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THE PATIENT PACKAGE INSERT AND PHARMACIST LIABILITY

I. INTRODUCTION

New patient labeling regulations promulgated by the Commissioner of the Food and Drug Administration (FDA) became effective on April 3, 1978.¹ The regulations provide for revised and expanded labeling information on oral contraceptive drug products to give the consumer extensive "reports about the risk of blood clots, other problems of the circulatory system, cancer, and effects on the unborn child associated with the use of oral contraceptives."² The regulation further requires that the patient package insert (PPI) be provided by the pharmacist or other dispenser to each patient to whom the drug is delivered. At this time, a PPI is required only for the oral contraceptives, for products containing estrogen,³ and for the post-coital contraceptive, diethylstilbestrol.⁴ The Commissioner has, however, proposed patient labeling for all prescription drugs.⁵ Both Houses of Congress, in proposing comprehensive reforms of existing federal law governing drugs administered to humans, have introduced legislation requiring detailed labeling directed at the patient.⁶ The existing regulations and the proposed legislation may have far-reaching effects on the pharmaceutical delivery system, not only for the pharmaceutical manufacturer⁷ and for the prescribing physician,⁸ but also for the dispensing pharmacist and for the consumer. This comment will explore the increased potential liabilities of the pharmacist, both statutory⁹ and judi-

1. 21 C.F.R. § 310.501(a)(1).

2. *Id.* For an example of the required patient insert, see App. B & C.

3. 21 C.F.R. § 310.515 (1978).

4. 21 C.F.R. § 310.501(b) (1978).

5. 40 Fed. Reg. 15,392 (1975).

6. S. 2755, 95th Cong., 2d Sess. (1978). The House version, H.R. 8891, 95th Cong., 1st Sess. (1977) (cited in Gardner, *Increasing Patient Awareness in Drug Therapy: Ramifications of a Patient Package Insert Requirement*, 66 GEO. L.J. 837, 840 n.14 (1978)) provides that a drug will be deemed mislabeled if not dispensed with a patient package insert. *Id.* § 5(a). See notes 28-38 *infra* and accompanying text.

7. For a recent analysis of the impact of the PPI on the manufacturer see Gardner, *supra* note 6, at 855-60. This comment will expand Gardner's article to include the additional ramifications that the PPI may present to the dispensing pharmacist.

8. *Id.* at 860-67.

9. See notes 29-38 *infra* and accompanying text.

cially imposed,¹⁰ when delivery of a PPI to the patient is omitted. It will be shown that these liabilities can arise from the breach of a duty to warn the patient—using theories of negligence¹¹ and of strict liability¹²—as well as from the breach of a warranty.¹³

II. FEDERAL STATUTORY LIABILITY

When the Commissioner of the FDA first proposed PPI requirements,¹⁴ many comments were received expressing doubt that the Commissioner had the authority to promulgate those regulations.¹⁵ The comments argued that

the enactment of Section 503(b)(2) [of the Federal Food, Drug and Cosmetic Act (FDCA)]¹⁶ . . . in 1951, reflected a

10. See notes 40-88 *infra* and accompanying text.

11. See notes 54-88 *infra* and accompanying text.

12. See notes 60-88 *infra* and accompanying text.

13. See notes 89-129 *infra* and accompanying text.

14. 40 Fed. Reg. 15,392 (1975).

15. 43 Fed. Reg. 4,214 (1978). This comment does not attempt a complete statutory analysis of the FDA's rule-making authority. Only a brief synopsis of the issue is presented here. For a detailed discussion of the Commissioner's legal authority to promulgate PPI regulations, see Gardner, *supra* note 6, at 839, and McNamara, *The New Age of FDA Rule-Making*, 31 FOOD-DRUG-COSM. L.J. 393 (1976). For a complete presentation of the administrative comment procedure employed by the FDA, see generally Jurow, *A Look at FDA's History and Future*, 28 FOOD-DRUG-COSM. L.J. 518 (1973); Marcus, *The New FDA Hearing Regulations—An Analysis*, 29 FOOD-DRUG-COSM. L.J. 336 (1974); Peskoe, *Submissions and Petitions Under the FDA's Procedural Regulations*, 32 FOOD-DRUG-COSM. L.J. 216 (1977); Willig, *The Influence of the Federal Food, Drug and Cosmetic Act on the Pharmacists' Current Good Dispensing Practices*, 28 FOOD-DRUG-COSM. L.J. 636 (1973). "FDA's rule-making has been substantially the result of court litigation. It is not, as one would assume, rule-making followed by court challenges." Epstein, *New Directions for Administrative Regulations*, 30 FOOD-DRUG-COSM. L.J. 384, 384-85 (1975). See also Shapiro, *The Judicial Review of Rule Making*, 28 FOOD-DRUG-COSM. L.J. 756 (1973). For an excellent forum on FDA rule making, see Austern, *Philosophy of Regulation: A Reply to Mr. Hutt*, 28 FOOD-DRUG-COSM. L.J. 189 (1973); Hagan, *Remarks on the Regulatory Philosophy of the FDA*, 28 FOOD-DRUG-COSM. L.J. 195 (1973); Hutt, *The Philosophy of Regulation Under the Federal Food, Drug and Cosmetic Act*, 28 FOOD-DRUG-COSM. L.J. 177 (1973); Kennedy, *The New Vogue in Rulemaking at FDA: A Foreword*, 28 FOOD-DRUG-COSM. L.J. 172 (1973); Montgomery, *Comments on the Philosophy of Regulation Under the Federal Food, Drug and Cosmetic Act*, 28 FOOD-DRUG-COSM. L.J. 201 (1973). Peter Hutt, past Assistant General Counsel for the FDA, developed the Federal Register notice system with commentary for each proposed regulation. Epstein, *New Directions for Administrative Regulations*, 30 FOOD-DRUG-COSM. L.J. 384, 394 (1973). The system, although lauded by some, has critics within the food and drug bar. See Merrill, *Administrative Rule Making*, 30 FOOD-DRUG-COSM. L.J. 478, 479-81 (1975). But see Austern, *The Regulatory Gospel According to Saint Peter*, 29 FOOD-DRUG-COSM. L.J. 316 (1974).

16. 21 U.S.C. § 353(b)(2) (1970). Section 353(b)(2) provides:

(2) Any drug dispensed by filling or refilling a written or oral prescription of a practitioner licensed by law to administer such drug shall be exempt from the requirements of section 352 of this title, except subsections (a), (i) (2) and (3), (k), and (l) of said section, and the packaging requirements of subsections (g), (h), and (p) of said section, if the drug bears a label containing the name and address of the dispenser, the serial number and date of the prescription or of its filling, the name of the prescriber, and, if

clear understanding by Congress that prescription drugs need not bear labeling containing directions for patient use and that this section exempts prescription drugs at the time the drug is dispensed by the pharmacist from any requirement that the labeling bear adequate directions for use and warnings under Section 502(f) of the Act.¹⁷

The Commissioner responded to this comment by pointing out that “[t]he primary purpose of the provision in section 503(b)(2) of the Act exempting a prescription drug from adequate directions for use and warnings is to avoid self-diagnosis and self-administration of drugs that require professional supervision for safe use.”¹⁸ The Commissioner contends that a PPI will not encourage self-diagnosis or administration but, instead, “will inform the patient of the advantages and risks associated with the use of these drugs and insure safe and effective use . . . after it has been prescribed by the physician.”¹⁹

At any rate, it is arguable that the self-medication problem will exist to the same extent even after a PPI delivery requirement is instituted. Patients may frequently save the last of a prescription for use the next time the same symptoms occur. The patient is thus self-diagnosing and self-medicating. Since a PPI would detail the indications for the drug’s use,²⁰ it is conceivable that a PPI would *increase* the incidence of self-medication, rather than limit it as the Commissioner contends.²¹

Although the self-medication argument appears inconclusive, an-

stated in the prescription, the name of the patient, and the directions for use and cautionary statements, if any, contained in such prescription. This exemption shall not apply to any drug dispensed in the course of the conduct of a business of dispensing drugs pursuant to diagnosis by mail, or to a drug dispensed in violation of paragraph (1) of this subsection.

17. 42 Fed. Reg. 37,656 (1977).

18. *Id.*

19. See also Guarino, *Patient Package Inserts*, 34 FOOD-DRUG-COSM. L.J. 116 (1979).

20. See App. A.

21. 42 Fed. Reg. 37,636 (1977). This semantic distinction tends to break down when considering a refillable prescription drug. When first dispensed to the patient, a PPI would seem to function as the Commissioner contends, as a concise statement of the effects of the drug and the purpose for which the physician has prescribed it. Any unused portion of the original prescription or an authorized refill, however, may be used contrary to the use envisioned by the Commissioner’s rationale for the PPI. For example, when seemingly similar symptoms appear, the patient may consult his PPI from the original prescription, conclude that the etiology is therefore similar, and begin to self-medicate with a potentially dangerous pharmaceutical. Even worse, perhaps, is the situation where the patient transfers the unused portion to a third person who exhibits similar symptoms. The knowledge the patient acquires concerning the advantages and risks of his prescription is heavily outweighed by the possibility of self-medication, thereby defeating any meritorious purpose of a PPI.

other position taken by the Commissioner is more substantial and, with the reinforcement of case law, does justify FDA rule-making authority regarding drug labeling. It was argued in comments to the proposed regulations on estrogenic drug products labeling²² that section 701(a)²³ of the FDCA authorizes only the promulgation of substantive regulations on subjects specifically authorized by the Act. In *National Nutritional Foods Association v. Weinberger*,²⁴ the court recognized that "if the administrative process is to be practically effective, specific regulations promulgated pursuant to a general statutory delegation of authority must be treated as authoritative, whether labeled 'substantive' or 'interpretive,' especially in areas where the agency possesses expertise not shared by the courts."²⁵ Based on this, the Commissioner concluded that section 701(a) empowers him to issue substantive rules to facilitate enforcement of the Act; therefore, a regulation issued pursuant to section 701(a) "may lawfully establish a requirement for patient labeling for a prescription drug product."²⁶

Assuming that the Commissioner does possess the authority to promulgate labeling rules and that the rules do have the force and effect of statutory law, the impact on the dispensing pharmacist must next be considered.²⁷ Statutory liability for misbranding of a drug product is controlled by section 502 of the FDCA.²⁸ A dispensing

22. 42 Fed. Reg. 37,636 (1977).

23. 21 U.S.C. § 371(a) (1976).

24. 512 F.2d 688 (2d Cir.), *cert. denied*, 423 U.S. 827 (1975) (injunctive relief sought by manufacturers against regulations classifying high level vitamins as prescription drugs).

25. 512 F.2d at 696.

26. 42 Fed. Reg. 37,636 (1977). *See also* *Weinberger v. Hynson, Westcott, & Dunning, Inc.*, 412 U.S. 609 (1973); *Ciba Corp. v. Weinberger*, 412 U.S. 640 (1973); and *USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655 (1973), decided the same day and upholding the validity of FDA administrative summary judgment procedures as applied to withdrawal of new drug applications.

27. Although the regulation as finally written requires that the dispenser distribute the PPI, this article will be limited to the dispensing pharmacist. The Commissioner has stated that the PPI regulation, 21 C.F.R. § 310.501(a)(1) (1978), for oral contraceptives applies to "physicians, nurses, lay persons or semi-professionals in a family planning clinic or student health department, as well as a pharmacist." 43 Fed. Reg. 4,214-215 (1978). The textual material will apply to each if he is functioning in a dispensing capacity.

28. 21 U.S.C. § 352 (1976). Section 352 reads:

A drug or device shall be deemed to be misbranded—

(a) If its labeling is false or misleading in any particular.

(b) If in package form unless it bears a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count: *Provided*, That under clause (2) of this subsection reasonable variations shall be permitted, and exemptions as to small packages shall be established, by regulations prescribed by the Secretary.

(c) If any word, statement, or other information required by or under authority of

pharmacist would be in violation of section 502(p) if he dispenses a

this chapter to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

(d) If it is for use by man and contains any quantity of the narcotic or hypnotic substance alpha eucaine, barbituric acid, betaeucaine, bromal, cannabis, carbromal, chloral, coca, cocaine, codeine, heroin, marihuana, morphine, opium, paraldehyde, peyote, or sulphonmethane; or any chemical derivative of such substance, which derivative has been by the Secretary, after investigation, found to be, and by regulations designated as, habit forming; unless its label bears the name and quantity or proportion of such substance or derivative and in juxtaposition therewith the statement "Warning—May be habit forming."

(f) Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users: *Provided*, That where any requirement of clause (1) of this subsection, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement.

(g) If it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein: *Provided*, That the method of packing may be modified with the consent of the Secretary. Whenever a drug is recognized in both the United States Pharmacopoeia and the Homoeopathic Pharmacopoeia of the United States, it shall be subject to the requirements of the United States Pharmacopoeia with respect to packaging and labeling unless it is labeled and offered for sale as a homoeopathic drug, in which case it shall be subject to the provisions of the Homoeopathic Pharmacopoeia of the United States, and not to those of the United States Pharmacopoeia: *Provided further*, That, in the event of inconsistency between the requirements of this subsection and those of subsection (e) of this section as to the name by which the drug or its ingredients shall be designated, the requirements of subsection (e) of this section shall prevail.

(h) If it has been found by the Secretary to be a drug liable to deterioration, unless it is packaged in such form and manner, and its label bears a statement of such precautions, as the Secretary shall by regulations require as necessary for the protection of the public health. No such regulation shall be established for any drug recognized in an official compendium until the Secretary shall have informed the appropriate body charged with the revision of such compendium of the need for such packaging or labeling requirements and such body shall have failed within a reasonable time to prescribe such requirements.

(i) (1) If it is a drug and its container is made, formed, or filled as to be misleading; or (2) if it is an imitation of another drug; or (3) if it is offered for sale under the name of another drug.

(j) If it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.

(k) If it is, or purports to be, or is represented as a drug composed wholly or partly of insulin, unless (1) it is from a batch with respect to which a certificate or release has been issued pursuant to section 356 of this title, and (2) such certificate or release is in effect with respect to such drug.

