Teaching Monograph

Tissue Reactions to Drugs

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Registry of Tissue Reactions to Drugs
The Armed Forces Institute of Pathology
Washington, D.C.

The American Journal of Pathology
Official publication of The American Association of
Pathologists and Bacteriologists and The American
Society for Experimental Pathology

Published by The American Association of Pathologists and Bacteriologists, Department of Pathology,
Duke University Medical Center, Durham, North Carolina

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Foreword to Teaching Monographs

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The Editorial Board

Tissue Reactions to Drugs

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A NEW FACET has been added to the practice of medicine in the last several decades: the adverse drug reaction (ADR). This has come about with the development and the use of many new and potent drugs and chemicals that have been added to the older armamentarium of therapeutic, diagnostic, and prophylactic agents.

As a generalization, there is hardly any drug or chemical that will not be associated with an adverse reaction at some time, at some place, and under some circumstance. Generally, there is a greater probability of the occurrence of ADRs with the more potent drugs, such as the cytostatics and the antiinfectives. Their adverse effects on normal host tissues may produce degenerative changes and necrosis in many anatomic sites, particularly where absorption, metabolism, storage, and excretion take place (i.e., the gastrointestinal tract, the liver, and the kidneys). Some drugs, either by themselves or in combination with body proteins, may induce antibody formation, leading to hypersensitivity reactions.

In addition to these toxic and hypersensitivity types of ADRs, the full spectrum of all the other well-known disease patterns may be produced by drugs and chemicals in a wide variety of target organs and tissues: congenital and developmental abnormalities; benign and malignant tumors; hyperplasias, hypoplasias, and aplasias; acute, subacute, chronic, and granulomatous inflammations; vascular alterations; and functional changes without evident morphologic variations from the normal.

These relatively few reaction patterns are the final common pathways into which *all* causes of human disease funnel, whether they are in the physical, *chemical,* or biologic categories. As a consequence, the clinicopathologic pictures presented by drug-related illnesses resemble many, if not most, of the non-drug-induced diseases. Put another way, although many drug-induced diseases are new to the physician, they do not have any new, distinctive, or unique features that would identify them per se as being caused by drugs. This point illustrates and emphasizes the limited capability of biologic organisms to react to injury, whatever the damaging agent may be.

From the Registry of Tissue Reactions to Drugs, The Armed Forces Institute of Pathology, Washington, DC 20306.

The Registry of Tissue Reactions to Drugs is sponsored by the Food and Drug Administration (under Contract FDA 223-73-3178) of the Department of Health, Education, and Welfare, and by the Armed Forces Institute of Pathology, and is under the auspices of Universities Associated for Research and Education in Pathology, Inc.

It is apparent from the above that the recognition, identification, and the diagnosis of ADRs pose a differential diagnostic problem to the practitioner of medicine, and it is the purpose of this monograph to present a methodology of use in the evaluation of ADRs.

The basic principles used in diagnosing ADRs are the same as in other areas of medicine: the physician integrates the symptoms, signs, and laboratory data (including morphologic findings, when available), and reaches a conclusion epitomized by a diagnostic word or phrase.

While history taking and the techniques of physical examination have remained fairly constant, there has been a tremendous increase in the information-furnishing capabilities of the clinical and the toxicologic laboratories over the past several decades. The number and the sophistication of instruments and techniques has been greatly increased, and many are of material assistance in analyzing and diagnosing ADRs—e.g., single- and multiple-channel autoanalyzers; spectrophotometry (ultraviolet, visible-light, atomic-absorption, and fluorometry); chromatographic analysis (gas, gas–liquid, gelatin, and paper); x-ray diffraction; electron-spin resonance; immunologic techniques in hematology and blood banking; and special stains in histochemistry, to mention but a few.

The accumulation of more and more detailed information, from whatever source, does not lead per se to diagnostic success, however. While the patient's history, physical findings, and laboratory data are important elements in establishing a diagnosis, of equal importance is the methodology or analytic plan adopted by the physician to digest the multitude of details that may be available from these multiple sources.

It is the purpose of this discussion to present an *algorithm* (a special method of solving a particular kind of problem) that will furnish guidelines for analyzing and diagnosing ADRs. The use of this methodology should enable the physician, when faced with a possible ADR case, to make one of three responses as to the presence of an ADR: an assured *yes*, a firm *no*, or a reasoned *admission of uncertainty*.

Reaching one of these three alternative conclusions (validation) is important to both the patient and the physician because a) the immediate treatment of the patient may depend on this judgment, b) future avoidance of the implicated drug may be imperative, c) there are potential, if not actual, medicolegal implications in every case of ADR, and d) the data base for meaningful studies on the status of adverse drug-reaction problems in modern medicine depends on the accumulation of individual cases of ADRs on whom validated diagnoses have been established.

Further, the methodology to be presented is one that is applicable to

physicians generally, whether they are general practitioners or specialists, clinicians or laboratorians. This methodology (algorithm or schema) is pertinent to the problems presented in the postmarketing phase of drug usage, i.e., to clinically occurring, unexpected adverse events related to the use of therapeutic, diagnostic, and prophylactic drugs.

Parenthetically, it is in this postmarketing phase that maximum patient exposure occurs and there is the greatest likelihood for the occurrence of ADRs. This is in sharp contrast to the relatively few ADR cases that are generated in the premarketing phases of drug studies, i.e., limited clinical trials and studies of safety and efficacy.

It is pertinent to emphasize three statements: a) A new area of diagnostic problems has been added to the practice of modern medicine—the adverse drug reaction. b) The possibility of an ADR should be included in the modern physician's differential diagnosis along with the possibility of infectious, neoplastic, metabolic, and other well-established categories of human illness. c) The clinicopathologic picture of ADRs is not readily distinguishable from those of non-drug-induced diseases.

The preceding points indicate the need for a methodology or algorithm that will operationally define an ADR and will confirm, deny, or admit uncertainty over linkage of the drug with the clinicopathologic findings.

The following quotations point out this need for standardization and agreement on definitions and analytic approaches in the field of adverse drug reactions.

> The fundamental problem in attempting to assess an individual clinical situation for an adverse drug reaction is thus the establishment of a clear cause–effect relationship between the drug and the reaction.[1]

> The first main step toward developing a valid biostatistical science of pharmaceutical surveillance will not be in creating additional technologies of surveillance. The first step is to arrive at reproducible methods for identifying an adverse drug reaction. . . . We have no idea of the amount of variability among physicians whose nondescript judgment is used to decide whether an observed event is or is not an adverse drug reaction.[2]

The Methodology

Fundamental Concepts and Relationships of a Time-Oriented Algorithm

There are undoubtedly a number of systems that could be set up for guidance in analyzing ADRs. Each would give emphasis to some particular factor or element that would become the focal point or base for its development.

The algorithm to be presented here is *time* oriented, with the fourth dimension in central position.

The emphasis on time springs from the importance of temporal

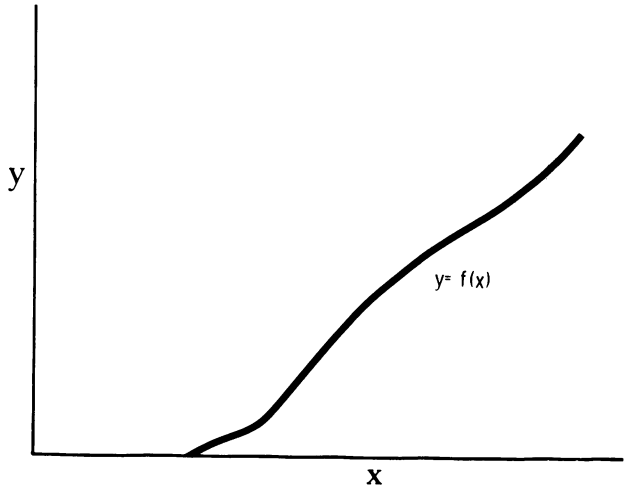
relationships, which has become evident in the experience with over 3000 cases of ADR. The practical tool that has evolved from the appreciation of this factor has been the *time-flow chart.*

Before going into the applicatory phase of this tool it will be of orientation value to start with a few fundamental concepts and relationships, building up the system from the simple to the complex.

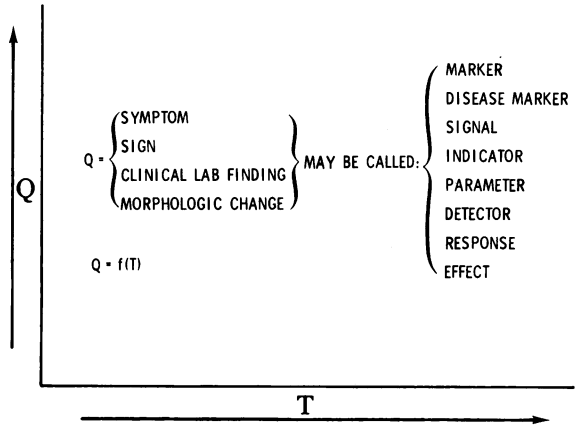
Keeping in mind that the ultimate object of this time-oriented methodology is to confirm or deny a linkage between a drug and an ADR, we start with Text-figure 1. This presents the familiar algebraic concept of a *function*: the dependent variable y being a function of the independent variable x. In the operational definition that will be developed, x will be related to the drug, and y will represent the adverse drug reaction, these two being *empiric correlates* if an ADR is present.

