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## COMMENT

# Drug Synergism and Potential Medical Liability

**M**EDICAL MALPRACTICE litigation is currently of great interest not only to the medical and legal professions, but to the general public as well. The increased demand for health care services by all segments of society, exemplified by Medicare,<sup>1</sup> will continue to place a greater premium on the time a physician may spend with an individual case. To cope with the rising case load, science is continually developing new and more powerful drugs to allow the physician more flexibility in his treatment.<sup>2</sup> However, new drugs can pose additional problems for the practitioner. Among these is the possibility of synergistic interaction<sup>3</sup> and its effect on both the success of the therapy selected and the patient's overall health.

Traditionally the doctor has not been considered to warrant the success of a particular therapeutic regimen. In the cases where liability has attached for adverse drug reactions, there has been sufficient evidence to allow the jury to consider whether the injury was at least partially caused by the physician's negligence.<sup>4</sup> In order for a synergistic response<sup>5</sup> to drug therapy to form the basis of a negligence action, it has been necessary to establish that the doctor knew or should have known that there was a high probability that the drugs being administered could produce potentially harmful effects, and that he prescribed the combination of drugs through carelessness or failed to take adequate precautions to detect adverse effects at an early stage.

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<sup>1</sup> 42 U.S.C. § 1395 *et seq.* (1964, Supp. V, 1970).

<sup>2</sup> Current antibiotic therapy for infectious diseases (*e.g.*, gonorrhea, syphilis) has greatly reduced the quantum of time necessary for the individual physician to devote to the individual patient.

<sup>3</sup> Synergism may be defined as "the cooperative action of two discrete, or individually distinct agencies or substances, which results in a total effect greater than the sum of their two effects when taken independently." *Metropolitan Life Ins. Co. v. Main*, 383 F.2d 952, 956 (5th Cir. 1967).

<sup>4</sup> *Tozer & Kasik, The Medical-Legal Aspects of Adverse Drug Reactions*, 8 *CLINICAL PHARMACOLOGY & THERAPEUTICS* 637 (1967).

<sup>5</sup> Substances may have a synergistic effect although not pharmacologically synergistic. An example of *clinical* synergism "is the use of the vasoconstrictor epinephrine in a solution of procaine hydrochloride for local anesthesia. The vasoconstriction diminishes the blood supply to the area injected and thereby prolongs the time required for the dissipation of the local anesthetic. Hence, the anesthetic activity is prolonged." *J. KRANTZ, C. CARR & B. LA DUE, THE PHARMACOLOGIC PRINCIPLES OF MEDICAL PRACTICE* 22 (7th ed. 1969).

It is a well accepted fact in pharmacology that no drug produces a single effect on a given patient.<sup>6</sup> Side effects, which result from drug interactions, have been a topic of much controversy within the medical profession. For example, monamine oxidase (MAO) inhibitors<sup>7</sup> were introduced in the late 1950's primarily as antidepressants, but MAO has caused surprising side effects.<sup>8</sup> Other drugs were found to modify the effects of MAO and these posed a serious risk to the patient.<sup>9</sup> This has led to a renewed interest in the field of drug interactions, motivating an increased amount of research in this area.<sup>10</sup>

This intensified inquiry into the interaction of chemically synthesized drugs<sup>11</sup> is consequently expanding the information available to the practitioner. With increasing frequency, articles appearing in medical literature are not only outlining interactions between specific drugs, but they are also presenting lists and tables of drug interactions.<sup>12</sup> These strong, unexpected reactions, which may be encountered when increasing or decreasing<sup>13</sup> drug therapy, may provide a basis for establishing a physician's liability. A patient may be able to recover damages for physical injuries sustained owing to the adverse synergistic reaction, the attendant pain and suf-

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<sup>6</sup> A. GOTH, *MEDICAL PHARMACOLOGY* 9 (5th ed. 1970).

<sup>7</sup> Grosshandler, Henschel & Kampine, *Toxic Reactions Due to Drug Synergism and Antagonism*, 47 *ANESTHESIA & ANALGESIA* 345 (1968).

<sup>8</sup> "One of the serious disadvantages of MAO inhibitors is the increased likelihood of adverse reactions to ingested foods and to drugs that may release monamines in the body. The ingestion of aged cheese, beer, and certain wines has caused hypertensive emergencies in patients who were being treated with MAO inhibitors." J. KRANTZ, C. CARRY & B. LA DUE, *supra* note 5, at 13.

<sup>9</sup> "Chronic administration of furazolidone [an antibacterial agent used in the treatment of various bacterial and protozoal infections] causes a cumulative inhibition of MAO and could predispose to a serious risk of hypertensive crises if an indirect-acting sympathomimetic amine were administered." Solomon, *Clinical Disorders of Drug Interaction*, 16 *ADVANCES IN INTERNAL MED.* 285, 291 (1970).