(l) If it is, or purports to be, or is represented as a drug (except a drug for use in animals other than man) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof, unless (1) it is from a batch with respect to which a certificate or release has been issued pursuant to section 357 of this title, and (2) such certificate or release is in effect with respect to such drug: *Provided*, That this subsection shall not apply to any drug or class of drugs exempted by regulations promulgated under section 357(c) or (d) of this title.

....

pharmaceutical product that is labeled contrary to FDA regulation.²⁹ The applicable FDA regulation³⁰ requires the manufacturer (in this case, of the oral contraceptive) to supply the pharmacist with the current PPI for that product³¹ and for the pharmacist to then deliver the PPI to the patient.³² Failure to do so would constitute violation of the regulation and therefore a violation of section 502(p). The omission would be a federal offense, punishable by up to one year imprisonment or a fine of not more than \$1,000.00, or both.³³

A serious question of liability to the consumer is raised by violation of a misbranding statute. If section 502 is determined to be a safety statute,³⁴ its violation through misbranding could constitute neg-

(n) In the case of any prescription drug distributed or offered for sale in any State, unless the manufacturer, packer, or distributor thereof includes in all advertisements and other descriptive printed matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to that drug a true statement of (1) the established name as defined in subsection (e) of this section, printed prominently and in type at least half as large as that used for any trade or brand name thereof, (2) the formula showing quantitatively each ingredient of such drug to the extent required for labels under subsection (e) of this section, and (3) such other information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in regulations which shall be issued by the Secretary in accordance with the procedure specified in sections 371(e) of this title: *Provided*, That (A) except in extraordinary circumstances, no regulation issued under this subsection shall require prior approval by the Secretary of the content of any advertisement, and (B) no advertisement of a prescription drug, published after the effective date of regulations issued under this subsection applicable to advertisements of prescription drugs, shall, with respect to the matters specified in this subsection or covered by such regulations, be subject to the provisions of sections 52 to 57 of Title 15. This subsection (n) shall not be applicable to any printed matter which the Secretary determines to be labeling as defined in section 321(m) of this title.

(p) If it is a drug and its packaging or labeling is in violation of an applicable regulation issued pursuant to section 1472 or 1473 of Title 15.

29. 21 U.S.C. § 352(p) (1976).

30. 21 C.F.R. § 310.501(a)(1) (1978).

31. The FDA intends to publish updated versions of the PPI in the Federal Register as changes occur. The manufacturer is thus effectively put on notice that changes may occur and failure to revise will result in misbranding by the manufacturer. *Id.* § 310.501(a)(8).

32. This delivery requirement presents practical and economic disadvantages to the use of PPIs. For the manufacturer, the cost of development and distribution of the PPI will inevitably be reflected in the prescription cost. Also, and perhaps more significantly, the requirement of the PPI may prolong the approval of the new drug application process, a procedure that already takes many years and millions of dollars. See generally Goldstein, *On the Road with American Drug Companies*, 12 TRIAL 43 (1976), and Parker, *Regulating Pharmaceutical Innovation: An Economist's View*, 32 FOOD-DRUG-COSM. L.J. 160, 172-74 (1977).

The pharmacist will have to develop an efficient distribution system to insure that each patient receives the required labeling, with resulting cost increases in prescription pricing. See generally Weigel, *New Regulatory Concepts in Rx Labeling for Patients*, 31 FOOD-DRUG-COSM. L.J. 531 (1976). From a legal point of view, the pharmacist should also develop a system to prove that the patient received the PPI, perhaps by requiring a signature from the patient at the time of prescription delivery to serve as proof that a PPI was delivered.

33. 21 U.S.C. § 333(a) (1976).

34. "Violation of a pure food and drug act has been held sufficient to show negligence and

ligence *per se*.³⁵ “The effect of such a rule is to stamp the [defendant pharmacist’s] conduct as negligence, with all the effects of common law negligence.”³⁶ If a court should find that the FDCA was “so clearly intended to protect a particular class of persons against their own inability to protect themselves . . . the policy of the legislature is interpreted to mean that [ordinary negligence defenses of contributory negligence and assumption of the risk] are not available [to a defendant].”³⁷ Thus, it can be seen that failure to deliver a PPI to a patient, clearly a misbranding violation under section 502, can potentially give rise to tort liability which would not exist in the absence of such a statute.³⁸

permit a recovery since these statutes are enacted for the public’s protection from the very harm suffered.” Cotton, *A Note on the Civil Remedies of Injured Consumers*, 1 L. & CONTEMP. PROB. 67, 72, n.37 (1933) (citing *Armour v. Wanamaker*, 202 F. 423 (3d Cir. 1913), and *Meshbesher v. Channellene Oil & Mfg. Co.*, 107 Minn. 104, 119 N.W. 428 (1909)). See also *United States v. Various Quantities of Articles of Drug*, 83 F. Supp. 882 (D.D.C. 1949).

35. W. PROSSER, HANDBOOK OF THE LAW OF TORTS § 36, at 200 (4th ed. 1971).

Once a statute is determined to be applicable—which is to say, once it is interpreted as designed to protect the class of persons in which the plaintiff is included, against the risk of the type of harm which has in fact occurred as a result of the violation—the great majority of the courts hold that an unexcused violation is conclusive on the issue of negligence.

Id. The classic case interpreting when a plaintiff is included in the “class of persons to be protected” is *Gorris v. Scott*, [1874] 9 Ex. D. 125, holding that a statute requiring footholds and pens on a cattleship to prevent disease would not operate to create liability when the defendant failed to so equip his ship and cattle were subsequently washed overboard in a storm. For a general discussion on the issue of negligence *per se*, see Kennelly, *Safety Statutes and Ordinances—Their Application and Construction*, 19 TRIAL LAW GUIDE 323 (1975); Lowndes, *Civil Liability Created by Criminal Legislation*, 16 MINN. L. REV. 361 (1932); Comment, *Negligence—Violation of Safety Regulations as Negligence Per Se: The Perishable Sanction*, 62 KY. L.J. 254 (1973). It seems clear that violation of the FDCA will result in *personal* criminal liability, as was held in *United States v. Dotterweich*, 320 U.S. 277 (1943) (imposing vicarious criminal liability on the president of a drug company for shipping misbranded and adulterated drugs in interstate commerce). The question of whether a court should imply a private cause of action for violation of a federal regulatory statute has been debated for many years. “If a plaintiff can prove to a court that the defendant’s violation of the Act [the FDCA] proximately caused him physical or economic harm, a court should imply a remedy on his behalf. . . . [T]here is nothing in the Act or its history to prevent a court from doing this.” Cole & Shapiro, *Private Litigation Under the Federal Food, Drug and Cosmetic Act: Should the Right to Sue Be Implied?*, 30 FOOD-DRUG-COSM. L.J. 576, 610 (1975). *Contra*, Sales, *Does the Food, Drug and Cosmetic Act Create a Private Right of Action?*, 28 FOOD-DRUG-COSM. L.J. 501, 511 (1973) (“The inescapable conclusion is that the [FDCA] does not provide a private right of action nor may one be implied. Congress expressly rejected all proposals that might have justified such an action.”). See generally O’Neill, *Public Regulation and Private Rights of Action*, 52 CALIF. L. REV. 231 (1964); Words, *The Effect of the Food, Drug, and Cosmetic Act on Private Litigation*, 18 FOOD-DRUG-COSM. L.J. 511 (1963); Note, *Implying Civil Remedies from Federal Regulatory Statutes*, 77 HARV. L. REV. 285 (1963).

36. W. PROSSER, *supra* note 35, § 36, at 200

37. *Id.* at 201. See also Morris, *The Role of Administrative Safety Measures in Negligence Actions*, 28 TEX. L. REV. 143 (1949).

38. See discussion of informed consent at notes 78-82 *infra* and accompanying text.

III. TORT LIABILITY

A. *Negligence and Strict Liability—The Duty to Warn*

To recover under the tort theory of negligence, a plaintiff must show (1) a duty, (2) a breach of that duty, (3) causation or proximate cause, and (4) actual damage or loss resulting from the breach.³⁹ The historical standard of care owed to the patient by the pharmacist requires "such precautions as are liable to prevent death or serious injury to those who may, in the ordinary course of events, be exposed to the dangers incident to traffic in which he is engaged"⁴⁰ The concept may also be stated in the classical tort language of professional duty: "[The pharmacist is] required to have that reasonable degree of learning and skill which is ordinarily possessed by other druggists in good standing as to qualifications in similar communities."⁴¹ The pharmacist's duty of care encompasses a duty to warn the patient of dangers connected with the drugs and medicines he compounds and sells.⁴² This duty, combined with the special knowledge of the drugs he dispenses,⁴³ creates unique liabilities for the pharmacist. It has been held that a pharmacist who sells a drug which is "harmless in itself, but is to be mixed with, or used in connection with, another which would then have an injurious effect, of which the purchaser has no knowledge, should advise the purchaser of it, and a failure to do so would make him liable for the consequences."⁴⁴ *Gibson v. Torbert*,⁴⁵ decided in

39. W. PROSSER, *supra* note 35, § 30. For purposes of this comment, it will be presumed that these four elements are present. Therefore, it must also be presumed that, not only did the pharmacist breach his statutory duty to deliver a PPI, but also that the patient was harmed by administration of the drug. The incidence of these two conditions occurring remains to be seen. The remainder of this comment explores possible causes of action a patient/plaintiff might have against the dispensing pharmacist if these two conditions are met.

40. *Corona Coal Co. v. Sexton*, 21 Ala. App. 52, —, 105 So. 716, 717 (1925). See also *Johnson v. Primm*, 74 N.M. 597, 396 P.2d 426 (1964) (pharmacist might be liable for plaintiff's addiction caused by providing drug in excess of prescribed dosage if there was a showing that pharmacist knew of habit-forming nature of drug).

41. *Tremblay v. Kimball*, 107 Me. 53, —, 77 A. 405, 407 (1910).

42. "One dealing in dangerous drugs owes to the public a positive and active duty to limit the danger by labeling or otherwise conveying knowledge thereof." *Miller v. New Zealand Ins. Co.*, 98 So. 2d 544, 546 (La. 1957). Cf. *Love v. Wolf*, 226 Cal. App. 2d 378, 38 Cal. Rptr. 183 (1964) (overpromotion may counteract warning given).

43. "A druggist is undoubtedly held to a special degree of responsibility . . . corresponding with his superior knowledge of the business." *Marigny v. Dejoie*, 172 So. 808, 810 (La. 1937) (citing *Thomas v. Winchester*, 6 N.Y. 397 (1852) (pharmacist delivered poisonous pills by mistake)).

44. *Krueger v. Knutson*, 261 Minn. 144, —, 111 N.W.2d 526, 532 (1961).

45. 115 Iowa 163, 88 N.W. 443 (1901).

Iowa at the turn of the century, however, severely limited the pharmacist's duty to warn by stating that

[i]t has been said that when a person who has reached the age of discretion, and who is apparently in possession of his mental faculties, applies to the druggist for a certain drug, he represents to the dealer, by implication, at least, that he knows its properties and uses, and that he is a fit person to whom sale thereof may be made, and that unless there is something . . . to indicate that the would-be purchaser cannot be entrusted with the substance, a sale . . . , may be made without explaining its properties or the manner in which it may be safely used or handled and . . . the seller is not liable in damages for injuries . . . , no matter how little knowledge the purchaser may in fact have had of its properties, or of the manner in which it could safely be handled.⁴⁶

Although *Gibson* has never been expressly overruled or judicially limited, it is doubtful that a court today would go to such extremes in light of prevalent consumer protection attitudes. The *Gibson* decision has several interesting analogies to the PPI. First, again using the Commissioner's reasons for instituting PPI delivery, the purpose of the PPI is to better enable the patient to participate in the prescription drug regimen delivery system.⁴⁷ If the patient is supplied with an accurate, up-to-date PPI (applying the *Gibson* holding), the liability of the dispensing pharmacist is actually decreased because he may assume, within the limitations of the information actually contained in the PPI, that the patient knows the drug's properties and the manner in which the drug may safely be used.

In California, it has been held that failure to follow instructions given by a physician constitutes a complete defense of contributory negligence in a medical malpractice case.⁴⁸ It is possible that, if the PPI

46. *Id.* at 164, 88 N.W. at 445.

47. 43 Fed. Reg. 4,214-215 (1978). The prescription system as it now operates for all nonsteroid pharmaceuticals includes primarily the physician diagnosing and prescribing the drug and the pharmacist, following the physician's orders, then dispensing the prescription. The patient, though the beneficiary of this delivery system, has little input about what is dispensed to him. Apparently, the Commissioner intends, by requiring PPIs, to give the patient a greater role in the delivery system, at least to the extent that the patient has the information at hand to participate in the decision to assent to a prescription drug regimen.

48. *Preston v. Hubbell*, 87 Cal. App. 2d 53, 196 P.2d 113 (1948) (plaintiff was contributorily negligent in failing to follow post-operative care instructions). *See also Maertins v. Kaiser Found. Hosp.*, 162 Cal. App. 2d 661, 328 P.2d 494 (1958) (plaintiff ignored instructions to return for treatment). *See Kouri, The Patients Duty to Cooperate*, 3 REVUE DE DROIT UNIVERSITE DE SHERBROOKE 43 (1972).

is delivered and the instructions and warnings are not followed, a defense of contributory negligence may be raised effectively by the pharmacist if injury results.⁴⁹

If the patient received the PPI and was harmed as a result of the prescription, assumption of risk should also operate to cut off the pharmacist's liability. The patient is presumed to know the possible adverse effects of the drug which are listed in the PPI and, by continuing therapy, gives free and informed consent to that drug treatment.⁵⁰ Thus, it can be seen that, *if the PPI is delivered*, the liability of the pharmacist may actually be decreased because the pharmacist's duty to warn is fulfilled. Conversely, failure to deliver a PPI would leave the patient without information about the drug prescribed for him. It is probable that the courts would presume the pharmacist to have been aware of the fact that the patient was uninformed about the properties of the drug and therefore hold him liable for any adverse effects caused by his omission.⁵¹

Without the delivery of a PPI, assumption of risk as a defense may be raised only upon a showing that the patient voluntarily took the drug after learning, by means other than the PPI, all information that the PPI would have disclosed.⁵² Such a showing would be difficult at best. *Gibson* notwithstanding, it would be a rare patient who would have the requisite specialized knowledge of a drug's hazards, and it would be unrealistic to assume as much.

