reporting format (previously illustrated) was chosen which would enable a physician or a pharmacist to effectively review a patient's previous medication history as well as the present drug therapy for suspected drug-drug interactions. A unique advantage of this system is that it reports important drug-drug interactions with each drug entity the patient is receiving. The system is not limited to the reporting of specific interactions with the concomitant use of two drugs.

A retrospective review of a patient's previous medication history is a valuable exercise in light of the extended biological half-life of many drugs and the many structural similarites which exist. This is extremely important since so many of the reported drug interactions exhibit structure activity relationships and are not specific for any one drug entity. The sulfonamides are a class of drugs in

which a number of the drug interactions involving these compounds are structure dependent. This information is of practical value in a patient care environment, because it provides the physician with drug interaction information which will enable him to make an intelligent choice as to the appropriate class of drugs to prescribe.

This sort of information is also helpful in predicting unknown reactions which may occur with new drugs. There are many instances when it is impossible to predict a possible drug-drug interaction based on the structure activity relationship to a parent compound. For example, a new drug with a phenothiazine nucleus would be expected to potentiate the effects of central nervous system depressants. In the majority of instances so-called new drugs are merely molecular modifications of an existing generic drug or are compounds which are transformed to a pharmacologically active compound which in itself is commercially available.

The importance of knowing beforehand when two drugs given together will result in an interaction cannot be overemphasized. Since drug interactions unknown to-date cannot be predicted in patients taking two or more drugs at the same time, only those interactions already reported in the literature offer any clue as to what drugs make a rational combination.

LITERATURE EVALUATION:

Drugs which exert a similar pharmacological action and which

are prescribed for the same therapeutic purposes were not considered as examples of drug-drug interactions having additive or synergistic pharmacological effects (e.g. epinephrine and levarterenol). Another broad area which was not included in this file is the rationale of combining both bacteriostatic and bactericidal antibiotics in the same therapeutic regimen. Jawetz (18) has reported that antibiotic antagonism may occur but the net effect plays a minor role in clinical medicine. This has been an extremely controversial subject for years and still has not been resolved. The inclusion of this sort of material in a drug interaction compilation is of no practical value.

One of the major difficulties in evaluating drug interactions is the occurrence of contradictory reports concerning a specific interaction. For example, a drug interaction of considerable interest to neurologists is the reported inhibition of diphenylhydantoin and phenobarbital metabolism by methylphenidate. Recent studies (19, 20) indicate that during the period of concurrent drug administration there is no elevation in diphenylhydantoin plasma levels or clinical signs of drug toxicity. Based on the results of these two studies this suspected interaction was not included in the file. Although these studies do not preclude the possibility of an interaction of methylphenidate with the anticonvulsants they do suggest that if this interaction does exist it must occur infrequently.

A similar case is illustrated by the combination of a tricyclic

antidepressant and a monoamine oxidase inhibitor (MAOI) in the treatment of depression. This combination is often contraindicated in the literature as well as the respective product brochure. In certain instances a medication-free period of two weeks is recommended after discontinuance of the MAOI and the institution of a tricyclic antidepressant. However, there have been two recent publications (21, 22) concerning antidepressant therapy which indicate that the combined use of a tricyclic antidepressant and a MAOI may not be hazardous and that this method of treatment may be used with considerable benefit to the patient. Since it was listed as a caution in the product brochure it was decided to include it in the files despite the fact that the clinical significance of this interaction has not been demonstrated.

The interaction between chloral hydrate and warfarin sodium is even more complex. In 1966 Cucinall et al (23) suggested that the coadministration of bishydroxycoumarin and chloral hydrate resulted in a reduction in expected plasma levels of the anticoagulant with a decrease in prothrombin time. Sellers and Koch-Weser (24) showed that the administration of 1 Gm. chloral hydrate for one week increased the hypoprothrombinemic effect of warfarin sodium by 40 to 80 percent. Griner, P.F., et al (25) recently conducted a study to determine the effect of chloral hydrate in patients receiving long-term therapy with warfarin sodium. Their findings, unbelievable as

they may seem, indicated that chloral hydrate or its equivalent as chloral betaine, in doses of 0.5 to 1 Gm. daily, did not influence the anticoagulant effect of warfarin in such patients. Since the studies reported in the literature are not conclusive and the results remain contradictory it was decided to include in the file a statement to the effect that "chloral hydrate variably effects the anticoagulant response to oral anticoagulants." This statement merely points out the fact that chloral hydrate may in some way interfere with the hypoprothrombinemic effect of oral anticoagulants.

Diphenylhydantoin is one of many drugs metabolized by enzymes found in the microsomal fraction of hepatic cells. The drug phenobarbital, is known to stimulate these enzymes and thus the metabolism of diphenylhydantoin. Apparently, the ability of phenobarbital to lower plasma levels of diphenylhydantoin is not so great as to offset its own anticonvulsant activity. Although a biochemical antagonism exists the net result is a potentiation of the desired pharmacological effects. This particular combination is the drug regimen of choice for grand mal epilepsy. A suspected or reported drug interaction can not be evaluated solely on the basis of biochemical data. It must be remembered that combination drug therapy attempts to achieve one or more therapeutic effects with a minimum of adverse effects. The ultimate clinical objective of the therapeutic regimen must always be considered. On the other hand, this antagonism may be significant if the patient

was receiving large doses of diphenylhydantoin (common to hospitalized patients in psychiatric hospitals) and then had the phenobarbital discontinued. In this particular case, the diphenylhydantoin plasma levels may well rise to a toxic level.

Isolated case reports (one or two patients) were excluded except the reports concerning methotrexate and small pox vaccination. Methotrexate, a antineoplastic agent, may inhibit the immunological response to smallpox vaccine resulting in generalized vaccinia. The decision to include this interaction was strictly subjective and not based on any rational scientific data. Regardless of the severity of the reaction one would not expect to find numerous cases or controlled studies since the use of this combination is very limited. An important consideration is that by reporting this interaction it may alert the prescriber to possible difficulties with other immunosuppressive drugs, namely the corticosteroids.

There are a number of interactions which are well known in medical circles but specific clinical documentation is lacking. The major area of concern to the clinician is that although the clinical data is lacking they are included in the pharmaceutical brochure which brings about a potential legal liability. From a medicolegal standpoint it is wise to include these in a drug interaction file in order that the physician will be forewarned about a possible adverse effect. If the drug interaction is included in the product literature

as a caution or warning the physician is faced with a legal dilemma. In this situation the physician may wish to select another drug or decide to run the risk to the patient. This situation is applicable to the following examples of drug-drug interactions: Propoxyphene-orphenadrine, meperidine-isoniazid, and allopurinol-iron.

CURRENT APPLICATIONS:

The system is designed in a manner which enables it to be incorporated into a program using computerized medication profiles. The messages or supplementary notes pertaining to possible drug-drug interactions immediately follow the cumulative medication profile (Illustration I). In the first example (Illustration I) the information presented in the accompanying messages does not suggest any specific drug interactions with the drug regimen outlined in the medication profile. However, the information would be extremely useful to the physician if he were considering adding additional drugs to the present therapeutic regimen. The information previously presented may forewarn him of an interaction. In the second example (Illustration II) the messages describe pertinent drug-drug interactions which are possible with the current therapeutic regimen. If a medication has been discontinued the drug interaction summary is not printed. This check is built into the computer program. For example, in Illustration I the message summary for diphenhydramine hydrochloride (an antihistamine) was printed while it was not in the

second illustration since the drug had been discontinued.

The program of instructions designed to print the cumulative medication profile and search the drug interaction file for the appropriate drug interaction message code is included (Appendix VI). The computer program is written in COBAL.

From a practical viewpoint it is difficult to justify a computer program which does not always produce a tangible result. It is much more difficult to implement a program limited to professional objectives as opposed to a cost accounting program designed to process medication charges. As with most organizations computer time is expensive and is limited. An additional feature of the cumulative patient medication profile described in this project is that it can be used as a dispensing record for a medication distribution system.

All that is necessary to incorporate this file into an ongoing computerized system is to place the file in storage and then assign message codes to drug names listed in a computerized drug product file or a drug data file. In order to facilitate this task the specific generic entities are cross-indexed to the appropriate message codes (Appendix II). The drug product file can be compiled by the individual institution or a commercially available file can be purchased. The American Society of Hospital Pharmacists Drug Product Information File (DPIF) serves as a master drug code dictionary and is adapt-

able to each individual system. The DPIF is a data bank composed of terms and code numbers for commercially available drug products which is organized to facilitate automated processing of drug data. This particular multi-functional drug coding system is based on a 5-digit generic drug product number that completely identifies the generic drug product.

Retrieval may be accomplished by one of two basic methods: (1) As an integral component of a computerized medication profile and/or pricing system. (2) Manual selection of pre-punched cards.

The file can be easily utilized by individuals who do not have a computerized profile system. They can create a tub file of pre-punched index cards and then select the applicable cards upon special request. A prospective review of drug interactions can then be conducted by running a program to search the file in storage. A system similar to this is utilized by the Drug Information Center, Mercy Hospital, Pittsburgh, Pennsylvania (25).

FUTURE APPLICATIONS:

It is possible to prepare a manual from the drug-drug interaction file. This aspect of the system would be especially useful to individuals without access to electronic data processing facilities. This would serve as a supplementary reference source which would enable the user to rapidly screen a medication profile in lieu of a computerized system. Under certain circumstances a request for

an immediate computer search is impractical, e.g. servicing a drug information request VIA the telephone or while participating in work and teaching rounds. The major sections, namely, the Source Document, Indexes, and Selected References can be cross-indexed, typed and then photoreduced.

Another valuable application of this file is that a drug-induced laboratory test interference file can be used in conjunction with the present system or incorporated into it. Drugs may possess the inherent ability to alter laboratory test values through a variety of pharmacological, physical or chemical mechanisms (27). A drug may affect the normal physiological levels of the particular substance being measured. Through physical or chemical interference, a drug may not only alter a test's value but may prevent its determination by a particular method. The extended biological half-life of drugs as well as intermediate or end products of drug metabolism may often be responsible for unsuspected alteration in laboratory test values. The reporting format and retrieval system is compatible with a program conducted by the Pathology Department of the Rhode Island Hospital, Providence, Rhode Island (28) for reporting possible drug-induced modifications of laboratory test values. In this particular program a computerized cumulative report of all laboratory tests is prepared for every patient who had a test conducted. Immediately following the cumulative report are supplementary

notes pertaining to drug-induced laboratory interferences for the tests outlined in the report. Although it is ideal to include this information in a cumulative laboratory report there are instances when this may not be practical and it would be preferable to include this information in the medication profile. A prime example would be a situation where a patient obtains health care services from an ambulatory patient care facility. Usually after the initial battery of laboratory tests only a few tests, if any, are conducted for continued surveillance of a particular physiological parameter. In this situation, it would not be economically feasible to run a specific program for laboratory tests.

The file is compatible with existing computerized drug information services. Another advantage of this type of drug-drug interaction file is that its use is not limited to an institutional setting. The system may be incorporated into a computerized drug information service coordinated by a regional drug information network and offered to community practitioners on a subscription basis VIA on-line computer terminals.

ILLUSTRATION I

Patient Medication Profile. Example I

MODERN HOSPITAL

DEPARTMENT OF PHARMACY

CUMULATIVE MEDICATION PROFILE FOR KAREN SMITH

NO. 6572810 ROOM 602 AGE 26

START	STOP	MEDICATION ORDERED	PHYSICIAN
2/08		DIAZEPAM 5 MG. PO TID PC	ALLEN
2/08		LITHIUM CARBONATE 0.3 GM. PO TID PC	CAMPBELL
2/08		ISOCARBOXAZID 10 MG. PO TID	CAMPBELL
2/10		SULFISOXAZOLE 0.5 GM. PO TID	STEINBERG
2/11		DIPHENHYDRAMINE HCL 50 MG. PO HS PRN	CAMPBELL
2/11		METAMUCIL 5 GM. PO TID	CAMPBELL
2/11	2/14	BETHANECHOL CHLORIDE 10 MG. PO TID	STEINBERG

END OF PROFILE 2/17/72

PROBABLE DRUG-DRUG INTERACTIONS FOR KAREN SMITH NO. 6572810

LITHIUM EXCRETION IS INCREASED BY AMINOPHYLLINE, SODIUM BICARBONATE AND LARGE DOSES OF SODIUM CHLORIDE. LOW SODIUM INTAKE MAY PRECIPITATE LITHIUM TOXICITY.

MONOAMINE OXIDASE INHIBITORS POTENTIATE THE PHARMACOLOGICAL EFFECTS OF AMPHETAMINES, METHYLPHENIDATE (RITALIN), TRICYCLIC ANTIDEPRESSANTS, HYPOGLYCEMICS AND SYMPATHOMIMETICS SUCH AS EPHEDRINE, METARAMINOL (ARAMINE), PHENYLEPHRINE AND PHENYLPROPANOLAMINE. CONCOMITANT USE WITH MEPERIDINE OR LEVODOPA INCREASES INCIDENCE OF ADVERSE EFFECTS.

SULFONAMIDES MAY POTENTIATE THE HYPOGLYCEMIC RESPONSE TO ORAL HYPOGLYCEMICS AND ELEVATE SERUM LEVELS OF METHOTREXATE. CONCOMITANT USE WITH METHENAMINE COMPOUNDS FREQUENTLY RESULTS IN CRYSTALLURIA AND THE FORMATION OF A PRECIPITATE.