The next step, illustrated in Text-figure 2, is to transform the initial relationship from the rather nonspecific $y = f(x)$ to a *time-quantity diagram,* in which Q (the ADR) is a function of time: $Q = f(T)$. As indicated in Text-figure 2, Q is a symbol representing any one of the four major categories of clinicopathologic evidences of ADRs: a) a symptom (pain, dizziness, nausea, diplopia, etc.); b) a sign (hepatomegaly, fever, icterus, papular skin eruption, etc.); c) a clinical laboratory finding (a white blood cell count, an SGOT serum level, a BUN level, a blood salicylate level, etc.); and d) a morphologic change (hepatic cholestasis; pulmonary fibrosis, etc.).

In addition, Text-figure 2 lists synonyms that may be used to designate Q: marker, disease marker, signal, indicator, parameter, detector, response, and effect.



TEXT-FIGURE 1—A graphic representation of the concept of y as a function of x. This is the first step in the development of time-flow chart.

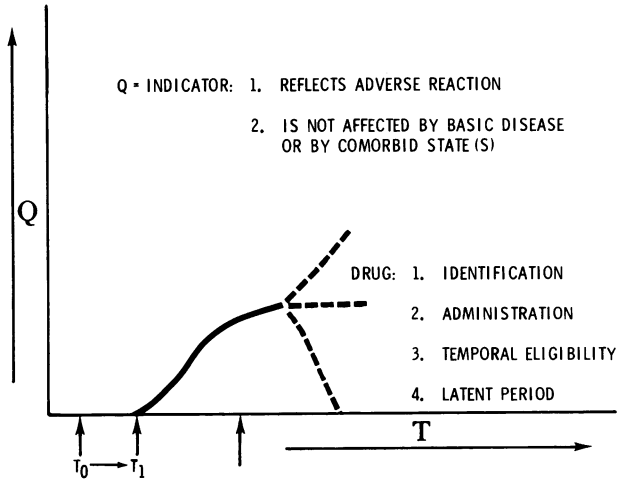


TEXT-FIGURE 2—Substitution of $Q = f(T)$ for $y = f(x)$, where Q, representing the adverse drug reaction and the dependent variable, is further defined, and the abscissa becomes T(time).

Since any of the clinicopathologic evidences of ADRs identified by the above terms are usually dynamic and changing with the passage of time, the expression $Q = f(T)$ is quite pertinent to the development of our concept of the time-flow chart.

Going on to Text-figure 3, the curve rising from the abscissa can be described as a map of Q (the drug reaction) through time. The three dotted extensions of this curve demonstrate the three courses that an ADR can take: increasing severity to death, leveling off to chronicity, or return to the abscissa, indicating recovery.

The second point to be made about Text-figure 3 is that Q (the disease marker of the ADR) should be selected because it is not affected by either the basic disease of the patient or by any concurrent comorbid state. If this requirement is not met, it will be impossible to decide whether the



TEXT-FIGURE 3—An adverse drug reaction (the curve, Q) is plotted against time (the abscissa, T). Dotted lines show the three courses of ADR can take: increasing severity to death, leveling off to chronicity, or return to the abscissa, indicating recovery. Four criteria that must be met before the drug is eligible to be an empiric correlate of Q (the adverse drug reaction) are listed.

variation in Q reflects the adverse drug action, the basic disease, the comorbid state, or some combination of these three factors.

Criteria for Eligibility as an Independent Variable

There are four items listed in Text-figure 3 concerning the "drug;" these are the criteria that have to be met before the drug is eligible to become the independent variable (one of the empiric correlates) in the operational definition of the ADR:

Identification

This refers to the need for accurate labeling of the medication and the need for assurance that what was ordered is what was actually received by the patient. This is usually assumed, without qualitative or quantitative verification by laboratory examination of body fluids or tissues. That this assumption may not always be true is illustrated by the following case, as reported by Golbert and Patterson.[3]

> EXAMPLE. A patient complained of recurrent urticaria associated at times with dyspnea, wheezing, nausea, and vomiting. He was taking two drugs: thyroid extract and ascorbic acid. Since this clinical profile is not easily explained by this drug regimen, the case remained an enigma until it was found, by laboratory analysis, that the ascorbic acid was mislabeled and actually was benzyl penicillin. Such occasional mislabeling may occur at any point along the pharmaceutical-manufacturer–pharmacy–physician–nurse–patient chain, and while it is not practicable or feasible to confirm the drug identity in day-to-day medical practice, the possibility of mislabeling should be kept in mind in circumstances in which there are unpredicated, unexpected, or unusual clinical and/or morphologic findings in alleged or possible drug-reaction cases.

Administration

As with proper drug identification, it is usually assumed, usually without proof, that the patient was indeed taking the drug(s) as ordered. This assumption is not always valid.

> EXAMPLE. A diabetic said to have been receiving tolbutamide developed renal dysfunction. Kidney biopsy revealed an interstitial granulomatous nephritis. Since sulfonylurea compounds (of which tolbutamide is one) may at times be associated with such lesions, follow-up information was requested, particularly if this agent were to be discontinued. It was then found that the patient never had taken the tolbutamide, even though it had been prescribed for him for 2 years.

Temporal Eligibility

A drug cannot be responsible for an ADR if given after its onset. This is a simple point, but one that is frequently ignored by those evaluating

alleged ADR cases. Temporal ineligibility is illustrated in Text-figure 3 by the short vertical arrow below the abscissa, to the right of T-1.

EXAMPLE. A 50-year-old white man with a long history of rheumatoid arthritis had a terminal illness of 5 weeks' duration that was dominated by cardiac and cerebral symptomatology. Thrombocytopenia was a laboratory feature, and the patient had been receiving indomethacin. The case was submitted as an example of an indomethacin-induced thrombotic thrombocytopenic purpura.

The autopsy revealed vascular lesions in the heart and brain that were quite compatible with thrombotic thrombocytopenic purpura. In regard to indomethacin, however, time relationships available in the patient's chart indicated that this drug was not given for the first time until the beginning of the fourth week of his terminal 5-week illness. This agent, therefore, was temporally ineligible to have initiated his final illness.

EXAMPLE. Another instance of temporal ineligibility is that of a jaundiced middle-aged man who had been receiving prochlorperazine. The alleged etiologic relationship of this agent to the liver cholestasis, however, was ruled out because the chart revealed that his jaundice appeared 3 days before he received his first dose of prochlorperazine.

Latent Period

This refers to the time interval between the beginning of the therapy with the drug and the onset of the ADR (T_0–T_1, in Text-figure 3). This interval, of course, is not rigidly fixed for any specific drug or type of ADR. For many drugs, however, the latent period falls for the most part within certain limits. Deaths from cyanide usually occur within seconds to minutes; most deaths from anaphylactic shock occur within 20 minutes of contact with the lethal antigen; jaundice associated with chlorpromazine usually has its onset in the range of 3 days to 4 weeks after this medication is started; the fatal aplastic anemia from chloramphenicol appears in from 1 to 3 months; the latent period for thorium-induced angiosarcoma of the liver is in the range of one to three decades; and the ultimate in latent-period length is the one to several generations time lag for drug-induced mutational change in the germ cell to become manifested in the conceptus.

In some instances the latent period may have an extremely wide range and thereby be of little analytic value, as with thromboembolism in association with oral contraceptives, in which the interval from drug exposure to this complication may vary from 5 weeks to several years; the development of serious consequences of ergot-induced arterial spasm may vary from several days to several years; and the agranulocytosis secondary to phenylbutazone may have a latent period varying from "soon" to

months or years, even after the drug has been taken without any apparent adverse effect over such an extended period of time.

Under certain circumstances, however, and with certain drug–site–process combinations, the length of the latent period may be of considerable analytic value.

EXAMPLE. An overly long latent period was considered to eliminate meprobamate from consideration as the cause of death in a 4-year-old male child. He had been inadvertently given an adult dose (400 mg) of this agent and suffered a sudden cardiorespiratory arrest 16 hours later, with no evidence of any clinical abnormality during the intervening 16 hours. Since this drug ordinarily reaches a peak blood level within 2 hours followed by a slow decline over the next 10 hours, it was considered that the cardiorespiratory arrest had some other cause. The child's history and subsequent autopsy findings tended to substantiate this interpretation. He had suffered several similar spontaneous episodes of non-drug-related cardiorespiratory arrest in the past, and the autopsy revealed multiple congenital anomalies of the brain, including hypoplasia of the cerebellum and the spinal cord, polymicrogyria and pachygyria, and hydrocephalus *ex vacuo*. In this case, consideration of the latent period was of critical importance and was a major factor in disqualifying the drug as the cause of death.