As will be shown, the pharmacist today should have an affirmative duty to warn,⁵³ and breach of that duty will subject him to liability, the extent of which the remainder of this section will examine. Traditionally, the concept of a duty to warn as applied to prescription pharmaceuticals sounded in negligence and suit was brought primarily against the manufacturer.⁵⁴ The manufacturer's duty to warn has been

49. See generally W. PROSSER, *supra* note 35, § 65; Note, *Contributory Negligence as a Defense to Medical Malpractice in California*, 8 U.S.F.L. REV. 386 (1973).

50. See generally Keeton, *Assumption of Risk in Products Liability Cases*, 22 LA. L. REV. 122 (1961). Informed consent is discussed at notes 78-82 *infra* and accompanying text.

51. See notes 60-88 *infra* and accompanying text.

52. W. PROSSER, *supra* note 35, § 68, at 440. See also Keeton, *supra* note 50, at 145-46.

53. *Krueger v. Knutson*, 261 Minn. 144, 111 N.W.2d 526 (1961). See RESTATEMENT (SECOND) OF TORTS § 402A, comment k, at 353 (1965), and notes 67-88 *infra* and accompanying text.

54. *Salmon v. Parke, Davis & Co.*, 520 F.2d 1359 (4th Cir. 1975) (manufacturer must exercise reasonable care commensurate with the risk, to warn physicians); *Schenebeck v. Sterling Drug, Inc.*, 423 F.2d 919 (8th Cir. 1970) (manufacturer has continuous duty to warn physicians of dangers of drug); *Sterling Drug, Inc. v. Cornish*, 370 F.2d 82 (8th Cir. 1966) (duty to warn doctors even though only a small number of people would experience the particular side effect).

held repeatedly to be a duty to warn only the prescribing physician, not the ultimate consumer, the patient.⁵⁵ This duty was fulfilled mainly through the use of the package insert⁵⁶ included with each pharmaceutical packaged by the manufacturer (though given to the pharmacist and usually not to the physician) and compiled in the *Physicians' Desk Reference*. The manufacturer's duty to warn is also met through drug advertising which is required to detail all the drug's uses, contraindications, and adverse effects, and through the promotional efforts of the "detail man," the manufacturer's representative who personally contacts the physician to promote the manufacturer's drug products.⁵⁷ Liability has been based on the assumption that the manufacturer is "in the best position to prevent injuries resulting from the use of prescription drugs."⁵⁸ The prescribing physician, on the other hand, if effec-

55. See, e.g., *Salmon v. Parke, Davis & Co.*, 520 F.2d 1359 (4th Cir. 1975); *Schenebeck v. Sterling Drug, Inc.*, 423 F.2d 919 (8th Cir. 1970). But see *Cunningham v. Charles Pfizer & Co.*, 532 P.2d 1377 (Okla. 1974) (manufacturer's duty to warn extends to ultimate consumer—the polio vaccine recipient).

The FDCA has been used by the courts to impose negligence upon a manufacturer based upon a failure to adhere to the Act's requirements. See *Toole v. Richardson-Merrell, Inc.*, 251 Cal. App. 2d 689, 60 Cal. Rptr. 398 (1967) (violation of new drug reporting provision, codified in 21 C.F.R. § 330.10 (1978), gave rise to a presumption of negligence); *McEwen v. Ortho Pharmaceutical Corp.*, 270 Or. 375, 528 P.2d 522 (1974) (liability imposed for injuries caused by inadequate FDA approved labeling, i.e., the physician package insert). The *McEwen* court went on to hold that FDCA requirements "may be only minimal in nature when the manufacturer or supplier knows of, or has reasons to know of, greater dangers not included in the warning, its duty to warn may not be fulfilled. . . ." *id.* at —, 528 P.2d at 534 (citing *Stevens v. Parke, Davis & Co.*, 9 Cal. 3d 51, 507 P.2d 643, 107 Cal. Rptr. 45 (1973)), and that the warnings given by an ethical drug manufacturer may be found inadequate, "[a]lthough all the government's regulations and requirements have been satisfactorily met in the production and marketing of the pharmaceutical and in the changes made in the literature." *Id.* at 534 (citing *Yarrow v. Sterling Drug, Inc.*, 263 F. Supp. 159, *aff'd*, 408 F.2d 978 (8th Cir. 1969)). See Henteleff, *The Interrelationships of FDA Laws and Regulations with Product Liability Issues*, 32 BUS. LAW. 1029 (1977).

56. See App. C.

57. One consistent theme of the *Parke, Davis/Chloromycetin* cases is the effect of manufacturer overpromotion on physician liability. Though the package insert gave adequate warnings, the "detail" men of the manufacturer (i.e., the manufacturer's sales representatives) negated the warnings by minimizing the risks in their presentations to the physicians, resulting in over-prescribing of Chloromycetin in situations where the antibiotic was of little or no use or even contraindicated, with attendant fatalities caused by drug-induced blood dyscrasias. See, e.g., *Stevens v. Parke, Davis & Co.*, 9 Cal. 3d 51, 67, 507 P.2d 653, 662, 107 Cal. Rptr. 45, 54 (1973); *Incollingo v. Ewing*, 444 Pa. 263, 289, 282 A.2d 206, 220 (1971). See generally Note, *Torts—Products Liability—Manufacturer Held Negligently Liable for Failure to Warn of Ethical Drug's Dangers By "Watering Down" Its Warning and Overpromoting Its Drug*, 23 CATH. U.L. REV. 189 (1973); Note, *Products Liability—Drug Manufacturer Liable for Overpromotion of the Use of a Prescription Drug*, 10 GA. S.B.J. 450 (1974); Comment, *The Ubiquitous Detailman: An Inquiry Into His Function and Activities and the Laws Relating to Them*, 1 HOFSTRA L. REV. 183 (1973); Note, *Torts—Products Liability—FDA Required Warning Nullified by Manufacturer Overpromotion of Drug*, 43 U. CINN. L. REV. 224 (1974).

58. Gardner, *supra* note 6, at 855. See *Leibowitz v. Ortho Pharmaceutical Corp.*, 224 Pa. Super. Ct. 418, 307 A.2d 449 (1973), discussing the standard placed on the manufacturer to re-

tively warned by the manufacturer about the use and effects of the drug, has been held liable for negligent malpractice if he either disregarded or was unfamiliar with the available information.⁵⁹

The concept of the duty to warn has now evolved from use in negligence to use in strict liability as embodied in section 402A of the *Restatement (Second) of Torts*.⁶⁰ Drug manufacturers who had failed to provide adequate warnings about their products to the prescribing physician have been held strictly liable for adverse effects suffered by a patient as a result of taking the drug.⁶¹ Strict liability and prescription drugs seem made for each other. Comment j to section 402A⁶² makes

search effects of the drug and the resulting inadequacy of the package insert warnings if such research is not continually performed, with liability accordingly imposed.

59. *McCue v. Norwich Pharmacal Co.*, 453 F.2d 1033 (1st Cir. 1972) (manufacturer liability cut off by physician's negligently prescribing a drug in spite of adequate warning by manufacturer). See also Carleton, *Physician Liability for Adverse Drug Reactions*, 24 MED. TRIAL TECH. Q. 184 (1978). The package insert directed to the physician has frequently been held to be the standard of care in prescription writing. One case resulting from the Chloromycetin litigation held that a deviation from the package insert labeling directions is prima facie evidence of negligence. *Mulder v. Parke, Davis & Co.*, 288 Minn. 332, 339, 181 N.W.2d 882, 887 (1970). See generally Comment, *Package Inserts for Rx Drugs as Evidence in Medical Malpractice Suits*, 44 U. CHI. L.J. 398 (1977). The introduction of physician package inserts as evidence in medical malpractice trials has been excluded as hearsay when used to prove the truth of the statements they contain. See, e.g., *Allen v. Leonard*, 270 Cal. App. 2d 209, 75 Cal. Rptr. 840 (1969) (*dictum*).

60. RESTATEMENT (SECOND) OF TORTS § 402A, at 347 (1965). Section 402A provides:

- (1) One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm thereby caused to the ultimate user or consumer, or to his property, if:
 - (a) the seller is engaged in the business of selling such a product, and
 - (b) it is expected to and does reach the user or consumer, without substantial change in the condition in which it is sold.
- (2) The rule stated in Subsection (1) applies although
 - (a) the seller has exercised all possible care in the preparation of his product, and
 - (b) the user or consumer has not bought the product from or entered into any contractual relation with the seller.

Id.

61. *Hoffman v. Sterling Drug, Inc.* 485 F.2d 132 (3d Cir. 1973) (breach of duty to warn would result in liability to user under both negligence and strict liability theories); *Sterling Drug, Inc., v. Yarrow*, 408 F.2d 978 (8th Cir. 1969) (if drug is manufactured without negligence, but is unreasonably dangerous if warning is not given, manufacturer may be held liable); *Basko v. Sterling Drug, Inc.*, 416 F.2d 417 (2d Cir. 1969) (manufacturer must have actual or constructive knowledge of the hazards before the duty to warn attaches); *Sindell v. Abbott Laboratories*, 149 Cal. Rptr. 138 (1978) (drug manufacturers are not entitled to more lenient treatment than other manufacturers in the area of products liability). The *Basko* court noted that comment k to § 402A of the *Restatement (Second) of Torts* adopts the ordinary negligence duty to warn standard. 416 F.2d at 426. For further discussion of manufacturer liability, see Gardner, *supra* note 6, at 855.

62. RESTATEMENT (SECOND) OF TORTS § 402A, comment j, at 353 (1965). Comment j provides:

Where . . . the product contains an ingredient to which a substantial number of the population are allergic . . . the seller is required to give warning against it, if he has knowledge, or by the application of reasonable, developed human skill and foresight should have knowledge, of the presence of the ingredient and the danger. . . . Where warning is given, the seller may reasonably assume that it will be read and heeded; and a

the failure to warn adequately of a defect in the product itself a basis for imposing strict liability. The drafters of the *Restatement (Second)*, however, chose to provide an exemption for prescription drugs. Comment k, when read together with comment j, specifically exempts prescription drugs, provided adequate warning is given. While admitting that drugs are unsafe, they are termed "unavoidably unsafe" and therefore not defective or unreasonably dangerous if accompanied by proper directions and warnings.⁶³

With the inception of the *patient* package insert, it becomes possible that a duty to give proper directions and warnings will now apply to the pharmacist as well. The courts have long been hesitant to hold a pharmacist strictly liable for the performance of his duties. Before the PPI, the pharmacist was held not to be an insurer, making him immune to strict liability theories of recovery and leaving him answerable only for his negligence.⁶⁴ The information contained in the PPI, however, may be viewed as the "proper directions and warnings" required by

product bearing such a warning, which is safe for use if it is followed, is not in defective condition, nor is it unreasonably dangerous.

63. *Id.*, comment k. Comment k provides:

There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. . . . Such a product, properly prepared, and accompanied by proper directions and warnings, is not defective, nor is it unreasonably dangerous.

For a discussion of the duty to warn regarding polio vaccines, see Note, *Duty to Warn Extended to Bystander in Close Contact to Polio Vaccinee*, 29 MERCER L. REV. 643 (1978).

64. *Faulkner v. Birch*, 120 Ill. App. 281, 284-86 (1905) (instruction for plaintiff erroneous in that it made defendant pharmacist an insurer of the accuracy of his prescriptions). See also *McLeod v. W.S. Merrell*, 174 So.2d 736 (Fla. 1965); *Bichler v. Willig*, 58 A.D.2d 331, 397 N.Y.S.2d 57 (1977); *Singer v. Oken*, 193 Misc. 1058, 87 N.Y.S.2d 686 (1949); *Batiste v. American Home Prod. Corp.*, 32 N.C. App. 1, 231 S.E.2d 269 (1977).

Very few recent cases concerning pharmacist liability have been heard. One possible explanation for this is the changing system of pharmaceutical delivery. "Originally a prescription drug could be requested from the druggist. A physician who was knowledgeable in pharmacology would tell a patient what drug might be best for him, but it was not necessary to have a prescription to obtain many hazardous drugs." M. DIXON, *DRUG PRODUCTS LIABILITY* § 801, at 8-2 (1977). The pharmacist then advised among the many products available. Today's delivery system usually requires the pharmacist to be only a "distributor of prepackaged products." *Id.* at 8-34. Although the duty of care is still high, there is less chance of error and therefore, less litigation. Strict liability has not been resorted to as a means of recovery in the few cases reported. Negligence and negligence *per se* remain the chief causes of action with plaintiffs seldom resorting to strict liability. See *Cox v. Laws*, 244 Miss. 676, 145 So. 2d 703 (1962) (deliberate violation of statute removes bar of privity of contract); *Duensing v. Huscher*, 431 S.W.2d 169 (Mo. 1968) (nonpharmacist employee negligently dispensed wrong drug, in violation of statute requiring either a pharmacist to be on duty or notice to the patient that no pharmacist was on duty. Plaintiff suffered brain damage and was awarded punitive damages). In *McLeod v. W.S. Merrell Co.*, 174 So. 2d 736 (Fla. 1965), the Florida Supreme Court refused to extend strict liability to retail pharmacists, restricting their liability to improper compounding, adulteration, and failure to use due care in filling a prescription. The holding seems out of line with the trend toward strict liability

section 402A to avoid strict liability to the patient for adverse effects caused by the prescription. The pharmacist who fails to deliver a PPI with the unavoidably unsafe (by definition)⁶⁵ prescription medicine may be deemed to have dispensed an unreasonably dangerous and defective product. Therefore, he would become subject to the liability without fault sanctions of section 402A, not for an error in dispensing the prescription itself, but for nondelivery of the PPI.⁶⁶

The Commissioner of the FDA denied that increased liability for the dispensing pharmacist would result in all cases with the inception of the PPI.⁶⁷ Instead, he proposed that a case-by-case determination be made according to state judicial and legislative standards.⁶⁸ Considering that most states have adopted some form of strict liability patterned, at least roughly, on section 402A⁶⁹ and have adopted the Uniform Commercial Code,⁷⁰ strict liability for the pharmacist may be found in the majority of jurisdictions, despite the Commissioner's statements to the contrary.⁷¹ Where the plaintiff has been harmed but the usual defendant, the drug manufacturer, is absolved from liability because it provided the PPI to the pharmacist as required, a jury may be inclined to find someone liable rather than allow the innocent plaintiff to be denied recovery. It is reasonable to conclude that the pharmacist who failed to deliver the PPI will have to bear the liability. Of course, if the pharmacist does deliver a PPI as required, and the manufacturer has provided adequate warnings to the prescribing physician, section 402A may work against the plaintiff to deny relief completely.