<sup>10</sup> See generally AMA Council on Drugs, *Fixed-Dose Combination of Drugs*, 213 *J. AM. MED. ASS'N* 1172 (1970); Bowles, *Better Drug Histories Avoid Adverse Reactions*, 112 *MOD. HOSP.* 128 (1969); Hunninghake, *Drug Interactions*, 47 *POSTGRAD. MED.* 71 (1970); *Interaction of Drugs*, *BRIT. MED. J.* 811 (April 2, 1966); Jick, Miettinen, Shapiro, Lewis, Siskind & Slone, *Comprehensive Drug Surveillance*, 213 *J. AM. MED. ASS'N* 1455 (1970); Soffer, Editorial, *International Drug Fads and Clinical Vigilance*, 57 *CHEST* 213 (1970).

<sup>11</sup> *Drug Synergism* was added as a major topic heading to the *INDEX MEDICUS* in 1966.

<sup>12</sup> Hussar, *Tabular Compilation of Drug Interactions*, 141 *AM. J. PHARM.* 109 (1969).

<sup>13</sup> Removal of a drug during multidrug therapy may pose a hazard. As an example, "phenobarbital promotes the rate of destruction of bishydroxy-coumarin and warfarin. By this mechanism it increases the effective dose of these drugs for anticoagulation. This becomes very dangerous when phenobarbital is suddenly discontinued without decreasing the coumarin dosage. Severe hemorrhagic episodes may follow." A. GOTH, *supra* note 6, at 616.

fering, and the prolonged treatment necessitated. A physician is normally held to the standard of care of the average practitioner in his speciality in the locality in which the physician is practicing. With the increased dangers to the patient flowing from the management of multiple drug therapy, the "locality rule" for the standards of medical practice may be insufficient to protect the physician from civil liability.<sup>14</sup>

There has been a trend over the past decade to place the burden for the risks arising from drug therapy on the pharmaceutical industry. Prompted in part by the thalidomide disaster,<sup>15</sup> the Ke-fauver-Harris drug amendments of 1962<sup>16</sup> increased the testing requirements of the drug industry for marketed drugs. The drug manufacturers have correspondingly intensified their efforts to provide notice to the physician of the potential side effects that may be expected with the use of a specific drug. Such notice has consisted of advertisements in medical periodicals, personal correspondence to individual physicians ("Dear Doctor" letters), and package stuff-er warnings. The clear intent of this flood of information is to provide a legally sufficient notice to the physician of the side effects of a particular drug.<sup>17</sup> If the doctor is on notice, he may be able to look for symptoms of such side effects.<sup>18</sup> This notice provided by the drug industry would tend to bar his plea of lack of knowledge of the potential reaction, creating a higher standard of care in his selection and prescription of the more dangerous drugs. On its face, notice of potentially dangerous side effects of a drug would appear to place the physician in a more informed position from which to exercise his medical judgment. However, if this type of notice is effective, then the overall result will be to shift the pecuniary liability for adverse therapeutic results from the deep pocket of the drug industry to the deep pocket of the physician. The principal obstacle to this development would appear to be the same as that underlying the *Sterling Drug, Inc. v. Yarrow*<sup>19</sup> case. Prior to the diagnosis of the plaintiff's retinopathy, the drug company had published indications of adverse side effects on its product cards

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<sup>14</sup> *Bruce v. United States*, 167 F. Supp. 579 (S.D. Cal. 1958); *Gielski v. State*, 155 N.Y.S. 2d 863, 3 Misc. 2d 578 (Ct. Cl. 1956).

<sup>15</sup> *Id.*

<sup>16</sup> 21 U.S.C. § 321 *et seq.* (1964, Supp. V, 1970).

<sup>17</sup> Drug companies are apparently so anxious to notify physicians of side effects that warnings may be issued on mere rumors of adverse effects. See Pearson & Salter, *Drug Interaction? — Orphenadrine with Propoxyphene*, 282 N. Eng. J. MED. 1215 (1970).

<sup>18</sup> *Sterling Drug, Inc. v. Yarrow*, 408 F.2d 978 (8th Cir. 1969).

<sup>19</sup> *Id.*

and in the *Physician's Desk Reference*,<sup>20</sup> as well as having circulated a "Dear Doctor" letter. Despite the drug company's efforts, the court held that the attempted notice was insufficient to have alerted the physician. The court noted that general practitioners "receive so much literature on drugs that it is impossible to read all of it. . . . [Physicians are] inundated with literature and product cards of various manufacturers [and] a change in literature and an additional letter were insufficient to present new information [to the treating physician]."<sup>21</sup>

An individual intent on suing a physician may be able to overcome this question of effective notice by extending the doctrine of strict liability in tort<sup>22</sup> to this area of adverse synergistic effects. For a prescription drug, effective notice of harmful effects is satisfied if the manufacturer informs the physician. The doctor may then balance the benefit against the risk, using his own medical judgment. Although a physician is not normally considered the seller of a drug he prescribes, under section 402A of the *Restatement (Second) of Torts*<sup>23</sup> this interpretation is possible if the medical judgment factor is deemphasized.