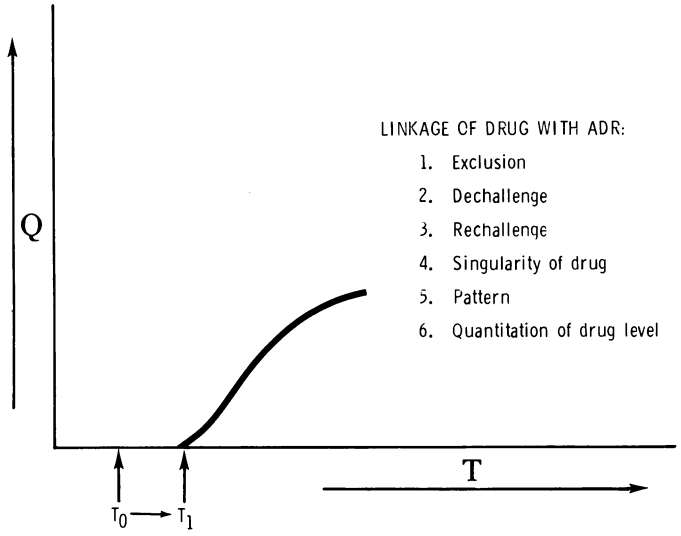
EXAMPLE. Too short a latent period was of differential value in the case of a death from complications stemming from pancytopenia. A 52-year-old woman received sulfamethoxazole for a urinary tract infection. The subsequent pancytopenia and death were at first attributed to the use of this drug. Chart information, however, revealed that 6 days after this agent was initially administered, she was described as weak, anemic, and with an "abnormal blood count;" and 4 days later her hemoglobin level was reported as 6.6 g. Considering the half life of the red blood cell, and in the face of no evidence of either hemorrhage or hemolytic disease, this 10-day interval was considered too short a time for a drop of hemoglobin from a normal level to 6.6 g if the pancytopenia were secondary to bone marrow toxicity and subsequent hypoplasia.

Demonstration of Empiric Correlation

To this point, the development of a schema for evaluating ADRs has included the formation of a time-quantity diagram; the *Q* element has been defined as a selected marker or indicator of an ADR that is plotted against time; and four criteria have been listed for determing the eligibility of a drug to be entered in the time line (the abscissa) as the independent variable.

In order to operationally define the drug reaction, it must now be shown that there is a linkage between the drug and the adverse reaction (Q). This linkage can be made by demonstrating that the drug and the reaction are *empiric correlates*.

This correlation may be accomplished by any one or a combination of several of the following methods, as shown in Text-figure 4: exclusion, dechallenge, rechallenge, singularity of the drug, pattern, and quantitative determination of the drug.



TEXT-FIGURE 4—The six methods of linking a drug with an adverse drug reaction.

These six methods to establish empiric correlates between the drug and the marker of the ADR will be successively defined and illustrated.

Exclusion

Exclusion may be on a *time* or a *precedent* basis.

Time Basis. This is essentially a method involving time-related elimination of all but one of the potential drug candidates, plus the negative factor of assuming or demonstrating that a non-drug-related cause is not present.

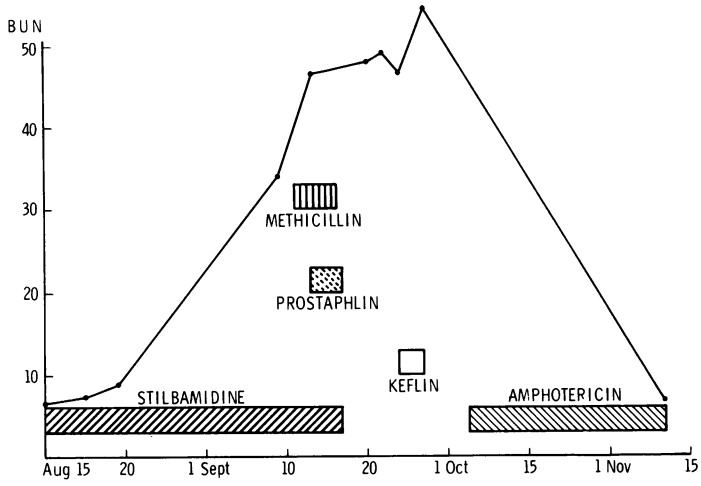
EXAMPLE. A 15-year-old black man with pulmonary blastomycosis was treated with a succession of five drugs over a 3-month period. During this interval he went into renal failure. A renal biopsy was done at the height of the BUN elevation, and it revealed an interstitial nephritis with a granulomatoid character. Cultures from this open biopsy specimen were subsequently negative for fungi, acid-fast bacilli, and anaerobic organisms.

From the time-flow chart (Text-figure 5), a number of points are evident:

1. The only drug eligible to have induced the renal dysfunction was stilbamadine. The other four agents were received after the initial rise in the disease marker. The latter agents are therefore temporally ineligible to have caused the BUN elevation.

2. The latent period of several weeks is not inconsistent with the time for development of the observed renal changes.

3. The question of whether or not the basic disease (blastomycosis)



TEXT-FIGURE 5—Time-flow chart demonstrating the temporal eligibility of stilbamidine to have produced the elevation of the BUN in the case described.

might have been the cause of the kidney changes is properly raised. Considerable evidence prompts a negative answer to this question: a) Cultures of blood and urine were negative for fungi, as well as for acid-fast bacilli and anaerobic pathogens. b) Renal tissue obtained at open biopsy failed to show histologic evidence of blastomycotic organisms, and culture of a portion of this renal tissue was negative for fungi. c) The BUN returned promptly to normal level when the stilbamidine therapy was discontinued.

4. From this information, it is most likely that we have satisfied the two points listed in Text-figure 3 as to the *Q* factor: i.e., that the two disease markers utilized in this case (the BUN levels and the morphologic changes in the kidney) reflected an ADR and that they were not affected by the basic disease (pulmonary blastomycosis).

5. Further, it appears fairly firm, for the analytic reasons given, that a linkage has been established between stilbamidine and the ADR and that these may be considered to be *empiric correlates.*

Precedent Basis. If a patient had been exposed to more than one drug, and if other methods of selecting the responsible agent are denied (rechallenge, dechallenge, etc.), then the drug candidates may be placed in an order of likelihood of causation based on a combination of the personal experience of the investigator and that found in the literature for their respective frequencies in association with the particular ADR.

EXAMPLE. A 77-year-old white woman with arthritis, hypertension, and Parkinson's disease was treated with three drugs over a year's time, at the end of which she died of aplastic anemia.

The last drug she received was oxyphenbutazone. After 1 month on this medication she developed skin petechiae. Her hemogram showed that the platelet count went as low as 3000, the white blood cell count to 800, and the red blood cell count to 2.7 million. She died 6 weeks after the petechiae appeared. Autopsy revealed multiple hemorrhagic foci in the brain, lungs, heart, adrenals, stomach, and urinary bladder.

While oxyphenbutazone has been associated with cases of aplastic anemia, the same is true of the other two drugs she had received during the last year of life: hydroflumethiazide and orphenadrine.

All three of these agents were temporally eligible. The latent periods were of no value in the differential because of their extreme variability (for oxyphenbutazone it varies up to several years), and the same might also be true of the other two drugs.

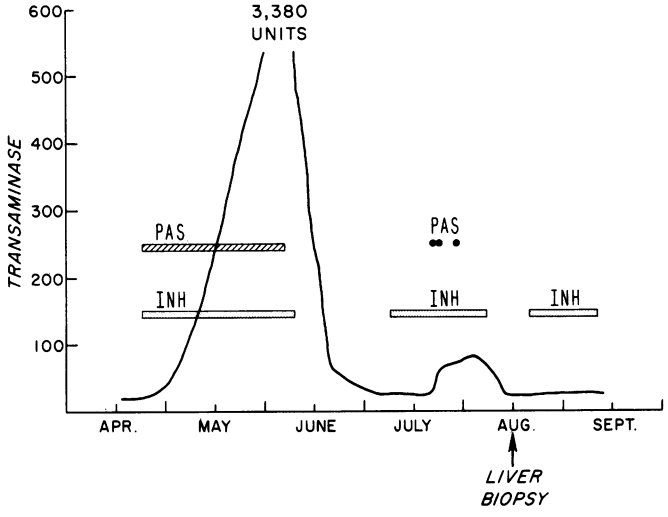
Consideration was then given to gaining an impression from the literature of the likelihood of an association between these drugs and aplastic anemia. Three authorities were consulted, with the following results: a) There was no mention of orphenadrine in association with aplastic anemia by two authorities, and it was credited with a "rare" association by the third; b) regarding hydroflumenthiazide, two authorities said "relatively rare" and "infrequent" and the third commented that this association did occur; and c) the association between oxyphenbutazone and aplastic anemia was mentioned by all three sources and in one of the three this type of ADR was mentioned first and was cited as "the most serious."

