PHYSICIAN'S LIABILITY FOR PRESCRIPTION DRUGS

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INTRODUCTION

The Registry of Tissue Reactions to Drugs located at the Armed Forces Institute of Pathology, Washington, D.C., reports findings that one in twenty beds in a general hospital is occupied by a patient suffering from a complication of chemotherapy, and that one in seven patients will suffer some kind of a drug reaction during hospitalization.¹

In a three month period at Johns Hopkins Hospital, 122 of 714 general medical service patients (17.1%) had an adverse reaction to medication.² In the same period, 97 patients (13.6%) acquired an adverse reaction during hospitalization. Of 36 patients admitted because of a drug reaction, 11 (30.4%) acquired another reaction in the hospital. Eight of the 36 patients died, five from the reaction for which they were admitted to the hospital and three of a reaction acquired in the hospital.

In the year beginning July, 1965, all patients admitted to a public medical service of the Montreal General

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¹Cluff, et. al., Studies on the Epidemiology of Adverse Drug Reactions, 188 J.A.M.A. 976 (1964), reports the same ratio in a four week study of admittances due to adverse responses to drugs.

²CLIN-ALERT Nos. 2, 142 (1967).
Hospital were surveyed for drug reactions occurring during hospitalization. Of 731 patients, 132 (18%) experienced 193 reactions, the majority of which were severe enough to require specific corrective therapy, prolonged hospitalization or which were life threatening or fatal. One-quarter of the 67 deaths on the service were the result of adverse drug reaction. In addition to the above, 48 patients were admitted because of drug reactions outside the hospital and of these, 15 had further reactions in the hospital.

These statistics are from hospital services alone in special studies designed to measure the incidence of drug reactions. No such measurement has been attempted in the case of the general populace, but it is reasonable to suppose that presently, and in the years ahead, hundreds of thousands of people will be injured or killed through the media of supposed life preserving medications. Anaphylactic reactions to penicillin alone are said to occur in one to five out of every 1,000 patients and it has been estimated that there are about 90,000 such anaphylactic reactions annually. The figure is deemed conservative because of the incidence of unreported cases.

The problem of gathering statistics is further complicated by the fact that a drug reaction may mimic a serious disease and thus go unrecognized. Also, drugs are often given in concert with other drugs so that it may be impossible to pinpoint the cause of an untoward result.

In the years 1952-1961 alone, 4,562 new drug products were marketed in the United States. New pills (not all

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3 97 CAN. M.A.J. 1458 (1967); CLIN-ALERT No. 1 (1968).
4 There is a similar report from the University of Western Ontario of 104 persons who at some time during a 59 day period occupied a 31 bed medical ward. In all, 23 errors in drug administration in 20 patients were noted and 30% of the 104 patients had adverse drug reactions or were subject to error in the administration of drugs. See CLIN-ALERT No. 273 (1967). A follow-up study of the same Montreal investigators produced a slightly better result. See 98 CAN. M.A.J. 175 (1968); CLIN-ALERT No. 51 (1968).
miracle drugs) have been flooding the market at the rate of one a day. To compound matters further, 90% of the prescription drugs now in use did not even exist 20 years ago. Most of the antibiotics, steroids, antihistamines and tranquilizers have been developed and put on the market since the average-aged doctor left medical school.

Although the rule of law is that a physician must keep abreast of the times and follow approved methods in general use, the current crop of chemical creations has threatened to nullify his skills by antiquating his education and training by adding new lore at a rate he cannot hope to absorb while practicing his profession. The doctor cannot ignore the host of new drugs, but to keep up with published reports of them is out of the question.\(^7\)

It is patent that the role of the doctor in the purveying of drug products is of prime importance, since he is the vehicle by which the medication is transferred from the manufacturer to the consumer. The vice is that since the doctor cannot hope to ferret out all vital information concerning drugs for himself, he is usually consigned to obtaining his knowledge from the manufacturer. It is a fact that most information concerning drug products which comes to the attention of the average physician is heralded by the detail men of the drug companies whose design is to push their products, or from drug company advertising in one form or another. And this is where the problems of the doctor begin.

The human being is an extremely complicated dynamic system and there is considerable variation in the system from one person to another. As to any particular drug, the dosage form was once thought of as a pharmaceutical carrier used to deliver the labeled amount of active ingredient to the patient. Today, because of increased biological knowledge, the problem of the drug formulator is much more extended. He must be concerned with the

\(^7\) The National Library of Medicine has estimated that about 200,000 articles on drugs are published each year.
absorption, distribution, metabolism and excretion of the
drug in an intact biological system—a live human being. Thus, a particular drug dosage should be thought of as a
physical system which is entrusted with the task of de-
delivering the drug to the site of its absorption in the most
efficient, predictable and reproducible manner.