Section 402A is clearly intent on establishing the liability of the seller to the ultimate consumer of the product. Drugs as products are specifically mentioned in comments *j* and *k* to section 402A. When a drug manufacturer complies with the F.D.A. requirements for notifying physicians of adverse drug reactions to a specific product, he has done what is required by law to protect the consumer in this regard. The physician may be protected against allegations of negligence on his part for failure to heed the warnings by reasoning such as that used by the court in *Sterling Drug, Inc. v. Yarrow*.<sup>24</sup> The clear intent of comment *k* to section 402A is that,

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<sup>20</sup> *Id.* at 990. The court stated that, in that instance, notification by the detail men would have been more effective. In *Love v. Wolf*, 226 Cal. App. 2d 378, 38 Cal. Rptr. 183 (3rd Dist. 1964) (reversed on other grounds), the court refused to dismiss the drug manufacturer as a codefendant although the company had sent out two "Dear Doctor" letters, had placed full page notices in the *Journal of the American Medical Association*, and had placed a warning on all packages, labels, stuffers, and promotional material as required by the Food and Drug Administration. However, the actions of the detail men in not emphasizing the side effects to the physicians while promoting the drug (chloromycetin) were sufficient to take the question of the company's liability to the jury. Evidence of the company's profits on the sale of the drug was admissible to demonstrate overpromotion by the manufacturer.

<sup>21</sup> *Greenman v. Yuba Power Prod., Inc.*, 59 Cal. 2d 57, 377 P.2d 897, 27 Cal. Rptr. 697, (1963).

<sup>22</sup> RESTATEMENT (SECOND) OF TORTS (1965).

<sup>23</sup> Barring other actions on the part of the manufacturer such as overpromotion by other means. See *Love v. Wolf*, 226 Cal. App. 2d 378, 38 Cal. Rptr. 183 (Dist. Ct. 1964).

<sup>24</sup> 408 F.2d 978 (8th Cir. 1969).

with proper directions and warning, a drug will not be considered *unreasonably* dangerous. But at this juncture the drug has become unreasonably dangerous through the physician's failing to note the warning concerning the drug's use. There is in fact no medically recognized risk for the physician to balance as he is unaware of that risk. At that point, the physician is no longer exercising good medical judgment for he is not considering all of the information made available to him by the manufacturer and the government. If the physician will not be held liable for failure to read and heed all of the drug warnings sent to him, then he could be considered merely a necessary conduit in the manufacturer's chain of distribution of his product. As such, his failure in his new capacity to warn the customer may establish his liability under the doctrine of strict tort.<sup>25</sup>

It may be assumed that the amount of information available to physicians concerning adverse drug interactions will continue to increase rapidly as new drugs are introduced and additional research is conducted. If physicians are hard pressed today to integrate these additional factors into their daily clinical practice, they will find the problem growing more acute as time passes. The attempt by the drug industry to shift at least part of the burden for adverse drug reactions to the practitioner through increased notification efforts in all probability will succeed.

One possible solution to this problem would be to utilize available technology to shift at least a portion of the liability to a third party and to simultaneously increase the quality of patient care. This could be accomplished through establishment of a local automatic data processing facility whose sole purpose would be the collection and dissemination of drug information. This center would, along with the members of the medical profession, receive all current advisories published by the government and the drug manufacturers. In addition, it would collect all published papers dealing with drug interactions and side effects. The physician would use a multipart form when writing a prescription in place of the currently used

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<sup>25</sup> This would place the physician in the position of either being legally responsible for knowledge of all warnings issued and required by the government in the sale of distribution of drugs (much as an ordinary citizen is presumed to know the law) or lose his status as a physician for that transfer. He would also become liable under strict tort liability for failure to warn the consumer of dangerous side effects. In either event, when the government and the manufacturers have done what is legally required of them to notify of side effects, the responsibility for the management of the drug therapy is the physician's.

An argument may be made that the results in products liability cases decided under the doctrine of strict tort liability could have been more profitably decided under the sales article of the *Uniform Commercial Code* with no loss of effect. See Shanker, *Strict Tort Theory of Products Liability and the Uniform Commercial Code*, 17 W. RES. L. REV. 5 (1965).

blanks. The top copy would serve the function of the current prescription blank. The second copy could be used for his office records. The third copy would serve as a data processing card. A locally assigned patient identification number could be entered by the physician in lieu of the patient's name. The card could be either encoded by his office staff or forwarded to the center for encoding. A similar card could be submitted for the discontinuance of a particular drug therapy. This system would provide a method by which the physician could determine the status of a particular drug in the context of a specific patient's therapy program prior to prescribing the drug. The doctor would also establish in the computer a drug history for each of his patients through the use of the encoded cards. He would then periodically receive a printout sheet indicating all current warnings in force and a synopsis of experimental findings on the drugs and drug combination he was currently prescribing. The center could be established on a county or metropolitan basis by either the government or local medical societies. Use of such a center for distribution of information to the physician could provide him with current, detailed information relevant to his practice and increase the quality of patient care.

The expanding demands for medical care and the increasing number of drugs available for therapy will place progressively greater demands on the skill of the physician. Every effort should be made to insure that he has information necessary to exercise sound medical judgment, for the law is placing increasing emphasis on the proper exercise of that judgment. An error in therapy due to unexpected reactions could lead to disastrous results for the patient and the physician. Such adverse results could be avoided through the creation and use of a computer based system.

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