Placing oxyphenbutazone as the number one candidate, in this case, and excluding the other two drugs on the basis of literature precedent is presumptive and speculative at best, because statistics and probability cannot be applied with surety to a particular case. In this instance, however, a qualitative impression was obtained from literature sources that oxyphenbutazone caused aplastic anemia more frequently than the other two agents.

Dechallenge and Rechallenge

This method uses the line of reasoning implied in the phrase *post hoc ergo propter hoc* (after this, therefore because of this).

EXAMPLE. A 31-year-old white woman was treated for pulmonary tuberculosis with combined *p*-aminosalicylic acid–isoniazid (PAS-INH) therapy. A pretreatment serum transaminase level was within normal limits. As shown in Text-figure 6, there was a great initial elevation in this disease marker after therapy was begun, followed by a return to normal range on the first dechallenge. Rechallenge with INH alone produced no rise in serum transaminase, but when PAS was added to the drug regimen there was again a rise in this enzyme level. Dechallenge again was associated with transaminase normality, and a final rechallenge with INH alone was associated with no evident liver dysfunction.



TEXT-FIGURE 6—Time-flow chart of patient receiving PAS and INH, showing rise in the transaminase level on rechallenge with PAS and absence of rise on rechallenge with INH.

This succession of dechallenges and rechallenges with concurrent transaminase fluctuations is rather strong circumstantial evidence favoring the interpretation that PAS was the agent responsible for the liver damage. Put another way, this time-flow chart prompts the opinion that PAS and the transaminase elevation are *empiric correlates.*

One must hasten to add that there is another interpretation of this data: that the ADR was due to the combination of PAS-INH therapy. To confirm or deny this possibility, rechallenge with PAS alone would have to be resorted to. Such a trial, in this case, would probably carry a high risk of repeated liver damage and would not be condoned. In either event, this liver damage would appear to be drug related.

To reiterate the major analytic features of this case: a) The criteria listed in Text-figure 3 appear to have been met—the indicator (serum transaminase) reflected abnormality (an ADR) in the liver; it is unlikely that this indicator would be affected by or reflect the basic disease (pulmonary tuberculosis), and, conversely, hepatic biopsy obtained during the course of this illness contained no evidence of tuberculosis; in the liver the sequence of events as shown in Text-figure 6 clearly established the temporal eligibility of the PAS (or the combination PAS-INH); and the latent periods from drug administrations to appearance of the ADR indicator are within the limits as established by past experience with these agents. b) The linkage of the PAS (or PAS-INH) with the ADR indicator with circumstances of both dechallenge and rechallenge would appear to establish them as empiric correlates.

(Parenthetically, rechallenge may fail to reflect the actuality of the

existence of an ADR in some hypersensitivity-type cases. In these, the mechanism involved is that of desensitization occurring prior to the rechallenge, thus producing a falsely negative response. This phenomenon is seen with some of the phenothiazine-related jaundice cases, for example.)

Singularity of the Drug

The validity of this method of establishing empiric correlation between the drug and the ADR is based on two assumptions: a) that the patient was exposed to only one drug, and b) that there was no basic disease or comorbid state that could be related to the disease marker or indicator being used in the analysis.

EXAMPLE. A 34-year-old black female epileptic had been on long-term therapy with diphenylhydantoin. Hospitalized under the care of another physician, she was placed on this same agent. Continuing to take diphenylhydantoin from her own previously prescribed supply, as well as the newly prescribed anticonvulsant, she developed in 12 hours a syndrome including fever of 103 F, ataxia, nystagmus, confusion, hallucinations, slurred speech, and somnolence.

On the discovery of this double jeopardy, both sources of the drug were discontinued, and in 12 hours a distinct clinical improvement was noted; 12 days later she was completely recovered.

In this case, there were multiple indicators of an ADR: a systemic reaction (fever) plus a complex of symptoms and signs that related to the central nervous system. The timetable established the temporal eligibility of the drug, and the 8-day latent period was a reasonable one. In this case, the linkage of the diphenylhydantoin with the bizarre neurologic and psychiatric picture can be based not only on the singularity of the drug but also on the rapid return to normalcy after discontinuation of this agent (dechallenge).

It should be noted that the use of several of the methods of linking a drug with an ADR (as listed in Text-figure 4) strengthens the likelihood of their empiric correlation (as in this case).

Parenthetically, in regard to the term *singularity of drug*, the assumption that there is only one drug candidate in the problem should be confirmed or denied by active search of the record. Unless this is done, diagnostic error may result.

EXAMPLE. A 30-year-old woman, an alcoholic and epileptic with a duodenal ulcer, developed painful feet and blurring of vision 6 months before death. These symptoms diagnosed by the contributor as being on the basis of peripheral optic neuritis secondary to alcoholism. Her terminus was associated with a severe and generalized exfoliative dermatitis.

Scanning the available record revealed that she had received diphenylhydantoin for 8 years prior to death and that this medication had been replaced by carbamazepine in the terminal 4 months. There is precedent in the literature for the association between both diphenylhydantoin and carbamazepine and peripheral neuritis and blurring of vision. Thus, these were three possible empiric correlates to be considered in this instance.

While it was not possible with the present information and diagnostic methodology to single out any one of these three candidates (and it might actually have been a combined drug action by any two or all three), it would have been a diagnostic error not to have considered all three agents, and the case was ultimately coded under all three for later retrieval and comparative purposes.

In addition, there is a possibility that the severe terminal exfoliative dermatitis was related to the carbamazepine, and not *cause undetermined*, as originally thought by the contributor of the case.

Particularly in these days of polypharmacy, *singularity of drug* is infrequent, must be carefully confirmed, and will often be found to be an incorrect assertion.

Pattern

The pattern method of establishing empiric correlation shifts the emphasis from the drug factor to the adverse consequences of the drug action. These indicators or end results of an adverse drug reaction, when taken together, form a profile or picture that may be fairly distinctive of a particular drug–site–process combination.

Up to this point, the establishment of empiric correlates has concentrated on selecting and identifying a particular drug as the cause of the reaction. This selection was made possible because of unique time relationships (exclusion, rechallenge, dechallenge) and by unique historical data (singularity of drug), and it is to be noted that in most such instances, only one or a limited few indicators or disease markers was utilized in the analysis.

In the pattern method, being denied such methodology (as exclusion, rechallenge, dechallenge), we are forced to depend on the recognition of an aggregation of indicators that, when taken as a unit, is sufficiently distinctive to permit it to be labeled as a particular drug–site–process combination.

Such pattern diagnosis has its counterpart in the practice of medicine in areas unrelated to drugs. This is particularly true in diseases the causes of which are unknown or uncertain but in which a unique aggregate of

symptoms, signs, laboratory, and morphologic findings or parameters makes a particular diagnosis most likely. Since the identification of the causative drug or drugs is emphasized in analyzing ADRs, the pattern method in the drug-reaction area is relatively less definitive, but in some instances it is necessary to use it because we are barred from other means of establishing empiric correlates.

EXAMPLE. A 36-year-old white man, while under the influence of alcohol, was exposed to vapors of carbon tetrachloride while working in a small and poorly ventilated space. He subsequently became jaundiced. During hospitalization, a liver biopsy was done. This revealed a universal zonal change characterized by centrilobular loss of hepatocytes, central sinusoidal dilatation and congestion, collapse of reticulin network centrally, and prominence of Kupffer cells containing both lipofuscin and hemosiderin.

These histologic changes are seen with a large number of hepatotoxic agents, including various hydrocarbons, and are not themselves distinctive or diagnostic for any specific drug or chemical.

In this case, the diagnosis of carbon tetrachloride hepatocellular damage was based on the combined clinicopathologic pattern: the presumably accurate history of exposure to a particular agent, development of jaundice, and morphologic changes in the liver that were themselves nonspecific but were consistent with past experience with this agent.

The pattern method may also be used in a negative manner, i.e., to rule out the likelihood of an ADR associated with a particular drug. If a clinical and/or morphologic picture that is alleged to be an ADR has no precedent in past experience for an association with the agent in question, this would militate against their being empiric correlates. (This presumes, of course, that what you are seeing is not a new ADR being seen for the first time.)

EXAMPLE. A 65-year-old man had been receiving prednisone for several years and suffered an episode of congestive heart failure. It was thought that the congestive failure might have been induced by the steroid therapy. While the administration of glucocorticoids with mineralocorticoid activity may be associated with water and salt retention and edema, prednisone is said to have no significant mineralocorticoid activity.