As to the individual physician, his problem is that
he knows of the medication only what the manufacturer
has seen fit to tell him. Thus, when a new drug comes
on the market, the dispensation of it is to use the patient
as a guinea pig in the testing process. The physician
cannot know of the long range effect of the therapy, nor of the results possible when drugs are used in combi-

8 See Tingstad, The Use of Biological Data in the Design of Phar-
maceutical Dosage Forms, 5 LEX ET SCIENTIA 105 (1968).
9 Id.

For example, that Chloroquine (Aralen) induced ocular damage is
apparently related to the amount of the drug taken rather than the daily
dose. The drug is stored in the melanin-bearing tissues of the eye where
it remains long after it has been eliminated from the other parts of the
body. Even small doses exert a cumulative effect. See Leading Articles,
1 BRITISH MED. J. 254 (1967).

10 See CLIN-ALERT No. 103 (1968).
11 MacDonald & Robinson, Clinical Observations of Possible Barbituate
Interference With Anti-Coagulation, 204 J.A.M.A. 97 (1968).

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journals, brochures mailed to the practitioner's office replete with samples, and by the detail men.

A psychiatrist\textsuperscript{13} reviewed 133 referrals sent to him for evaluation and/or treatment. All patients had been under the care of non-psychiatrist physicians. Of 93 patients who had been on some type of drug therapy, 90 were considered unresponsive. The greatest source of drug failure was inappropriate prescribing. There were 42 cases in which drugs were misused and nearly as many patients had chronic illnesses which could not reasonably have expected to improve with medication. In addition to the 42 cases, there were 30 in which nonpsychotherapeutic drugs were used for emotional disorders. In many instances drugs were given without objective evidence of an organic condition to justify their use, \textit{e.g.}, thyroid for euthyroid patients, anti-convulsants for patients without seizures, hormones for women without menopausal symptoms, iron for patients without anemia, etc. The schizophrenics received inadequate or no treatment. Of these, 8 had been to their family doctor without psychiatric care or referral, 19 had received inappropriate psycho-pharmacologic drugs and 7 received nonpsychopharmacologic drugs.\textsuperscript{14}

It is an understatement to allege that our present day society is drug conscious. We are exposed to drugs not only for the treatment of disease entities, but for manifold other purposes. They are used for anesthesia as well as analgesia, to put us to sleep, to wake us up, to tranquilize the over-anxious, to stimulate the depressed, as well as for the diagnosis of specific ailments. Drugs have been developed which modify one's personality by expanding memory functions and which change life cycles by affecting menstrual and menopausal functions.

There is a growing recognition that all drug usage involves some risk.\textsuperscript{15} Drug induced injury is the price paid by society for development of drug technology. What

\textsuperscript{13} Lynn, 57 IND. M.A.J. 1229 (1964).
\textsuperscript{14} See CLIN-ALERT No. 357 (1964).
\textsuperscript{15} See Modell, \textit{Hazards of New Drugs}, 139 SCIENCE 1180 (1963).
is more important is that the public is becoming drug reaction conscious. It is becoming increasingly clear that people at large will continue to support new drug development only to the extent that the law provides appropriate and adequate remedies for those injured and killed by drug products. The victim is clearly entitled to compensation from those responsible, the doctor, the drug company, the pharmacist, the hospital or the nurse, if the injury could have been avoided in the exercise of reasonable care.

In recent years there have been many verdicts in drug reaction cases totaling millions of dollars. Similar awards and settlements in startling amounts have been reported in cases involving chloromycetin, polio vaccine, MER/29, measles vaccine, and many others. Awards have been made for neurotoxicity related to penicillin, renal damage caused by methicillin, deafness related to neomycin and kanamycin, and vestibular dysfunction caused by streptomycin.

