Contents

1. Diagnostic problems in drug-induced diseases

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With the development of many new therapeutic and diagnostic agents in the past several decades, a new diagnostic facet has been added to the practice of medicine: the drug reaction. Because of the increasing frequency of this group of iatrogenic diseases, it is becoming as important to recognize the presence of a drug reaction as it is to recognize a malignancy, an inflammatory disease, or any other major disease category. The drug reaction is now included in the modern physician's differential-diagnosis list.

The diagnostic problems relating to drug-induced diseases are the subject of this discussion. The background for this analysis is the experience with over 1,600 cases studied in the Registry of Tissue Reactions to Drugs. In all cases, biopsy or autopsy material was available for morphologic correlation with clinical and clinical-laboratory features.

Drug reactions usually pose a difficult diagnostic problem that should be shared between the clinician and his supporting pathologist. Integration of the clinical with the pathologic information is necessary in most instances for adequate and valid analysis. Since the morphologic changes associated with drug reactions are not usually agent-specific, the need for fusing the historical, clinical, and clinical-laboratory findings will be evident.

Implicit in the term 'drug reaction' is the presence of a drug and its causative relationship to the reaction. Emphasis on the importance of identifying the responsible drug is a reasonable extension of this implication. A drug reaction may be related to an inborn error of metabolism, to an allergic or hypersensitivity state, or to a concurrent visceral disease involving alteration of the functions of absorption, metabolism, storage, or excretion. It may also occur on the basis of direct toxic action or as an exaggeration of a therapeutic effect. Regardless of the background or mechanism, identification of the drug responsible for the reaction is of primary importance.

This emphasis on pinpointing the causative agent is a shift in point of view from that which dominates much of the practice of general pathology. In the latter, many of the diagnostic entities are made up of a group of supporting criteria that are often primarily microscopic, are frequently unique combinations, and consist of observations made at the same point in time. Identification of the cause of the particular pathologic state is frequently not an integral part of the diagnostic problem. This approach constitutes diagnosis by 'pattern'.

In contrast, the histologic pattern of a drug reaction is usually nonspecific and does not have a one-to-one correspondence with any one agent; it is one of a limited number of reaction patterns by which the body responds to all disease-producing agents, and it may suggest only a class or type of drug.

To solve the drug reaction problem, the base of information must be enlarged far beyond the microscopic findings and must include sequential time-related drug and disease-marker data.

Toxic (enzymatic, etc.)	Degenerative and infiltrative
Inflammatory	Vascular (edema, congestion, thrombosis)
Developmental (congenital)	Functional (morphologic changes not necessarily demonstrable)
Hyperplasia, hypoplasia, aplasia	
Neoplasia	

Fig. 1. Categories of basic reaction patterns to injury

Before going into the specific methodology of drug-reaction problems, it is important to place 'tissue pattern' in broad perspective for basic orientation. The rather limited number of responses to injury constitute a final common path of reaction to a large number of disease-producing agents. These are listed in Figure 1. Drugs may produce any one of these patterns of response, as symbolized in Figure 2.

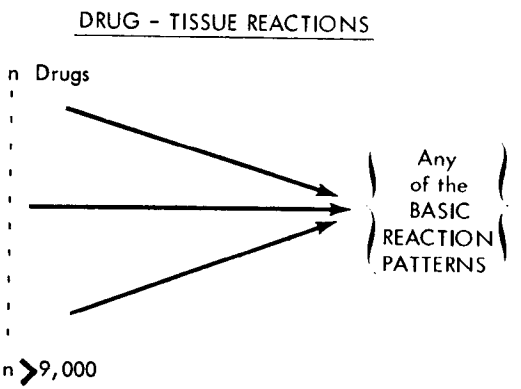

Fig. 2. A diagrammatic representation of the large number of drugs now available in comparison to the limited number of reaction patterns to them.

These reaction categories, however, are the same responses as to any of the other types of disease-producing agents (mechanical, thermal, radiation, viral, bacterial, spirochetal, etc.). This 'final *common* path' is emphasized when the drug category is placed with the other major classes of disease-producing agents, as shown in Figure 3.

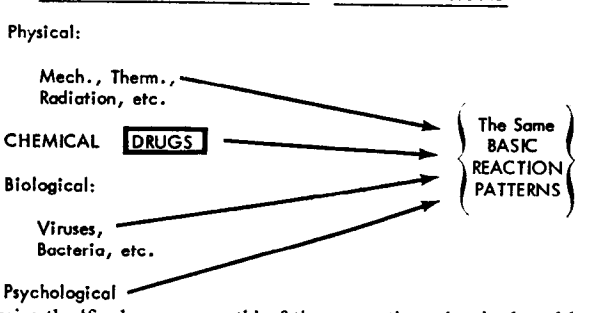

Fig. 3. To emphasize the 'final *common* path' of tissue reactions that is shared between drugs and all other categories of disease-producing agents.