Causation must next be considered in determining a pharmacist's potential liability. The problem of causation in strict liability cases has created some confusion in the courts,⁷² particularly in cases involving

for retailers and has been criticized. See Comment, *Torts—Strict Products Liability for Retailers?*, 45 WASH. L. REV. 431 (1970); Annot., 13 A.L.R. 3d 1057, 1099 (1967).

65. RESTATEMENT (SECOND) OF TORTS § 402A, comment k, at 353 (1965).

66. For limitations to § 402A liability, see notes 71-87 *infra* and accompanying text.

67. 43 Fed. Reg. 4,214 (1978).

68. *Id.* A trend in pharmacist-patient consultation seems to be emerging. In at least six states, the legislature has included oral consultation with the patient as a mandatory step in the compounding and dispensing of a prescription. See KANSAS STATE BD. OF PHARMACY RULES AND REGS. 68-2-20(2); ME. REV. STAT. ANN. tit. 32, § 2911(1) (1978); N.J. AD. CODE §§ 13.39-6.3(b) & 13.39-8.14; N.D. CENT. CODE § 43-15-31.2 (1978); WASH. AD. CODE § 360-16-250(1); WIS. AD. CODE PHARMACY § 1.19. See generally Valentino, *Legal Implications of U.S.P. Dispensing Information*, U.S. PHARMACIST, August 1978, at 24, 28-29.

69. W. PROSSER, *supra* note 35, § 98, at 657-58.

70. See notes 89-129 *infra* and accompanying text.

71. See 43 Fed. Reg. 4,214 (1978).

72. "Nor, despite the manifold attempts which have been made to clarify the subject, is there

unavoidably unsafe products such as pharmaceuticals.⁷³ The *Restatement (Second)* requires only actual, not proximate, causation under section 402A,⁷⁴ but many courts continue to include proximate causation as an element of strict liability.⁷⁵ Causation required in pharmaceutical cases should be limited to that postulated by the *Restatement (Second)* in section 402A. With the limitations placed upon section 402A by comment k, the legal cause required for drug products liability is that the injuries flow from a breach of the duty to warn of the danger which caused the injury. If the patient would have continued taking the prescription drug after having been warned of the possible adverse reactions, the legal cause of the harm is insufficiently related to the pharmacist to hold him liable even if no warning was given. An Oklahoma case, *Cunningham v. Charles Pfizer & Co.*,⁷⁶ held that proving merely that the polio vaccine in question was the cause in fact of the plaintiff's injury was not enough. Not only must it be established that the vaccine caused the injury, but it must also be shown that, had an adequate warning been given to the plaintiff, he would not have taken the drug.⁷⁷

The *Cunningham* test for causation appears to bring the doctrine of informed consent from the operating room into the pharmacy.⁷⁸ The plaintiff must prove "that had the needed disclosures been made,

yet any general agreement as to the proper approach." W. PROSSER, *supra* note 35, § 41, at 236, and articles cited.

73. See, e.g., *Parke, Davis & Co. v. Stromsodt*, 411 F.2d 1390 (8th Cir. 1969) (drug was probable cause of injuries as illicit by medical testimony under North Dakota law). See also *Rexall Drug Co. v. Nihill*, 276 F.2d 637 (9th Cir. 1960) (applying North Dakota and California law); *Carmichael v. Reitz, Searle & Co.*, 17 Cal. App. 3d 958, 95 Cal. Rptr. 381 (1971). See generally Rheingold, *The Expanding Liability of the Product Supplier: A Primer*, 2 HOFSTRA L. REV. 521, 547-48 (1974); Note, *Unavoidably Unsafe Drugs—An Oklahoma Modification*, 29 OKLA. L. REV. 252, 258-59 (1976).

74. See generally RESTATEMENT (SECOND) OF TORTS § 402A(1), at 348 (1965). See also Maleson, *Negligence Is Dead But Its Doctrines Rule Us from the Grave: A Proposal To Limit Defendant's Responsibilities in Strict Products Liability Actions Without Resort to Proximate Cause*, 51 TEMP. L.Q. 1 (1978).

75. See *Basko v. Sterling Drug, Inc.*, 416 F.2d 417 (2d Cir. 1969). See also Comment, *Strict Products Liability: The Irrelevance of Foreseeability and Related Negligence Concepts*, 14 TULSA L.J. 338, 360 n.112 (1978).

76. 532 P.2d 1377 (Okla. 1974).

77. *Id.* at 1382. The court went on to state, however, that plaintiff was entitled to a rebuttable presumption that the patient would have heeded any warning which might have been given. Direct evidence on this point was not required, following the holding of *Reyes v. Wyeth Laboratories*, 498 F.2d 1264 (5th Cir. 1974). Receipt of the insert also presumes that the patient has read the insert. 532 P.2d at 1382.

78. Mr. Justice Cardozo first commented on what evolved into the doctrine of informed consent in *Schloendorff v. Society of N.Y. Hosp.*, 211 N.Y. 125, 105 N.E. 92 (1914), by stating that "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body" *Id.* at 129, 105 N.E. at 93

his course of conduct would not have included the [drug] therapy which resulted in his injury."⁷⁹ In other words, had the patient been told what effects the particular drug might cause, a different course of action would have been chosen.⁸⁰ This is especially true with regard to contraindications⁸¹ of a drug. For example, a patient, knowing that he is hypersensitive to penicillin, is given a prescription for Keflex, an antibiotic similar to penicillin which may cause cross-sensitivity reactions in patients also sensitive to penicillin. Upon reading the contraindication information contained in a Keflex PPI, the patient would be alerted to the danger and another antibiotic could be prescribed. If, however, the pharmacist omitted the PPI from the prescription, the patient would be unaware of the contraindication (assuming the physician had not inquired before prescribing, which is a separate cause of

79. Note, *Unavoidably Unsafe Drugs—An Oklahoma Modification*, 29 OKLA. L. REV. 252, 258 (1976). See also *Gobbs v. Grant*, 8 Cal. App. 3d 229, 502 P.2d 1, 104 Cal. Rptr. 505 (1972); *Canterbury v. Spence*, 464 F.2d 772 (D.C. Cir. 1972); *Funke v. Dieldman*, 212 Kan. 524, 512 P.2d 539 (1973); *Trogun v. Fruchtman*, 58 Wisc. 2d 569, 207 N.W.2d 297 (1973); *Gravis v. Parke, Davis & Co.*, 502 S.W.2d 863 (Tex. Civ. App. 1973). For a general discussion of informed consent as applied to the physician in a medical malpractice setting, see M. DIXON, *supra* note 64, § 7.23, at 7-109 to 7-113; Markham, *The Doctrine of Informed Consent—Fact or Fiction?*, 10 FORUM 1073 (1975); Plant, *Decline of Informed Consent*, 35 WASH. & LEE L. REV. 91 (1973); Seidelson, *Medical Malpractice: Informed Consent in "Full Disclosure" Jurisdictions*, 14 DUQ. L. REV. 309 (1976); Comment, *Who's Afraid of Informed Consent, An Affirmative Approach to the Medical Malpractice Crisis*, 44 BROOKLYN L. REV. 241 (1978); Note, *Informed Consent Liability*, 26 DRAKE L. REV. 696 (1977); Note, *Evolution of the Doctrine of Informed Consent*, 12 GA L. REV. 581 (1978); Comment, *Informed Consent and the Patient's Right to Say "No"*, 6 LOY. L.A.L. REV. 384 (1973); Comment, *New Trends in Informed Consent*, 54 NEBR. L. REV. 66 (1975); Comment, *A New Standard of Informed Consent in Medical Malpractice Cases—The Role of the Expert Witness*, 18 ST. LOUIS U.L.J. 256 (1973).

Informed consent and the delivery of the PPI present questions which could possibly change the status of health care delivery today. First, after having been given a prescription by the physician following a thorough examination, would the patient rely on the PPI and forego the prescription treatment or instead rely on the physician's knowledge and authority that the physician-patient relationship carries with it? Second, will health care suffer if a PPI does promote a reconsideration of prescription drug therapy by the patient? "Doctors believe that patients are neither emotionally nor intellectually equipped to play a significant role in decisions affecting their medical fate, that they must be guided past childish fears into 'rational' therapy, and that disclosures of uncertainty, gloomy prognosis, and due risks often seriously undermine cure." Katz, *Informed Consent—A Fairy Tale? Law's Vision*, 39 U. PITT. L. REV. 137, 148 (1977). "We [the medical profession] are all committed to providing patients with considerate and respectful care, competent medical advice, high quality medications, . . . and as much information as it is reasonably possible to convey with regard to both treatment and illness." Guarino, *Patient Package Inserts*, 34 FOOD-DRUG-COSM. L.J. 116 (1979). The questions of patient rights, FDA regulations, and the physician are fully discussed, against the backdrop of the Laetrile issue, in Note, *Freedom of Choice in Medical Treatment: Reconsidering the Efficacy Requirement of the FDCA*, 9 LOY. CHI. L.J. 205 (1977).

80. See generally Hirsch, *Patient Package Inserts*, 6 MED. L.J.2d 227 (1978).

81. A contraindication is an absolute warning that the drug must not be used in certain patients, for example, patients with a known hypersensitivity to the drug.

action)⁸² and would therefore be unaware that he could possibly suffer an allergic, often fatal, anaphylactic reaction for which the pharmacist could be held liable.

The pharmacist would not be liable in tort for nondelivery of a PPI if his omission was not the legal cause of the patient's injury. A classic example would arise with failure to deliver a PPI with a prescription of an oral contraceptive. While the pharmacist might be liable if a patient with a history of thrombophlebitis⁸³ developed a clot after taking the new prescription without adequate patient warning, he would not be liable if the patient became pregnant while taking the pill. The pregnancy could not be viewed as a result of the pharmacist's failure to deliver the PPI.⁸⁴

The limitation of foreseeability has some bearing on the extent of the pharmacist's liability.⁸⁵ When the consequences of the act (or in the pharmacist's case, the omission) could not reasonably be anticipated, no legal causation exists, and there can be no liability. Though difficulties with the language persist, foreseeability can best be defined here as liability "only if the harm suffered is the 'natural and probable' consequence of . . . [the pharmacist's] act."⁸⁶ Prosser defines natural as being intended to "refer to consequences which are normal, not extraordinary, not surprising in the light of ordinary experience. Probable, if it is to add anything to this, must refer to consequences which were to be anticipated at the time of the defendant's conduct."⁸⁷ Foreseeability as a limiting factor can best be demonstrated in the example above. When the pharmacist dispenses a supply of oral contraceptives

82. See, e.g., *Rotan v. Greenbaum*, 273 F.2d 830 (D.C. Cir. 1959) (physician held liable for death resulting from anaphylactic reaction to penicillin injection); *Dickens v. Everhart*, 284 N.C. 95, 199 S.E.2d 440 (1973) (standard of care of physician extends to selection and use of drugs and knowledge of dangers inherent in their use).

83. Thrombophlebitis is a listed contraindication in the presently required PPI labeling. 21 C.F.R. § 301.501(a) (1978). See App. B. It has been held, however, that if the patient knew of the contraindication and did not inform his prescribing physician, the physician would not be liable for adverse effects. *Vaughn v. G.D. Searle & Co.*, 272 Or. 367, 536 P.2d 17, cert. denied, 423 U.S. 1054 (1975).

84. In an action against the manufacturer of an oral contraceptive, it was held that "manufacturers of products are not liable . . . to persons, who, having taken or received drugs, contract that which the drug was designed to prevent. . . ." *Whittington v. Eli Lilly & Co.*, 333 F. Supp. 93, 100 (S.D.W. Va. 1971).

85. W. PROSSER, *supra* note 35, § 43, at 250. See Polelle, *The Foreseeability Concept and Strict Products Liability: The Odd Couple of Tort Law*, 8 RUT.-CAM. L.J. 101 (1976); Comment, *Strict Products Liability: The Irrelevance of Foreseeability and Related Negligence Concepts*, 14 TULSA L.J. 338 (1979).

86. W. PROSSER, *supra* note 35, § 43, at 252.

87. *Id.*

without delivering a PPI as well, the risk of developing thrombophlebitis in a sensitive patient is natural and probable and, hence, a foreseeable consequence of his omission. By no stretch of a court's imagination could a patient's pregnancy be termed a natural and probable consequence of his failure to deliver the PPI.⁸⁸

B. Breach of Warranty

The omission of a PPI may also impose liability upon the dispensing pharmacist in the form of a warranty action, a relief that originated in tort⁸⁹ and has since been written into most state codes through the Uniform Commercial Code (U.C.C.). This action, which bases relief on the express or implied representations by the manufacturer or the seller of goods to the purchaser, approaches strict liability and indeed

88. Pregnancy would be a foreseeable consequence for which the pharmacist is liable if he failed to dispense the oral contraceptive prescribed and, instead, mistakenly dispensed some other drug. *Troppi v. Scarf*, 31 Mich. App. 240, 187 N.W.2d 511 (1971) (pharmacist may be required to make child support payments).