Prednisone was therefore an unlikely candidate for a relationship to the episode of congestive failure. In this example, then, the pattern observed in the patient (congestive failure) did not fit with the known ADR patterns of the suspected drug, and the empiric correlate of the congestive failure was more likely cardiac dysfunction related to a previously documented myocardial infarction (several years prior) and subsequent atrial fibrillation.

Quantitation of the Drug Level

This method moves back to centering on the drug factor as of primary importence in establishing empiric correlates. Here linkage of the drug with the reaction is based on quantitative and objective data based on laboratory examination of body fluids and/or viscera.

This method is essentially limited to drug-overdose cases. A *sine qua non* of this method is the availability of data based on previous cases of drug overdose deaths that will furnish baselines of the lethal range for comparative purposes. Without dependable information of this sort, the quantitation method cannot be utilized.

Quantitation of drug levels is of no diagnostic use in ADRs that fall into the hypersensitivity, idiosyncratic, and pharmacogenetic categories. In these instances, drugs are given in therapeutic (not toxic) amounts, and in the face of therapeutic levels in body fluids and viscera, one is still left with the differential diagnostic problem, which must be solved by other methods.

EXAMPLE. A 21-year-old white man was admitted to a medical facility in acute respiratory distress. He stated that he was "sensitive" to chloroquine, and had shortly before taken one tablet of this malarial prophylactic drug. Cardiorespiratory failure ensued. Autopsy revealed no anatomic cause of death. Based on the history and the nonspecific autopsy findings, the initial diagnostic impression was death from chloroquine hypersensitivity.

The autopsy prosector had submitted samples of blood and viscera for toxicologic examination, however, and the following concentrations of chloroquine (in milligrams per 100 milliliters or per gram) were obtained: blood, 6.5; liver, 23.0; kidney, 24.0; brain, 2.5; and lung, 23.0. These levels lie in the lethal range for chloroquine-related overdose, as reported elsewhere.[4]

Based on this quantitation of the drug, the case was considered to belong in the toxicity (overdose) category, rather than in the hypersensitivity group.

Incidentally, the optimum time to obtain diagnostic material (blood and urine samples and vomitus) on suspected drug-related cases is in the hospital emergency room. Since blood and tissue levels of drugs and chemicals are progressively reduced with the passage of time by metabolic breakdown and excretion, available evidence on the cause thus progressively decreases.

Before leaving this section on the contribution of the chemical laboratory to the analysis of ADR cases, a word should be said about the qualitative test for the presence of a drug, i.e., determining its presence but not quantitating it.

While we have previously cited an instance of a drug prescribed for but not actually taken by a patient, and while in this example and generally speaking it would be of diagnostic value to confirm the presence of a drug qualitatively in an ADR case, such laboratory confirmation is not practicable under most clinical circumstances. There are some situations, however, in which the qualitative identification of a a drug or chemical *is* of material aid in establishing a diagnosis.

EXAMPLE. A 22-year-old woman developed multiple subcutaneous masses in the anterior abdominal wall. On excision, multiple cystic spaces were found containing clear viscid fluid. Silicone injections had previously been made into her breasts, and there was a possibility that these lesions in the abdominal wall represented gravitational migration of some of the silicone. Infrared spectrophotometric analysis of the aspirated contents of these cysts revealed silicone. In this case, there was no value in determining how much of this agent was there, but the need was to determine its identity—a qualitative determination only.[5]

EXAMPLE. A 2-year-old white male child accidentally ingested an estimated 6 g of ferrous sulfate. The iron level in his serum rose to a maximum of 810 μ/100 ml (normal, 40 to 140 μg/100 ml). Iron stains on sections of small intestine demonstrated heavy deposits or iron in the mucosa. While this qualitative demonstration of iron in the tissues was not critical to establishing the diagnosis of iron toxicity in this particular case (since serum levels were available), such a qualitative procedure would have been of diagnostic value in a similar case if quantitated levels of iron in serum had not been determined and if there were a history of iron ingestion.

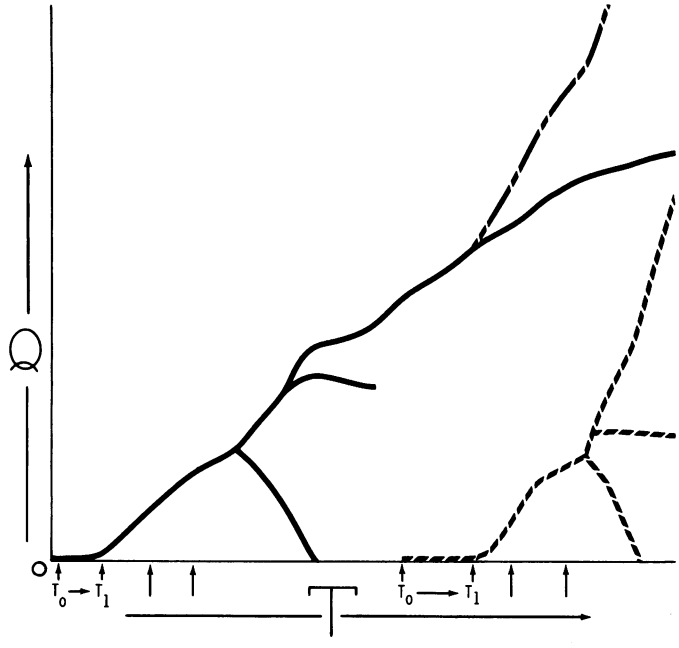
So far, in the development of an algorithm for evaluating ADR cases, the emphasis has been on a) criteria for drug selection and b) establishing linkage between the selected drug and the indicator of the ADR (empiric correlation between these two elements).

The next major consideration in the analysis of an ADR is the determination of whether or not the basic disease or any comorbid states of the patient might be responsible for what has been, to this point, considered to be drug induced.

Text-figure 7 plots both basic disease and ADR and shows the composite Q that results when an ADR is added to the primary illness. The mingling of these two processes evident on this graphic illustration is representative of the situation in clinical medicine, in which the problem of selecting the evidence supporting an ADR from that due to the basic disease is a real and usually, or at least quite often, a difficult one.

EXAMPLE. Text-figure 8 is a time-flow chart representing a case in which a drug met the criteria for empiric correlation to a certain point but was ultimately disqualified from such relationships because a comorbid state was found to be the empiric correlate of the selected indicator.

The case illustrating this situation is that of a 70-year-old white man who had an excision of an atherosclerotic abdominal aneurysm. He received tetracycline post-



TEXT-FIGURE 7—Representation of the basic disease and the composite curve that appears when an adverse drug reaction occurs. (Basic disease, *solid line*; drug-induced disease, *dotted line*; combined basic and drug-induced diseases, *dashed line*)

operatively and then developed successively oliguria, anuria, and azotemia and died about 1 month after the operation.

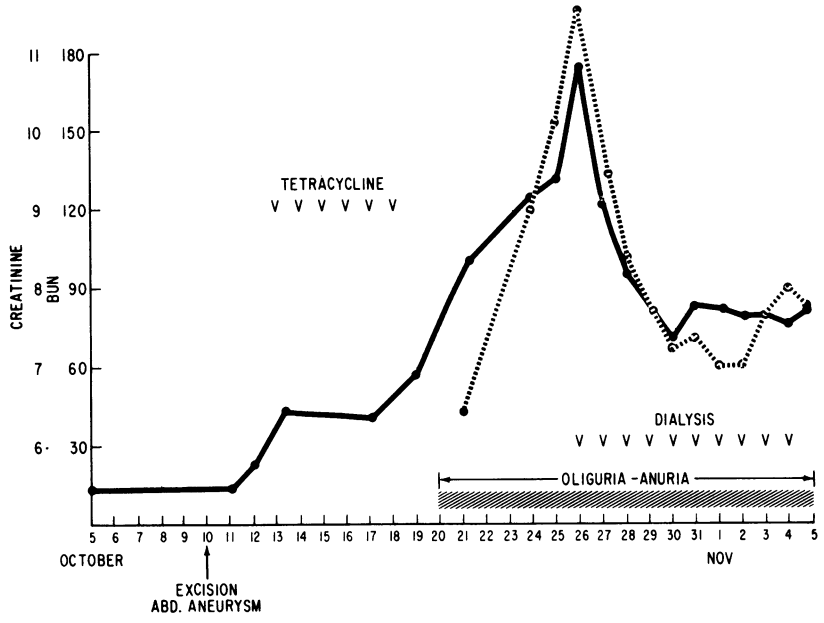
As shown in Text-figure 8, tetracycline preceded the onset of the elevations in creatinine and BUN, the week-long latent period is a reasonable one for renal toxicity to have developed, and there is precedent in the literature for an association between this drug and renal toxicity.