ANTIHISTAMINES MAY PRODUCE ADDITIVE CNS DEPRESSANT EFFECTS WHEN USED CONCOMITANTLY WITH ETHYL ALCOHOL, BARBITURATES AND PHENOTHIAZINES. THEY MAY POTENTIATE THE PHARMACOLOGICAL ACTIVITY OF ANTICHOLINERGICS AND THE ADVERSE EFFECTS OF TRICYCLIC ANTIDEPRESSANTS.

FOR FURTHER INFORMATION CALL DRUG INFORMATION CENTER EXT 1234

ILLUSTRATION II

Patient Medication Profile. Example II

MODERN HOSPITAL

DEPARTMENT OF PHARMACY

CUMULATIVE MEDICATION PROFILE FOR ROBERT E. JOHNSON

NO. 8363820 ROOM 723 AGE 78

START	STOP	MEDICATION ORDERED	PHYSICIAN
2/02	2/03	DIGOXIN 0.25 MG. PO TID	RILEY
2/02	2/02	BISACODYL 5 MG. PO BID	VINCENT
2/03	2/03	BISACODYL 10 MG. R	VINCENT
2/03	2/03	CASTOR OIL 30 ML. PO	VINCENT
2/03		DIGOXIN 0.25 MG. PO QD	RILEY
2/03	2/03	PENTOBARBITAL SODIUM 100 MG. PO HS	VINCENT
2/04	2/04	DIGOXIN 0.25 MG. IM	VINCENT
2/04	2/04	ATROPINE SULFATE 0.4 MG. IM PRE-OP	VINCENT
2/04	2/04	MEPERIDINE HYDROCHLORIDE 50 MG. IM PRE-OP	VINCENT
2/04	2/04	PROMETHAZINE HYDROCHLORIDE 25 MG. IM PRE-OP	VINCENT
2/04	2/05	MEPERIDINE HYDROCHLORIDE 100 MG. IM Q 4H PRN	RILEY
2/04	2/06	POTASSIUM CHLORIDE 40 MEQ. IV IN D5W 500 ML.	VINCENT
2/04	2/06	MULTIVITAMINS 10 ML. IV IN D5W 1000 ML.	VINCENT
2/05	2/11	METAMUCIL 5 GM. PO BID	RILEY
2/05	2/07	PENICILLIN G POTASSIUM 1,000,000 UNITS IV Q 6H	RILEY
2/05	2/06	MEPERIDINE HYDROCHLORIDE 50 MG. IM Q 4H PRN	VINCENT
2/06	2/08	PENTAZOCINE 30 MG. IM Q 4H PRN	VINCENT
2/07	2/11	AMPICILLIN 0.5 GM. IV Q 6H	RILEY
2/07	2/08	TRIMETHOBENZAMIDE HCL 0.2 GM. R Q 6H PRN	HOLLOND
2/08	2/11	PROCHLORPERAZINE MALEATE 10 MG. IM Q 6H PRN	VINCENT
2/10	2/15	MAALOX 30 ML. PO QID	RILEY
2/11	2/13	CHLORDIAZEPOXIDE HYDROCHLORIDE 10 MG. PO TID	RILEY

CONTINUED ON NEXT PAGE

ROBERT E. JOHNSON NO. 8363820 ROOM 723 PAGE 2

2/11	2/15	GENTAMICIN SULFATE 40 MG. Q 12H	CUTTS
2/11	2/11	LIDOCAINE HYDROCHLORIDE 2 GM. IN D5W 1000 ML.	CUTTS
2/11	2/11	FUROSEMIDE 40 MG. IV	CUTTS
2/11	2/11	SODIUM BICARBONATE 50 PCT, 150 ML IV	CUTTS
2/11	2/11	MAGNESIUM SULFATE 10 PCT, 10 ML IV	CUTTS
2/11	2/12	HYDROCORTISONE SODIUM SUCCINATE 100 MG. IV Q6H	CUTTS
2/11	2/11	METARAMINOL 10 MG. IV	CUTTS
2/11	2/11	METHYLPREDNISOLONE SOD. SUCCINATE 0.5 GM. IV	CUTTS
2/11	2/11	FUROSEMIDE 200 MG. IV	CUTTS
2/11		POTASSIUM CHLORIDE SYRUP 25 MEQ. PO TID	RILEY
2/11	2/15	FUROSEMIDE 40 MG. PO QD	CUTTS
2/12	2/14	NEOSPORIN GU IRRIGANT	VINCENT
2/12	2/16	CEPHALOTHIN SODIUM 2 GM. IV Q 6H	RILEY
2/13	2/15	HEPARIN SODIUM 1000 UNITS IV Q 6H	VINCENT
2/14	2/15	DIPHENHYDRAMINE HCL 50 MG. PO HS PRN	RILEY
2/16		PHENOBARBITAL 32 MG. PO QID	RILEY
2/16		CHLORAL HYDRATE 0.5 GM. PO HS	RILEY
2/16		WARFARIN SODIUM 10 MG. PO QD	RILEY

END OF PROFILE 2/17/72

PROBABLE DRUG-DRUG INTERACTIONS FOR ROBERT E. JOHNSON NO. 8363820

DIGITALIS GLYCOSIDES ARE PHARMACOLOGICALLY POTENTIATED BY PARENTERAL CALCIUM PREPARATIONS AND DIURETICS PRODUCING POTASSIUM AND MAGNESIUM DEFICIENCIES. AMPHOTERICIN B (FUNGIZONE) MAY PRODUCE HYPOKALEMIA PRECIPITATING DIGITALIS TOXICITY. SYMPATHOMIMETICS MAY INCREASE INCIDENCE OF CARDIAC ARRHYTHMIAS.

BARBIURATES-ADDITIVE EFFECTS MAY BE SEEN WITH THE CONCOMITANT USE OF ANTIHISTAMINES, PHENOTHIAZINES AND OTHER CNS DEPRESSANTS. THEY MAY BE POTENTIATED BY PROCARBAZINE (MATULANE). THEY MAY DECREASE THERAPEUTIC EFFECTS OF ORAL ANTICOAGULANTS, TRICYCLIC ANTIDEPRESSANTS AND GRISEO-FULVIN. THEY MAY VARIABLY EFFECT SERUM DIPHENYLHYDANTOIN LEVELS.

CHLORAL HYDRATE VARIABLY EFFECTS THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS.

ORAL ANTICOAGULANTS ARE POTENTIATED BY ACETAMINOPHEN, ESTROGENS, ANABOLIC STEROIDS, CHLORAMPHENICOL, CHOLESTYRAMINE (CUEMID), CLOFIBRATE (ATROMID S), D-THYROXINE, PHENYLBUTAZONE (BUTAZOLIDIN) AND PHENYRAMIDOL (ANALEXIN). THEY MAY BE POTENTIATED BY AMINOGLYCOSIDE ANTIBIOTICS, DI-PHENYLHYDANTOIN, INDOMETHACIN, QUINIDINE AND SALICYLATES. THEY ARE ANTAG-ONIZED BY ETHYL ALCOHOL, BARBITURATES, ETHCHLORVYNOL, GRISEOFULVIN AND GLUTETHIMIDE. THEY ARE VARIABLY AFFECTED BY CHLORAL HYDRATE.

FOR FURTHER INFORMATION CALL DRUG INFORMATION CENTER EXT 1234

IV. CONCLUSIONS

The design of this computerized drug-drug interaction file offers several unique features.

1. The program reports important drug-drug interactions with each drug entity the patient is receiving. The system is not limited to the reporting of specific interactions which may occur with the patient's current therapeutic regimen.
2. The reporting format is designed to provide practical information in a concise summary which can be easily understood and utilized in any patient care environment.
3. The printout may be incorporated into a patient's medical record or used strictly as a reference source to screen for drug-drug interactions.
4. The file is compatible with existing computerized medication profiles and record systems as well as computerized drug information services.
5. The use of the drug-drug interaction file is not limited to a hospital or a comprehensive ambulatory patient care facility. The system may be incorporated into a computerized drug information service coordinated by a regional drug information network and offered to community practitioners on a subscription basis.

6. The various components of the system can be assembled in a manner which would create a cross-idexed manual of human drug-drug interactions. This aspect of the system would be especially useful to individuals without access to electronic data processing facilities.

7. As an added feature the cumulative patient medication profile can be used as a dispensing record for a medication distribution system.

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APPENDIX I

Source Document

00086 Acetaminophen

Acetaminophen elevates the anticoagulant response to oral anticoagulants. (3, 4)

00124 Acetazolamide

Acetazolamide (Diamox), urinary alkalinizing agent, elavates serum levels of amphetamines (42), tricyclic antidepressants (33, 37) and quinidine (78) by enhancing renal reabsorption. It may antagonize the activity of methenamine compounds. (79)

00167 Alcohol, Ethyl

Ethyl alcohol-additive effects may be seen with CNS depressants (26, 54) and antihistamines (26). It may antagonize the pharmacological effects of the oral anticoagulants (28) and diphenylhydantoin (104). It may enhance the adverse effects of guanethidine (29), nitroglycerin (27), disulfiram (Antabuse) (30), metronidazole (Flagyl) (31) and tricyclic antidepressants (21). It prolongs the action of insulin. (129)

00205 Allopurinol

Allopurinol potentiates the effects of bishydroxycoumarin (10), and mercaptopurine (11, 58). It may increase hepatic

iron concentration. (140)

00299 Antacids

Antacids containing divalent and trivalent cations decrease oral absorption of tetracyclines. Antacids should not be administered simultaneously with enteric coated products. (6) Sodium polystyrene resin (Kayexalate) binds magnesium and calcium ions found in antacids resulting in systemic alkalosis. (176)

00337 Amantadine

Amantadine (Symmetrel) potentiates the pharmacological effects produced by levodopa. (9)

00434 Aminophyllin

Aminophyllin may impair the therapeutic response to lithium carbonate by increasing the renal excretion of lithium ions. (80)

00515 Aminosalicylic Acid

Aminosalicylic acid plasma levels are elevated by probenecid (Benemid). (81)

00566 Ammonium chloride

Ammonium chloride (urinary acidifier) may decrease renal reabsorption of amphetamines (42) and tricylic antidepressants (33, 37).

00604 Amphotericin B

Amphotericin B (Fungizone) may produce hypokalemia

precipitating digitalis toxicity. (82) It may potentiate neuromuscular blockade of skeletal muscle relaxants. (82)

00647 Ampicillin

Ampicillin plasma levels are increased by concomitant use of probenecid (Benemid). (43, 56)

00698 Amphetamines

Amphetamines potentiate MAOI (20) and antagonize the effects of guanethidine (40). Phenothiazines may antagonize the central effects of amphetamines (41). Urine acidifying agents decrease renal reabsorption and urinary alkalinizers such as acetazolamide (Diamox), sodium bicarbonate and thiazide diuretics increase reabsorption. (42)

00744 Angiotensin Amide

Angiotensin amide (Hypertensin)-induced antidiuresis and antinatriuresis is reversed by ethacrynic acid (Edecrin) and furosemide (Lasix). (44)

00752 Anabolic Steroids

Anabolic steroids may potentiate the activity of oral anticoagulants (63), phenylbutazone (Butazolidin) and oxyphenbutazone (Tandearil) (155, 156) They may decrease insulin requirements in diabetics. (188)

00787 Anticholinergic Drugs

Anticholinergic drugs may potentiate quinidine (83) and the

secondary pharmacological effects of antihistamines and tricyclic antidepressants. Propranolol (Inderal)-induced adverse effects are antagonized by anticholinergics. (84) They may produce extrapyramidal symptoms when used simultaneously with methotrimeprazine (Levoprome). (149)

00825 Anticoagulants, Oral

Oral anticoagulants are potentiated by acetaminophen (3, 4) estrogens (98), anabolic steroids (63), chloramphenicol (64), cholestyramine (Cuemid) (68), clofibrate (Atromid S) (63), Phenylbutazone (Butazolidin) (28, 39) and phenyramidol (Analexin) (72). They may be potentiated by aminoglycoside antibiotics (64), diphenylhydantoin (69), indomethacin (71), quinidine (28, 185) and salicylates (13). They are antagonized by ethyl alcohol (28), barbiturates (49), ethchlorvynol (117), griseofulvin (28, 72) and glutethimide (49, 70). They are variably affected by chloral hydrate (38, 65, 66).

00876 Antidepressants, Tricyclic

Tricyclic antidepressants may potentiate the adverse effects of MAOI (21) and ethyl alcohol (21, 59) and the pharmacological effects of sympathomimetics (36), thyroid preparations (35), antihistamines and anticholinergics. They may antagonize guanethidine (60, 61, 62). Barbiturates appear to decrease therapeutic activity. (38) They are potentiated by

methylphenidate. (34) Urine acidifying agents decrease renal reabsorption and urine alkalinizing agents increase reabsorption. (33, 37)

00884 Antihistamines

Antihistamines may produce additive CNS depressant effects when used concomitantly with ethyl alcohol (26), barbiturates (55) and phenothiazines (157). They may potentiate the pharmacological activity of anticholinergics and the adverse effects of tricyclic antidepressants.

00892 Antihypertensive Agents

Antihypertensive agents may be potentiated by methotrimeprazine (Levoprome) (149), procainamide (Pronestyl) (125, 168) and propranolol (Inderal) (84, 126).

00914 Ascorbic Acid

Ascorbic acid (urinary acidifier) may antagonize amphetamines (42) and tricyclic antidepressants (33, 37).