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The evaluation of drug-related cases by the clinician and the pathologist is a retrospective problem. Each case is usually an unexpected event, an unplanned experiment, a therapeutic misadventure, and the diagnostic emphasis is on tracing the symptoms, signs, and morphologic findings back to their point of origin, the causative drug. Understanding the individual case comes from the precedent of past experience derived from such sources as:

1. Animal experimentation.
2. Carefully studied and documented individual human cases.
3. Limited clinical trials on groups of patients.
4. Epidemiologic and statistical studies.

For further orientation, the relationship between the *retrospective* drug-reaction case facing the practicing clinician and pathologist and the earlier *prospective* drug studies is brought out in Figure 4, which lists the successive stages in drug development.

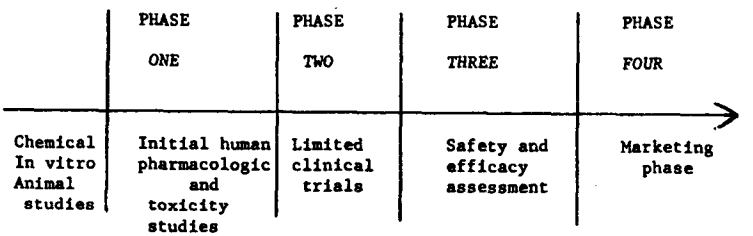

Fig. 4. The successive stages in new drug development.

The preclinical studies and Phases One and Two of the above sequence function primarily to detect toxic reactions and efficacy in animals and man, and Phase Three assesses safety and efficacy in more extensive clinical investigations. These initial phases are planned prospective studies. It is only in Phase Four, when there is widespread use of a drug by the public and when the number of persons at risk becomes large, that the relatively rare hypersensitivity, idiosyncratic, and pharmacogenetic reactions appear. The difference in incidence between these latter relatively uncommon categories and the toxic-type reactions is highlighted in Figure 5.

The earlier drug studies in Phases One and Two are designed to eliminate agents causing purely toxic reactions, and such compounds are thereby excluded from medical usage. Thus,

Relative incidence of drug reactions

Toxicity (overdose)	Exaggeration of therapeutic action Secondary pharmacologic action (Therapeutic doses)	Hypersensitivity Idiosyncrasy Pharmacogenetic (Therapeutic doses)
95+		a few
100	5 % or less	10,000–150,000

Numerators: Cases of drug reactions
Denominators: Persons at risk

Fig. 5. Illustrating the relatively high incidence of reactions to drug overdose (toxicity) as compared to therapeutic doses. The latter have a relatively low incidence if the reaction is an exaggeration of the therapeutic action of the drug, or is a secondary pharmacologic action. An even lower incidence with therapeutic doses is associated with hypersensitivity, idiosyncratic, and pharmacogenetic reactions.

except for accidental, suicidal, and homicidal overdoses and circumstances of occupational hazard, the majority of drug-reaction cases coming to the attention of the clinician and pathologist in the post-marketing phase are in the hypersensitivity, idiosyncratic, and pharmacogenetic categories. In addition, three other types of drug reactions may occur and should be included for completeness: those based on an exaggeration of therapeutic action; those related to the dominance of a secondary pharmacologic action; and those related to the potentiation of one drug by the action of another.

There are three points worth emphasizing about the post-marketing phase of drug problems. The first is their magnitude. The number of persons suffering from drug reactions has become increasingly large over the past several decades. Estimates of the number admitted to hospitals for drug reactions or those developing reactions while hospitalized vary from 1 or 2 % to as high as 15 %. It follows that the number of clinicians and pathologists involved in evaluating these problems is correspondingly large. A second point is that the clinical and pathologic judgments made on these cases have more than academic import; they have medical significance and may have medicolegal consequences. A third point to be emphasized is the complex character of the analytical problem presented by these retrospective cases.

To expand on the latter point, the retrospective case has little or no 'control' in the usual laboratory and experimental meaning of the word; many of the pertinent factors are only partly known or may be completely unknown; and much of the required information is either incomplete or is of questionable validity. The existence of these difficulties, however, does not mean that retrospective-type drug reactions can be avoided or that attempts to solve them should not be made, particularly in view of their medical and medicolegal significance.

To compare the drug-reaction problem in the pre- and post-marketing phases and to emphasize the difficulties in analyzing the retrospective case, the major elements in these two situations are placed in parallel in the skeletonized framework presented in Figure 6.

The primary elements in a mathematical relationship are shown in the first equation: an independent variable (X); a constant factor (K); and the dependent variable (Y).

In the experimental and prospective equation, the 'drug' is the independent variable and is a firmly known and definite factor under these controlled conditions. The 'biologic system' on which the drug acts is the 'K' or constant. This 'K' connotes environmental control and also implies an attempt to rule out intrinsic variations in the biologic systems by running parallel studies with animal or human subjects who have not been exposed to the drug in question. The 'dependent' variable, or result, consists of the 'action and effects' of the agent. These can be determined in considerable detail and depth with currently available clinical and laboratory methods.