Prior to death, however, there was evidence suggesting a nondrug cause for the renal dysfunction: a translumbar aortogram done 9 days before death was reported as showing "no flow in the left kidney and minimal or no flow in the right kidney."

Necropsy revealed a morphologic cause for the decreased renal blood flow and the renal failure: Both renal arteries were occluded by thrombotic material that had propagated from a second abdominal aneurysm located above the level of the previously excised aneurysm.

This case illustrates the point that *post hoc ergo propter hoc* is not always valid. Also, it illustrates the virtue of including the pathologic findings when available and integrating them with the clinical and laboratory data.

In this instance, then, the renal vascular compromise was the empiric correlate of the elevated levels of BUN and creatinine, and the role of tetracycline was relegated to the coincidental category.



TEXT-FIGURE 8—Time-flow chart illustrating the temporal eligibility of tetracycline in relation to the subsequent renal failure. (Creatinine, *dotted line*; BUN, *solid line*)

Use of Several Methods to Establish Empiric Correlation

Before concluding the discussion of the various methods that may be utilized to establish empiric correlates in alleged ADR cases, it is important to emphasize that the solution of many diagnostic problems in the drug area involves the use of a combination of points listed in Text-figures 3 and 4. In fact, the use of more than one method of establishing empiric correlates tends to strengthen either the confirmation or the denial of the existence of an ADR.

While some of the previous case examples did use more than one method, the following case is particularly useful as an example of this point.

EXAMPLE. A 55-year-old Oriental woman sustained multiple and serious injuries in an automobile accident. She died in 7 weeks of hepatic failure. In the intervening time, she suffered three episodes of hypotension, had multiple transfusions, and underwent halothane anesthesia twice.

Put in the preceding fashion, and with the known capabilities of these three factors to produce liver damage, the determination of which one had caused the hepatic damage and failure would appear to be a virtually insoluble problem.

Table 1—Timetable of Treatment of Accident Victim Who Later Died of Hepatic Failure

March 9	Auto accident, one blood transfusion, one episode of hypotension and shock
March 14 & 22	Surgical procedures carried out under halothane anesthesia
March 25	Fever of undetermined origin
April 1	Jaundice first noted; SGOT, 3300 Karmen units; SGPT, 2100 Karmen units
April 10	Exchange transfusion
April 20 & 24	Hypotensive episodes
April 25	Death

Using *time* as a base for analysis, there are certain aids to be derived. The patient's timetable is shown in Table 1. Put in this time frame (Table 1), certain eliminative points can be made:

Hypotension. There were three recorded episodes. Two of these occurred after liver damage was already evident, so those recorded on April 20 and 24 can be eliminated as initiating the liver damage (temporal ineligibility). The third hypotensive period occurred on the day of the auto accident. This, too, can be discarded as being related to the liver necrosis, because it occurred 21 days before the first clinical evidence of liver dysfunction (too long a latent period).

Blood Transfusions. These were multiple; only one preceded the evidence of liver damage, however, and this is felt to be an unlikely cause of the hepatosis, primarily on the basis of the morphologic changes found in the liver at necropsy (pattern method). While it is essentially impossible to differentiate on histologic grounds between drug injury and viral hepatitis in instances of massive liver necrosis, in submassive necrosis (which was found in this patient), the finding of universal and dominant centrilobular necrosis of hepatocytes is more in favor of a drug-related injury, since the viral injury (in submassive necrosis) is more often focal and not zonal.

Halothane. This is favored as the cause of the liver damage for several reasons: a) Evidence of liver dysfunction was found only after the second exposure to this agent (multiple exposures are not infrequent in association with halothane-related hepatosis). b) Fever of undetermined origin occurred on the third day following this second exposure to halothane. c) The pattern of the liver changes was of zonal distribution (itself consistent with hepatocellular damage by a drug).

Thus, in this case, the analytic points most probably implicating halothane included considerations relating to latent periods, temporal eligibility, exclusion, and pattern (both clinical and morphologic).

Operational Definitions of Degrees of Certainty

Theoretically, applying the methodology criteria just outlined to an ideal case of alleged ADR should result in an unequivocal confirmation or denial of the presence of an ADR, with no room for uncertainty.

This ability to separate all alleged ADRs into clear-cut *yes* or *no* categories would imply the unrealistic assumption that in all cases there would be such a sufficiency of broad-based and essentially complete information that there could be no doubt about the affirmative or negative opinion rendered.

In actual practice, however, it has been found necessary to interpose three shades of relative certainty between these extremes of assuredness. These additional categories are: *probable, possible,* and *coincidental.* These three categories and the causative and negative groups will be defined and illustrated in the following discussion.

Causative

There are three subgroups in this category.

1. The first is essentially limited to instances of drug overdose. The following criteria apply to this group: a) The latent period for the reaction falls within the limits consistent with past experience with the particular drug, b) drug levels in body fluids and viscera are within the lethal range found in previously validated cases, and c) no anatomic or morphologic cause of death is demonstrated at necropsy.

The empiric correlates in this category are: death and quantitated laboratory-derived drug levels that lie within the lethal range.

This category constitutes a hard core of ADRs with a diagnostic base in the chemical laboratory, with data that are objective and reproducible and lead to a definite and unequivocal diagnosis.

EXAMPLE. The death from overdose of chloroquine previously cited (p 632) serves as an example of an ADR in the causative category.

2. A second type of case in this class also lies in the toxicity and overdose group, but the basis for the diagnosis relies heavily on the total clinicopathologic picture rather than primarily on the findings of the toxicology laboratory.

This group has the following characteristics: a) The identity of the drug and the corroboration of the patient's exposure to it are based on the patient's history (though the chemical identification and even the quantitation may be carried out but are not a *sine qua non*); b) there is temporal eligibility; c) the latent period is short (this is essentially a requirement, since long latent periods tend to obscure the relationship between the drug or chemical and the ADR); d) singularity of the drug is established by reliably reported circumstances; and e) if the ADR is fatal, autopsy fails to reveal any previously undisclosed basic disease or comorbid condition that would explain the illness; if the ADR is not fatal,

the subsequent clinicolaboratory findings likewise fail to disclose any preexisting disease that would account for the illness.

EXAMPLE. A 46-year-old man, in good health and gainfully employed, ingested with suicidal intent a large quantity (estimated at 50 ml) of fiberglass or resin catalyst (containing 60% methyl ethyl ketone peroxide and cyclohexane peroxide). Within minutes he became very ill and went into shock; gastrointestinal bleeding occurred and he became comatose shortly. His subsequent course was dominated by jaundice and anuria, and he died in hepatorenal failure. Autopsy revealed hemorrhagic gastroenteritis, nephrosis, and hepatic cholestasis.

In this example, the agent causing the ADR was identified by the victim's associates, who saw him drink it; temporal eligibility was established by the sequence of events; the latent period was very short; and the autopsy was highlighted by morphologic changes in three target organs that are frequently the site of acute toxic reactions and alterations—the gastrointestinal tract, the liver, and the kidneys.

In this instance, it is difficult to escape the interpretation that the ingested chemicals and the death were empiric correlates, even in the absence of laboratory identification and quantitation of the agents. In fact, should the latter have been done, we would probably have been unable to find base line lethal levels in the literature for comparison.

EXAMPLE. The previously cited case (p 629) of the epileptic who inadvertently received twice the recommended dosage of diphenylhydantoin would also serve as an instance of a causative relationship between the drug and the ADR. This case and that of ingestion of the resin catalyst are similar in principle, with the exception of the differences in their latent periods and in their ultimate outcomes.

3. The third type of case in the causative category is not currently applicable but is mentioned for potential future use. At such time as newly developed objective and reproducible laboratory procedures become available in the ADR field (immunologic, enzymatic, and/or histochemical techniques) that would be recognized as specific and distinctive diagnostic tests for the identification of empiric correlates with particular ADRs, then cases in which such procedures were applicable would be classed in the causative category.

Probable (Equivalent to Consistent With)

Cases in this category are considered to be essentially drug related but to differ in one critical respect from the previous (causative) group: they lack any unique, objective, reproducible, and usually laboratory-derived cornerstone on which to rest the unequivocal diagnosis of ADR.

Cases in this category do have a *combination* of findings that, taken

together, add up to a very high degree of probability that a particular drug or combination of drugs has caused an adverse reaction.

Probable ADR cases have the following characteristics: a) The requirements of temporal eligibility and latent period (as previously defined) are met, b) the clinical and morphologic findings resemble those associated with the particular drug or chemical as found in previous experience, c) other than drug causes (the basic disease and/or comorbid states) have been eliminated with reasonable assurance, and d) one or several of the six previously listed means of linkage of the drug with the ADR (Text-figure 4) has identified the drug in question as an empiric correlate of the ADR.