Thirty years ago drugs were used almost indiscriminately, but then it was of lesser consequence, for fewer drugs were available for prescription, and, of those that were, most were inconsequential so that if the patient was not benefited by the prescription, at least he was not hurt. In those days, the physician did not see the

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16 In Stromsodt v. Parke, Davis & Co., 257 F. Supp. 991 (N.D.N.D. 1966), an award of $651,783 was made in the case of an 8 year old boy who at the age of 3 months was immunized with Quadrigen, a quadruple vaccine. He was left with irreversible brain damage, mental retardation and right-sided paralysis. In Morgan v. Sterling Drug, Inc., an award of $550,000 was made to a 38 year old woman who became blind as the result of the administration of Aralen for rheumatoid arthritis. In Kershaw v. Sterling Drug, Inc., a companion case, a plaintiff was awarded $150,000. 11 A.T.L. Ass'n Newsletter 152 (May 1968). Other awards in reported Aralen cases are: Sterling Drug, Inc. v. Cornish, 370 F.2d 82 (8th Cir. 1967) ($80,000); Yarrow v. Sterling Drug, Inc., 263 F. Supp. 159 (S.D.S.D. 1967) ($180,000); Bine v. Sterling Drug, Inc., 422 S.W.2d 603 (Mo. 1968) ($175,000 reduced on remittitur to $125,000); Krug v. Sterling Drug, Inc., 416 S.W.2d 143 (Mo. 1967) ($125,000).

17 The role of the pharmacist today has been reduced from the careful compounding of prescribed elixirs to interpretation of the doctor's handwriting, counting the requisite number of pills, and typing the directions for use.
necessity of informing his patient of the medication he was administering. When a new drug came on the market, e.g., penicillin, it was considered a panacea and was prescribed for all ailments, even when the supply of it was scarce, in amounts which by modern standards would be considered inadequate, because not enough was known of it.

Literature on drug toxicity did not begin to accumulate until the late 1930's with the advent of the sulfonamides which greatly enlarged the scope of chemotherapy. The greatly increased availability of antibiotics in the '40's and '50's gave greater rein to physicians generally in their combat against disease, but actual knowledge of therapeutic misadventure was largely confined to medical journals and the medical profession. The great misadventure which alerted the general public to drug toxicities, allergies and idiosyncracies was the thalidomide disaster which produced grotesque birth defects in the early 1960's. Even now they are the subject of much comment and concern in the fields of sociology, psychology and economics as well as medicine.

DRUG TOXICITY

Every physician knows that the use of a drug involves at least a remote possibility of an unfavorable response to it. Not only may a patient's intrinsic hypersensitivity cause a reaction, but there is a possibility that the amount of the dosage, the mode of administration and even the speed of the injection may cause an unfortunate reaction. It may be that a great percentage of such reactions are unpredictable, but there are occasions where a physician, in proper medical practice, can prophesize the possibilities of a reaction with a great degree of probability.

On the other hand, the pharmacologist regards all dosages as toxic and he views the undesirable effect of a drug merely as one which is not beneficial. The pharmacologist knows that all dosages achieve their effect by the disturbance of one organ system in preference to an-
other. According to the Food and Drug Administration definition, an adverse drug reaction is one that is noxious, unintended, and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological functions. More simply put, it is a reaction to a drug in a patient which was not intended. The results of the administration of a drug which are severe enough to be called side effects or toxic reactions are always present to some degree although they may be so minor as not to be noticed by a person taking them. But it matters little to the pharmacologist whether the incidence of reaction is high or low, for he is aware that there is a dosage in which, in a given situation, any drug will produce toxicity.

"Idiosyncracy" is a word used more by the courts than by those in the field and it is largely employed as a waste basket term to describe an allergic or toxic reaction. It implies that there is some built-in mechanism in a person which causes him to respond abnormally to a medication. There are some cases which fall into this category, but the pharmacologist avoids the use of the word since it has implications which he would describe otherwise.19

The pharmacologist places drug toxicities into three general categories:

1. Where the reaction is minor. As indicated, there is always some complication to drug administration, even if so minor as not to be readily noticed. If there is a noticeable response to the drug, it usually takes the form of a headache, nausea, fatigue or of just not feeling well. Unless the symptoms are severe, the physician usually disregards the complaint on the theory that the patient will be more benefitted by the drug than the slight discomfort he might have to endure. Such minor toxicities are not often the subject of lawsuits except under unusual

19 Id.
circumstances. One such circumstance which has given rise to litigation is in the prescription of antihistamines without appropriate warnings that the user might become drowsy.  

2. Where the reaction is reversible in most instances. The examples are skin rashes, fever and the like. The symptoms disappear on withdrawal of the drug without permanent injury. Unless there is some harmful residual, this type of reaction does not usually give rise to litigation.