In sharp contrast is the third equation, the retrospective-type problem. In this, the drug is labelled 'X' because its presence and its responsibility for the reaction are not initially a certainty, and because this factor is further clouded by the possibility of combined action with another agent or agents. The patient is in the position of the 'K' factor, though he or

Basic elements of problem
1. $X \cdot (K) \rightarrow Y$
2. Experimental and controlled clinical (prospective): Drug · (Biologic system) → (Action effects)
3. Clinical case (retrospective; post-marketing phase): X (Drug?) · (Patient) → Reaction

Fig. 6. A comparison between prospective- and retrospective-type drug reaction cases.

she is generally anything but constant, either intrinsically or environmentally, and in fact is receiving therapy because of illness. The patient does represent the 'biologic system', however, and labelling him thus keeps the retrospective equation in parallel with its prospective counterpart. The relative inconstancy of this 'K' factor serves only to accent the difficulty of the problem. The 'reaction' is the dependent variable, and this is frequently the most reliable element in the retrospective equation, consisting as it does of objective and, frequently, of measurable clinical, pathologic, and chemical abnormalities.

Figure 7 puts these comparative relationships in non-mathematical terms.

Basic elements of problem
1. $X \cdot (K) \rightarrow Y$
2. Experimental and controlled clinical (prospective): Drug · Does → What
3. Clinical case (retrospective; post-marketing phase): What · Did → It

Fig. 7. Another comparison between the major elements of prospective- and retrospective-type drug reaction cases.

Note that in the prospective equation the unknown factor is on the right side, designated as the 'what', and that the verb is in the present tense, indicating present action. In contrast, the 'what' or unknown of the retrospective equation is on the opposite side. This location of the major unknown factor accents the diagnostic emphasis placed on determining the cause of the reaction in the retrospective case and the relatively minor diagnostic significance of the resultant 'it', which is generally a nonspecific morphologic (and clinical) picture.

Having compared the relative clarity and obscurity of the primary factors in drug-related cases in the several phases of drug development and usage, the next step is to outline some of the practical difficulties in evaluating retrospective-type reaction cases. There are at least four:

1. Incomplete time-related drug and disease-marker information.
2. The multiplicity of drugs administered in most cases.
3. The lack of an objective means of demonstrating a causal relationship between a drug and a reaction in most instances.
4. The limited number of reaction patterns of the body to the entire range of physical, chemical, biologic, and psychologic causes of disease.

On the first point, insufficiency of information is nothing new in the practice of medicine. Diagnosis by histologic pattern alone, however, has more limitation in the drug field than in general pathology, and most drug-reaction cases require supplementation of the microscopic picture by time-orientated clinical and clinico-laboratory data.

A history of taking multiple drugs is the second hurdle. Analysis of the first 1,000 cases in the Registry reveals a range of from 1 to 32 drugs per case. Narrowing down to one drug is almost always difficult, frequently impossible, and the likelihood of combined or synergistic action of several agents further complicates the problem.

The third difficulty is the lack of an objective means of demonstrating a causal relationship between the drug and the reaction. At this time, the equivalent of the special stains and culture methods available for demonstrating specific causative organisms in some of the

granulomatous diseases is not available in the study of most drug reactions. The future may bring such specific means to drug pathology through advances in techniques for histochemical, enzymatic, and ultrastructural study.

The fourth major difficulty, the limited number of reaction patterns, has already been discussed and is repeated here only for emphasis.

In the analysis of cases with possible drug causation, there are four successive determinations to be made:

I. Is the drug eligible as to temporal factors?
II. Have 'other than drug' causes been eliminated with reasonable certainty (the differential diagnosis)?
III. Can the responsible agent be selected from the multiple drugs usually received by a patient and be firmly linked to the reaction?
IV. What is the degree of certainty of this analysis and diagnosis?

Evaluation of drug-reaction cases is most complex, and a methodical and comprehensive approach is required to avoid both 'overcall' and 'undercall'. Morphologic findings must be supplemented with time-related historical, clinical, and laboratory information. Drug 'timetables' and dated 'disease-marker' data are fundamental requisites for adequate analysis of a drug-reaction case.

I. TEMPORAL ELIGIBILITY

Temporal eligibility of the drug must be established. The interval between initiation of drug administration and a subsequent reaction varies within wide limits: seconds for death from cyanide; minutes to several hours for anaphylactic death from penicillin hypersensitivity; days to weeks for jaundice related to one of the phenothiazines; one to three or four months for the fatal aplastic anemia caused by chloramphenicol; and decades for hepatic malignancy following thorium dioxide. Regardless of its duration, there must be an interval of time between the initiation of administration of the drug and the subsequent reaction. This is an obvious point, but one that is frequently ignored.

Example: A case of thrombotic thrombocytopenic purpura (TTP) was attributed to indomethacin. A 50-year-old Caucasian man with a long history of rheumatoid arthritis and possibly lupus erythematosus developed substernal pain, fatigue, and malaise. These symptoms were followed by progressively increasing disorientation, dizziness, and fever. Terminally (five weeks later) he was semicomatose, with associated convulsive seizures. Two platelet counts in the last week of life were recorded as 30,000/cu mm and 16,000/cu mm. Autopsy revealed vascular lesions morphologically consistent with the diagnosis of TTP. These were found in the heart, brain, lungs, liver, pancreas, kidneys, and adrenals. As to the temporal relationship between indomethacin and TTP, however, he had not received the first dose of this drug until the beginning of the fourth week of his terminal five weeks. Assuming that his final and acute illness was a progression of one basic process, indomethacin could not have initiated the TTP, having been given three weeks after the onset of the final illness.