89. A more notable example of legal miscegenation could hardly be cited than that which produced the modern action for breach of warranty. Originally sounding in tort, yet arising out of the warrantor's consent to be bound, it later ceased necessarily to be consensual and at the same time came to lie mainly in contract.

Note, *Necessity for Privity of Contract in Warranties by Representation*, 42 HARV. L. REV. 414, 414-15 (1929) (citations omitted).

The action of implied warranty began in tort as a means of recovery against the marketing of defective food products, although throughout the common law the seller of food and drink possessed a special, but fluctuating, responsibility. See Cotton, *A Note on the Civil Remedies of Injured Consumers*, 1 L. & CONTEMP. PROB. 67 (1933).

With the coming of the Industrial Revolution and its accompanying accentuation of individualism, *caveat emptor* replaced the doctrine of the common calling, especially in American courts, and protection for consumers of food and drugs was a matter of exception to be granted guardedly. Thus, though Blackstone had recognized an implied warranty of fitness where food was sold, the Massachusetts court in 1813 interpreted him to mean this to apply only where a dealer *knew* that he was selling impure food, and disguised it, a construction which appears to unduly limit Blackstone's text.

Id. at 68 (emphasis in original) (citations omitted). *Nazetti v. Armour & Co.*, 75 Wash. 622, 135 P. 633 (1913), became the first case to discard the necessity of contract and the steady march was on to hold sellers of defective food and drink strictly liable. W. PROSSER, *supra* note 35, § 97, at 653. For a detailed development of the trend from warranty (requiring contract) to strict products liability, see Prosser, *The Assault Upon the Citadel (Strict Liability to the Consumer)*, 69 YALE L.J. 1099 (1960).

Items for intimate bodily use, such as cosmetics, became the next group of products to which an implied warranty was extended until, in 1958, "the Michigan court found a warranty, without privity and without negligence, of cinder building blocks when the user's home collapsed." W. PROSSER, *supra* note 35, at 654 (citing *Spence v. Three Rivers Builders & Masonry Supply, Inc.*, 353 Mich. 120, 90 N.W.2d 873 (1958)). Other products quickly followed, and privity is not currently required in most jurisdictions in an action of implied warranty. The warranty action has completed its full circle from tort to contract and back again. See Prosser, *The Fall of the Citadel (Strict Liability to the Consumer)*, 50 MINN. L. REV. 791 (1966). The remainder of this article will deal with the implied warranty of merchantability under the Uniform Commercial Code as an alternative theory of recovery against the dispensing pharmacist.

has been viewed as an intermediate step between negligence and pure strict liability.⁹⁰ Though the action had its origin in tort and has retained some of its tort character,⁹¹ contract principles as governed by the U.C.C. provide the primary basis of recovery. This is true even though many courts have returned to tort principles to escape the harsher provisions required by the U.C.C.⁹² By examining the warranty provisions of the U.C.C.⁹³ and by applying them to the requirements and purposes of the FDCA, it will be shown that the PPI may allow additional theories of recovery against the dispensing pharmacist that would have been unavailable before a PPI was required.

The pharmacist, as a prescription drug dispenser, has historically been liable for breach of warranty even when the rule of caveat emptor flourished.⁹⁴ The pharmacist has been held to warrant "the good quality of the drug sold; that the article is of the kind he contracted [through the prescription form presented by the patient to the pharmacist] to sell; and, as to sale of a prescription, that he used due and proper care and skill."⁹⁵ The "good quality of the drug sold" requirement has been modified and expanded into the U.C.C. article 2 requirement of merchantability of goods.⁹⁶ For purposes of this discussion, it will be assumed that the sale of a prescription is a sale of goods and not of services.⁹⁷ Because the pharmacist is a "merchant with respect to goods

90. W. PROSSER, *supra* note 35, § 97.

91. *Id.* at 654. See note 89 *supra*.

92. W. PROSSER, *supra* note 35, § 97, at 655. See notes 113-24 *infra* and accompanying text.

93. U.C.C. §§ 2-313, 2-314.

94. *Jacobs Pharmacy Co. v. Gibson*, 116 Ga. App. 760, —, 159 S.E.2d 171, 173 (1967). See also note 89 *supra*.

95. *Jacobs Pharmacy Co. v. Gibson*, 116 Ga. App. 760, —, 159 S.E.2d 171, 173 (1967).

96. U.C.C. § 2-314. Section 2-314 provides:

(1) Unless excluded or modified (Section 2-316), a warranty that the goods shall be merchantable is implied in a contract for their sale if the seller is a merchant with respect to goods of that kind. Under this section the serving for value of food or drink to be consumed either on the premises or elsewhere is a sale.

(2) Goods to be merchantable must be at least such as

(a) pass without objection in the trade under the contract description; and

(b) in the case of fungible goods, are of fair average quality within the description;

and

(c) are fit for the ordinary purposes for which such goods are used; and

(d) run, within the variations permitted by the agreement, of even kind, quality and quantity within each unit and among all units involved; and

(e) are adequately contained, packaged, and labeled as the agreement may require; and

(f) conform to the promises or affirmations of fact made on the container or label if any.

(3) Unless excluded or modified (Section 2-316) other implied warranties may arise from course of dealing or usage of trade.

97. "Outside of a few examples of what might be considered purely services, in most cases

of that kind [prescription drugs and medicines],”⁹⁸ an implied warranty is created by the sale of the prescription to the patient.⁹⁹ For goods to be merchantable, they must be “adequately contained, packaged, and labeled as the agreement may require.”¹⁰⁰ If the PPI regulations, either presently in force¹⁰¹ or proposed,¹⁰² constitute the required agreement, it is then possible that by omitting the required PPI the pharmacist has dispensed an inadequately labeled product.

Thus, by the operation of U.C.C. section 2-314(2)(e), the pharmacist has breached an implied warranty of merchantability for which he may be liable. The agreement is between the pharmacist and the patient for U.C.C. purposes, but the implied warranty is formed when section 2-314 of the U.C.C. is read together with section 352 of the FDCA. Thus, the agreement implies to the patient that the pharmacist will fill the prescription in accordance with all applicable pharmacy regulations. The Official Comments to section 2-314¹⁰³ provide that sub-paragraph (e) “applies only where the nature of the goods and of the transaction requires a certain type of . . . label.”¹⁰⁴ Section 352(f)

pharmacists services will entail the sale of a product and warranty law will apply.” C. DEMARCO, *PHARMACY AND THE LAW* 229 (1975). This is to be contrasted with the controversy found in the blood transfusion/serum hepatitis cases where the transfusion was held to be a service and not the sale of a product. See *Perlmutter v. Beth David Hosp.*, 308 N.Y. 100, 123 N.E.2d 792 (1954).

The art of healing frequently calls for a balancing of risks and dangers to a patient.

Consequently, if injury results from the course adopted, where no negligence or fault is present, liability should not be imposed upon the institution or agency actually seeking to save or otherwise assist the patient.

Id. at 107, 123 N.E.2d at 795. The idea of a blood transfusion as a sale did not emerge until 1966 in *Community Blood Bank, Inc., v. Russell*, 196 So. 2d 115 (Fla. 1967), which involved a commercial blood bank as compared to a hospital. A hospital was first found strictly liable for serum hepatitis transmitted by a transfusion in *Cunningham v. MacNeal Memorial Hosp.*, 47 Ill 2d 443, 266 N.E.2d 897 (1970). See also *Schmaltz v. Saint Luke's Hosp.*, 33 Colo. App. 351, 521 P.2d 787 (1974). See generally Comment, *Blood Transfusions and the Transmission of Serum Hepatitis: The Need for Statutory Reform*, 24 AM. U.L. REV. 367 (1975); Comment, *Products Liability—Blood Transfusions—“Implied Warranty” Action Against Blood Suppliers Requires Showing of Detectable Defect and Negligence*, 3 FLA. ST. L. REV. 483 (1975).

98. U.C.C. § 2-314(1) (1972 version).

99. The warranty liability has been limited to drugs that are compounded by the pharmacist personally and unmerchantable drugs that have expired or decomposed and are nevertheless dispensed. The liability has never been applied to an adverse effect caused, not by some act or omission of the pharmacist, but by the drug itself. *McLeod v. W.S. Merrell Co.*, 174 So. 2d 736 (Fla. 1965) (pharmacist would not be liable for patient's adverse effect when the prescription was filled precisely in accordance with the doctor's order and manufacturer's directions). See also *Batiste v. American Home Products Corp.*, 32 N.C. App. 1, 231 S.E.2d 269 (1977).

100. U.C.C. § 2-314(2)(e) (1972 version).

101. 21 C.F.R. § 310.501(a) (1978).

102. See note 6 *supra* and accompanying text.

103. U.C.C. § 2-314, comment 10 (1972 version).

104. *Id.*

of the FDCA, as amended by section 310.501(a),¹⁰⁵ requires a label giving directions and warnings, in other words a PPI, to avoid misbranding. The U.C.C. imposes an obligation on the seller "not to deliver mislabeled articles."¹⁰⁶ Reading these two provisions together indicates that liability may be imposed on a pharmacist for delivery of a mislabeled prescription under a theory of breach of an implied warranty of merchantability.

*Reddick v. White Consolidated Industries, Inc.*¹⁰⁷ addressed the question of merchantability as applied to an instruction manual accompanying a gas heater and is instructive by analogy. The plaintiffs claimed that the instructions supplied were inadequate, and that as a direct result of this defect the heater was improperly installed, causing asphyxiation. In deciding the implied warranty question, the district court had to determine if the instruction manual could be classified as a "label" within the meaning of the U.C.C. After examining the FDCA definition of "label,"¹⁰⁸ the court held that the manual was not a label under the FDCA; therefore, the U.C.C. implied warranty of merchantability would not apply.¹⁰⁹ The FDCA defines labeling as "all . . . written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) *accompanying such article.*"¹¹⁰ It seems clear that a PPI is to be included as labeling under the FDCA; therefore, the U.C.C. implied warranty of merchantability would apply to the PPI, unlike the instruction manual in the *Reddick* case.

The plaintiffs in *Reddick* recovered, however, because the court applied the second form of implied warranty, that of fitness for a particular use.¹¹¹ "If a manufacturer furnishes instructions as to a manner

105. 21 C.F.R. § 310.501(a) (1978).

106. U.C.C. § 2-314, comment 10 (1972 version).

107. 295 F. Supp. 243 (S.D. Ga. 1969).

108. *See United States v. 24 Bottles*, 338 F.2d 157, 158 (2d Cir. 1964).

109. 295 F. Supp. at 249-50.

110. 21 U.S.C. § 321(m) (1976) (emphasis supplied). A label is defined as a display of written, printed, or graphic matter upon the immediate container or any article; and a requirement made by or under authority of this chapter that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

Id. § 201(k). *See generally* C. DEMARCO, *supra* note 97, at 127.

111. 295 F. Supp. at 250. The implied warranty of fitness for a particular use is found in U.C.C. § 2-315 (1972 version).

Section 2-315 provides:

Where the seller at the time of contracting has reason to know any particular purposes for which the goods are required and that the buyer is relying on the seller's skill or

in which a product is to be used, the consumer is entitled to think that so used it will not injure him. There is an implied warranty that the goods are fit for that particular use."¹¹² A PPI should *not* subject a pharmacist to liability if the drug does not act as intended. The implied warranty of fitness for a particular purpose should apply to the physician or manufacturer because the patient/buyer is not relying on the pharmacist/seller's skill or judgment, but "on the skill and judgment of the physician, the person who chooses the prescription."¹¹³ Instead, only the warranty of merchantability would apply to the pharmacist for dispensing a misbranded prescription.

Using a contractual theory of implied warranty under the U.C.C. presents problems that a tort action does not. The U.C.C. requires the buyer to give notice to the seller within a reasonable time after he knew or should have known of the breach.¹¹⁴ Additionally, the U.C.C. allows a disclaimer of all express or implied warranties to be effective. The implied warranty of merchantability may be disclaimed "by expressions like 'as is,' 'with all faults' or other language which in common understanding calls the buyer's attention to the exclusion of warranties"¹¹⁵ If such terms are not used, specific requirements must be met, including conspicuous language (if in writing) mentioning merchantability. The PPI¹¹⁶ contains "no reference to 'as is,' 'with all faults' or other common commercial terms synonymous with dis-

judgment to select or furnish suitable goods, there is . . . an implied warranty that the goods shall be fit for such purpose.

See Corman, *Implied Sales Warranty for Fitness for Particular Purpose*, 1958 WIS. L. REV. 219; Note, *Commercial Law—Implied Warranties Under the Uniform Commercial Code—The Implied Warranty of Fitness for a Particular Purpose*, 10 WAKE FOREST L. REV. 169 (1974). For a discussion of implied warranties in general as applied to suppliers of services, see Greenfield, *Consumer Protection in Service Transactions—Implied Warranties and Strict Liability in Tort*, 1974 UTAH L. REV. 661; Singal, *Extending Implied Warranties Beyond Goods: Equal Protection for Consumers of Services*, 12 NEW ENG. L. REV. 859 (1977).

112. 295 F. Supp. at 250.

113. Frey, *The Pill and the Code*, 15 J. FAM. L. 1 (1976). See generally Carleton, *Physician Liability for Adverse Drug Reactions*, 24 MED. TRIAL TECH. Q. 184 (1978); Comment, *Prescriptions as an Extension of the Doctor-Patient Relationship*, 22 CLEV. ST L. REV. 549 (1973); Comment, *Liability for Failure of Birth Control Methods*, 76 COLUM. L. REV. 1187 (1976). See also Incollingo v. Ewing, 444 Pa. 263, 282 A.2d 206 (1971) (physician held liable for repeated administration of Chloromycetin without adequate testing).