It should be noted, however, that drug reactions sometimes do not commence promptly following the institution of drug therapy. Correspondingly, they sometimes do not stop immediately after administration of the medication is halted. It is not like turning a light on and off.

3. Where the reaction is irreversible. This type of situation is always a potential embryonic lawsuit. The examples are: teeth staining in the case of tetracyclines; cataracts in the case of MER/29; visual impairment in the case of Chloroquine (Aralen); aplastic anemia in the case of sulfonimides; and many others.

CONSIDERATIONS BASIC TO SUIT

Cases of allergic toxicity are always difficult to prepare and prove. Unless the patient has suffered a substantial, irreversible injury, it is usually better to forego the claim than to take on the case. The usual intangibles which plague the plaintiff's attorney are whether the possibility of a reaction could have been determined before the drug was prescribed, whether the reaction was due to a condition inherent in the person for which no one could be blamed (the true "idiosyncracy"), or whether the medication, once started, could or should have been stopped in time to avoid the undesirable consequence.  

Most drugs, reactions to which are capable of pre-testing, do not need that prerequisite. Furthermore, such determinations are frequently uncertain. In all cases however, it is valid to inquire whether the blame for a drug reaction was due to the drug, the patient or the physician.

Under ordinary circumstances, assuming that the drug was wholesome when placed on the market, and that warnings and contraindications as to its use should have been known, or were plainly indicated, or readily available, the inquiry of the attorney should be somewhat along the following lines:

1. The manufacturer's literature, or PHYSICIAN'S DESK REFERENCE, should be examined to ascertain whether the drug was contraindicated in the case, whether by foresight or hindsight. The literature concerning the drug should then be carefully researched. The concern is improvement of the attorney's knowledge with a view to determining the substance of the case. It should be kept in mind that the package insert is concerned with a drug and that it is not intended to instruct the physician in the diagnosis of diseases or in the recognition of pathological states. It is not intended to replace the doctor's basic learning as to pharmacology or drug therapy.

2. The next point of inquiry, sometimes the most fertile one, should be whether the drug prescribed was medically indicated in the case, or whether the physician

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22 The following texts may be found useful: BECKMAN, DILEMMAS IN DRUG THERAPY (1967); BECKMAN, DRUGS, THEIR NATURE & USE (1958); GOODMAN & GILMAN, THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (1958).

At intervals, The Medical Clinics of North America publishes a volume on "Efficacy of New Drugs." The two most recent are the issues for March, 1964 and September, 1967.

See also Robinson, Antimicrobial Drugs, Their Action, Use and Adverse Effects, in CANTOR, TRAUMATIC MEDICINE AND SURGERY FOR THE ATTORNEY 141 (Supp. Serv. 1964).


Two services to which reference should be made are: CLIN-ALERT, published by Science Editors, Inc., Morrisville, Ky. and the MEDICAL LETTER ON DRUGS AND THERAPEUTICS, published by Drug and Therapeutic Information, New York, N.Y.
should have, in the exercise of reasonable care, prescribed a more benign or perhaps longer established drug.\textsuperscript{23}

3. The attorney should then ascertain whether, in the exercise of due care, the reaction sustained should have sooner been discovered in the particular patient. Inquiry should be directed as to whether proper treatment was promptly instituted following the reaction.

Attorneys handling drug claims against physicians must realize that inevitably the defense will be that whatever error occurred was the exercise of judgment for which there could be no liability. To support the defense, there will be available as much expert medical testimony as may seem to be required.

In a representative case,\textsuperscript{24} it was held that a trial court properly directed verdicts in favor of two physicians and the manufacturer of Dilantin, a drug used to control convulsive seizures. The physicians, general practitioners, in consultation with a neurologist, diagnosed the plaintiff’s ailment as a severe type of epilepsy and they prescribed $\frac{3}{2}$ grains of the drug three times a day. Within three weeks the plaintiff developed a high fever and a rash over much of his body which was diagnosed as measles. Several weeks later he became feverish and jaundiced. He had a rash and his spleen and liver were enlarged and palpable. An allergic reaction to Dilantin was suspected, but on the basis of symptoms and laboratory tests the plaintiff’s ailment was diagnosed as infectious mononucleosis. He was hospitalized and the drug was discontinued to determine whether it was causing any re-

\textsuperscript{23}The Council on Drugs of the American Medical Association has frequently noted no discernible advantage to a newly marketed medication. For example, as to six of the newer minor tranquilizers, it stated:

On the basis of the current evidence, the Council can find no general advantage in the use of these newer agents; thus, the physician should use discretion when prescribing any of these in place of an older, well-established drug of similar therapeutic range and safety ratio with which he may already be thoroughly familiar.