In contrast, temporal eligibility does not necessarily mean causality, as illustrated by the case of a 70-year-old Caucasian man who had an excision of an aneurysm of the lower abdominal aorta. On the tenth postoperative day oliguria developed, progressing to anuria, azotemia, and death two weeks later. In the autopsy protocol, tetracycline was implicated as the probable causative agent. The initially received clinical information, however, had no drug 'timetable' on which to base an 'eligibility' judgment. On retrieval of the patient's chart, a time-flow graph was made (Fig. 8): this showed that tetracycline was given on the third to the eighth postoperative days. Since the renal dysfunction did not begin until the tenth postoperative day, drug 'eligibility' was thus established. The probability that basic vascular disease of the patient played a major role in the renal dysfunction, however, was brought out by further clinical and pathologic information. A radioactive renal scan had been done

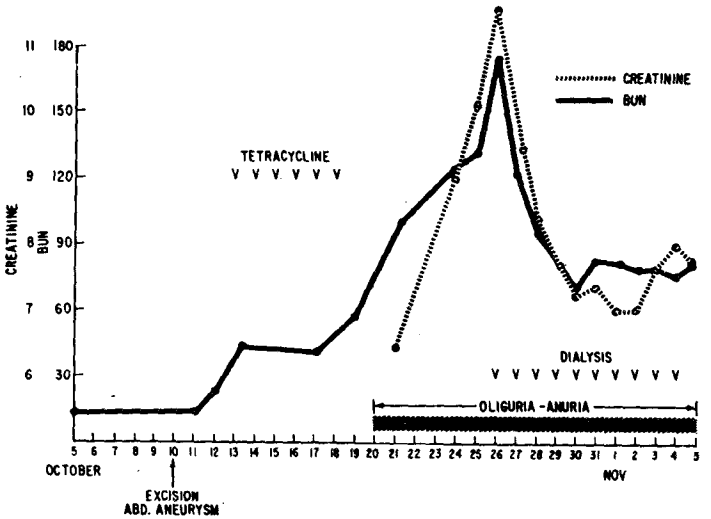

Fig. 8. 'Time flow chart' showing the temporal eligibility of tetracycline in relation to the subsequent renal failure.

nine days before death and was reported as 'showing no function bilaterally', and a translumbar aortogram done on that same day 'showed no flow in the left kidney and minimal or no flow in the right kidney'.

The autopsy revealed a second aortic aneurysm located above the level of the aneurysm previously resected. This was the site of rather extensive mural thrombosis, and the prosector reported that 'the gross autopsy findings would indicate at least a partial bilateral occlusion of the origins of the renal arteries by the mural thrombus of the aneurysm'.

That tetracycline may have had some effect on the function of these kidneys cannot be denied, but clinical and morphologic demonstrations of renal vascular compromise reduce the tetracycline relationship to the relatively weak 'possible' category, and in actuality it may have been only 'coincidental'.

II. THE DIFFERENTIAL DIAGNOSIS 'OTHER THAN DRUG CAUSES'

The following differential-diagnosis list is of assistance in ruling in or out factors other than the alleged drug that might be responsible for the clinical and morphologic changes:

1. Another drug not initially listed or considered.
2. The combined or synergistic action of several drugs.
3. The basic disease(s) of the patient.
4. The results of previous operations or diagnostic procedures.
5. Other methods of therapy known to have been used.
6. A placebo reaction.
7. A combination of several of the above items.

The reasonably certain elimination of the above factors should be based on *active* search into the historical, clinical, and pathologic features of the case, and not on passive acceptance of the sparse and inadequate information initially available in many cases.

This negative approach of elimination, when combined with the positive clinical and pathologic findings, results in a complementary system that aids in reducing diagnostic error. Parenthetically, the confirmed presence of one or several of these 'other than drug' factors does not mean, however, that drug action is necessarily ruled out. Morphologically similar drug and non-drug disease patterns might possibly co-exist in the same patient, which further emphasizes the diagnostic difficulties of the problem.

1. Another drug not initially listed or considered

Multiple drug therapy (polypharmacy) is the rule rather than the exception, and the initially received clinical data do not always list all agents administered. The importance of broadening the etiologic considerations beyond the alleged and initially mentioned drug or drugs is illustrated by the following case:

A three-year-old boy ingested 30 g of acetylsalicylic acid. No salicylate levels were recorded. Death occurred in 48 hours. The case was submitted to the Registry as one of salicylate intoxication. The autopsy findings were nonspecific. The history mentioned the use of ipecac to induce emesis. Retrieval of the patient's chart revealed that the child had indeed received ipecac: 10 ml of the syrup, and later 10 ml of the fluid extract. Since the adult dose of the fluid extract is only 0.5 to 1.0 ml, this three-year-old child received 10 to 20 times the adult dose. The final diagnosis was: salicylate and ipecac intoxication. Whether the child would have survived the salicylate toxicity alone is conjectural.