00957 Barbiturates

Barbiturates-additive effects may be seen with the concomitant use of antihistamines, phenothiazines and other CNS depressants. (55) They may be potentiated by procarbazine (Matulane) (48). They may decrease therapeutic effects of oral anticoagulants (49), tricyclic antidepressants (38) and griseofulvin (37).

They may variably effect serum diphenylhydantoin levels. (45, 46)

01058 Bishydroxycoumarin

Bishydroxycoumarin may potentiate the sulfonylureas and increase serum levels of diphenylhydantoin (50). It is potentiated by acetaminophen (3, 4), estrogens (98), anabolic steroids (63), chloramphenicol (64), cholestyramine (Cuemid) (68), clofibrate (Atromid S) (63), d-thyroxine (63), phenylbutazone (Butazolidin) (28, 39) and phenyramidol (Analexin) (72). It may be potentiated by aminoglycoside antibiotics (64), diphenylhydantoin (69), indomethacin (71) and salicylates (13). It is antagonized by ethyl alcohol (28), barbiturates (49), ethchlorvynol (117), griseofulvin (28, 73) and glutethimide (49, 70). It is variably affected by chloral hydrate. (38, 65, 66)

01090 Bisacodyl

Bisacodyl (Dulcolax) tablets should not be taken concomitantly with antacids. (182)

01139 Calcium Preparations (Parenteral)

Calcium ions administered parenterally may pharmacologically potentiate digitalis glycosides. (74, 75)

01147 Carbenicillin

Carbenicillin (Pyopen, Geopen) plasma levels may be elevated and prolonged by probenecid (Benemid) (186, 187)

01171 Cephalosporins

Cephalosporins, all-plasma levels are elevated by probenecid (Benemid) (43, 76). Concomitant administration of colistin increases incidence of nephrotoxicity. (96)

01236 Chloral Betaine

Chloral betaine (Beta-Chlor) variably effects the anticoagulant response to oral anticoagulants. (38, 65, 66)

01317 Chloral Hydrate

Chloral hydrate variably effects the anticoagulant response to oral anticoagulants. (38, 65, 66)

01368 Chloramphenicol

Chloramphenicol may potentiate oral anticoagulants (64), diphenylhydantoin (67) and sulfonylureas (67).

01406 Diuretics

Diuretics producing potassium and magnesium deficiencies may precipitate digitalis toxicity (94, 95). Concomitant use with corticosteroids may result in excessive potassium loss (102). Diuretics may antagonize the activity of oral hypoglycemics. (115, 163, 164)

01449 Cholestyramine

Cholestyramine (Cuemid) may elevate the anticoagulant response to oral anticoagulants. (68) It decreases absorption of thyroid preparations by binding thyroxine and triiodo-

thyronnine. (177)

01481 Clofibrate

Clofibrate (Atromid S) pharmacologically elevates the anticoagulant response to oral anticoagulants (63). It may inhibit platelet adhesiveness. (179)

01546 Colistin

Colistin (Coly-Mycin) enhances neuromuscular blockade of skeletal muscle relaxants. (97) Concomitant administration of parenteral cephalosporins increases incidence of nephrotoxicity. (96)

01589 Corticosteroids

Corticosteroids may be potentiated by estrogens. (99) They may pharmacologically antagonize hypoglycemics (77, 115) and decrease salicylate plasma levels (15). Diphenylhydantoin may decrease therapeutic response to corticosteroids. (100, 101) Concomitant use with diuretics may result in excessive potassium loss. (102)

01627 Corticotropin

Corticotropin (ACTH) may be potentiated by estrogens (99). It may pharmacologically antagonize hypoglycemics (77, 115) and decrease salicylate plasma levels (15). Diphenylhydantoin may decrease response to corticosteroids. (100, 101) Concomitant use with diuretics may result in excessive potassium loss. (102)

01678 Dapsone

Dapsone (Avlosulfon) plasma levels are increased by probenecid (Benemid). (103)

01759 Digitalis Glycosides

Digitalis glycosides are pharmacologically potentiated by parenteral calcium preparations (74, 75) and diuretics producing potassium and magnesium deficiencies (94, 95). Amphotericin B (Fungizone) may produce hypokalemia precipitating digitalis toxicity. (82) Sympathomimetics may increase incidence of cardiac arrhythmias. (94)

01791 Diphenylhydantoin

Diphenylhydantoin is potentiated by chloramphenicol (67), disulfiram (Antabuse) (105) and isoniazid (106, 107). It may be antagonized by ethyl alcohol (104) and phenyramidol (Analexin) (109). It may potentiate oral anticoagulants (69) and methotrexate (108). It may decrease the therapeutic response to corticosteroids. (100, 101)

01848 Dipyridamole

Dipyridamole (Persantine) may potentiate the anticoagulant activity of heparin. (110, 178)

01880 Disulfiram

Disulfiram (Antabuse) potentiates diphenylhydantoin. (105) Concomitant use with isoniazid (111), ethyl alcohol (30) and

metronidazole (Flagyl) (112, 113) enhances the incidence of adverse effects.

01929 Echothiophate Iodide

Echothiophate iodide (Phospholine iodide) potentiates the pharmacological effects of succinylcholine. (114)

01961 Ephedrine

Ephedrine potentiates hypertensive reactions with MAOI. (23) It antagonizes the adrenergic neuron blockade produced by guanethidine (Ismelin). (40)

02011 Epinephrine

Epinephrine, and to a lesser extent, other adrenergic agents may decrease activity of hypoglycemic agents. (115)

02062 Estrogens

Estrogens pharmacologically elevate the anticoagulant activity of oral anticoagulants. (98) They may potentiate corticosteroid activity. (99)

02100 Ethacrynic Acid

Ethacrynic acid potentiates ototoxicity of aminoglycoside antibiotics. (116) It may produce potassium and magnesium deficiencies precipitating digitalis toxicity. (94, 95) Concomitant use with corticosteroids may enhance potassium loss. (102) It may antagonize the activity of oral hypoglycemics. (163, 164)

02143 Ethchlorvynol

Ethchlorvynol (Placidyl) antagonizes the anticoagulant activity of oral anticoagulants. (117)

02194 Folic Acid

Folic acid antagonizes the antineoplastic activity of methotrexate. (118)

02232 Furosemide

Furosemide may produce potassium and magnesium deficiencies precipitating digitalis toxicity. (94, 95) Concomitant use with corticosteroids may enhance potassium loss. (102) It enhances the effects of tubocurarine. (119) It may antagonize the activity of oral hypoglycemics. (163, 164)

02275 Gentamicin

Gentamicin in combination with other aminoglycoside antibiotics increases incidence of ototoxicity and nephrotoxicity. (120) Ethacrynic acid potentiates the ototoxicity. (116) It enhances the blockade of skeletal muscle relaxants. (97)

02313 Glutethimide

Glutethimide (Doriden) decreases anticoagulant response to oral anticoagulants. (49, 70)

02364 Glyceryl Guaiacolate

Glyceryl guaiacolate may potentiate the anticoagulant

activity of heparin. (110, 118)

02402 Griseofulvin

Griseofulvin may decrease the anticoagulant activity of oral anticoagulants. (28, 73) It is antagonized by barbiturates which may impair absorption. (37)

02445 Guanethidine

Guanethidine may be potentiated by procainamide (125), propranolol (126) and quinidine (127). It is antagonized by amphetamines (40), tricyclic antidepressants (60, 61, 62), ephedrine (40) and methylphenidate (40, 122,123). It may potentiate phenylephrine (124) and decrease activity of hypoglycemics (88, 89). Ethyl alcohol (29), methotrimeprazine (Levoprome) (121), procarbazine (Matulane) (48) and thiazide diuretics (32) may potentiate orthostatic hypotension.

02496 Heparin

Heparin induced anticoagulant activity may be enhanced by dipyridamole (Persantine) (110) and glyceryl guaiacolate (110, 118).

02542 Hypoglycemic Agents, Oral

Oral hypoglycemic agents may be potentiated by chloramphenicol (67). MAOI (22), phenylbutazone (Butazolidin) (2, 165), propranolol (Inderal) (166, 169), bishydroxycoumarin (162),

phenyramidol (Analexin) (162) and salicylates (17). The hypoglycemic effects are antagonized by corticosteroids (77), diuretics (115, 163, 164) and guanethidine (Ismelin) (88, 89).

02585 Indomethacin

Indomethacin may pharmacologically elevate the activity of oral anticoagulants. (71) Indomethacin plasma levels may be increased by probenecid (Benemid) (128) and decreased by salicylates (53).

02623 Insulin

Insulin may be pharmacologically antagonized by guanethidine. (88, 89) Ethyl alcohol may prolong the action of insulin. (129) Glucocorticoids, thyroid, epinephrine and thiazide diuretics may increase insulin requirements. (115)

02674 Iron Salts

Iron salts should not be used simultaneously with allopurinol (Zyloprim). (140) Antacids may decrease iron absorption. (141) Iron salts may impair the absorption of oral tetracyclines. (183)

02712 Isoniazid

Isoniazid increases plasma levels of diphenylhydantoin. (106, 107) It may be antagonized by ethyl alcohol. (130) Concomitant use with disulfiram (Antabuse) (111) and meperidine (131) enhances incidence of adverse effects.

01716 D-Thyroxine

D-Thyroxine elevates the anticoagulant response to oral anticoagulants. (63)

02755 Isoproterenol

Isoproterenol is pharmacologically antagonized by propranolol (Inderal). (132)

02801 Kanamycin

Kanamycin in combination with other aminoglycoside antibiotics increases incidence of ototoxicity and nephrotoxicity. (120) Concomitant use with ethacrynic acid potentiates the ototoxicity. (116) It potentiates neuromuscular blockade of skeletal muscle relaxants. (97) When administered by the oral route it may increase the activity of oral anticoagulants. (64)

02852 Kaolin-Pectin

Kaolin-pectin mixtures inhibit the absorption of orally administered lincomycin (Lincocin), (133)

02895 Levodopa

Levodopa may be antagonized by methyldopa (137), pyridoxine (138, 139), reserpine (137) and phenothiazines (85). Concomitant use with MAOI may produce hypertension (136). Additive therapeutic effects may occur with amantadine (Symmetrel). (9)

02933 Lithium Carbonate

Lithium excretion is increased by aminophylline (134), sodium bicarbonate (134) and large doses of sodium chloride (135). Low sodium intake may precipitate lithium toxicity. (135)

02984 Magnesium Salts

Magnesium ions administered parenterally potentiate the neuromuscular blockade of skeletal muscle relaxants. (142)

03034 Meperidine

Meperidine should not be used simultaneously with isoniazid (131) and MAOI (25) - it enhances incidence of adverse effects. It is potentiated by other CNS depressants.

03077 Meprobamate

Meprobamate (Equanil, Miltown) is potentiated by ethyl alcohol. (180, 181)

03115 Mercaptopurine

Mercaptopurine (Purinethol) is potentiated by allopurinol (Zyloprim). (11, 58)

03166 Metaraminol

Metaraminol (Aramine) is pharmacologically potentiated by MAOI. (23)

03204 Methenamine Compounds

Methenamine compounds exhibit optimum activity in a

urine ph of 5.5 or lower. Urine acidifying agents are useful adjuncts while urine alkalinizers decrease activity. (143) Concomitant use with sulfonamides frequently results in crystalluria and the formation of a precipitate. (143, 144 145)

03247 Methoxyflurane

Methotrexate serum levels are elevated by diphenylhydantoin (108), salicylates (16, 146, 147) and sulfonamides (16, 146, 147). It may impair the immunological response to smallpox vaccine, resulting in vaccina. (148)

03298 Methotrimeprazine

Methotrimeprazine (Levoprome) potentiates the effects of antihypertensive agents (149), other CNS depressants (149) and skeletal muscle relaxants (149). It will produce extrapyramidal symptoms when used simultaneously with anticholinergics. (149)

03361 Methoxyflurane

Methoxyflurane anesthesia in conjunction with tetracycline therapy increases incidence of nephrotoxic effects. (93)

03344 Methyldopa

Methyldopa may antagonize the therapeutic effects of levodopa (137). Additive hypotensive effects may occur with propranolol (Inderal) (84, 150), procainamide (Pronestyl)

(125, 168), methotrimeprazine (Levoprome) (149) and thiazide diuretics (184).

03387 Methlyphenidate

Methylphenidate (Ritalin) potentiates tricyclic antidepressants. (34) It may be potentiated by MAOI. (20, 151) It antagonizes the pharmacological effects of guanethidine (Ismelin). (40, 122, 123)

03425 Metronidazole

Metronidazole (Flagyl) should not be used simultaneously with disulfiram (Antabuse) (112, 113) or ethyl alcohol (31) due to the increased incidence of adverse effects.

03476 Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors potentiate the pharmacological effects of amphetamines (20), methylphenidate (Ritalin) (20, 151). tricyclic antidepressants (21), hypoglycemics (22) and sympathomimetics such as ephedrine (23), metaraminol (Aramine) (24), phenylephrine and phenylpropanolamine. Concomitant use with meperidine (25) or levodopa (136) increases incidence of adverse effects.