\textbf{NEW AND NONOFFICIAL DRUGS—AN ANNUAL COMPILATION OF AVAILABLE INFORMATION ON DRUGS INCLUDING THEIR THERAPEUTIC, PROPHYLACTIC AND DIAGNOSTIC STATUS, AS EVALUATED BY THE COUNCIL ON DRUGS OF THE AMERICAN MEDICAL ASSOCIATION (1963).}

\textsuperscript{24}Fritz v. Parke, Davis & Co., 277 Minn. 210, 152 N.W.2d 129 (1967).
action. A week later the drug was started again at half the prior dosage and, when the plaintiff was released from the hospital ten days later, it was discontinued. He was told to see his physicians periodically for observation and he returned twice. He died more than a year later while undergoing surgery.

On the trial of the case, a neurologist testified that it was highly probable that the Dilantin caused toxic damage to the plaintiff's liver which was responsible for his death.

The defendants' evidence was that there are at least five drugs, including Dilantin, on the market which are commonly used to control epilepsy and that all five could produce serious side effects in certain persons; that there is disagreement among physicians as to which drug is preferable; and, that the drug does control certain types of epilepsy and did control the plaintiff's seizures.

The court held that the physicians clearly were not negligent in the initial prescribing of Dilantin, that a physician may adopt a mode of treatment approved by a considerable number of physicians. The evidence was that the use of Dilantin to control epilepsy was widespread and that the neurologist's opinion that it was highly probable that the drug had damaged the plaintiff's liver and contributed to his death was not sufficient to establish that the doctors were negligent in continuing to use it. The defendants' expert testimony was that their care and treatment of their patient was in accord with accepted standards of practice and thus there was no evidence to support a finding of negligence.

A further consideration of the plaintiff's attorney in a proper case is application of the doctrine of informed consent. In its usual sense, this doctrine holds that the

25 Probably the leading and certainly the most quoted from case on informed consent is Salgo v. Leland Stanford Jr. Univ. Bd. of Trustees, 154 Cal. App. 2d 560, 578, 317 P.2d 170, 181 (1957), wherein it was said:

A physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment. Likewise the physician may not minimize the known dangers of a procedure or operation in order to induce his patient's consent.
right of a person to control what is to be done to his body is inviolate, that in medical cases a physician cannot force his attendance upon his patient no matter how badly he may conceive him to be in need of treatment. As a corollary, the rule requires explanation to the patient of the form of the treatment proposed and what risks may be involved so that the patient may make an informed choice as to whether to submit to the treatment.

As applied to medical therapy, it may be the physician's duty to inform his patient that there may be some risk or discomfort in connection with the administration of certain drugs. Oddly enough, the suggested application of the doctrine came first from pharmacologists and pathologists. The parallel is that it is now considered necessary to secure the consent of the patient to even a minor operation where the risk may be relatively small. Why then should it be any the less reasonable to exact the requirement of consent for the administration of a drug where the risk may be considerably greater than for ordinary surgery? No clinically useful drug is devoid of toxicity and no human being should be exposed to needless risk. The necessary inference is that as the risks of drug therapy become more defined, it may be necessary to obtain informed consents prior to the administration of drugs with potentially dangerous propensities.

**The Package "Stuffer"**

Essential to an understanding of cases against physicians and drug manufacturers is knowledge of the regulations of the Food and Drug Administration with reference to package inserts, or "package stuffers," the manufacturer's literature packaged with the drug which, among other things, describes drug dosages and contraindications.

A judicial decision was the touchstone of a controversy between physicians and the Food and Drug Administration which still lingers, and which had and will have tremendous legal repercussions on the liability of doctors in drug cases. In *Sanzari v. Rosenfeld,* a dentist administered lidocaine,

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an anesthetic, with epinephrine to a patient suffering from high blood pressure and chronic myocarditis. She suffered a stroke and thereafter died. The manufacturer's package insert stated that the use of epinephrine with the anesthetic was contraindicated in the presence of hypertension. The plaintiff was unable to obtain the requisite expert testimony to prove that the dentist was negligent in administering the drug. The package insert, however, was allowed in evidence in that warning of a possible side effect was given and the jury was allowed to find against the defendant on the ground that the manufacturer's literature stated the contraindication.