2. The combined or synergistic action of several drugs

In toxic-type drug reactions, several drugs in combination may cause death even though their individual levels in blood or tissue are not in lethal ranges.

A 39-year-old Caucasian man was found dead, an apparent suicide. The autopsy findings were nonspecific. Pulmonary edema and congestion were the only positive pathologic findings. Toxicologic examination revealed the following secobarbital levels: blood—0.25 mg/100 ml; in the liver—1.34 mg/100 g. The ethanol blood level was 2.5 mg/ml. The individual levels of these two agents are below the usually accepted lethal range but, taken together, were considered to be responsible for the death.

Many additional examples of drug interaction or combined action might be cited, such as the enhancement of the hypoglycemic effect of the sulfonylureas by coumarin anticoagulants.

3. The basic disease or diseases of the patient

The possibility that the tissue reaction was caused by the primary or concomitant disease present, and not by the drug received, is an important point in the differential diagnosis. This is illustrated by the following case:

A 64-year-old man had thrombosis of the common iliac artery, and an arteriotomy and by-pass were done. A regimen of warfarin therapy was begun. Subsequently he had several episodes of hematuria and melena. These were attributed to the anticoagulant therapy. Cessation of these bleeding episodes was noted with discontinuance of the anticoagulant. Later, autopsy revealed 'incidental' findings of a primary carcinoma of the urinary bladder (Fig. 9) and an adenomatous polyp of the rectum, neither of which had been demonstrated prior to death.

That the hematuria and melena were possibly related to the anticoagulant therapy acting on these two 'loci minoris resistentiae' cannot be denied, but clinically they were assumed to have been *purely* drug related, and no search had been made for other causes of these hemorrhagic episodes.

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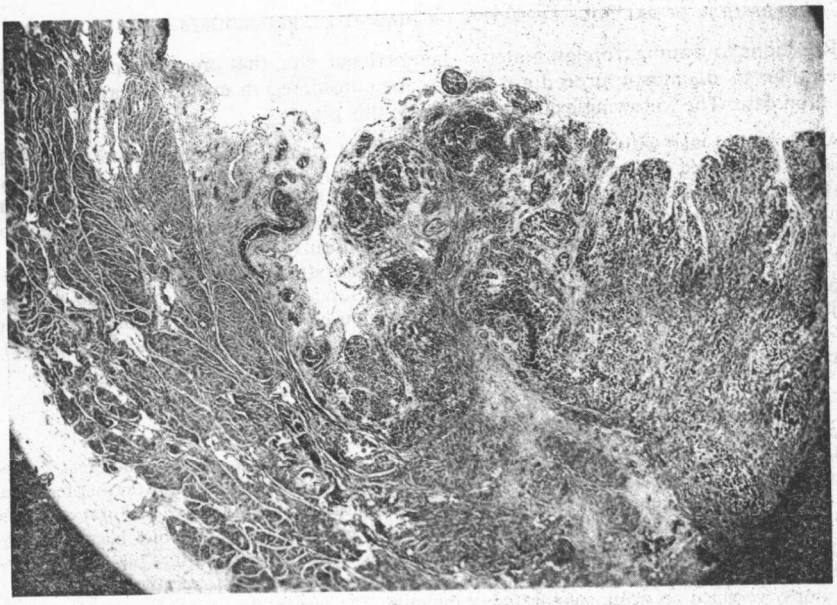

Fig. 9. Urinary bladder: primary carcinoma. Case of hematuria associated with anticoagulant therapy; × 9.8.

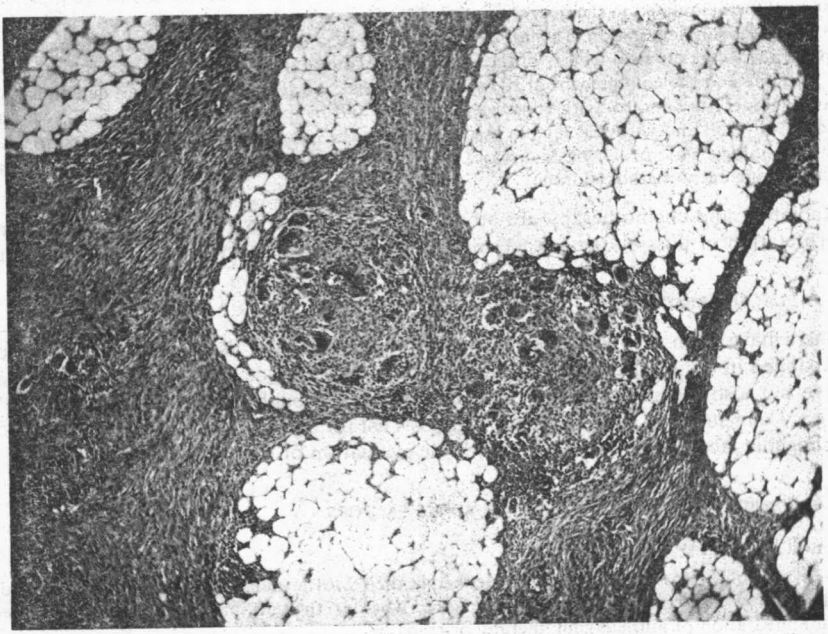

Fig. 10. Peritoneal biopsy. Granulomata and fibrosis. Case of intestinal obstruction originally attributed to lincomycin. Talc identified in these tissues by X-ray diffraction; × 40.