In this probable category, circumstances of exclusion, dechallenge, rechallenge, and singularity of the drug are commonly used to diagnostic advantage.

EXAMPLE. The previously presented case of blastomycosis treated with stilbamidine (and four other drugs) (p 625) and the case of pulmonary tuberculosis treated with PAS-INH (p 628) serve as examples of probable ADRs. Both these cases meet the requirements of the operational definition of probable given previously.

Possible

Cases of adverse drug reaction in this group fall into an uncertain diagnostic area in which the allegation of the presence of an ADR can be neither confirmed nor denied with the information at hand. It is important to recognize cases in this category and to avoid placing a possible case in either the causative–probable or the coincidental–negative groups.

A possible ADR case has the following characteristics: a) criteria for temporal eligibility and latent period are met; b) the clinical and morphologic patterns are similar to those cases having an association with the particular drug in question; c) drug (or drug–drug) singularity is assured by historical and time-related information; and d) linkage of the drug(s) with the ADR can be accomplished by one or several of the six methods previously cited (Text-figure 4), *but* the clinicopathologic picture presented by the case could also have been produced by other potential empiric correlates, i.e., by the basic disease or by comorbid states present in the patients, *or* by other modes of therapy received by the patient, and elimination of all but one of these candidates for causation cannot be accomplished.

Another type of potential ADR case that is placed in the possible group is that in which some of the criteria for the probable category are met, but data needed to meet the remaining criteria are insufficent or unavailable. Pending receipt of additionally needed information, the case is coded as possible.

Another type of case included in this group is that in which there is no precedent in the literature for such a drug–site–process combination. Such a case might be a new ADR, and it is designated possible for later retrieval and comparative purposes, should similar instances appear in the future. This type of case is coded as conditional by Karch and Lasagna.[1]

EXAMPLE. A case that meets the criteria of the first definition cited in the possible group is that of a 45-year-old white man who underwent an abdominoperineal resection for a carcinoma of the rectum. He had a bilateral inguinal dissection 3 weeks later, and this was associated with an episode of hypotension and shock. Subsequently he became jaundiced, and his serum transaminase levels were elevated. He survived an additional 2 weeks, then died. Necropsy revealed submassive necrosis of the liver.

He had undergone halothane anesthesia twice in his terminal month of life, and a halothane-related hepatocellular damage was one major consideration in the diagnosis. The hepatocellular necrosis following halothane anesthesia cannot be differentiated from the changes related to hypotension and shock, however, as both are capable of producing essentially similar morphologic hepatic changes (centrilobular necrosis).

In this instance, then, the consequences of a comorbid state could not be differentiated from changes related to a halothane-induced ADR. The relationship of the halothane to the hepatic necrosis, therefore, could be neither confirmed nor denied, and the case was coded no higher than the possible category for the role that halothane may have played.

Coincidental

Cases in this category are illnesses in which there was exposure to a drug or chemical but in which clinical and/or morphologic studies reveal another cause for the illness that was initially ascribed to a drug or chemical.

EXAMPLE. A 52-year-old white man with a history of occupational exposure to several organic solvents (including tetrahydrofuran and dimethylformamide) became jaundiced.

While there is precedent in the literature for an association between these compounds and liver damage, laparotomy was performed to attempt to rule out some form of extrahepatic obstruction as the cause of the jaundice. No form of extrahepatic obstruction was found, and a liver biopsy taken at that time showed, in addition to severe cholestasis, periductal lamellar fibrosis in the portal triads and an occasional bile lake. These microscopic findings, taken together, are practically pathognomonic of extrahepatic obstruction of the bile flow, though no such lesion had been found at the laparotomy.

The patient's course was progressively downhill, with increase in jaundice (total bilirubin up to 42.0 mg/100 ml) and hepatic failure, and he died 7 months after the laparotomy.

Necropsy revealed a primary adenocarcinoma of the common hepatic duct, with numerous metastatic lesions in the viscera.

This case was coded in the coincidental category for the relationship between the previously mentioned organic solvents and the changes in the liver. While those chemicals were presumed to be potential candidates, an extrahepatic neoplasm obstructing the common hepatic duct was demonstrated by autopsy, and this constituted an "other than drug cause" that fully explained the clinicopathologic findings and course of the patient's illness. It is also interesting that his occult lesion, which was not demonstrated at surgery, was predicted (in principle if not in specific type and location) by the earlier biopsy.

Parenthetically, in this case, the chemical candidates for causation of the jaundice and hepatic failure were not in the class of therapeutic, diagnostic, or prophylactic agents. The use of this case as an illustration in this discussion of ADRs is considered justified, however, as a means of broadening the scope of our attention to include environmental sources of some of the chemical etiologies of human adverse reactions to drugs and chemicals, which are becoming an increasing problem in our modern technologic and industrialized society. Other examples include: vinyl chloride associated with hepatic angiosarcoma; asbestos, with mesothelioma; herbicides and insecticides, with adverse reactions in the lungs, liver, or central nervous system; and beryllium, with pulmonary and lymph node granulomata, to mention a few.

Negative

This category of certainty for the relationship between a drug or chemical and an adverse reaction is reserved for those cases in which additional clinicopathologic and/or laboratory studies clearly show that the alleged drug could not have been responsible. This disqualification takes one of the following three forms: a) the drug was mislabeled; b) it was not administered as initially presumed; or c) the drug was temporally ineligible.

EXAMPLE. An instance of misidentification is illustrated by the case of the previously cited patient (p 622),[3] in which benzyl penicillin was mislabeled as ascorbic acid and the empiric correlate of the ADR (urticaria, dyspnea, nausea, and vomiting) was not disclosed until the "ascorbic acid" was analyzed and found to be penicillin.

EXAMPLE. An instance of failure to take the prescribed drug is illustrated by another previously cited case (p 622): the diabetic who had been presumed to be taking tolbutamide developed renal dysfunction and showed granulomatoid interstitial lesions on renal biopsy. It was only after further clinical information revealed that the patient had never used the agent that had been prescribed for him for several years that an incorrect linkage of empiric correlates was averted.

EXAMPLE. A third type of the negative category is illustrated by the case of a 33-year-old white man who developed jaundice while receiving prochlorperazine. The initial presumption of drug-related jaundice was shown to be impossible when it was

found that his jaundice was present 3 days before he had taken the first dose of this tranquilizer.

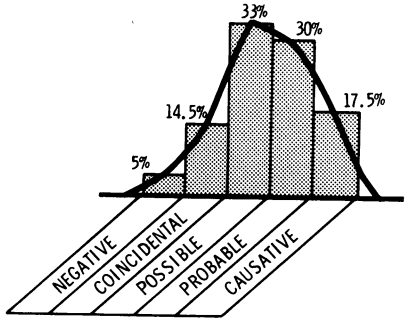
The application of these five categories of certainty, as operationally defined here, to the first 2500 cases in the Registry yielded the results shown in Text-figure 9. For practical purposes, these five categories may be reduced to three: *drug-related* (causative plus probable) cases; *non-drug-related* (coincidental plus negative); and *possible*. Put more briefly, these three consolidated categories amount to: *yes*, *no*, and *maybe*.

It is evident from Text-figure 9 that validation of these originally alleged ADR cases was made in almost 50% of the cases, that about one-fifth were disqualified as ADRs, and that in one-third of the cases neither confirmation nor denial was possible with the available information.

There are at least four reasons for the difficulties encountered in evaluating ADR cases and for the relative dominance of the uncertain group in these 2500 patients: a) Inadequate information. b) Polypharmacy. c) The lack of objective and reliably reproducible methods of establishing a casual relationship between a drug or chemical and the alleged reaction, i.e., difficulty in linking the drug and the reaction as empiric correlates. d) The limited number of reaction patterns of the body to all disease-producing agents.

Given that the evaluation of ADRs is often complex and difficult, given that the possible (uncertain) group is the numerically dominant one of the five categories of certainty, and given that we know four major reasons for these difficulties, what measures can be taken to improve our diagnostic capabilities?

Three of the four difficulties previously enumerated appear to be uncorrectable or unimprovable, at least at this time. Polypharmacy is such an integral part of modern medical practice that there is little likelihood of reducing this difficulty; objective means (reliable and reproducible laboratory-based tests) of linking a drug with an ADR may be developed in the



TEXT-FIGURE 9—Graph showing distribution of degrees of certainty as to the relationship between the drug and the adverse drug reaction as found in 2500 cases of alleged drug reactions.