Under the Federal Food, Drug and Cosmetic Act, and rules and regulations promulgated by the Food and Drug Administration, the basis of drug prescription is the manufacturer's literature which is placed in the package which contains the drug.

The Federal Food, Drug and Cosmetic Act of 1938 required the labeling of all drugs, with adequate directions for use, but made no distinction between over-the-counter and prescription items. Thereafter, prescription drugs were exempt from the requirement because it was felt that physicians, being experts in drug dosage, did not need labeling directions. A tremendous number of new drugs came on the market after World War II and the average practicing physician was then thought not to be able to keep abreast of the times with respect to drugs through traditional medical communications media. The fear was that he would be touted onto drugs by manufacturer's promotion without always being aware of the dangers of them, and their side effects and contraindications. Ostensibly to

28 Act of June 25, 1938, ch. 675, §§ 501, et seq., 52 Stat. 1049. The law was tightened after a sulfa drug elixir, distributed without testing by a small Tennessee manufacturer, was found to have a poisonous ingredient, not the sulfa, which resulted in the death of nearly 100 persons.
29 In Yarrow v. Sterling Drug, Inc., 263 F. Supp. 159 (S.D.S.D. 1967), the drug house had satisfied all government regulations in producing and marketing Aralen, and had used the traditional methods of drug manufacturers in providing information and warnings to physicians (descriptive literature, direct mail and detail men). It was held, on the record made in the case, that the defendant's detail men did not bring the side effects
remedy this situation, in 1961, the FDA promulgated a new regulation, the essence of which was that an insert be put on or within prescription drug packages. It required that [1]abeling on or within the package from which the drug is to be dispensed bears adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or presented...

The Act contemplates proof by the manufacturer that a drug, before being placed on the market, is safe and effective for the purpose for which it was intended. This proof is submitted to the FDA in the form of a New Drug Application. It is in effect a report of controlled studies of the drug conducted by experienced investigators with the training necessary for them to interpret those studies.

Following FDA approval of a drug, it comes on the market with a package insert, or stuffer, usually a single sheet of paper, in compliance with the labeling regulation.

of the drug to the attention of the plaintiff's doctor and that the defendant's conduct did not constitute a proper warning. Very recently, on appeal, this judgment was affirmed by the Eighth Circuit Court of Appeals. See N.Y.L.J., March 19, 1969, at 1, col. 1.

In Incollingo v. Ewing and Parke, Davis & Co., (Court of Common Pleas, Philadelphia, Pa., Dec. 1967), a six year old child treated with Chloromycetin developed aplastic anemia and died. The plaintiff contended that the defendant pediatrician prescribed Chloromycetin for a minor infection, that the defendant osteopath authorized refilling of the prescription without examining the child, and that the manufacturer was guilty of over-promoting the drug via its detail men whose efforts, in effect, diluted inadequate printed warnings. The thrust of the complaint was that the manufacturer, in producing over 7½ tons of Chloromycetin knew that inadequate warnings as to the use of the drug were not being heeded by the medical profession. The jury brought in a verdict of $215,000 against both physicians and the drug company. All the manufacturer's labeling, including the package insert, brochures and advertising was against the use of the drug in "trivial" infections, yet the total sales of the drug were $72,000,000 in 1966.


To illustrate the complexity of gaining new drug approval, a manufacturer drew a chart which listed 125 steps to be taken before a drug is ready for submission.

The content of the stuffer is usually arranged in the following order: name of the drug, description, actions, indications, contraindications, warnings, precautions, adverse reactions, dosage and administration, and references.

After initial testing and release by the FDA, the reports of the side effects of drugs appear in professional journals. Although both the FDA and the American Medical Association have set up "early warning" systems so as to become aware as soon as possible of severe reactions to newer pharmaceutical agents, the process of compiling seemingly isolated reactions into meaningful trends is painfully slow.3

As news of adverse reactions to drugs comes to the FDA, it may require revision of the package insert or even withdrawal of the drug from the market. Where a major change is to be made in the precautionary provision of the insert, the FDA requires this information to be transmitted to the physician in a distinctively marked envelope. These have come to be known as "Dear Doctor" letters.