4. THE RESULTS OF PREVIOUS OPERATIVE OR DIAGNOSTIC PROCEDURES

Reactions to trauma, foreign material, hemorrhage, etc., that are consequent to previous operations or diagnostic procedures have to be considered in evaluating an alleged drug-reaction case. The following example illustrates this point:

A 33-year-old man with a chronic duodenal ulcer had a partial gastrectomy. As a prophylactic measure he received intravenous lincomycin postoperatively. One month later signs and symptoms suggesting intestinal obstruction developed. At the second laparotomy, multiple foci of edema and induration were found throughout the abdominal cavity. Biopsy of several of these revealed fibrosis and chronic inflammation, including multinucleated giant cells (Fig. 10).

The pathologist submitting the case quoted the surgeon as strongly implicating lincomycin as being responsible for this peritoneal reaction. The latter cited several other patients who had had similar peritoneal reactions after receiving lincomycin intravenously. Histochemical studies on the tissue of this case revealed the presence of talc and silica. In view of this finding, the multiple peritoneal granulomata were considered to be secondary to talc (glove powder) and not to the lincomycin.

5. OTHER METHODS OF THERAPY KNOWN TO HAVE BEEN USED

A case illustrating this point is that of a 23-year-old woman with an 'acute abdomen'. The white cell count on admission was 20,500/cu mm with 90% polymorphonuclear leukocytes; her temperature was 101.6° F. Seven hours after admission, laparotomy was done under methoxyflurane anesthesia. Her pulse, initially 120, rose to 160/min soon after the skin incision, and her color became dusky. By the time the surgeon was ready to enter the abdominal cavity, her temperature had risen to 109° F. At this point the operation was discontinued. She died seven hours postoperatively.

Autopsy revealed an acute suppurative salpingitis. The possibility of death from the anesthetic agent methoxyflurane was at issue.

After detailed operative and anesthesia records had been studied and after consultation with several anesthesiologists, the death was judged not to have been caused by the anesthetic agent *per se*, but by several factors related to the operative procedure, in combination with the patient's systemic reaction to her tubal inflammation. The initially high pulse rate and relatively elevated temperature, when combined with the physical factors of the surgical procedure (decreased sweating from the preoperative atropine and the confinement of the surgical drapes), led to increased oxygen demands and decreased temperature control with consequent hypoxia and hyperthermia. This vicious cycle was the result of physical and chemical factors associated with the operative procedure interacting with the pathophysiologic state of her basic disease, and her death was not considered to be directly related to the specific agent methoxyflurane.

Radiation and chemotherapy are other methods of therapy whose effects might confuse interpretation of possible drug reactions, particularly in the evaluation of blood dyscrasias.

6. A PLACEBO REACTION

There have been no recognized examples of placebo-type tissue reactions in the cases accessioned in the Registry to date. That placebo-induced side effects may not only be subjective but also include objective reactions has been brought out by Schindel, 1968. This category is included in the differential diagnosis list for completeness, and to emphasize that psychogenic factors cannot be ignored in the evaluation of drug-reaction cases.

7. A COMBINATION OF SEVERAL OF THE ABOVE FACTORS

As an illustrative case:

A 61-year-old man with myelogenous leukemia died with terminal uremia. He had received busulfan therapy. The contributor of this case asked whether 'the terminal uremia was precipitated by the administration of antileukemic therapy principally'.

Time-oriented information was plotted on a 'time-flow chart' (Fig. 11).

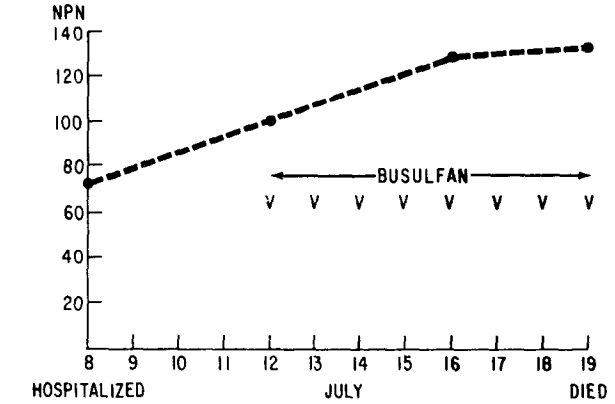

Fig. 11. 'Time flow chart' demonstrating temporal ineligibility of busulfan to have initiated the elevation of NPN found on admission to hospital.

This showed that the NPN was already elevated more than two times above the normal level on admission to the hospital, and was rising prior to the first administration of busulfan. As noted on the graph, there was no appreciable effect on the rising slope of the NPN curve after administration of this drug was begun.

In this instance, busulfan was not temporally eligible to have caused the initial elevation in the NPN. In addition, the kidneys at autopsy revealed the presence of three major pathologic changes (heavy leukemic infiltration, severe arterial and arteriolonephrosclerosis, and old pyelonephritis). The combination of the temporal ineligibility, the three pre-existing basic diseases, and the unchanged slope of the NPN curve after receiving busulfan, all pointed away from the implication of this agent as being related to the terminal renal failure.