03514 Nafcillin

Nafcillin (Unipen) plasma levels are increased by concomitant use of probenecid (Benemid). (154)

03557 Neomycin

Neomycin in combination with other aminoglycoside antibiotics

increases incidence of ototoxicity and nephrotoxicity. (120) Concomitant use with ethacrynic acid potentiates the ototoxicity. (116) It potentiates neuromuscular blockade of skeletal muscle relaxants. (97) When administered by the oral route it may increase the activity of oral anticoagulants. (64)

03603 Nitroglycerin

Nitroglycerin may produce hypotension following combined use with ethyl alcohol. (27) Chronic administration of pentaerythritol tetranitrate (Peritrate) may produce a tolerance to nitroglycerin. (152, 153)

03697 Orphenadrine

Orphenadrine (Norflex) in combination with propoxyphene (Darvon) may produce mental confusion and anxiety. (169, 170)

03735 Oxyphenbutazone

Oxyphenbutazone (Tandearil) elevates the anticoagulant response to oral anticoagulants. (28, 39) Oxyphenbutazone plasma levels may be elevated by anabolic steroids. (155, 156)

03743 Penicillin G and Derivatives

Penicillin G and derivatives-plasma levels are elevated by probenecid (Benemid) (8, 43) and salicylates (14).

03751 Pentaerythritol Tetranitrate

Pentaerythritol tetranitrate (Peritrate) therapy may produce a tolerance to nitroglycerin. (152, 153)

03786 Phenothiazines

Phenothiazines may antagonize levodopa (85) and the central effects of amphetamines (41). Additive effects occur with concomitant use of other CNS depressants (161) and antihistamines (157). Additive cardiac depressant effects are possible with quinidine. (158, 159, 160) Procarbazine (Matulane) may potentiate the CNS depressant effects of phenothiazines. (48)

03824 Phenylbutazone

Phenylbutazone (Butazolidin) elevates the anticoagulant response to oral anticoagulants (28, 39) and potentiates the hypoglycemic response to sulfonylureas (2, 165). Phenylbutazone plasma levels may be elevated by anabolic steroids. (155, 156)

03867 Phenylephrine

Phenylephrine administered nasally or systemically may be potentiated by guanethidine (Ismelin) (124) and MAOI (23).

03905 Phenylpropanolamine

Phenylpropanolamine may be potentiated by MAOI. (23)

03956 Phenyramidol

Phenyramidol (Analexin) elevates the anticoagulant response to oral anticoagulants (72) and potentiates the activity of diphenylhydantoin (109) and sulfonylureas) (162).

03999 Polymyxin B

Polymyxin B (Aerosporin) enhances neuromuscular blockade of skeletal muscle relaxants. (97) In combination with other

aminoglycoside antibiotics it increases incidence of ototoxicity and nephrotoxicity. (120)

04230 Probenecid

Probenecid (Benemid) elevates plasma levels of aminosalicylic acid (81), dapsone (Avlosulfon) (103), cephalosporins (43, 77), penicillin G and derivatives (8, 43) and indomethacin (128). Salicylates inhibit uricosuric activity of probenecid. (19)

04073 Procainamide

Procainamide (Pronestyl) - additive hypotensive effects may occur with concomitant use of antihypertensive agents. (125, 168)

04138 Procarbazine

Procarbazine (Matulane) may potentiate the effects of phenothiazines and CNS depressants. (48) It may produce additive hypotensive effects with guanethidine (Ismelin). (48)

04170 Propoxyphene

Propoxyphene (Darvon) in combination with orphenadrine (Norflex) may produce mental confusion and anxiety. (169, 170)

04219 Propranolol

Propranolol (Inderal) may potentiate oral hypoglycemics (166, 167) and antihypertensives (84, 126). It antagonizes pharmacological actions of sympathomimetics. (132) Propranolol-induced adverse effects are antagonized by anticholinergics. (84) Additive cardiac depressant effects are possible with quinidine (171,

172) and phenothiazines (158, 159, 160)

04251 Pyridoxine

Pyridoxine (Vitamin B6) antagonizes the pharmacological effects of levodopa. (138, 139)

04308 Quinidine

Quinidine may potentiate guanethidine (127), oral anticoagulants (28, 185) and the neuromuscular blockade of muscle relaxants (173). It may be potentiated by anticholinergics (83). Acetazolamide (Diamox), sodium bicarbonate and thiazide diuretics increase renal reabsorption (5, 78, 175). Additive cardiac depressant effects are possible with propranolol (171, 172) and phenothiazines (158, 159, 160).

04340 Reserpine

Reserpine is potentiated by methotrimeprazine (Levoprome). (149) It may antagonize the effects of levodopa. (137)

04383 Salicylates

Salicylates elevate the anticoagulant response to oral anticoagulants (13), increase plasma levels of unbound penicillin G and derivatives (14) and potentiate methotrexate (16) and sulfonylureas (17). Salicylate plasma levels may be decreased by corticosteroids. (15) They may decrease serum levels of indomethacin (Indocin) (53) and inhibit uricosuric activity of sulfinpyrazone (Anturane) (18) and probenecid (Benemid) (19).

04421 Skeletal Muscle Relaxants

Surgical skeletal muscle relaxants are potentiated by aminoglycoside antibiotics (97), amphotericin B (82), furosemide (119), magnesium ions (142), methotrimeprazine (Levoprome) (149), quinidine (173) and thiazide diuretics (174). Echothiophate iodide potentiates the effects of succinylcholine. (114)

04472 Small Pox Vaccine

Small pox vaccination may result in generalized vaccina with concomitant use of methotrexate. (148)

04510 Sodium Bicarbonate

Sodium bicarbonate elevates serum levels of amphetamines (42), tricyclic antidepressants (33, 37) and quinidine (5, 78, 175) by enhancing renal reabsorption. It may antagonize methenamine compounds (143) and lithium carbonate (134) and decrease oral absorption of tetracyclines (91).

04553 Sodium Chloride

Sodium chloride in large doses may antagonize pharmacological effects of lithium carbonate. (135) Low sodium intake may precipitate lithium toxicity. (135)

04618 Sodium Polystyrene Sulfonate

Sodium polystyrene sulfonate resin (Kayexalate) binds magnesium and calcium ions found in antacids resulting in systemic alkalosis. (176)

04650 Streptomycin

Streptomycin in combination with aminoglycoside antibiotics increases incidence of ototoxicity and nephrotoxicity. (120) Ethacrynic acid potentiates the ototoxicity. (116) It potentiates neuromuscular blockade of skeletal muscle relaxants. (97)

04693 Sulfinpyrazone

Sulfinpyrazone (Anturane) induced uricosuria is inhibited by salicylates. (18)

04731 Sulfonamides

Sulfonamides may potentiate the hypoglycemic response to oral hypoglycemics (1) and elevate serum levels of methotrexate (16, 146, 147). Concomitant use with methenamine compounds frequently results in crystalluria and the formation of a precipitate. (143, 144, 145)

04782 Tetracyclines

Tetracycline absorption is decreased by antacids (90) containing divalent or trivalent cations, sodium bicarbonate (91) and iron salts (183). It may elevate anticoagulant response to oral anticoagulants (92) and potentiate nephrotoxic effects of methoxyflurane (Penthrane) (93).

04820 Thiazide Diuretics

Thiazide diuretics may precipitate digitalis toxicity (94, 95) and antagonize the effects of hypoglycemics (115, 163, 164). Neuro-

muscular blockade produced by surgical muscle relaxants may be enhanced. (174) Concomitant use with corticosteroids may result in excessive potassium loss. (162) They may produce additive hypotensive effects with guanethidine (Ismelin) (32) and methyldopa (Aldomet) (184).

04863 Thyroid Preparations

Thyroid preparations may potentiate the anticoagulant response to oral anticoagulants. (63) Cholestyramine decreases absorption by binding thyroxine and triiodothyronnine. (177) They may decrease activity of hypoglycemic agents. (115)

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APPENDIX III

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00124	Acetazolamide
00167	Ethyl Alcohol
00205	Allopurinol
00256	Alphaprodine
00299	Antacids
00337	Amantadine
00434	Aminophyllin
00515	Aminosalicylic Acid
00566	Ammonium Chloride
00604	Amphotericin B
00647	Ampicillin Hetacillin
00698	Amphetamine Sulfate Biphetamine-T Desbutal Dexamyl Dextroamphetamine Sulfate Eskatrol Methamphetamine HCL
00744	Angiotensin
00752	Ethylestrenol Methandriol Methandrostenolone Nandrolone Decanoate Nandrolone Phenpropionate Norethandrolone Oxymetholone Stanozolol
00787	Adiphenine HCL Alverine Citrate Atropine Sulfate Biperiden Cycrimine HCL Dibutoline Sulfate l-Hyoscyamine Sulfate Methylatropine Nitrate Piperidolate Scopolamine HBr Trihexyphenidyl Procyclidine HCL
00825	Acenocoumarol Ethyl Biscoumacetate Phenindione Phenprocoumon Warfarin Sodium

Message Code	Drug
00876	Amitriptyline HCL
	Desipramine HCL
	Doxepin HCL
	Imipramine
	Nortriptyline HCL
	Protriptyline HCL
00884	Cyproheptadine Hydrochloride
	Diphenhydramine Hydrochloride
	Methdilazine Hydrochloride
	Trimeprazine
	Tripelennamine
00892	Azapetine Hydrochloride
	Phenoxybenzamine Hydrochloride
	Tolazoline Hydrochloride
	Trimethaphen Camsylate
00914	Ascorbic Acid
00957	Amobarbital
	Aprobarbital
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	Barbital Sodium
	Butabarbital Sodium
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	Desbutal
	Dexamyl
	Hexobarbital
	Mephobarbital
	Pentobarbital Sodium
	Phenobarbital
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01139	Calcium Chloride, Injection
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01147	Carbenicillin
01236	Chloral Betaine
01317	Chloral Hydrate
01368	Chloramphenicol
01406	Chlormerodrin
	Chlorthalidone
	Meralluride
	Merethoxylline
	Mercaptomerin Sodium
	Mercurophylline
	Quinethazone
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01449	Cholestyramine
01481	Clofibrate
01546	Colistin
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	Fluprednisolone
	Hydrocortisone
	Methylprednisolone
	Paramethasone
	Prednisolone
	Prednisone
	Triamcinolone

Message Code	Drug
01627	Corticotropin
01678	Dapsone
01716	D-Thyroxine
01759	Acetyldigitoxin
	Deslanoside
	Digitalis
	Digitalis Glycosides
	Digitoxin
	Digoxin
	Lanatoside C
	Quabain
01791	Diphenylhydantoin
01848	Dipyridamole
01880	Disulfiram
01929	Echothiophate Iodide
01961	Ephedrine
02011	Epinephrine
02062	Benzestrol
	C-Quens
	Chlorotrianisene
	Dienestrol
	Diethylstilbestrol
	Diethylstilbestrol Diphosphate
	Estradiol
	Estradiol Benzoate
	Estradiol Dipropionate
	Estrone
	Ethinyl Estradiol
	Methallenestril
	Ortho-Novum
	Ovral
	Ovulen
	Polyestradiol Phosphate
	Promethestrol Dipropionate
02100	Ethacrynic Acid
02143	Ethchlorvynol
02194	Folic Acid
02232	Furosemide
02275	Gentamicin
02313	Glutethimide
02364	Glyceryl Guaiacolate
02402	Griseofulvin
02445	Guanethidine
02496	Heparin
02542	Acetohexamide
	Chlorpropamide
	Tolbutamide
	Tolinase
	Phenformin
02585	Indomethacin
02633	Insulin
02674	Ferrous Fumarate
	Ferrous Gluconate
	Ferrous Sulfate
02712	Isoniazid

Message Code	Drug
02755	Isoproterenol
02801	Kanamycin
02852	Kaolin-Pectin
02895	Levodopa
02933	Lithium Carbonate
02984	Magnesium Sulfate, Injection
03034	Meperidine
03077	Equagesic Meprobamate
03115	Mercaptopurine
03166	Metaraminol
03204	Methenamine Hippurate Methenamine Mandelate Methenamine Sulfosalicylate
03247	Methotrexate
03298	Methotrimeprazine
03344	Methyldopa
03361	Methoxyflurane
03387	Methylphenidate
03425	Metronidazole
03476	Isocarboxazid Nialamide
	Phenelzine Sulfate
	Tranylcypromine
03514	Nafcillin Sodium
03557	Neomycin Sulfate
03603	Nitroglycerin
03697	Norgesic Orphenadrine
03735	Oxyphenbutazone
03743	Penicillin G Phenoxymethyl Penicillin Procaine Penicillin
03751	Pentaerythritol Tetranitrate
03786	Acetophenazine Maleate Butaperazine Maleate Carphenazine Maleate Chlorpromazine HCL Combid Eskatrol Fluphenazine Enanthate Fluphenazine HCL Perphenazine Piperactazine Prochlorperazine HCL Promazine HCL

Message Code	Drug
	Promethazine HCL
	Thiopropazate Dihydrochloride
	Thioridazine HCL
	Trifluoperazine HCL
	Triflupromazine
03824	Butazolidin Alka
	Phenylbutazone
03867	Phenylephrine
03905	Naldecon
	Phenylpropanolamine
03956	Phenyramidol
03999	Polymyxin B
04030	Probenecid
04073	Procainamide
04138	Procarbazine
04170	Darvon Compound
	Darvon Compound-65
	Propoxyphene HCL
	Propoxyphene Napsylate
04219	Propranolol
04251	Pyridoxine
04308	Quinidine
04340	Diupres
	Hydropres
	Reserpine
	Ser-Ap-Es
04383	APC
	Aspirin
	Empirin
	Equagesic
	Norgesic
	Salicylamide
	Sodium Salicylate
04421	Dimethyl Tubocurarine Iodide
	Decamethonium Bromide
	Succinylcholine Chloride
	Tubocurarine Chloride
04472	Small Pox Vaccine
04510	Sodium Bicarbonate
04553	Sodium Chloride
04618	Sodium Polystyrene Sulfonate Resin
04660	Streptomycin
04693	Sulfinpyrazone
04731	Azo-Gantrisin
	Azo-Gantanol
	Sulfadiazine
	Sulfaethidole
	Sulfachlorpyridazine
	Sulfadimethoxine
	Sulfamerazine
	Sulfameter
	Sulfamethizole

Message Code	Drug
	Sulfamethoxazole
	Sulfamethoxypyridazine
	Sulfapyridine
	Sulfisoxazole
04782	Chlortetracycline
	Demethylchlortetracycline
	Doxycycline
	Methacycline
	Oxytetracycline
	Tetracycline
04820	Aldactazide
	Bendroflumethiazide
	Benzthiazide
	Chlorothiazide
	Cyclothiazide
	Diupres
	Dyazide
	Hydrochlorothiazide
	Hydroflumethiazide
	Hydropres
	Methyclorthiazide
	Polythiazide
	Ser-Ap-Es
	Trichlormethiazide
04863	Liothyronine
	Liotrix
	Levothyroxine
	Thyroid
	Thyroglobulin

APPENDIX IV

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APPENDIX V

Drug-Drug Interaction Printout

ACETAMINOPHEN ELEVATES THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS.