From the viewpoint of the FDA, the burden of proving the safety and effectiveness of a drug is on the manufacturer. Thus, when a new drug comes into the hands of a physician, the package insert is deemed prima facie proof that the drug is safe and effective for the uses for which it is intended. The great issue presented by the package insert is that when the physician exercises his judgment to prescribe the drug beyond the limits of the package insert, it is presumed that he is aware that a scientific basis for doing so has not been established by information submitted by the manufacturer through the procedures established by law. It is at once apparent that an awesome moral responsibility has been placed on the drug houses not to attempt to market their products for financial gain until there is assurance that they will do no harm.4

The difficulties thus presented are the subject of controversy in that the opportunity is presented to the drug

3 See Balmer, Manning the Early-Warning Systems for Adverse Reactions to Drugs, 37 Medical Record News 362 (1966).

4 One of the bases of the MER/29 cases was that the product was inadequately tested on humans.
manufacturer to understate effective dosages of its product, and, in effect, to "disclaim," by flooding the physician with letters and brochures with "more" information about the drug, replete with rumors and warnings, and by frequent visits from detail men. In a collateral sense, the effect is also to prevent authors from publishing articles based on experience which do not coincide with the current FDA approved package stuffer. The issue is the extent to which the manufacturer's literature is to be considered inviolate and the extent to which the FDA is to be the sole arbiter of drug dosage.

From a practical legal standpoint, it would seem that the doctor is now "it," i.e., on the spot where there has been a compensible drug reaction. How the package stuffer may create liability for a physician where none existed before is easy of illustration. For example, the package insert for Vibramycin, a new tetracycline, a broad spectrum antibiotic, contained the following directions for dosage:

The usual dose of Vibramycin (doxycycline) is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended. . .

As to Vibramycin, The Medical Letter, a responsible publication, reported to its readers that:

Most Medical Letter Consultants believe that a dosage schedule of 100 mg. once daily is inadequate and recommend 100 mg. doses twice daily throughout the course of therapy. Because the urinary excretion of doxycycline is slower than with other tetracyclines, the urinary concentration of the antibiotic may be

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35 1968 Physician's Desk Reference at 943. When a new drug is placed on the market, it is usually accompanied by an extensive promotional campaign. Wide use of the drug may uncover additional adverse effects which were unknown and unsuspected in the premarketing investigation. The reasons are that: 1.) When the drug is marketed many more people will receive it than in the testing period; and 2.) in the investigative process, trial dosages are usually administered to carefully-selected persons, while, after it is marketed, it will be prescribed at random.
too low, even with twice daily dosages, to be effective in infections of the urinary tract.\textsuperscript{36}

The point to be made is that it is possible that a physician who follows the manufacturer's recommendation in prescribing a drug may provide inadequate therapy for his patient. But, if he deviates from the package insert, he may be providing the basis of liability in a lawsuit against himself.

**THE DOCTOR'S LIABILITY**

A great hue and cry arose from the medical profession with respect to the FDA intervention in drug prescription and much of it seems justified. On the other hand, it is utterly impossible today for the average medical man to keep abreast of current literature on drugs and, even if he could, he runs the risk of injuring his patients while information is collated. The preferred method would seem to be to place the burden on the manufacturer to keep the physician informed and then to make him "it" when the drug is prescribed. After all, the manufacturer cannot know how sick the patient is. The manufacturer cannot balance the hazards of leaving the disease state untreated as against prescribing an indicated medication. While in some instances it may be that the doctor does not have at hand all information which might be considered desirable in prescribing a particular drug for a particular ailment, he does have a better opportunity than the manufacturer to calculate the odds and to obtain more information to make a reasonable judgment.

Again, it must be remembered that all drugs have toxic effects as well as therapeutic benefits. Most of them depend on their toxicity for their therapeutic action since they act by depression of some natural metabolic process. The difference is that the toxic proneness of the drug must be selective to be useful. It must be capable of destroying one form of living cell without harming another even though the two forms of cell are in close proximity. The ideal drug is that which is toxic to the infectious agent but

\textsuperscript{36} Medical Letter, Feb. 23, 1968, at 13.
not to the normal cells of the person to whom it is administered. That state of perfection has not often been achieved and so it is possible to allege that the number of cases of adverse reactions to drugs would diminish if the drugs were prescribed only where indicated and proper precautions were then observed. As a doctor-lawyer has written:

It has always been the physician's responsibility to weigh risks against benefits when administering drugs—all drugs. This has been part of his educational foundation. Perhaps, in the past, the test may not have been consciously applied by physicians as often as would have been desirable; however, comprehensive information has not always been readily available to physicians, and it is probable the previously known risks were considered so mild or infrequent that they seldom generated concern. Nevertheless, increased efforts to identify and to publicize drug hazards require physicians to be more alert today to the application of this test for every drug prescribed or administered. Failure to do so may lead to legal as well as medical repercussions.37

Tozer (J.D.) and Kasik (M.D.) have made several suggestions to minimize the physician's risk in drug prescription.38 Parenthetically, it should be noted that the suggestions also provide standards against which to judge the doctor's conduct in potential malpractice cases.