III. SELECTION OF THE RESPONSIBLE DRUG

Up to this point, the discussion has been concerned with the establishment of 'temporal eligibility' of the alleged drug or drugs and with the identification or elimination of 'other than drug' causes for the reaction.

The next step in the analysis is an attempt to select the responsible drug or drugs from among those that are eligible. Since most patients have received more than one drug, not only may more than one be eligible, but the reaction may be on a multidrug base. The selection of the responsible agent and its identification with the reaction may be accomplished by any one or several of the following methods:

1. By identification of agent
   A. (i) Qualitative; (ii) Quantitative
   B. By demonstration of the pathologic mechanism (enzymatic deficiency; in vitro identification of agglutinins, lysins, etc.; immunofluorescent techniques). (No illustrative cases to be cited.)

2. By pattern
   A. Pathologic: morphologic (primarily microscopic)
   B. Clinicopathologic: the total features of a case

3. By exclusion
4. By singularity of the drug
5. By re-challenge
6. By de-challenge

It is to be noted that most of the above methods require the use of clinical and time-related data. It is not uncommon to use more than one of these methods in an individual case, and such combination strengthens the validity of the diagnosis.

1. By identification of agent

This approach is primarily of use in cases of toxicity and drug overdose. Except to confirm the presence of a particular drug, it is of little value in other drug-reaction categories (hypersensitivity, idiosyncratic, and pharmacogenetic) in the selection of the responsible agent from among the many that are present. Even if blood and tissue levels are determined in a multi-drug case in these latter categories, one is still left with the problem of selecting the responsible agent by other means, since these levels are not usually in 'toxic' ranges.

Before citing case examples of 'agent identification' as an analytic tool, it must be pointed out that the tacit acceptance of the drug history is not always a safe one, as the following case will illustrate:

A 49-year-old Caucasian man complained of increasing fatigability. His BUN was 42 mg %; creatinine: 4.1 mg %; and his creatinine clearance was 25 ml/min. A renal biopsy revealed multiple non-caseating microgranulomata in which were interspersed a few eosinophilic leukocytes. Since sulfonylurea compounds may in some instances be associated with granulomata in the liver, heart, and kidneys (Bloodworth, 1963), inquiry was made as to what drugs he had received. The response indicated that the patient was a diabetic and that he had been on tolbutamide for several years. At this point, there was a possibility that the renal lesions were on a hypersensitivity basis and due to tolbutamide. We next requested follow-up information on the renal-function studies, particularly if tolbutamide therapy were to be stopped. Response to this inquiry included the following statement: 'The physician in charge of the patient has just informed us that the patient never took tolbutamide, and the physician was under the impression that he was taking tolbutamide. We would like to apologize for this rather embarrassing situation'.

Another stumbling block in the way of accurate analysis is the occasional mislabelling that may occur anywhere in the chain from drug production and distribution to the ultimate consumer. A case in point is that of a patient with a history of penicillin allergy who inadvertently received penicillin that had been erroneously labelled as ascorbic acid (Golbert and Patterson, 1968).

A. (i) Qualitative A 62-year-old woman with carcinoma of the endometrium submitted to lymphangiogram studies for evidence of metastasis. Radiopaque material (ethiodized oil) was injected into the dorsal lymphatics of the foot. The patient died later the same day from massive pulmonary embolism from a pre-existing thrombophlebitis of the opposite leg.

Lipid emboli were demonstrated in glomerular and pulmonary alveolar capillaries. These emboli were positive for halogenated lipids (Felton stain), and were oil red O positive. Identity between the fat-positive and radiopaque material was established by demonstrating them both in the same quadrant of a glomerulus by successive microradiograph and fat stain on the same kidney section (Fig.12)

While it was considered that this halogenated lipid embolization was not the cause of death and its demonstration in these several tissues was of only academic interest, the case serves to illustrate the special methods that may be used to demonstrate the presence of an agent qualitatively.

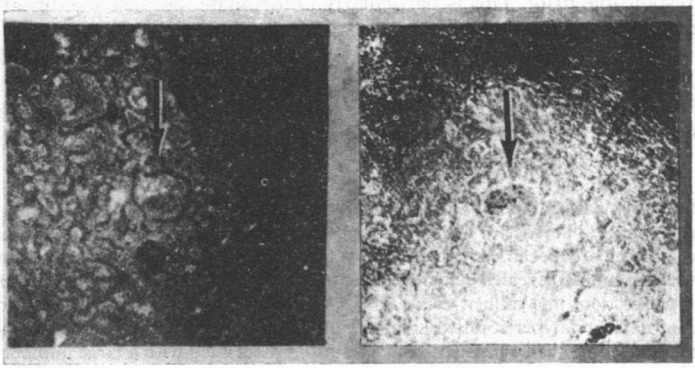

Fig. 12. Companion microradiograph (left) and fat stain (right) of the same glomerulus, demonstrating the identity between the radio-opaque and the fat-positive material embolic to the left upper quadrant of the glomerulus (halogenated radio-opaque lipid); × 24.