114. U.C.C. § 2-607(3) (1972 version). New York, however, has held that goods sold for human consumption are not subject to § 2-607. See *Fischer v. Mead Johnson Laboratories*, 41 A.D.2d 737, 341 N.Y.S.2d 257 (1973). Illinois has upheld the notification requirement saying that the plain meaning of the statute requires such an interpretation. *Berry v. G.D. Searle & Co.*, 56 Ill. 2d 548, —, 309 N.E.2d 550, 554-55 (1974).

115. U.C.C. § 2-316(3)(a) (1972 version).

116. See App. A & B.

claimer. Nor is there mention of merchantability."¹¹⁷ Thus, it appears that the PPI is not a disclaimer of liability, but is instead only a warning, with no effect on U.C.C. liability.¹¹⁸ In any event, the nondelivery of a PPI could result in liability under any of the above theories of recovery, since no label that could be classed as either a warning or a disclaimer was given to the patient.

Section 2-715 of the U.C.C. expressly provides for the recovery of consequential damages including injury to "person or property proximately resulting from any breach of warranty."¹¹⁹ This raises the question of legal causation that was first presented in the discussion of the duty to warn liability concept.¹²⁰ The comments to section 2-715 define this causation factor somewhat differently than the standard tort usage:

Where the injury involved follows the use of goods without discovery of the defect [in this case, the non-delivery of the PPI, resulting in unmerchantability of the prescription] causing the damage, the question of "proximate cause" turns on whether it was reasonable for the buyer to use goods without such inspection as would have revealed the defects. If it was not reasonable for him to do so, or if he did in fact discover the defect prior to his use, the injury would not proximately result from the breach of warranty.¹²¹

Where there is nondelivery of the PPI causing the prescription to be misbranded and therefore unmerchantable, it must also be shown that the patient would not reasonably have been expected to inspect the prescription in order to discover the defect.¹²² This theory of causation is a difficult one for the pharmacist to overcome. The defect caused by the misbranding is one brought about by omission, not by an overt, physical act. Therefore, unless the patient had received the drug before and was expecting to receive a PPI and did not, there is nothing unusual about the prescription that would put the patient on notice of the hidden defect. The patient must also show that the nondelivery of the

117. Frey, *supra* note 113, at 19. For a general discussion of warranty disclaimers, see McNichols, *Who Says That Strict Tort Disclaimers Can Never Be Effective? The Courts Cannot Agree*, 28 OKLA. L. REV. 494 (1975); Parker, *The Warranty Disclaimer v. Manufacturers' Products Liability—Steiner Aero AB v. Page Airmotive, Inc.: Did the Tenth Circuit Bury the Disclaimer Alive?*, 10 TULSA L.J. 612 (1975); Weintraub, *Disclaimer of Warranties and Limitations of Damages for Breach of Warranty Under the U.C.C.*, 5 TEX. L. REV. 60 (1974).

118. See Frey, *supra* note 113, at 18-19.

119. U.C.C. § 2-715(2)(b) (1972 version).

120. See notes 39-87 *supra* and accompanying text.

121. U.C.C. § 2-715, comment 5 (1972 version).

122. See *Dunlap v. Oakcliff Pharmacy Co.*, 288 S.W. 236 (Tex. Civ. App. 1926) (layman will not appreciate that substituted drug would not have same label).

PPI was the proximate cause of the injury itself,¹²³ in addition to showing that it was reasonable for him to take the prescription without inspecting for defects. It becomes more difficult for the patient to recover under the U.C.C. for consequential damages in that certain requirements must be complied with in addition to proximate causation, most notably, that of notice of the breach.¹²⁴ While the requirement of notice has been modified and extensively limited by some courts,¹²⁵ it still presents a barrier to recovery for the unknowing plaintiff. The statute of limitations in a warranty action may cause disadvantages as well. Though longer¹²⁶ than most two-year tort statutes, the cause of action accrues when tender of delivery is made.¹²⁷ Thus, it is possible that the plaintiff's cause of action may be barred before any injury has occurred.¹²⁸ On the other hand, if the particular jurisdiction recognizes liability under section 402A,

a plaintiff who is injured more than four years after the sale of the defective product, although barred from recovery in a breach of warranty action pursuant to the Code, will nevertheless have two years to bring an action based on strict tort liability, provided she can show that the defective product was unreasonably dangerous as required under 402A.¹²⁹

IV. CONCLUSION

Once the pharmacist was liable to the patient only for negligent performance of his duties.¹³⁰ It now appears possible that FDA and congressional action to require patient labeling for most drugs will in-

123. One causal problem relates to the statistical probability for injury due to the pill. Women may suffer heart attacks and strokes whether or not they use oral contraceptives. The pill only increases the rate at which these events occur. Must the injured consumer establish that her stroke was not the one in eight which still would have occurred had she not taken the pill? This issue has not reached the reported decisions. It would seem, however, that the causal chain must be established with more information than merely the higher incidences of heart attack and stroke due to the pill.

Frey, *supra* note 113, at 16 n.11. See generally, J. WHITE & R. SUMMERS, HANDBOOK OF THE LAW UNDER THE UNIFORM COMMERCIAL CODE 296 (1972).

124. See Frey, *supra* note 113, at 10-11.

125. See Fischer v. Mead Johnson Laboratories, 41 A.D.2d 737, 341 N.Y.S.2d 257 (1973). *Contra*, Berry v. G.D. Searle & Co., 56 Ill. 2d 548, 309 N.E.2d 550 (1974).

126. U.C.C. § 2-725(1) (1972 version) prescribes a period of four years from the time tender of delivery is made.

127. U.C.C. § 2-725(2) (1972 version).

128. Frey, *supra* note 113, at 10. Compare the U.C.C. accrual of a cause of action with that under a tort statute requiring the cause of action to begin when the injury was sustained. See, e.g., ILL. REV. STAT. ch. 83, § 15 (1966).

129. Frey, *supra* note 113, at 10 (citation omitted).

130. See notes 39-59 *supra* and accompanying text.

crease the liability of the pharmacist up to and including strict liability. In this age of awareness and consumer reform, perhaps this is a laudable development. As before, the pharmacist must still practice with a high degree of skill and competency. The PPI requirement will do nothing to change this standard of care. Now, however, a pharmacist must also dispense additional labeling to make the prescription complete. New and efficient distribution systems must be developed by each pharmacy to insure that a PPI is delivered with each prescription to reduce exposure to liability for nondelivery.

If the PPI will act as a means of educating the patient about his drug regimen and encourage him to ask meaningful questions of both the physician and the pharmacist, the labeling will have served its purpose admirably and will enhance medical health care dramatically. Physicians will be more mindful of what they prescribe, and pharmacists will be able to provide a more professional service to the general public. Though it may be doubted that the Commissioner of the FDA intended such a result when the PPI was proposed, the increased liability has a sound, theoretical basis in the law. Whether a court would use the PPI as grounds for imposing liability remains to be seen. A number of factors may control the outcome, particularly the relationship between the injury and the omission by the pharmacist as well as the availability of a more desirable defendant such as the pharmaceutical manufacturer. It appears, however, that potential liability based on the PPI will be available when the issue comes to court.

Craig Harman Walker

APPENDIX A

Required Labeling for the Patient Taking Pharmaceuticals Containing Estrogen 21 C.F.R. § 310.515 (1978)

WHAT YOU SHOULD KNOW ABOUT ESTROGENS

Estrogens are female hormones produced by the ovaries. The ovaries make several different kinds of estrogens. In addition, scientists have been able to make a variety of synthetic estrogens. As far as we know, all these estrogens have similar properties and therefore much the same usefulness, side effects, and risks. This leaflet is intended to help you understand what estrogens are used for, the risks involved in their use, and how to use them as safely as possible.

This leaflet includes the most important information about estrogens, but not all the information. If you want to know more, you should ask your doctor for more information or you can ask your doctor or pharmacist to let you read the package insert prepared for the doctor.

USES OF ESTROGEN**THERE IS NO PROPER USE OF ESTROGENS IN A PREGNANT WOMAN.**

Estrogens are prescribed by doctors for a number of purposes, including:

- 1 To provide estrogen during a period of adjustment when a woman's ovaries stop producing a majority of her estrogens, in order to prevent certain uncomfortable symptoms of estrogen deficiency. (With the menopause, which generally occurs between the ages of 45 and 55, women produce a much smaller amount of estrogens.)
- 2 To prevent symptoms of estrogen deficiency when a woman's ovaries have been removed surgically before the natural menopause.
- 3 To prevent pregnancy. (Estrogens are given along with a progestogen, another female hormone; these combinations are called oral contraceptives or birth control pills. Patient labeling is available to women taking oral contraceptives and they will not be discussed in this leaflet.)
- 4 To treat certain cancers in women and men.
- 5 To prevent painful swelling of the breasts after pregnancy in women who choose not to nurse their babies.

ESTROGENS IN THE MENOPAUSE

In the natural course of their lives, all women eventually experience a decrease in estrogen production. This usually occurs between ages 45 and 55 but may occur earlier or later. Sometimes the ovaries may need to be removed before natural menopause by an operation, producing a "surgical menopause."

When the amount of estrogen in the blood begins to decrease, many women may develop typical symptoms: feelings of warmth in the face, neck, and chest or sudden intense episodes of heat and sweating throughout the body (called "hot flashes" or "hot flushes"). These symptoms are sometimes very uncomfortable. Some women may also develop changes in the vagina (called "atrophic vaginitis") which cause discomfort, especially during and after intercourse.

Estrogens can be prescribed to treat these symptoms of the menopause. It is estimated that considerably more than half of all women undergoing the menopause have only mild symptoms or no symptoms at all and therefore do not need estrogens. Other women may need estrogens for a few months, while their bodies adjust to lower estrogen levels. Sometimes the need will be for periods longer than six months. In an attempt to avoid overstimulation of the uterus (womb), estrogens are usually given cyclically during each month of use, such as three weeks of pills followed by one week without pills.

Sometimes women experience nervous symptoms or depression during menopause. There is no evidence that estrogens are effective for such symptoms without associated vasomotor symptoms. In the absence of vasomotor symptoms, estrogens should not be used to treat nervous symptoms, although other treatment may be needed.

You may have heard that taking estrogens for long periods (years) after the menopause will keep your skin soft and supple and keep you feeling young. There is no evidence that this is so, however, and such long-term treatment carries important risks.

ESTROGENS TO PREVENT SWELLING OF THE BREASTS AFTER PREGNANCY

If you do not breast-feed your baby after delivery, your breasts may fill up with milk and become painful and engorged. This usually begins about 3 to 4 days after delivery and may last for a few days to up to a week or more. Sometimes the discomfort is severe, but usually it is not and can be controlled by pain-relieving drugs such as aspirin and by binding the breasts up tightly. Estrogens can be used to try to prevent the breasts from filling up. While this treatment is sometimes successful, in many cases the breasts fill up to some degree in spite of treatment. The dose of estrogens needed to prevent pain and swelling of the breasts is much larger than the dose needed to treat symptoms of the menopause and this may increase your chances of developing blood clots in the legs or lungs (see below). Therefore, it is important that you discuss the benefits and the risks of estrogen use with your doctor if you have decided not to breast-feed your baby.

THE DANGERS OF ESTROGENS

1. **Endometrial cancer.** There are reports that if estrogens are used in the postmenopausal period for more than a year, there is an increased risk of endometrial cancer (cancer of the lining of the uterus). Women taking estrogens have roughly 5 to 10 times as great a chance of getting this cancer as women who take no estrogens. To put this another way, while a postmenopausal woman not taking estrogens has 1 chance in 1,000 each year of getting endometrial cancer, a woman taking estrogens has 5 to 10 chances in 1,000 each year. For this reason it is important to take estrogens only when they are really needed.

The risk of this cancer is greater the longer estrogens are used and when larger doses are taken. Therefore you should not take more estrogen than your doctor prescribes. It is important to take the lowest dose of estrogen that will control symptoms and to take it only as long as it is needed. If estrogens are needed for longer periods of time, your doctor will want to reevaluate your need for estrogens at least every six months.

Women using estrogens should report any vaginal bleeding to their doctors; such bleeding may be of no importance, but it can be an early warning of endometrial cancer. If you have undiagnosed vaginal bleeding, you should not use estrogens until a diagnosis is made and you are certain there is no endometrial cancer.

NOTE: If you have had your uterus removed (total hysterectomy), there is no danger of developing endometrial cancer.

2. **Other possible cancers.** Estrogens can cause development of other tumors in animals, such as tumors of the breast, cervix, vagina, or liver, when given for a long time. At present there is no good evidence that women using estrogen in the menopause have an increased risk of such tumors, but there is no way yet to be sure they do not; and one study raises the possibility that use of estrogens in the menopause may increase the risk of breast cancer many years later. This is a further reason to use estrogens only when clearly needed. While you are taking estrogens, it is important that you go to your doctor at least once a year for a physical examination. Also, if members of your family have had breast cancer or if you have breast nodules or abnormal mammograms (breast x-rays), your doctor may wish to carry out more frequent examinations of your breasts.

3. **Gallbladder disease.** Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens. Birth control pills have a similar effect.

4. **Abnormal blood clotting.** Oral contraceptives increase the risk of blood clotting in various parts of the body. This can result in a stroke (if the clots in the brain), a heart attack (clot in a blood vessel of the heart), or a pulmonary embolus (a clot which forms in the legs or pelvis, then breaks off and travels to the lungs). Any of these can be fatal.

At this time use of estrogens in the menopause is not known to cause such blood clotting, but this has not been fully studied and there could still prove to be such a risk. It is recommended that if you have had clotting in the legs or lungs or a heart attack or stroke while you were using estrogens or birth control pills, you should not use estrogens (unless they are being used to treat cancer of the breast or prostate). If you have had a stroke or heart attack or if you have angina pectoris, estrogens should be used with great caution and only if clearly needed (for example, if you have severe symptoms of the menopause).

The larger doses of estrogen used to prevent swelling of the breasts after pregnancy have been reported to cause clotting in the legs and lungs.