1. It is suggested that a doctor should give pause in prescribing a drug with which he is not thoroughly familiar. The physician should be current with the literature on adverse reactions.

2. He should know the history of his patient on adverse reactions.

3. He must be prepared to justify the use of the drug which he prescribes and its dangers, as opposed to other drugs, or other methods of treatment.

4. He must be prepared to observe and follow the signs and symptoms of adverse reactions. If laboratory

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38 Tozer & Kasik, *The Medical-Legal Aspects of Adverse Drug Reaction*, 8 CLINICAL PHARMACOLOGY AND THERAPEUTICS 637 (1967), a recommended article.
tests should be made prior to the administration of a drug, he must make them.

5. He should consider keeping a diary of all patients receiving drugs so that if there is a warning with respect to a particular drug, he can pass it on to his patient.

The conclusions reached by these authors are:

None of these conclusions is easy. All of them will further burden the already overburdened practitioner and inevitably will place increasing demands on his time and raise the cost of care for the patient. They may, however, have one desirable consequence; they may reduce some of the enthusiasm for the use of drugs in any and all circumstances.?

A review of the numerous adverse reactions which are possible following the administration of drugs is frightening. At the same time, one must be realistic, for although drug reactions may be serious or fatal, they are not the usual result of such therapy. The fact that three reactions in ten million doses of penicillin may be expected to be fatal should not be a reason for deleting the drug from the doctor's medical arsenal. Neither does it mean, however, that the public should be complacent about penicillin deaths nor that the attorney should not seek to ascertain if the legal causation was negligence.

It is a rare occurrence that a physician will be found liable for the administration of a drug which seemed reasonable in the light of foresight, although disastrous in terms of hindsight. There are occasions where the risk in the use of the drug would seem small as compared to the benefit expected for the patient. There are also hypersensitivities and idiosyncrasies which cannot be reasonably predicted in individual patients.

On the other hand, the patient is in no position to judge the virtues and perils of the remedy prescribed by his doctor. He expects relief from his ailment if for no other reason than favorable drug propaganda. He has faith in the ability of his doctor to heal and cure.

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39 Id. at 645.
The unalterable conclusion is that it is the physician, and he alone, who has the responsibility for selecting the right agent for the relief and cure of his patient's ailment. The role of the doctor is the most important for it is on his prescription that the drug is administered. He must be held responsible for knowing that which is known about the drug he prescribes.

Obviously, the plaintiffs' cases against physicians which have the greatest potential are those in which irreversible damage has resulted from the administration of a known potentially toxic drug in one of five instances:

1. Where the use of the drug was contraindicated under the circumstances.

2. Where, in any event, the indications for use were dubious.

3. Where the ailment to be treated was misdiagnosed.

4. Where the ailment was so minor as not to require the drug.

5. Where an improper dosage was prescribed or the patient was given improper or inadequate instructions for use.

There are an increasing number of gross medical errors in administering a drug or where there has been a failure to exercise proper precautions.\(^4\) Drug toxicity is all too common where directions for use are followed to the letter without regard to the individuality of the patient. It is almost inevitable when such instructions are disregarded.

Drug houses and public and private research institutions are advancing toward a goal of the production of medications which will have a lower toxicity propensity.

\(^4\) E.g., Koury v. Follo, 272 N.C. 366, 158 S.E.2d 548 (1968). An infant lost his hearing following five injections by a pediatrician of Strepcombiotic for bronchitis. The manufacturer had marked the drug container "Not for Pediatric Use" and the attending physician knew that Streptomycin contained in the compound could impair the auditory nerves. The plaintiff's expert witness testified that the dosage administered was approximately twice the upper safe limit of dosage for an infant and five times the standard dosage for children as recommended in standard tests.
Ultimately, the public will benefit from their research and testing. Drugs are the chief weapon in the fight against disease. They must be used, but with judgment and caution, and the attorney must be critical of the process. The trial attorney in order to protect a drug-injured client must be ever alert to the published warnings of adverse drug reactions and to the expanding role of liability of the physician as pronounced by courts everywhere.