A. (ii) Quantitative Toxicologic studies with determination of blood and tissue levels are the basis for the establishment of a firm diagnosis in cases of overdose and may separate the toxic from the hypersensitivity reactions, as illustrated by the following case:

A 21-year-old Caucasian man was brought into the dispensary in acute respiratory distress with an alleged history of allergy to chloroquine-primaquin malarial prophylactic. He claimed to have taken one such tablet, followed in two hours by emesis and dyspnea. Cardiac arrest followed. He died four days later in a respirator. The case was initially signed out as a hypersensitivity reaction, based on the history and the nonspecific autopsy findings. Fortunately, frozen tissues were included in the material submitted. Toxicologic examination revealed the following:

Chloroquine -	Blood:	6.5 mg/100 ml
	Brain:	2.5 mg/100 g
	Kidney:	24.0 mg/100 g
	Liver:	23.0 mg/100 g
	Lung:	23.0 mg/100 g
Gastric contents:		12.5 mg in total sample of 240 ml.

The distribution of chloroquine in the blood and tissues in this case is similar to the distribution found in a series of 13 fatal cases of chloroquine suicide (Kiel, 1964). The toxicologic studies permitted its recognition as an overdose case rather than one of anaphylactic death.

2. By pattern

Diagnosis by pattern is common practice in pathology as well as in clinical medicine. In the field of tumors, certain morphologic patterns connote a benign course; others point to malignancy. These combinations of findings constitute the criteria on which diagnoses are based and set precedents for future judgments. Similarly, in clinical medicine certain combinations of historical, clinical, and laboratory findings form patterns or profiles that become designated as particular diagnostic entities.

In drug pathology, past experience with documented cases may reveal a fairly constant relationship between certain agents or classes of agents and particular pathologic and clinicopathologic patterns, serve as guides for evaluating future cases, suggest the likelihood of certain causative agents, and permit reasonably certain prognostication in many instances. The weakness of this approach by pattern is its nonspecificity and its inability to pinpoint

the specific responsible drug. This is particularly unfortunate, because identification of the causative agent is one of the major issues in evaluating drug-related cases.

To apply the pattern of past experience to a specific and current case is not without diagnostic risk. Such a step must include supplementation of the pathologic findings with confirmation of the 'eligibility' of the drug and the ruling out of other possible etiologic factors, such as those listed in the differential diagnosis list. Pattern diagnosis, both clinical and pathologic, is of value in drug-reaction problems, but its limitations must be kept in mind.

An example of this 'pattern' method is afforded by the case of a 36-year-old Caucasian male alcoholic who was under the influence of alcohol while using carbon tetrachloride in a small unventilated enclosure. He subsequently became jaundiced and was hospitalized with evident liver damage. In his recovery phase, liver biopsy revealed evidence of centralobular zonal necrosis, with central sinusoidal dilatation and congestion, fine-caliber vacuolation of liver cells, collapse and condensation of reticulum fibers centrally, and hypertrophied Kupffer cells containing lipofuscin and hemosiderin. These centralobular zonal changes are consistent with alterations associated with a large number of hepatotoxins, including hydrocarbons, but are not themselves specific for any particular agent.

The diagnosis of carbon tetrachloride toxicity was made in this case by the combination of the documented history of a single and particular drug exposure plus morphologic changes consistent with past experience with this particular agent.

3. By exclusion

This method employs the use of a 'time-flow' chart on which are plotted drug and disease-marker information. Drugs administered after the appearance of the disease marker cannot be the initiators of a reaction. Parenthetically, however, it should be pointed out that they may in some instances interact with the initiating drug and therefore cannot be eliminated from a potential relationship to the subsequent problem.

It is to be emphasized that the establishment of temporal 'eligibility' itself is not proof of causation, and 'other than drug' factors must be eliminated with reasonable certainty before the presumption of drug causation when using the exclusion method.

An illustrative case is that of a 15-year-old Negro male with pulmonary blastomycosis, proven by culture, and with no prior evidence of any renal dysfunction. His BUN rose, as shown on the time-flow chart (Fig. 13). Renal biopsy revealed an acute and chronic interstitial nephritis, and the infiltrate

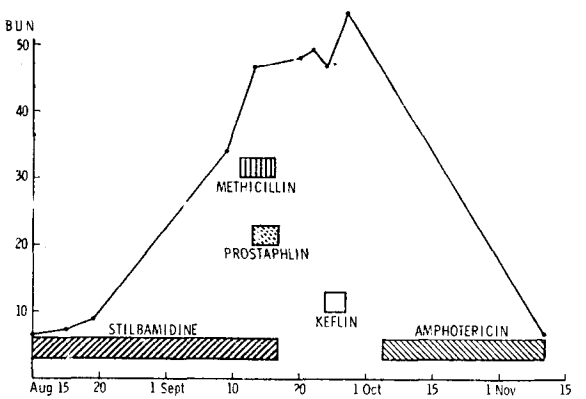

Fig. 13. 'Time flow chart' demonstrating temporal eligibility of stilbamidine for the production of the BUN elevation and the interstitial nephritis.

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