SPECIAL WARNING ABOUT PREGNANCY

You should not receive estrogen if you are pregnant. If this should occur, there is a greater than usual chance that the developing child will be born with a birth defect, although the possibility remains fairly small. A female child may have an increased risk of developing cancer of the vagina or cervix later in life (in the teens or twenties). Every possible effort should be made to avoid exposure to estrogens during pregnancy. If exposure occurs, see your doctor.

OTHER EFFECTS OF ESTROGENS

In addition to the serious known risks of estrogens described above, estrogens have the following side effects and potential risks:

- 1 **Nausea and vomiting.** The most common side effect of estrogen therapy is nausea. Vomiting is less common.
- 2 **Effects on breasts.** Estrogens may cause breast tenderness or enlargement and may cause the breasts to secrete a liquid. These effects are not dangerous.
- 3 **Effects on the uterus.** Estrogens may cause benign fibroid tumors of the uterus to get larger.
- 4 **Effects on liver.** Women taking oral contraceptives develop on rare occasions a tumor of the liver which can rupture and bleed into the abdomen and

may cause death. So far, these tumors have not been reported in women using estrogens in the menopause, but you should report any swelling or unusual pain or tenderness in the abdomen to your doctor immediately.

Women with a past history of jaundice (yellowing of the skin and white parts of the eyes) may get jaundice again during estrogen use. If this occurs, stop taking estrogens and see your doctor.

5. *Other effects.* Estrogens may cause excess fluid to be retained in the body. This may make some conditions worse, such as asthma, epilepsy, migraine, heart disease, or kidney disease.

SUMMARY

Estrogens have important uses, but they have serious risks as well. You must decide, with your doctor, whether the risks are acceptable to you in view of the benefits of treatment. Except where your doctor has prescribed estrogens for use in special cases of cancer of the breast or prostate, you should not use estrogens if you have cancer of the breast or uterus, are pregnant, have undiagnosed abnormal vaginal bleeding, clotting in the legs or lungs, or have

had a stroke, heart attack or angina, or clotting in the legs or lungs in the past while you were taking estrogens.

You can use estrogens as safely as possible by understanding that your doctor will require regular physical examinations while you are taking them and will try to discontinue the drug as soon as possible and use the smallest dose possible. Be alert for signs of trouble including.

1. Abnormal bleeding from the vagina.
2. Pains in the calves or chest or sudden shortness of breath, or coughing blood.
3. Severe headache, dizziness, faintness, or changes in vision.
4. Breast lumps (you should ask your doctor how to examine your own breasts).
5. Jaundice (yellowing of the skin).

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

APPENDIX B

Required Labeling for the Patient Taking Oral Contraceptives, 21 C.F.R. § 310.501(a) (1978)

R-643-10-000-6

Detailed Patient Labeling

ORTHO-NOVUM 1/50 □ 21

Each tablet contains 1 mg norethindrone and 0.05 mg mestranol.

ORTHO-NOVUM 1/50 □ 28 Day Regimen

Each yellow tablet contains 1 mg norethindrone and 0.05 mg mestranol.

Each green tablet contains inert ingredients.

ORTHO-NOVUM 1/80 □ 21

Each tablet contains 1 mg norethindrone and 0.08 mg mestranol.

ORTHO-NOVUM 1/80 □ 28 Day Regimen

Each white tablet contains 1 mg norethindrone and 0.08 mg mestranol.

Each green tablet contains inert ingredients.

MODICON

Each tablet contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol.

MODICON 28 Day Regimen

Each white tablet contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol.

Each green tablet contains inert ingredients.

ORTHO-NOVUM 2 mg □ 21

Each tablet contains 2 mg norethindrone and 0.10 mg mestranol.

ORTHO-NOVUM 10 mg

Each tablet contains 10 mg norethindrone and 0.06 mg mestranol.

MICRONOR

Each tablet contains 0.35 mg norethindrone.

What You Should Know About Oral Contraceptives

Oral contraceptives ("the pill") are the most effective way (except for sterilization) to prevent pregnancy. They are also convenient and, for most women, free of serious or unpleasant side effects. Oral contraceptives must always be taken under the continuous supervision of a physician.

The information in this leaflet under the headings "Who Should

Not Use Oral Contraceptives," "The Dangers of Oral Contraceptives," and "How to Use Oral Contraceptives As Effectively As Possible, Once You Have Decided to Use Them" is also applicable when these drugs are used for other indications.

ORTHO-NOVUM 2 mg may be prescribed for you for the treatment of hypermenorrhea.

ORTHO-NOVUM 10 mg may be prescribed for you for the treatment of hypermenorrhea and endometriosis.

It is important that any woman who considers using an oral contraceptive understand the risks involved. Although the oral contraceptives have important advantages over other methods of contraception, they have certain risks that no other method has. Only you can decide whether the advantages are worth these risks. This leaflet will tell you about the most important risks. It will explain how you can help your doctor prescribe the pill as safely as possible by telling him about yourself and being alert for the earliest signs of trouble. And it will tell you how to use the pill properly, so that it will be as effective as possible. There is more detailed information available in the leaflet prepared for doctors. Your pharmacist can show you a copy; you may need your doctor's help in understanding parts of it.

Who Should Not Use Oral Contraceptives

A. If you have now, or have had in the past, any of the following conditions you should not use the pill:

1. Heart attack or stroke.
2. Clots in the legs or lungs.
3. Angina pectoris.
4. Known or suspected cancer of the breast or sex organs.
5. Unusual vaginal bleeding that has not yet been diagnosed.

B. If you are pregnant or suspect that you are pregnant, do not use the pill.

C. Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

D. If you have scanty or irregular periods or are a young woman without a regular cycle, you should use another method of contraception because, if you use the pill, you may have difficulty becoming pregnant or may fail to have menstrual periods after discontinuing the pill.

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PHARMACIST LIABILITY

617

- E Although it is your decision, since many risks increase with age, birth control pills are not recommended for women past the age of 40

Deciding To Use Oral Contraceptives

If you do not have any of the conditions listed above and are thinking about using oral contraceptives, to help you decide, you need information about the advantages and risks of oral contraceptives and of other contraceptive methods as well. This leaflet describes the advantages and risks of oral contraceptives. Except for sterilization, the IUD and abortion, which have their own exclusive risks, the only risks of other methods of contraception are those due to pregnancy should the method fail. Your doctor can answer questions you may have with respect to other methods of contraception. He can also answer any questions you may have after reading this leaflet on oral contraceptives.

1. What Oral Contraceptives Are and How They Work. Oral Contraceptives are of two types. The most common, often simply called "the pill," is a combination of an estrogen and progesterone, the two kinds of female hormones. The amount of estrogen and progesterone can vary, but the amount of estrogen is most important because both the effectiveness and some of the dangers of oral contraceptives are related to the amount of estrogen. This kind of oral contraceptive works principally by preventing release of an egg from the ovary. When the amount of estrogen is 50 micrograms or more, and the pill is taken as directed, oral contraceptives are more than 99% effective (i.e., there would be less than one pregnancy if 100 women used the pill for one year). Pills that contain 20 to 35 micrograms of estrogen vary slightly in effectiveness, ranging from 93% to more than 99% effective.

The second type of oral contraceptive, often called the "mini-pill," contains only a progesterone. It works in part by preventing release of an egg from the ovary but also by keeping sperm from reaching the egg and by making the uterus (womb) less receptive to any fertilized egg that reaches it. The mini-pill is less effective than the combination oral contraceptive, about 97% effective. In addition, the progesterone-only pill has a tendency to cause irregular bleeding which may be quite inconvenient, or cessation of bleeding entirely. The progesterone-only pill is used despite its lower effectiveness in the hope that it will prove not to have some of the serious side effects of the estrogen-containing pill (see below) but it is not yet certain that the mini-pill does in fact have fewer serious side effects. The discussion below, which is based mainly on information about the combination pills, should be considered to apply as well to the mini-pill.

2. Other Nonsurgical Ways to Prevent Pregnancy. As this leaflet will explain, oral contraceptives have several serious risks. Other methods of contraception have lesser risks or none at all. They are also less effective than oral contraceptives, but, used properly, may be effective enough for many women. The following table gives reported pregnancy rates (the number of women out of 100 who would become pregnant in one year) for these methods:

Pregnancies Per 100 Women Per Year

- Intrauterine device (IUD), less than 1-6;
- Diaphragm with spermicidal products (creams or jellies), 2-20;
- Condom (rubber), 3-36; Aerosol foams, 2-29;
- Jellies and creams, 4-36;
- Periodic abstinence (rhythm) all types, less than 1-47;
 1. Calendar method, 14-47;
 2. Temperature method, 1-20;
 3. Temperature method — intercourse only in postovulatory phase, less than 1-7;
 4. Mucus method, 1-25;
- No contraception, 60-80.

The figures (except for the IUD) vary widely because people differ in how well they use each method. Very faithful users of the various methods obtain very good results, except for users of the calendar method of periodic abstinence (rhythm). Except for the IUD, effec-

tive use of these methods requires somewhat more effort than simply taking a single pill every morning, but it is an effort that many couples undertake successfully. Your doctor can tell you a great deal more about these methods of contraception.

3. The Dangers of Oral Contraceptives.

a. Circulatory disorders (abnormal blood clotting, heart attack, and stroke due to hemorrhage). Blood clots (in various blood vessels of the body) are the most common of the serious side effects of oral contraceptives. A clot can result in a stroke (if the clot is in the brain), a heart attack (if the clot is in a blood vessel of the heart), or a pulmonary embolus (a clot which forms in the legs or pelvis, then breaks off and travels to the lungs). Any of these can be fatal. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impairment of vision in that eye. There is evidence that the risk of clotting increases with higher estrogen doses. It is therefore important to keep the dose of estrogen as low as possible, so long as the oral contraceptive used has an acceptable pregnancy rate and doesn't cause unacceptable changes in the menstrual pattern. Furthermore, cigarette smoking by oral contraceptive users increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and begins to become quite marked in women over 35 years of age. For this reason, women who use oral contraceptives should not smoke.

The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

Even without the pill the risk of having a heart attack increases with age and is also increased by such heart attack risk factors as high blood pressure, high cholesterol, obesity, diabetes, and cigarette smoking. Without any risk factors present, the use of oral contraceptives alone may double the risk of heart attack. However, the combination of cigarette smoking, especially heavy smoking, and oral contraceptive use greatly increases the risk of heart attack. Oral contraceptive users who smoke are about five times more likely to have a heart attack than users who do not smoke and about ten times more likely to have a heart attack than nonusers who do not smoke. It has been estimated that users between the ages of 30 and 39 who smoke have about a 1-in-10,000 chance each year of having a fatal heart attack compared to about a 1-in-50,000 chance in users who do not smoke, and about a 1-in-100,000 chance in nonusers who do not smoke. In the age group 40 to 44, the risk is about 1 in 1,700 per year for users who smoke compared to about 1 in 10,000 for users who do not smoke and to about 1 in 14,000 per year for nonusers who do not smoke. Heavy smoking (about 15 cigarettes or more a day) further increases the risk. If you do not smoke and have none of the other heart attack risk factors described above, you will have a smaller risk than listed. If you have several heart attack risk factors, the risk may be considerably greater than listed.

In addition to blood-clotting disorders, it has been estimated that women taking oral contraceptives are twice as likely as nonusers to have a stroke due to rupture of a blood vessel in the brain.

One report suggests that the risk of circulatory diseases appears to increase the longer you are on the pill and may continue after you stop.

b. Formation of tumors. Studies have found that when certain

animals are given the female sex hormone estrogen, which is an ingredient of oral contraceptives, continuously for long periods, cancers may develop in the breast, cervix, vagina, and liver.

These findings suggest that oral contraceptives may cause cancer in humans. However, studies to date in women taking currently marketed oral contraceptives have not confirmed that oral contraceptives cause cancer in humans. Several studies have found no increase in breast cancer in users, although one study suggested oral contraceptives might cause an increase in breast cancer in women who already have benign breast disease (e.g., cysts).

Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms or who were exposed to DES (diethylstilbestrol), an estrogen, during their mother's pregnancy must be followed very closely by their doctors if they choose to use oral contraceptives instead of another method of contraception. Many studies have shown that women taking oral contraceptives have less risk of getting benign breast disease than those who have not used oral contraceptives. Recently, strong evidence has emerged that estrogens (one component of oral contraceptives), when given for periods of more than one year to women after the menopause, increase the risk of cancer of the uterus (womb). There is also some evidence that a kind of oral contraceptive which is no longer marketed, the sequential oral contraceptive, may increase the risk of cancer of the uterus. There remains no evidence, however, that the oral contraceptives now available increase the risk of this cancer.

Oral contraceptives do cause, although rarely, a benign (non-malignant) tumor of the liver. These tumors do not spread, but they may rupture and cause internal bleeding, which may be fatal. A few cases of cancer of the liver have been reported in women using oral contraceptives, but it is not yet known whether the drug caused them.

c. Dangers to a developing child if oral contraceptives are used in or immediately preceding pregnancy. Oral contraceptives should not be taken by pregnant women because they may damage the developing child. An increased risk of birth defects, including heart defects and limb defects, has been associated with the use of sex hormones, including oral contraceptives, in pregnancy. In addition, the developing female child whose mother has received DES (diethylstilbestrol), an estrogen, during pregnancy has a risk of getting cancer of the vagina or cervix in her teens or young adulthood. This risk is estimated to be about 1 to 4 in 1000 exposures. Abnormalities of the urinary and sex organs have been reported in male offspring so exposed. It is possible that other estrogens, such as the estrogens in oral contraceptives, could have the same effect in the child if the mother takes them during pregnancy.