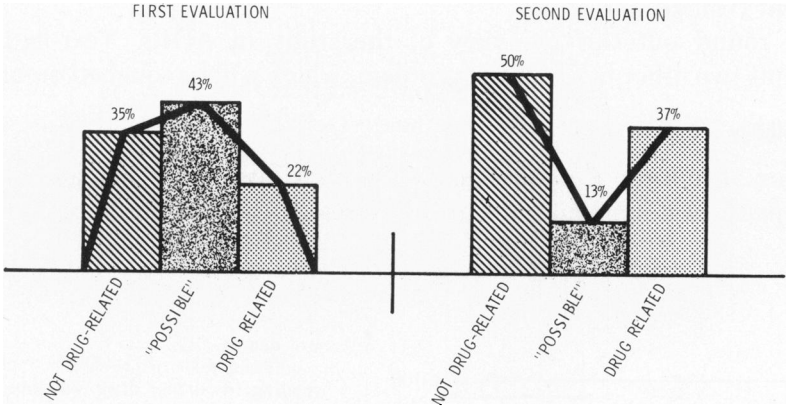
future, but currently there are few such means available to the practicing physician; and the limited number of reaction patterns of the body is a fixed and immutable biologic fact of long standing.

There remains only one of the four difficulties that has any practical chance of control and improvement—i.e., inadequate information.

To illustrate the part that improvement of the quality and quantity of data may play in evaluating ADR cases, a study of phenothiazine-related hepatoses is cited. This was carried out jointly by the Hepatic Registry of the Institute (Dr. Kamal G. Ishak, Registrar) and the Registry of Tissue Reactions to Drugs.[6] In this study, 94 cases with a possible relationship between this group of tranquilizers and subsequent jaundice were studied. As shown in Text-figure 10, the initial evaluation yielded confirmation of this alleged connection in only 22%, denial of this relationship was made in 35%, and in 43% it could be neither confirmed or denied.

Additional information was then obtained from the contributors of these cases, including such elements as more detailed histories with time-related drug and disease-marker information; operative and anesthesia records where pertinent; clinical laboratory information (particularly the results of liver-function studies); and in some instances, additional pathologic material for additional sections and/or special stains. Such additional information and material was obtained in over 95% of these cases.

Studying these same 94 cases in the light of this additional information



TEXT-FIGURE 10—Graph illustrating the value of more complete information in a study of 94 cases of phenothiazine-related hepatoses. First evaluation on left; second evaluation on right (after obtaining additional information). Note inversion of curve and reduction of possible group after a more complete study. Note large overcall group (50%) after second evaluation.

and using the methodology and operational definitions previously discussed yielded the following results; a) Confirmation of the drug relationship was raised from 22 to 37%. b) The negative-coincidental group rose from 25 to 50%. The other than drug causes that came to light in this group included viral hepatitis, calculi or neoplasms of the extrahepatic biliary tract; pancreatic tumors; metastatic tumors in the liver; the Dubin-Johnson syndrome; and tetracycline steatosis. c) The uncertain ("possible") group was reduced from 43 to 13%.

The main consequence of improving the inadequacy of information factor in this study was to reduce considerably the previously dominant possible (uncertain) group. In addition, the final opinion that in 50% of this group of cases the presence of an ADR was denied represents considerable diagnostic overcall, in light of the fact that most of these 94 cases were sent in for evaluation because they were considered to be likely ADR candidates.

Discussion and Summary

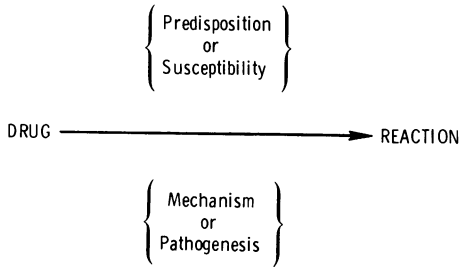
Thus far in the analysis and evaluation of alleged ADR cases we have been concerned with: a) confirming or denying that a particular drug was the empiric correlate of a particular clinicopathologic profile (with a methodology or algorithm that would aid in making this decision) and b) the operational definitions of the five degrees of certainty as to the part that a particular drug may have played in an illness alleged to have been an ADR.

In terms of Text-figure 11, we have been concerned with finding out whether the arrow or connection between drug and reaction was actually present (validation).

To round out this overview of the study of ADRs, Text-figure 11 presents two other facets of the problem, which will be touched on briefly.

Susceptibility or Predisposition

Many, if not most, people may take drugs (assuming they are taken in therapeutic amounts and not in overdoses) without suffering an ADR. If



TEXT-FIGURE 11—Other elements relating to adverse drug reactions.

they do have an ADR, in an estimated 70% of them it is a relatively minor one.[1] It is in the remaining 30% that more serious untoward events occur—the hypersensitivity, idiosyncratic, and pharmacogenetic categories.

There is something about the inherited or acquired metabolic pathways and processes in some persons (including also acquired visceral disease, which may alter the absorption, metabolism, storage, and excretion of drugs) that mark them as susceptible or predisposed to ADRs. Some we know; many we do not. For example, tens of thousands of patients have to be exposed to chloramphenicol before one case of fatal aplastic anemia will develop from it; women with Type A blood have a higher incidence of thromboembolic complications associated with oral contraceptives than those with Type O; the incidence of liver dysfunction and damage following isoniazid therapy is considerably higher in patients over the age of 50; agranulocytosis following the use of amidopyrine or phenylbutazone is higher in female than in male subjects.

In the framework of these susceptible or predisposing factors, the drug may be termed the *proximate* or *immediate* cause of the ADR, and regardless of whether or not we know these background (predisposing) factors, the preceding methodology for establishing empiric correlates is still applicable in relating the drug to the ultimate reaction.

Mechanism or Pathogenesis of an ADR

As with the predisposing factors just discussed, we know the mechanisms involved in some ADRs but not others. For example, the high-output renal failure sometimes associated with methoxyflurane anesthesia is thought to be related to the action of the fluoride portion of the anesthetic molecule in rendering the renal tubules unresponsive to the action of the antidiuretic hormone. Some patients taking both an anticoagulant (such as bishydroxycoumarin) and an antidiabetic agent (as tolbutamide) may go into hypoglycemic shock because the anticoagulant prolongs the half-life of the antidiabetic agent. A hemolytic anemia develops in certain persons receiving primaquine because of an inborn deficiency in glucose-6-phosphate-dehydrogenase; in some, chloroquine may be associated with visual changes because the drug tends to be deposited in melanin-bearing areas and because this agent inhibits alcohol dehydrogenase (the latter an important component in the chemistry of the visual cycle). Some infants may develop the gray syndrome when receiving chloramphenicol because this agent is detoxified by conjugation with glucuronic acid in the liver and infants have an insufficient quantity of glucuronyl transferase in the liver in the first few weeks of extrauterine life. The mechanism of action of

disulfiram (Antabuse) in the treatment of alcoholism is related to its interference with the oxidation of acetaldehyde (an intermediate metabolite of ethanol) and the consequent rise in the blood level of acetaldehyde, which produces a number of unpleasant adverse reactions (facial flush, dyspnea, nausea, vomiting, weakness, vertigo, and confusion). In cobalt-related myocardosis ("beer drinker's heart"), cobalt may combine with lipoic acid and produce a block in the Krebs cycle that is similar to a thiamine-deficiency state.

Increasing our knowledge of predisposing factors and mechanisms in the field of ADRs is important, because this may result in future rational treatment and control measures.

Another point worthy of emphasis is that there is no constancy in what the target organ will be for any particular drug, nor is there any predictability of the type of adverse reaction that any particular drug will cause. Chlorpromazine may cause hepatic damage in 1 patient and induce agranulocytosis in another. Cytostatic and immunosuppressive agents may induce bone marrow hypoplasia in some; in others, neoplasias may be induced by the reduction of the patient's immunologic surveillance capabilities. This inconstancy and unpredictability of target organs and types of adverse reactions that may be induced are additional elements in the complexity of this newly emerging field.

This monograph has been concerned with analysis of the individual ADR cases that has led to a judgment of drug causation. Judgment of drug causation in human illness may also be based on statistical and surveillance studies of groups of patients. It is not within the scope of this monograph to discuss such cluster studies, but they are mentioned briefly to emphasize that there are multiple methodologies in the field of adverse drug reactions. In this regard, reference is made to an article by Feinstein,[2] in which epidemiologic strategies and techniques, causes and cause signals, rates and rate signals, and goals and evaluations of surveillance methodologies are defined, discussed, and illustrated, and in which over forty references on this complex field are included.

Finally, it is essential in the evaluation of cases of adverse drug reactions that the successive steps of determining drug eligibility, of linking the drug to the markers of the reaction (establishing empiric correlates), and of placing the case in one of the five categories of certainty (as operationally defined) are all of critical importance in the validation of ADR cases. By these means

> . . .The causation by the drug will be confirmed in some and denied in others, and the remaining and uncertain group will be identified and so labeled. Validation is a requirement that should precede any coding action, statistical study, and special

technical procedures, if meaningful and valid conclusions are to be drawn from the study of restrospective-type drug-reaction cases.[7]

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Acknowledgments

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