ACETAZOLAMIDE (DIAMOX), URINARY ALKALINIZING AGENT, ELEVATES SERUM LEVELS OF AMPHETAMINES, TRICYCLIC ANTIDEPRESSANTS AND QUINIDINE BY ENHANCING RENAL REABSORPTION. IT MAY ANTAGONIZE THE ACTIVITY OF METHENAMINE COMPOUNDS.

ETHYL ALCOHOL-ADDITIVE EFFECTS MAY BE SEEN WITH CNS DEPRESSANTS AND ANTIHISTAMINES. IT MAY ANTAGONIZE THE PHARMACOLOGICAL EFFECTS OF THE ORAL ANTICOAGULANTS AND DIPHENYLHYDANTOIN. IT MAY ENHANCE THE ADVERSE EFFECTS OF GUANETHIDINE, NITROGLYCERIN, DISULFIRAM (ANTABUSE), METRONIDAZOLE (FLAGYL) AND TRICYCLIC ANTIDEPRESSANTS. IT PROLONGS THE ACTION OF INSULIN.

ALLOPURINOL POTENTIATES THE EFFECTS OF BISHYDROXYCOUMARIN, AND MERCAPTOPURINE. IT MAY INCREASE HEPATIC IRON CONCENTRATION.

ANTACIDS CONTAINING DIVALENT AND TRIVALENT CATIONS DECREASE ORAL ABSORPTION OF TETRACYCLINES. ANTACIDS SHOULD NOT BE ADMINISTERED SIMULTANEOUSLY WITH ENTERIC COATED PRODUCTS. SODIUM POLYSTYRENE RESIN (KAYEXALATE) BINDS MAGNESIUM AND CALCIUM IONS FOUND IN ANTACIDS RESULTING IN SYSTEMIC ALKALOSIS.

AMANTADINE (SYMMETREL) POTENTIATES THE PHARMACOLOGICAL EFFECTS PRODUCED BY LEVODOPA.

AMINOPHYLLIN MAY IMPAIR THE THERAPEUTIC RESPONSE TO LITHIUM CARBONATE BY INCREASING THE RENAL EXCRETION OF LITHIUM IONS.

AMINOSALICYLIC ACID PLASMA LEVELS ARE ELEVATED BY PROBENECID (BENEMID)

AMMONIUM CHLORIDE (URINARY ACIDIFIER) MAY DECREASE RENAL REABSORPTION OF AMPHETAMINES AND TRICYCLIC ANTIDEPRESSANTS.

AMPHOTERICIN B (FUNGIZONE) MAY PRODUCE HYPOKALEMIA PRECIPITATING DIGITALIS TOXICITY. IT MAY POTENTIATE NEUROMUSCULAR BLOCKADE OF SKELETAL MUSCLE RELAXANTS.

AMPICILLIN PLASMA LEVELS ARE INCREASED BY CONCOMITANT USE OF PROBENECID (BENEMID).

AMPHETAMINES POTENTIATE MAOI AND ANTAGONIZE THE EFFECTS OF GUANETHIDINE. PHENOTHIAZINES MAY ANTAGONIZE THE CENTRAL EFFECTS OF AMPHETAMINES. URINE ACIDIFYING AGENTS DECREASE RENAL REABSORPTION AND URINARY ALKALINIZERS SUCH AS ACETAZOLAMIDE (DIAMOX), SODIUM BICARBONATE AND THIAZIDE DIURETICS INCREASE REABSORPTION.

ANGIOTENSIN AMIDE (HYPERTENSIN)-INDUCED ANTIDIURESIS AND ANTINATRIURESIS IS REVERSED BY ETHACRYNIC ACID (EDECRIN) AND FUROSEMIDE (LASIX).

ANABOLIC STEROIDS MAY POTENTIATE THE ACTIVITY OF ORAL ANTICOAGULANTS, PHENYLBUTAZONE (BUTAZOLIDIN) AND OXYPHENBUTAZONE (TANDEARIL). THEY MAY DECREASE INSULIN REQUIREMENTS IN DIABETICS.

ANTICHOLINERGIC DRUGS MAY POTENTIATE QUINIDINE AND THE SECONDARY PHARMACOLOGICAL EFFECTS OF ANTIHISTAMINES AND TRICYCLIC ANTIDEPRESSANTS. PROPRANOLOL (INDERAL)-INDUCED ADVERSE EFFECTS ARE ANTAGONIZED BY ANTICHOLINERGICS. THEY MAY PRODUCE EXTRAPYRAMIDAL SYMPTOMS WHEN USED SIMULTANEOUSLY WITH METHOTRIMEPRAZINE (LEVOPROME).

ORAL ANTICOAGULANTS ARE POTENTIATED BY ACETAMINOPHEN, ESTROGENS, ANABOLIC STEROIDS, CHLORAMPHENICOL, CHOLESTYRAMINE (CUEMID), CLOFIBRATE (ATROMID S), D-THYROXINE, PHENYLBUTAZONE (BUTAZOLIDIN) AND PHENYRAMIDOL (ANALEXIN). THEY MAY BE POTENTIATED BY AMINOGLYCOSIDE ANTIBIOTICS, DIPHENYLHYDANTOIN, INDOMETHACIN, QUINIDINE AND SALICYLATES. THEY ARE ANTAGONIZED BY ETHYL ALCOHOL, BARBITURATES, ETHCHLORVYNOL, GRISEOFULVIN AND GLUTETHIMIDE. THEY ARE VARIABLY AFFECTED BY CHLORAL HYDRATE.

TRICYCLIC ANTIDEPRESSANTS MAY POTENTIATE THE ADVERSE EFFECTS OF MAOI AND ETHYL ALCOHOL AND THE PHARMACOLOGICAL EFFECTS OF SYMPATHOMIMETICS, THYROID PREPARATIONS, ANTIHISTAMINES AND ANTICHOLINERGICS. THEY MAY ANTAGONIZE GUANETHIDINE. BARBITURATES APPEAR TO DECREASE THERAPEUTIC ACTIVITY. THEY ARE POTENTIATED BY METHYLPHENIDATE. URINE ACIDIFYING AGENTS DECREASE RENAL REABSORPTION AND URINE ALKALINIZING AGENTS INCREASE REABSORPTION.

ANTIHISTAMINES MAY PRODUCE ADDITIVE CNS DEPRESSANT EFFECTS WHEN USED CONCOMITANTLY WITH ETHYL ALCOHOL, BARBITURATES AND PHENOTHIAZINES. THEY MAY POTENTIATE THE PHARMACOLOGICAL ACTIVITY OF ANTICHOLINERGICS AND THE ADVERSE EFFECTS OF TRICYCLIC ANTIDEPRESSANTS.

ANTIHYPERTENSIVE AGENTS MAY BE POTENTIATED BY METHOTRIMEPRAZINE (LEVOPROME), PROCAINAMIDE (PRONESTYL) AND PROPRANOLOL (INDERAL).

ASCORBIC ACID (URINARY ACIDIFIER) MAY ANTAGONIZE AMPHETAMINES AND TRICYCLIC ANTIDEPRESSANTS.

BARBIURATES-ADDITIVE EFFECTS MAY BE SEEN WITH THE CONCOMITANT USE OF ANTIHISTAMINES, PHENOTHIAZINES AND OTHER CNS DEPRESSANTS. THEY MAY BE POTENTIATED BY PROCARBAZINE (MATULANE). THEY MAY DECREASE THERAPEUTIC EFFECTS OF ORAL ANTICOAGULANTS, TRICYCLIC ANTIDEPRESSANTS AND GRISEOFULVIN. THEY MAY VARIABLY EFFECT SERUM DIPHENYLHYDANTOIN LEVELS.

BISHYDROXYCOUMARIN MAY POTENTIATE THE SULFONYLUREAS AND INCREASE SERUM LEVELS OF DIPHENYLHYDANTOIN. IT IS POTENTIATED BY ACETAMINOPHEN, ESTROGENS, ANABOLIC STEROIDS, CHLORAMPHENICOL, CHOLESTYRAMINE (CUEMID), CLOFIBRATE (ATROMID S), D-THYROXINE, PHENYLBUTAZONE (BUTAZOLIDIN) AND PHENYRAMIDOL (ANALEXIN). IT MAY BE POTENTIATED BY AMINOGLYCOSIDE ANTIBIOTICS, DIPHENYLHYDANTOIN, INDOMETHACIN AND SALICYLATES. IT IS ANTAGONIZED BY ETHYL ALCOHOL, BARBITURATES, ETHCHLORVYNOL, GRISEOFULVIN AND GLUTETHIMIDE. IT IS VARIABLY AFFECTED BY CHLORAL HYDRATE.

BISACODYL (DULCOLAX) TABLETS SHOULD NOT BE TAKEN CONCOMITANTLY WITH ANTACIDS.

CALCIUM ICNS ADMINISTERED PARENTERALLY MAY PHARMACOLOGICALLY POTENTIATE DIGITALIS GLYCOSIDES.

CARBENICILLIN (PYOPEN, GEOPEN) PLASMA LEVELS MAY BE ELEVATED AND PROLONGED BY PROBENECID (BENEMID).

CEPHALOSPORINS, ALL-PLASMA LEVELS ARE ELEVATED BY PROBENECID (BENEMID). CONCOMITANT ADMINISTRATION OF CEPHALOTHIN AND COLISTIN INCREASES INCIDENCE OF NEPHROTOXICITY.

CHLORAL BETAINE (BETA-CHLOR) VARIABLY EFFECTS THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS.

CHLORAL HYDRATE VARIABLY EFFECTS THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS.

CHLORAMPHENICOL MAY POTENTIATE ORAL ANTICOAGULANTS, DIPHENYLHYDANTOIN AND SULFONYLUREAS.

DIURETICS PRODUCING POTASSIUM AND MAGNESIUM DEFICIENCIES MAY PRECIPITATE DIGITALIS TOXICITY. CONCOMITANT USE WITH CORTICOSTEROIDS MAY RESULT IN EXCESSIVE POTASSIUM LOSS. DIURETICS MAY ANTAGONIZE THE ACTIVITY OF ORAL HYPOGLYCEMICS.

CHOLESTYRAMINE (CUEMID) MAY ELEVATE THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS. IT DECREASES ABSORPTION OF THYROID PREPARATIONS BY BINDING THYROXINE AND TRIIODOTHYRONNINE.

CLOFIBRATE (ATROMID S) PHARMACOLOGICALLY ELEVATES THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS. IT MAY INHIBIT PLATELET ADHESIVENESS.

COLISTIN (COLIMYCIN) ENHANCES NEUROMUSCULAR BLOCKADE OF SKELETAL MUSCLE RELAXANTS. CONCOMITANT ADMINISTRATION OF PARENTERAL CEPHALOSPORINS INCREASES INCIDENCE OF NEPHROTOXICITY.

CORTICOSTEROIDS MAY BE POTENTIATED BY ESTROGENS. THEY MAY PHARMACOLOGICALLY ANTAGONIZE HYPOGLYCEMICS AND DECREASE SALICYLATE PLASMA LEVELS. DIPHENYLHYDANTOIN MAY DECREASE THERAPEUTIC RESPONSE TO CORTICOSTEROIDS. CONCOMITANT USE WITH DIURETICS MAY RESULT IN EXCESSIVE POTASSIUM LOSS.

CORTICOTROPIN (ACTH) MAY BE POTENTIATED BY ESTROGENS. IT MAY PHARMACOLOGICALLY ANTAGONIZE HYPOGLYCEMICS AND DECREASE SALICYLATE PLASMA LEVELS. DIPHENYLHYDANTOIN MAY DECREASE RESPONSE TO CORTICOSTEROIDS. CONCOMITANT USE WITH DIURETICS MAY RESULT IN EXCESSIVE POTASSIUM LOSS.

DAPSONE (AVLOSULFON) PLASMA LEVELS ARE INCREASED BY PROBENECID (BENEMID).

DIGITALIS GLYCOSIDES ARE PHARMACOLOGICALLY POTENTIATED BY PARENTERAL CALCIUM PREPARATIONS AND DIURETICS PRODUCING POTASSIUM AND MAGNESIUM DEFICIENCIES. AMPHOTERICIN B (FUNGIZONE) MAY PRODUCE HYPOKALEMIA PRECIPITATING DIGITALIS TOXICITY. SYMPATHOMIMETICS MAY INCREASE INCIDENCE OF CARDIAC ARRHYTHMIAS.

DIPHENYLHYDANTOIN IS POTENTIATED BY CHLORAMPHENICOL, DISULFIRAM (ANTABUSE) AND ISONIAZID. IT MAY BE ANTAGONIZED BY ETHYL ALCOHOL AND PHENYRAMIDOL (ANALEXIN). IT MAY POTENTIATE ORAL ANTICOAGULANTS AND METHOTREXATE. IT MAY DECREASE THE THERAPEUTIC RESPONSE TO CORTICOSTEROIDS.

DIPYRIDAMOLE (PERSANTINE) MAY POTENTIATE THE ANTICOAGULANT ACTIVITY OF HEPARIN.

DISULFIRAM (ANTABUSE) POTENTIATES DIPHENYLHYDANTOIN. CONCOMITANT USE WITH ISONIAZID, ETHYL ALCOHOL AND METRONIDAZOLE (FLAGYL) ENHANCES THE INCIDENCE OF ADVERSE EFFECTS.

ECHOTHIOPHATE IODIDE (PHOSPHOLINE IODIDE) POTENTIATES THE PHARMACOLOGICAL EFFECTS OF SUCCINYLCHOLINE.

EPHEDRINE POTENTIATES HYPERTENSIVE REACTIONS WITH MAOI. IT ANTAGONIZES THE ADRENERGIC NEURON BLOCKADE PRODUCED BY GUANETHIDINE (ISMELIN).

EPINEPHRINE, AND TO A LESSER EXTENT, OTHER ADRENERGIC AGENTS MAY DECREASE ACTIVITY OF HYPOGLYCEMIC AGENTS.

ESTROGENS PHARMACOLOGICALLY ELEVATE THE ANTICOAGULANT ACTIVITY OF ORAL ANTICOAGULANTS. THEY MAY POTENTIATE CORTICOSTEROID ACTIVITY.

ETHACRYNIC ACID POTENTIATES OTOTOXICITY OF AMINOGLYCOSIDE ANTIBIOTICS. IT MAY PRODUCE POTASSIUM AND MAGNESIUM DEFICIENCIES PRECIPITATING DIGITALIS TOXICITY. CONCOMITANT USE WITH CORTICOSTEROIDS MAY ENHANCE POTASSIUM LOSS. IT MAY ANTAGONIZE THE ACTIVITY OF ORAL HYPOGLYCEMICS.

ETHCHLORVYNOL (PLACIDYL) ANTAGONIZES THE ANTICOAGULANT ACTIVITY OF ORAL ANTICOAGULANTS.

FOLIC ACID ANTAGONIZES THE ANTINEOPLASTIC ACTIVITY OF METHOTREXATE.

FUROSEMIDE MAY PRODUCE POTASSIUM AND MAGNESIUM DEFICIENCIES PRECIPITATING DIGITALIS TOXICITY. CONCOMITANT USE WITH CORTICOSTEROIDS MAY ENHANCE POTASSIUM LOSS. IT ENHANCES THE EFFECTS OF TUBOCURARINE. IT MAY ANTAGONIZE THE ACTIVITY OF ORAL HYPOGLYCEMICS.

GENTAMICIN IN COMBINATION WITH OTHER AMINOGLYCOSIDE ANTIBIOTICS INCREASES INCIDENCE OF OTOTOXICITY AND NEPHROTOXICITY. ETHACRYNIC ACID POTENTIATES THE OTOTOXICITY. IT ENHANCES THE BLOCKADE OF SKELETAL MUSCLE RELAXANTS.

GLUTETHIMIDE (DORIDEN) DECREASES ANTICOAGULLANT RESPONSE TO ORAL ANTICOAGULANTS.

GLYCERYL GUAIACOLATE MAY POTENTIATE THE ANTICOAGULANT ACTIVITY OF HEPARIN.

GRISEOFULVIN MAY DECREASE THE ANTICOAGULANT ACTIVITY OF ORAL ANTI-COAGULANTS. IT IS ANTAGONIZED BY BARBITURATES WHICH MAY IMPAIR ABSORPTION.

GUANETHIDINE MAY BE POTENTIATED BY PROCAINAMIDE, PROPRANOLOL AND QUINIDINE. IT IS ANTAGONIZED BY AMPHETAMINES, TRICYCLIC ANTIDEPRESSANTS, EPHEDRINE AND METHYLPHENIDATE. IT MAY POTENTIATE PHENYLEPHRINE AND DECREASE ACTIVITY OF HYPOGLYCEMICS. ETHYL ALCOHOL AND METHOTRIMEPRAZINE (LEVOPROME), PROCARBAZINE (MATULANE) AND THIAZIDE DIURETICS MAY POTENTIATE ORTHOSTATIC HYPOTENSION.

HEPARIN INDUCED ANTICOAGULANT ACTIVITY MAY BE ENHANCED BY DIPYRIDAMOLE (PERSANTINE) AND GLYCERYL GUAIACOLATE.

ORAL HYPOGLYCEMIC AGENTS MAY BE POTENTIATED BY CHLORAMPHENICOL, MAOI, PHENYLBUTAZONE (BUTAZOLIDIN) , PROPRANOLOL (INDERAL), BISHYDROXYCOUMARIN, PHENYRAMIDOL (ANALEXIN) AND SALICYLATES. THE HYPOGLYCEMIC EFFECTS ARE ANTAGONIZED BY CORTICOSTEROIDS, DIURETICS AND GUANETHIDINE (ISMELIN).

INDOMETHACIN MAY PHARMACOLOGICALLY ELEVATE THE ACTIVITY OF ORAL ANTI-COAGULANTS. INDOMETHACIN PLASMA LEVELS MAY BE INCREASED BY PROBENECID (BENEMID) AND DECREASED BY SALICYLATES.

INSULIN MAY BE PHARMACOLOGICALLY ANTAGONIZED BY GUANETHIDINE. ETHYL ALCOHOL MAY PROLONG THE ACTION OF INSULIN. GLUCOCORTICOIDS, THYROID, EPINEPHRINE AND THIAZIDE DIURETICS MAY INCREASE INSULIN REQUIREMENTS.

IRON SALTS SHOULD NOT BE USED SIMULTANEOUSLY WITH ALLOPURINOL (ZYLOPRIM). ANTACIDS MAY DECREASE IRON ABSORPTION. IRON SALTS MAY IMPAIR THE ABSORPTION OF ORAL TETRACYCLINES.

ISONIAZID INCREASES PLASMA LEVELS OF DIPHENYLHYDANTOIN. IT MAY BE ANTAGONIZED BY ETHYL ALCOHOL. CONCOMITANT USE WITH DISULFIRAM (ANTABUSE) AND MEPERIDINE ENHANCES INCIDENCE OF ADVERSE EFFECTS.

D-THYROXINE ELEVATES THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS.

ISOPROTERENOL IS PHARMACOLOGICALLY ANTAGONIZED BY PROPRANOLOL (INDERAL)

KANAMYCIN IN COMBINATION WITH OTHER AMINOGLYCOSIDE ANTIBIOTICS INCREASES INCIDENCE OF OTOTOXICITY AND NEPHROTOXICITY. CONCOMITANT USE WITH ETHACRYNIC ACID POTENTIATES THE OTOTOXICITY. IT POTENTIATES NEURO-MUSCULAR BLOCKADE OF SKELETAL MUSCLE RELAXANTS. WHEN ADMINISTERED BY THE ORAL ROUTE IT MAY INCREASE THE ACTIVITY OF ORAL ANTICOAGULANTS.

KAOLIN-PECTIN MIXTURES INHIBIT THE ABSORPTION OF ORALLY ADMINISTERED LINCOMYCIN (LINCOCIN).

LEVODOPA MAY BE ANTAGONIZED BY METHYLDOPA, PYRIDOXINE, RESERPINE AND PHENOTHIAZINES. CONCOMITANT USE WITH MAOI MAY PRODUCE HYPERTENSION. ADDITIVE THERAPEUTIC EFFECTS MAY OCCUR WITH AMANTADINE (SYMMETREL).

LITHIUM EXCRETION IS INCREASED BY AMINOPHYLLINE, SODIUM BICARBONATE AND LARGE DOSES OF SODIUM CHLORIDE. LOW SODIUM INTAKE MAY PRECIPITATE LITHIUM TOXICITY.

MAGNESIUM IONS ADMINISTERED PARENTERALLY POTENTIATE THE NEUROMUSCULAR BLOCKADE OF SKELETAL MUSCLE RELAXANTS.

MEPERIDINE SHOULD NOT BE USED SIMULTANEOUSLY WITH ISONIAZID AND MAOI- IT ENHANCES INCIDENCE OF ADVERSE EFFECTS. IT IS POTENTIATED BY OTHER CNS DEPRESSANTS.

MEPROBAMATE (EQUANIL,MILTOWN) IS POTENTIATED BY ETHYL ALCOHOL.

MERCAPTOPURINE (PURINETHOL) IS POTENTIATED BY ALLOPURINOL (ZYLOPRIM).

METARAMINOL (ARAMINE) IS PHARMACOLOGICALLY POTENTIATED BY MAOI.

METHENAMINE COMPOUNDS EXHIBIT OPTIMUM ACTIVITY IN A URINE PH OF 5.5 OR LOWER. URINE ACIDIFYING AGENTS ARE USEFUL ADJUNCTS WHILE URINE ALKALINIZERS DECREASE ACTIVITY. CONCOMITANT USE WITH SULFONAMIDES FREQUENTLY, RESULTS IN CRYSTALLURIA AND THE FORMATION OF A PRECIPITATE.

METHOTREXATE SERUM LEVELS ARE ELEVATED BY DIPHENYLHYDANTOIN, SALICYLATES AND SULFONAMIDES. IT MAY IMPAIR THE IMMUNOLOGICAL RESPONSE TO SMALLPOX VACCINE, RESULTING IN VACCINA.

METHOTRIMEPRAZINE (LEVOPROME) POTENTIATES THE EFFECTS OF ANTIHYPERTENSIVE AGENTS, OTHER CNS DEPRESSANTS AND SKELETAL MUSCLE RELAXANTS. IT WILL PRODUCE EXTRAPYRAMIDAL SYMPTOMS WHEN USED SIMULTANEOUSLY WITH ANTICHOLINERGICS.

METHYOXYFLURANE ANESTHESIA IN CONJUNCTION WITH TETRACYCLINE THERAPY INCREASES INCIDENCE OF NEPHROTOXIC EFFECTS.

METHYLDOPA MAY ANTAGONIZE THE THERAPEUTIC EFFECTS OF LEVODOPA. ADDITIVE HYPOTENSIVE EFFECTS MAY OCCUR WITH PROPRANOLOL (INDERAL), PROCAINAMIDE (PRONESTYL), METHOTRIMEPRAZINE (LEVOPROME) AND THIAZIDE DIURETICS.

METHYLPHENIDATE (RITALIN) POTENTIATES TRICYCLIC ANTIDEPRESSANTS. IT MAY BE POTENTIATED BY MAOI. IT ANTAGONIZES THE PHARMACOLOGICAL EFFECTS OF GUANETHIDINE (ISMELIN).

METRONIDAZOLE (FLAGYL) SHOULD NOT BE USED SIMULTANEOUSLY WITH DISULFIRAM (ANTABUSE) OR ETHYL ALCOHOL DUE TO THE INCREASED INCIDENCE OF ADVERSE EFFECTS.

MONOAMINE OXIDASE INHIBITORS POTENTIATE THE PHARMACOLOGICAL EFFECTS OF AMPHETAMINES, METHYLPHENIDATE (RITALIN), TRICYCLIC ANTIDEPRESSANTS, HYPOGLYCEMICS AND SYMPATHOMIMETICS SUCH AS EPHEDRINE, METARAMINOL (ARAMINE), PHENYLEPHRINE AND PHENYLPROPANOLAMINE. CONCOMITANT USE WITH MEPERIDINE OR LEVODOPA INCREASES INCIDENCE OF ADVERSE EFFECTS.

NAFCILLIN (UNIPEN) PLASMA LEVELS ARE INCREASED BY CONCOMITANT USE OF PROBENECID (BENEMID).

NEOMYCIN IN COMBINATION WITH OTHER AMINOGLYCOSIDE ANTIBIOTICS INCREASES INCIDENCE OF OTOTOXICITY AND NEPHROTOXICITY. CONCOMITANT USE WITH ETHACRYNIC ACID POTENTIATES THE OTOTOXICITY. IT POTENTIATES NEUROMUSCULAR BLOCKADE OF SKELETAL MUSCLE RELAXANTS. WHEN ADMINISTERED BY THE ORAL ROUTE IT MAY INCREASE THE ACTIVITY OF ORAL ANTICOAGULANTS.

NITROGLYCERIN MAY PRODUCE HYPOTENSION FOLLOWING COMBINED USE WITH ETHYL ALCOHOL. CHRONIC ADMINISTRATION OF PENTAERYTHRITOL TETRANITRATE (PERITRATE) MAY PRODUCE A TOLERANCE TO NITROGLYCERIN.

ORPHENADRINE (NORFLEX) IN COMBINATION WITH PROPOXYPHENE (DARVON) MAY PRODUCE MENTAL CONFUSION AND ANXIETY.

OXYPHENBUTAZONE (TANDEARIL) ELEVATES THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS. OXYPHENBUTAZONE PLASMA LEVELS MAY BE ELEVATED BY ANABOLIC STEROIDS.

PENICILLIN G AND DERIVATIVES-PLASMA LEVELS ARE ELEVATED BY PROBENECID (BENEMID) AND SALICYLATES.

PENTAERYTHRITOL TETRANITRATE (PERITRATE) THERAPY MAY PRODUCE A TOLERANCE TO NITROGLYCERIN.

PHENOTHIAZINES MAY ANTAGONIZE LEVODOPA AND THE CENTRAL EFFECTS OF AMPHETAMINES. ADDITIVE EFFECTS OCCUR WITH CONCOMITANT USE OF OTHER CNS DEPRESSANTS AND ANTIHISTAMINES. ADDITIVE CARDIAC DEPRESSANT EFFECTS ARE POSSIBLE WITH QUINIDINE. PROCARBAZINE (MATULANE) MAY POTENTIATE THE CNS DEPRESSANT EFFECTS OF PHENOTHIAZINES.

PHENYLBUTAZONE (BUTAZOLIDIN) ELEVATES THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS AND POTENTIATES THE HYPOGLYCEMIC RESPONSE TO SULFONYLUREAS. PHENYLBUTAZONE PLASMA LEVELS MAY BE ELEVATED BY ANABOLIC STEROIDS.

PHENYLEPHRINE ADMINISTERED NASALLY OR SYSTEMICALLY MAY BE POTENTIATED BY GUANETHIDINE (ISMELIN) AND MAOI.

PHENYLPROPANOLAMINE MAY BE POTENTIATED BY MAOI.

PHENYRAMIDOL (ANALEXIN) ELEVATES THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS AND POTENTIATES THE ACTIVITY OF DIPHENYLHYDANTOIN AND SULFONYLUREAS.

POLYMYXIN B (AEROSPORIN) ENHANCES NEUROMUSCULAR BLOCKADE OF SKELETAL MUSCLE RELAXANTS. IN COMBINATION WITH OTHER AMINOGLYCOSIDE ANTIBIOTICS IT INCREASES INCIDENCE OF OTOTOXICITY AND NEPHROTOXICITY.

PROBENECID (BENEMID) ELEVATES PLASMA LEVELS OF AMINOSALICYLIC ACID, DAPSONE (AVLOSULFON), CEPHALOSPORINS, PENICILLIN G AND DERIVATIVES AND INDOMETHACIN. SALICYLATES INHIBIT URICOSURIC ACTIVITY OF PROBENECID.

PROCAINAMIDE (PRONESTYL) - ADDITIVE HYPOTENSIVE EFFECTS MAY OCCUR WITH CONCOMITANT USE OF ANTIHYPERTENSIVE AGENTS.

PROCARBAZINE (MATULANE) MAY POTENTIATE THE EFFECTS OF PHENOTHIAZINES AND CNS DEPRESSANTS. IT MAY PRODUCE ADDITIVE HYPOTENSIVE EFFECTS WITH GUANETHIDINE (ISMELIN).

PROPOXYPHENE (DARVON) IN COMBINATION WITH ORPHENADRINE (NORFLEX) MAY PRODUCE MENTAL CONFUSION AND ANXIETY.

PROPRANOLOL (INDERAL) MAY POTENTIATE ORAL HYPOGLYCEMICS AND ANTI-HYPERTENSIVES. IT ANTAGONIZES PHARMACOLOGICAL ACTIONS OF SYMPATHOMIMETICS. PROPRANOLOL-INDUCED ADVERSE EFFECTS ARE ANTAGONIZED BY ANTICHOLINERGICS. ADDITIVE CARDIAC DEPRESSANT EFFECTS ARE POSSIBLE WITH QUINIDINE AND PHENO-THIAZINES.

PYRIDOXINE (VITAMIN B6) ANTAGONIZES THE PHARMACOLOGICAL EFFECTS OF LEVODOPA.

QUINIDINE MAY POTENTIATE GUANETHIDINE, ORAL ANTICOAGULANTS AND THE NEUROMUSCULAR BLOCKADE OF MUSCLE RELAXANTS. IT MAY BE POTENTIATED BY ANTICHOLINERGICS. ACETAZOLAMIDE (DIAMOX), SODIUM BICARBONATE AND THIAZIDE DIURETICS INCREASE RENAL REABSORPTION. ADDITIVE CARDIAC DEPRESSANT EFFECTS ARE POSSIBLE WITH PROPRANOLOL.

RESERPINE IS POTENTIATED BY METHOTRIMEPRAZINE (LEVOPROME). IT MAY ANTAGONIZE THE EFFECTS OF LEVODOPA.

SALICYLATES ELEVATE THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS, INCREASE PLASMA LEVELS OF UNBOUND PENICILLIN G AND DERIVATIVES AND POTENTIATE METHOTREXATE AND SULFONYLUREAS. SALICYLATE PLASMA LEVELS MAY BE DECREASED BY CORTICOSTEROIDS. THEY MAY DECREASE SERUM LEVELS OF INDOMETHACIN (INDOCIN) AND INHIBIT URICOSURIC ACTIVITY OF SULFINPYRAZONE (ANTURANE) AND PROBENECID (BENEMID).

SURGICAL SKELETAL MUSCLE RELAXANTS ARE POTENTIATED BY AMINOGLYCOSIDE ANTIBIOTICS, AMPHOTERICIN B, FUROSEMIDE, MAGNESIUM IONS, METHOTRIMEPRAZINE (LEVOPROME), QUINIDINE AND THIAZIDE DIURETICS. ECHOTHIOPHATE IODIDE POTENTIATES THE EFFECTS OF SUCCINYLCHOLINE.

SMALL POX VACCINATION MAY RESULT IN GENERALIZED VACCINA WITH CONCOMITANT USE OF METHOTREXATE.

SODIUM BICARBONATE ELEVATES SERUM LEVELS OF AMPHETAMINES, TRICYCLIC ANTIDEPRESSANTS AND QUINIDINE BY ENHANCING RENAL REABSORPTION. IT MAY ANTAGONIZE METHENAMINE COMPOUNDS AND LITHIUM CARBONATE AND DECREASE ORAL ABSORPTION OF TETRACYCLINES.

SODIUM CHLORIDE IN LARGE DOSES MAY ANTAGONIZE PHARMACOLOGICAL EFFECTS OF LITHIUM CARBONATE. LOW SODIUM INTAKE MAY PRECIPITATE LITHIUM TOXICITY.

SODIUM POLYSTYRENE SULFONATE RESIN (KAYEXALATE) BINDS MAGNESIUM AND CALCIUM IONS FOUND IN ANTACIDS RESULTING IN SYSTEMIC ALKALOSIS.

STREPTOMYCIN IN COMBINATION WITH AMINOGLYCOSIDE ANTIBIOTICS INCREASES INCIDENCE OF OTOTOXICITY AND NEPHROTOXICITY. ETHACRYNIC ACID POTENTIATES THE OTOTOXICITY. IT POTENTIATES NEUROMUSCULAR BLOCKADE OF SKELETAL MUSCLE RELAXANTS.

SULFINPYRAZONE (ANTURANE) INDUCED URICOSURIA IS INHIBITED BY SALICYLATES.

SULFONAMIDES MAY POTENTIATE THE HYPOGLYCEMIC RESPONSE TO ORAL HYPOGLYCEMICS AND ELEVATE SERUM LEVELS OF METHOTREXATE. CONCOMITANT USE WITH METHENAMINE COMPOUNDS FREQUENTLY RESULTS IN CRYSTALLURIA AND THE FORMATION OF A PRECIPITATE.

TETRACYCLINE ABSORPTION IS DECREASED BY ANTACIDS CONTAINING DIVALENT OR TRIVALENT CATIONS, SODIUM BICARBONATE AND IRON SALTS. IT MAY ELEVATE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS AND POTENTIATE NEPHROTOXIC EFFECTS OF METHOXYFLURANE (PENTHRANE).

THIAZIDE DIURETICS MAY PRECIPITATE DIGITALIS TOXICITY AND ANTAGONIZE THE EFFECTS OF HYPOGLYCEMICS. NEUROMUSCULAR BLOCKADE PRODUCED BY SURGICAL MUSCLE RELAXANTS MAY BE ENHANCED. CONCOMITANT USE WITH CORTICOSTEROIDS MAY RESULT IN EXCESSIVE POTASSIUM LOSS. THEY MAY PRODUCE ADDITIVE HYPOTENSIVE EFFECTS WITH GUANETHIDINE (ISMELIN) AND METHYLDOPA (ALDOMET).

THYROID PREPARATIONS MAY POTENTIATE THE ANTICOAGULANT RESPONSE TO ORAL ANTICOAGULANTS. CHOLESTYRAMINE DECREASES ABSORPTION BY BINDING THYROXINE AND TRIIODOTHYRONNINE. THEY MAY DECREASE ACTIVITY OF HYPOGLYCEMIC AGENTS.

APPENDIX VI

Computer Program

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LINE NO. SEQ. NO.          SOURCE STATEMENT                          CBD CL3-7 03/20/72

     1   OC1010 IDENTIFICATION DIVISION.
     2   OC1020 PROGRAM-ID. 'CDIRPT'.
     3   001030 AUTHOR. P E PLATIAU & C D MAHONEY.
     4   OC1040 REMARKS. SAMPLE PROGRAM FOR RETRIEVAL OF DRUG-DRUG INTERACTION
     5   OC1050         SUMMARIES WITH SAMPLE PROFILE.
     6   OC1060 ENVIRONMENT DIVISION.
     7   OC1070 CONFIGURATION SECTION.
     8   001080 SOURCE-COMPUTER. IBM-360 E30.
     9   001090 OBJECT-COMPUTER. IBM-360 E30.
    10   OC1100 INPUT-OUTPUT SECTION.
    11   OC1110 FILE-CONTROL.
    12   OC1120     SELECT CARD ASSIGN TO 'SYS004' UNIT-RECORD 2540R.
    13   OC1130     SELECT PRINT ASSIGN TO 'SYS005' UNIT-RECORD 1403.
    14   OC1140     SELECT DISK ASSIGN TO 'SYS013' DIRECT-ACCESS 2314
    15   OC1150         ACCESS IS RANDOM, ORGANIZATION IS INDEXED,
    16   OC1160         RESERVE NO ALTERNATE AREA, SYMBOLIC KEY IS REC-ID,
    17   OC1170         RECORD KEY IS DSK-NO.
    18   OC2010 DATA DIVISION.
    19   OC2020 FILE SECTION.
    20   002030 FD CARD
    21   002040     RECORD CONTAINS 80 CHARACTERS, LABEL RECORD IS OMITTED,
    22   002050     DATA RECORD IS CD, RECORDING MODE IS F.
    23   002060 01  CD.
    24   002061     02  CD-IN          PICTURE X(79).
    25   002062     02  CODE               PICTURE X.
    26   002063           88  HED  VALUE 'A'.
    27   002064           88  MED  VALUE 'B'.
    28   002065           88  DAT  VALUE 'C'.
    29   OC2070 FD PRINT
    30   002080     RECORD CONTAINS 133 CHARACTERS, LABEL RECORD IS OMITTED,
    31   002090     DATA RECORD IS PRT, RECORDING MODE IS F.
    32   OC2100 01 PRT                PICTURE X(133).
    33   OC2110 FD DISK
    34   OC2120     RECORD CONTAINS 671 CHARACTERS, LABEL RECORD IS STANDARD,
    35   OC2130     DATA RECORD IS DSK, RECORDING MODE IS F.
    36   OC2140 01 DSK.
    37   OC2150     02 DSK-NO          PICTURE X(5).
    38   OC2160     02 MSG, OCCURS 9 TIMES.
    39   OC2170         03 DSK-MSG PICTURE X(74).
    40   003010 WORKING-STORAGE SECTION.
    41   003020     77  A              PICTURE S9999   COMPUTATIONAL VALUE 0.
    42   003030     77  B              PICTURE S9999   COMPUTATIONAL VALUE 0.
    43   003040     77  C              PICTURE S9999   COMPUTATIONAL VALUE 0.
    44   003050     77  RDSW           PICTURE 99      COMPUTATIONAL-3 VALUE 1.
    45   003060     77  LIN-CNT        PICTURE 99      COMPUTATIONAL-3 VALUE 0.
    46   003070     77  CC             PICTURE X.
    47   003080     77  PAG-CNT        PICTURE 99      COMPUTATIONAL-3 VALUE 0.
    48   003090     77  NAME-STOR      PICTURE X(21).
    49   003100     77  PT-NO-STOR     PICTURE 9(7)    COMPUTATIONAL-3 VALUE 0.
    50   003110     77  PT-RM-STOR     PICTURE XXX.
    51   003120     77  REC-ID         PICTURE X(5).
    52   003125     77  DAY-STOR       PICTURE XX.
    53   003130 01  TABLE.
    54   003140     02 LINE, OCCURS 30 TIMES.
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LINE NO. SEQ. NO.          SOURCE STATEMENT

      55   0C3150          03  TBL-NO  PICTURE X(5).
      56   0C3160 01  HOSP-HED.
      57   0C3170      02  FILLER      PICTURE X(29)   VALUE SPACES.
      58   0C3180      02  TITLE       PICTURE X(22).
      59   0C3190      02  FILLER      PICTURE X(82)   VALUE SPACES.
      60   0C4010 01  PT-HED.
      61   0C4020      02  FILLER      PICTURE X(12)   VALUE SPACES.
      62   0C4030      02  FILLER      PICTURE X(35)   VALUE
      63   0C4040      'CUMULATIVE MEDICATION PROFILE FOR '.
      64   0C4050      02  PRT-NAM     PICTURE X(21).
      65   0C4060      02  FILLER      PICTURE X(65)   VALUE SPACES.
      66   0C4070 01  UNDERLIN1.
      67   0C4080      02  FILLER      PICTURE X(47)   VALUE SPACES.
      68   0C4090      02  FILLER      PICTURE X(21)   VALUE ALL '-'.
      69   0C4100      02  FILLER      PICTURE X(65)   VALUE SPACES.
      70   0C4110 01  PT-HED1.
      71   0C4120      02  FILLER      PICTURE X(12)   VALUE SPACES.
      72   0C4130      02  FILLER      PICTURE X(4)    VALUE 'NO. '.
      73   0C4140      02  PT-NO-PRT   PICTURE 9(7).
      74   0C4150      02  FILLER      PICTURE X(16)   VALUE '      ROOM    '.
      75   0C4160      02  PT-RM-PRT   PICTURE XXX.
      76   0C4170      02  FILLER      PICTURE X(16)   VALUE '         AGE    '.
      77   0C4180      02  PT-AG-PRT   PICTURE 99.
      78   0C4190      02  FILLER      PICTURE X(64)   VALUE SPACES.
      79   0C5010 01  COL-HED.
      80   0C5020      02  FILLER      PICTURE X(80)   VALUE
      81   0C5030 '    START  STOP   MEDICATION ORDERED
      82   0C5040-     ' PHYSICIAN      '.
      83   0C5050      02  FILLER      PICTURE X(53)   VALUE SPACES.
      84   0C5060 01  UNDERLIN2.
      85   0C5070      02  FILLER      PICTURE X(80)   VALUE
      86   0C5080 '    -----  ----   ------------------
      87   0C5090-     ' ---------      '.
      88   0C5100      02  FILLER      PICTURE X(53)   VALUE SPACES.
      89   0C5110 01  PRT-LIN.
      90   0C5120      02  FILLER      PICTURE XXX     VALUE SPACES.
      91   0C5130      02  MTH-IN1     PICTURE XX.
      92   0C5140      02  FILLER      PICTURE X       VALUE '/'.
      93   0C5150      02  DAY-IN1     PICTURE XX.
      94   0C5160      02  FILLER      PICTURE XX      VALUE SPACES.
      95   0C5170      02  MTH-OUT1    PICTURE XX.
      96   0C5180      02  SLASH       PICTURE X.
      97   0C5190      02  DAY-OUT1    PICTURE XX.
      98   0C5200      02  FILLER      PICTURE XX      VALUE SPACES.
      99   0C5210      02  PRT-ORD     PICTURE X(46).
     100   0C5220      02  FILLER      PICTURE XX      VALUE SPACES.
     101   0C5230      02  PRT-MD      PICTURE X(12).
     102   0C5240      02  FILLER      PICTURE X(56)   VALUE SPACES.
     103   0C6010 01  PT-HED2.
     104   0C6020      02  FILLER      PICTURE XXX     VALUE SPACES.
     105   0C6030      02  PRT-NAM2    PICTURE X(21).
     106   0C6040      02  FILLER      PICTURE X(8)    VALUE '    NO. '.
     107   0C6050      02  PT-NO-PRT2  PICTURE 9(7).
     108   0C6060      02  FILLER    PICTURE X(17)   VALUE '         ROOM    '.
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LINE NO. SEQ. NO.          SOURCE STATEMENT
     109   006070      02  PT-RM-PRT2  PICTURE XXX.
     110   006080      02  FILLER      PICTURE X(12)   VALUE '       PAGE '.
     111   006090      02  PAGE-NO     PICTURE ZZ9.
     112   006100      02  FILLER      PICTURE X(59)   VALUE SPACES.
     113   006110 01  PT-HED3.
     114   006120      02  FILLER      PICTURE X(41)   VALUE
     115   006130      '     PROBABLE DRUG-DRUG INTERACTIONS FOR '.
     116   006140      02  PRT-NAM3    PICTURE X(21).
     117   006150      02  FILLER      PICTURE X(5)    VALUE ' NO. '.
     118   006160      02  PT-NO-PRT3  PICTURE 9(7).
     119   006170      02  FILLER      PICTURE X(59)   VALUE SPACES.
     120   007010 01  MESSG.
     121   007020      02  FILLER      PICTURE XXX     VALUE SPACES.
     122   007030      02  PRT-MSG     PICTURE X(74).
     123   007040      02  FILLER      PICTURE X(56)   VALUE SPACES.
     124   007050 01  TEL-HED.
     125   007060      02  FILLER      PICTURE X(80)   VALUE
     126   007070 '          FOR FURTHER INFORMATION CALL DRUG INFORMATION CENTER E
     127   007080-    'XT 1234          '.
     128   007090      02  FILLER      PICTURE X(53)   VALUE SPACES.
     129   007100 01  DATE-HED.
     130   007110      02  FILLER      PICTURE X(29)   VALUE SPACES.
     131   007120      02  FILLER      PICTURE X(15)   VALUE 'END OF PROFILE '.
     132   007130      02  DATE-STOR   PICTURE X(8).
     133   007140      02  FILLER      PICTURE X(52)   VALUE SPACES.
     134   008010 01  CD-AREA.
     135   008020      02  PT-DATA.
     136   008030          03  PT-NAM      PICTURE X(21).
     137   008035          03  PT-NO       PICTURE 9(7).
     138   008040          03  PT-RM       PICTURE XXX.
     139   008050          03  PT-AGE      PICTURE 99.
     140   008060          03  FILLER      PICTURE X(46).
     141   008070      02  MED-DATA REDEFINES PT-DATA.
     142   008080          03  MED-CRD     PICTURE X(46).
     143   008090          03  MSG-NO      PICTURE X(5).
     144   008100          03  DAT-IN.
     145   008110              04  MTH-IN   PICTURE XX.
     146   008120              04  DAY-IN   PICTURE XX.
     147   008130          03  DAT-OUT.
     148   008140              04  MTH-OUT  PICTURE XX.
     149   008150              04  DAY-OUT  PICTURE XX.
     150   008160          03  MD           PICTURE X(12).
     151   008170          03  FILLER       PICTURE X(8).
     152   008180      02  DAT-DATA REDEFINES MED-DATA.
     153   008190          03  DATE.
     154   008200              04  MTH      PICTURE XX.
     155   008210              04  FILLER   PICTURE X.
     156   008220              04  DAY      PICTURE XX.
     157   008230              04  FILLER   PICTURE X.
     158   008240              04  YR       PICTURE XX.
     159   008250          03  FILLER       PICTURE X(71).
     160   009010 PROCEDURE DIVISION.
     161   009020 START.
     162   009025     PERFORM TBL-BLNK VARYING A FROM 1 BY 1 UNTIL A > 30.
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LINE NO. SEQ. NO.          SOURCE STATEMENT

     163   009030      OPEN INPUT CARD DISK OUTPUT PRINT.
     164   009040 CORD.
     165   009050      READ CARD AT END GO TO EOJ.
     166   009055      MOVE CD-IN TO CD-AREA.
     167   009056      IF DAT GO TO DATE-SAV.
     168   009060      IF RDSW = 1 GO TO FIRST-RTN.
     169   009070      IF MED GO TO SUMRY.
     170   009080 PROFILE.
     171   009090      IF LIN-CNT , 26 PERFORM MED-RTN2.
     172   009095      MOVE MTH-IN TO MTH-IN1. MOVE DAY-IN TO DAY-IN1.
     173   009100      MOVE MED-CRD TO PRT-CRD. MOVE MD TO PRT-MD.
     174   009105      IF DAY-OUT = ' ' MOVE ' ' TO SLASH ELSE MOVE '/' TO SLASH.
     175   009110      MOVE MTH-OUT TO MTH-OUT1. MOVE DAY-OUT TO DAY-OUT1.
     176   009115      PERFORM RITE-LINE. IF DAY-OUT = ' ' GO TO CHK-RTN.
     177   009120      IF DAY-OUT ) DAY-STOR GO TO CORD ELSE GO TO CHK-RTN.
     178   009130 RITE-LINE.
     179   009135      MOVE PRT-LIN TO PRT. PERFORM RITE-RTN. ADD 1 TO LIN-CNT.
     180   009140 CHK-RTN.
     181   009150      IF MSG-NO = ' ' GO TO CORD.
     182   009160      PERFORM MSG-CHK VARYING A FROM 1 BY 1 UNTIL TBL-NO (A) = ' '.
     183   009180      MOVE MSG-NO TO TBL-NO (A). GO TO CORD.
     184   010010 FIRST-RTN.
     185   010020      IF MED GO TO CORD. MOVE 0 TO RDSW.
     186   010030      PERFORM MED-RTN1. GO TO CORD.
     187   010040 MED-RTN1.
     188   010050      MOVE 1 TO CC. MOVE '   MODERN HOSPITAL    ' TO TITLE.
     189   010060      MOVE HOSP-MED TO PRT. PERFORM RITE-RTN. MOVE 0 TO CC.
     190   010070      MOVE 'DEPARTMENT OF PHARMACY' TO TITLE. MOVE HOSP-MED TO PRT.
     191   010080      PERFORM RITE-RTN. MOVE PT-NAM TO PRT-NAM NAME-STOR.
     192   010090      MOVE PT-MED TO PRT. PERFORM RITE-RTN. MOVE ' ' TO CC.
     193   010100      MOVE UNDERLIN1 TO PRT. PERFORM RITE-RTN. MOVE 0 TO CC.
     194   010110      MOVE PT-NO TO PT-NO-STOR PT-NO-PRT.
     195   010120      MOVE PT-RM TO PT-RM-STOR PT-RM-PRT.
     196   010130      MOVE PT-AGE TO PT-AG-PRT.
     197   010140      MOVE PT-MED1 TO PRT. PERFORM RITE-RTN.
     198   010150      MOVE COL-MED TO PRT. PERFORM RITE-RTN. MOVE ' ' TO CC.
     199   010160      MOVE UNDERLIN2 TO PRT. PERFORM RITE-RTN.
     200   010170      MOVE 0 TO CC, A, B.
     201   010175      MOVE 5 TO LIN-CNT. MOVE 1 TO PAG-CNT.
     202   011010 MED-RTN2.
     203   011015      MOVE 'CONTINUED ON NEXT PAGE' TO TITLE. MOVE HOSP-MED TO PRT.
     204   011016      PERFORM RITE-RTN.
     205   011020      MOVE 1 TO CC. MOVE 0 TO LIN-CNT.
     206   011030      MOVE NAME-STOR TO PRT-NAM2.
     207   011040      MOVE PT-NO-STOR TO PT-NO-PRT2.
     208   011050      MOVE PT-RM-STOR TO PT-RM-PRT2.
     209   011060      ADD 1 TO PAG-CNT. MOVE PAG-CNT TO PAGE-NO.
     210   011070      MOVE PT-MED2 TO PRT. PERFORM RITE-RTN. MOVE 0 TO CC.
     211   011080 MED-RTN3.
     212   011090      MOVE 1 TO CC. MOVE 0 TO LIN-CNT.
     213   011100      MOVE NAME-STOR TO PRT-NAM3.
     214   011110      MOVE PT-NO-STOR TO PT-NO-PRT3.
     215   011120      MOVE PT-MED3 TO PRT. PERFORM RITE-RTN.
     216   011130 DATE-SAV.
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LINE NO. SEQ. NO.          SOURCE STATEMENT

     217   011140      MOVE DATE TO DATE-STOR. MOVE DAY TO DAY-STOR. GO TO CORD.
     218   012010 SUMRY.
     219   012020      MOVE DATE-HED TO PRT. PERFORM RITE-RTN.
     220   012040 SUMRY1.
     221   012050      PERFORM HED-RTN3.
     222   012060 SUMRY-RITE.
     223   012070      ADD 1 TO B. IF TBL-NO (B) = ' ' GO TO END-RPT.
     224   012080      MOVE TBL-NO (B) TO REC-ID. MOVE 0 TO CC.
     225   012090      READ DISK INVALID KEY GO TO SUMRY-RITE.
     226   012100      PERFORM DSK-RITE VARYING C FROM 1 BY 1 UNTIL DSK-MSG (C) =
     227   012110      ' '. ADD 1 TO LIN-CNT.
     228   012120      IF LIN-CNT . 26 GO TO SUMRY1 ELSE GO TO SUMRY-RITE.
     229   012130 END-RPT.
     230   012140      MOVE TEL-HED TO PRT. MOVE '-' TO CC.
     231   012150      PERFORM RITE-RTN. IF RDSW = 3 GO TO CLOSE1.
     232   012160      PERFORM TBL-BLNK VARYING A FROM 1 BY 1 UNTIL A , 30.
     233   012170      PERFORM HED-RTN1. GO TO CORD.
     234   013010 DSK-RITE.
     235   013020      MOVE DSK-MSG (C) TO PRT-MSG.
     236   013030      MOVE MESSG TO PRT. PERFORM RITE-RTN.
     237   013040      MOVE ' ' TO CC. ADD 1 TO LIN-CNT.
     238   013050 TBL-BLNK.
     239   013060      MOVE ' ' TO TBL-NO (A).
     240   013070 MSG-CHK.
     241   013080      IF MSG-NO = TBL-NO (A) GO TO CORD.
     242   013090 RITE-RTN.
     243   013100      WRITE PRT AFTER ADVANCING CC LINES.
     244   013110 EOJ.
     245   013120      MOVE 3 TO RDSW. GO TO SUMRY.
     246   013130 CLOSE1.
     247   013150      CLOSE CARD PRINT DISK.
     248   013160      STOP RUN.
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