If you stop taking oral contraceptives to become pregnant, your doctor may recommend that you use another method of contraception for a short while, for example three months. The reason for this is that there is evidence from studies in women who have had "miscarriages" soon after stopping the pill, that the lost fetuses are more likely to be abnormal. Whether there is an overall increase in "miscarriage" in women who become pregnant soon after stopping the pill as compared with women who do not use the pill is not known, but it is possible that there may be. If, however, you do become pregnant soon after stopping oral contraceptives, and do not have a miscarriage, there does not appear to be evidence that the baby has an increased risk of being abnormal.

d. Gallbladder disease. Women who use oral contraceptives have a greater risk than nonusers of having gallbladder disease requiring surgery. The increased risk may first appear within one year of use and may double after four or five years of use.

e. Other side effects of oral contraceptives. Some women using oral contraceptives experience unpleasant side effects. Some of these may be temporary. Your breasts may feel tender, nausea and vomiting may occur, you may gain or lose weight, and your ankles may swell. A spotty darkening of the skin, particularly of the face, is

possible and may persist. You may notice unexpected vaginal bleeding or changes in your menstrual period. Irregular bleeding is frequently seen when using the mini-pill or combination oral contraceptives containing less than 50 micrograms of estrogen.

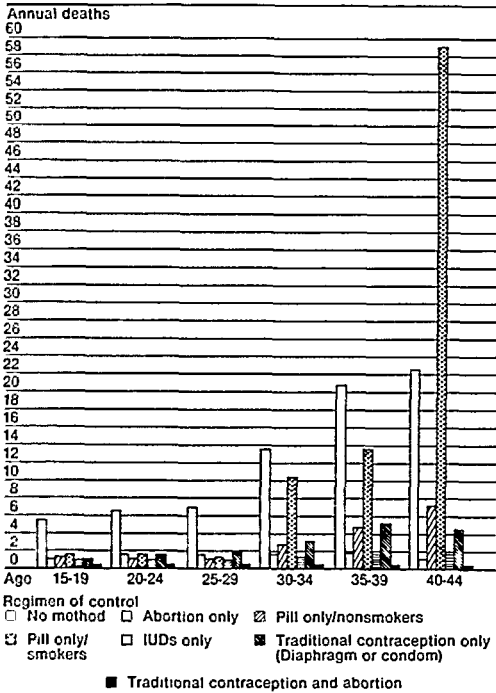
More serious side effects include worsening of migraine, asthma, epilepsy, and kidney or heart disease because of a tendency for water to be retained in the body when oral contraceptives are used. Other side effects are growth of preexisting fibroid tumors of the uterus; mental depression; and liver problems with jaundice (yellowing of the skin). Your doctor may find that levels of sugar and fatty substances in your blood are elevated; the long-term effects of these changes are not known. Some women develop high blood pressure while taking oral contraceptives, which ordinarily returns to the original levels when the oral contraceptive is stopped.

Other reactions, although not proved to be caused by oral contraceptives, are occasionally reported. These include more frequent urination and some discomfort when urinating, kidney disease, nervousness, dizziness, some loss of scalp hair, an increase in body hair, an increase or decrease in sex drive, appetite changes, cataracts, and a need for a change in contact lens prescription or inability to use contact lenses.

After you stop using oral contraceptives there may be a delay before you are able to become pregnant or before you resume having menstrual periods. This is especially true of women who had irregular menstrual cycles prior to the use of oral contraceptives. As discussed previously, your doctor may recommend that you wait a short while after stopping the pill before you try to become pregnant. During this time, use another form of contraception. You should consult your physician before resuming use of oral contraceptives after childbirth, especially if you plan to nurse your baby. Drugs in oral contraceptives are known to appear in the milk, and the long-range effect on infants is not known at this time. Furthermore, oral contraceptives may cause a decrease in your milk supply as well as in the quality of the milk.

4. Comparison of the Risks of Oral Contraceptives and Other Contraceptive Methods. The many studies on the risks and effectiveness of oral contraceptives and other methods of contraception have been analyzed to estimate the risk of death associated with various methods of contraception. This risk has two parts: (a) the risk of the method itself (e.g., the risk that oral contraceptives will cause death due to abnormal clotting), and (b) the risk of death due to pregnancy or abortion in the event the method fails. The results of this analysis are shown in the bar graph below. The height of the bars is the number of deaths per 100,000 women each year. There are six sets of bars, each set referring to a specific age group of women. Within each set of bars there is a single bar for each of the different contraceptive methods. For oral contraceptives, there are two bars—one for smokers and the other for nonsmokers. The analysis is based on present knowledge and new information could, of course, alter it. The analysis shows that the risk of death from all methods of birth control is low and below that associated with childbirth, except for oral contraceptives in women over 40 who smoke. It shows that the lowest risk of death is associated with the condom or diaphragm (traditional contraception) backed up by early abortion in case of failure of the condom or diaphragm to prevent pregnancy. Also, at any age the risk of death (due to unexpected pregnancy) from the use of traditional contraception, even without a backup of abortion, is generally the same as or less than that from use of oral contraceptives.

Figure 1. Estimated annual number of deaths associated with control of fertility and no control per 100,000 nonsterile women, by regimen of control and age of woman.



How to Use Oral Contraceptives As Effectively As Possible, Once You Have Decided to Use Them

1. What to Tell your Doctor.

You can make use of the pill as effectively as possible, by telling your doctor if you have any of the following:

- a. Conditions that mean you should not use oral contraceptives:

- Clots in the legs or lungs.
- Clots in the legs or lungs in the past.
- A stroke, heart attack, or angina pectoris.
- Known or suspected cancer of the breast or sex organs.
- Unusual vaginal bleeding that has not yet been diagnosed.
- Known or suspected pregnancy.

- b. Conditions that your doctor will want to watch closely or which might cause him to suggest another method of contraception.

- A family history of breast cancer.
- Breast nodules, fibrocystic disease of the breast, or an abnormal mammogram.
- Diabetes.
- High blood pressure.
- High cholesterol.
- Cigarette smoking.
- Migraine headaches.
- Heart or kidney disease.
- Epilepsy.
- Mental depression.
- Fibroid tumors of the uterus.
- Gallbladder disease.

- c. Once you are using oral contraceptives, you should be alert for signs of a serious adverse effect and call your doctor if they occur:

- Sharp pain in the chest, coughing blood, or sudden shortness of breath (indicating possible clots in the lungs).
- Pain in the calf (possible clot in the leg).
- Crushing chest pain or heaviness (indicating possible heart attack).
- Sudden severe headache or vomiting, dizziness or fainting, disturbance of vision or speech or weakness or numbness in an arm or leg (indicating a possible stroke).

- Sudden partial or complete loss of vision (indicating a possible clot in the eye).
- Breast lumps (you should ask your doctor to show you how to examine your own breasts).
- Severe pain in the abdomen (indicating a possible ruptured tumor of the liver).
- Severe depression.
- Yellowing of the skin (jaundice).

2. How to Take the Pill So That it is Most Effective.

To achieve maximum contraceptive effectiveness, ORTHO-NOVUM, MODICON and MICRONOR must be taken exactly as directed and at intervals not exceeding 24 hours.

21-Day Regimen: Counting the first day of menstrual flow as "Day 1," take one tablet daily from the 5th through the 25th day of the menstrual cycle. If the first tablet is taken later than the 5th day of the menstrual cycle or postpartum, contraceptive reliance should not be placed on ORTHO-NOVUM or MODICON until after the first seven consecutive days of administration. Take a tablet the same time each day, preferably at bedtime, for 21 days, then wait for 7 days during which time a menstrual period usually occurs. Following this 7-day waiting period, start taking a tablet each day for the next 21 days, thus using a three-weeks-on, one-week-off dosage regimen.

28-Day Regimen: The first white or yellow tablet should be taken on the first Sunday after the menstrual period begins. If period begins on Sunday, begin taking tablets that day. Take one white or yellow tablet at the same time each day for 21 consecutive days, then take one green tablet daily for 7 days during which time your menstrual period usually occurs. During the FIRST cycle, it is important that you use another method of birth control until you have taken a white or yellow tablet daily for seven consecutive days. After 28 tablets have been taken, (last green tablet will always be taken on a Saturday) take the first tablet (white or yellow) from your next package the following day (Sunday) whether or not you are still menstruating. With the 28-day regimen, pills are taken every day of the year.

20-Day Regimen: In the initial cycle, the dosage of ORTHO-NOVUM 10 mg for contraception is one tablet administered daily from the 5th through the 24th day of the menstrual cycle, counting the first day of the menstrual flow as "Day 1." If ORTHO-NOVUM 10 mg is first taken later than the fifth day of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on ORTHO-NOVUM 10 mg until after the first seven consecutive days of administration. In all subsequent cycles the first tablet is taken on the 7th day following completion of the previous 20-day course, i.e., 6 days without medication.

In the treatment of hypermenorrhea and endometriosis, your physician will discuss the regimen with you.

Continuous Regimen (MICRONOR): The first MICRONOR Tablet should be taken on the first day of the menstrual period.

Take one tablet at the same time each day without interruption for as long as contraceptive protection is desired.

The effectiveness of progestogen-only oral contraceptives, such as MICRONOR, is lower than that of the combination oral contraceptives containing both estrogen and progestogen. If 100 women utilized an estrogen-containing oral contraceptive for a period of one year, generally less than one pregnancy would be expected to occur; however, if MICRONOR had been utilized, approximately three pregnancies might occur.

Women who participated in the clinical studies with MICRONOR and who had not taken other oral contraceptives before starting MICRONOR had a higher pregnancy rate (four women out-of 100), particularly during the first six months of therapy, and to a large extent because they did not take their tablets correctly.

Of course, if you don't take your tablets as directed, or forget to take them every day, the chance you may become pregnant is naturally greater.

MICRONOR (norethindrone) will probably cause some changes

in your menstrual pattern. Your cycle, that is the time between menstrual periods, will vary. For example, you might have a 28-day cycle, followed by a 17-day cycle, followed by a 35-day cycle, etc. This is common with MICRONOR.

While using MICRONOR, your period may be longer or shorter than before. If bleeding lasts more than eight days, be sure to let your doctor know.

Occasionally women who are not taking the pill miss a period. This is also true for women taking the pill and it has been reported to occur as frequently as several times each year in some women, depending on various factors, such as age and prior history. Therefore, if you miss a period, or if you are taking mini-pills and it is 45 days or more from the start of your last menstrual period you may be pregnant and you should consult your physician before continuing to take the pill. (Your doctor is the best source of information about this.) The pill should not be used when you are pregnant because of some reports of the possibility of adverse effects on the developing child. Very rarely, women who are using the pill as directed become pregnant. The likelihood of becoming pregnant if you occasionally miss one or two pills is naturally higher. If you miss a period, especially if you have not taken the pill regularly, you should use an alternative method of contraception until pregnancy has been ruled out. If you have missed more than one tablet at any time, you should immediately start using an additional method of contraception and complete your pill cycle.

3. Periodic Examination.

Your doctor will take a complete medical and family history before prescribing oral contraceptives. At that time and about once a year thereafter, he will generally examine your blood pressure, breasts, abdomen, and pelvic organs (including a Papanicolaou smear, i.e., test for cancer).

Summary

Oral contraceptives are the most effective method, except sterilization, for preventing pregnancy. Other methods, when used consci-

entiously, are also very effective and have fewer risks.

Women who use oral contraceptives should not smoke.

In addition, if you have certain conditions or have had these conditions in the past, you should not use oral contraceptives because the risk is too great. These conditions are listed in the booklet. If you do not have these conditions and decide to use the "pill," please read the booklet carefully so that you can use the "pill."

Based on his or her assessment of your medical needs, your doctor has prescribed this drug for you. Do not give the drug to anyone else.

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APPENDIX C

The Physician Package Insert

P-631-10-000-4

ORTHO-NOVUM Tablets and MODICON Tablets MICRONOR

DESCRIPTION

ORTHO-NOVUM 1/50 □ 21 Tablets are a combination oral contraceptive. Each ORTHO-NOVUM 1/50 □ 21 Tablet contains 1 mg of the progestational compound, norethindrone (17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one), together with 0.05 mg of the estrogenic compound, mestranol (3-methoxy-19-nor-17 α -pregna-1,3,5 (10)-trien-20-yn-17-ol).

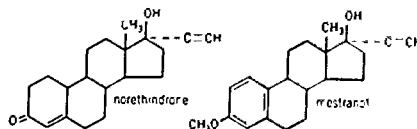
ORTHO-NOVUM 1/50 □ 28 Tablets are a combination oral contraceptive. Each yellow ORTHO-NOVUM 1/50 □ 28 Tablet contains 1 mg of the progestational compound, norethindrone (17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one), together with 0.05 mg of the estrogenic compound, mestranol (3-methoxy-19-nor-17 α -pregna-1,3,5 (10)-trien-20-yn-17-ol). Each green tablet contains inert ingredients.

ORTHO-NOVUM 1/80 □ 21 Tablets are a combination oral contraceptive. Each ORTHO-NOVUM 1/80 □ 21 Tablet contains 1 mg of the progestational compound, norethindrone (17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one), together with 0.08 mg of the estrogenic compound, mestranol (3-methoxy-19-nor-17 α -pregna-1,3,5 (10)-trien-20-yn-17-ol).

ORTHO-NOVUM 1/80 □ 28 Tablets are a combination oral contraceptive. Each white ORTHO-NOVUM 1/80 □ 28 Tablet contains 1 mg of the progestational compound, norethindrone (17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one), together with 0.08 mg of the estrogenic compound, mestranol (3-methoxy-19-nor-17 α -pregna-1,3,5 (10)-trien-20-yn-17-ol). Each green tablet contains inert ingredients.

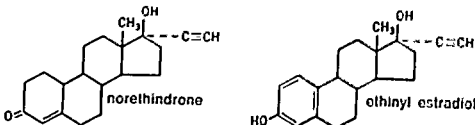
ORTHO-NOVUM 2 mg □ 21 Tablets are a combination oral contraceptive. Each ORTHO-NOVUM 2 mg □ 21 Tablet contains 2 mg of the progestational compound, norethindrone (17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one), together with 0.10 mg of the estrogenic compound, mestranol (3-methoxy-19-nor-17 α -pregna-1,3,5 (10)-trien-20-yn-17-ol).

ORTHO-NOVUM 10 mg Tablets are a combination oral contraceptive. Each ORTHO-NOVUM 10 mg Tablet contains 10 mg of the progestational compound, norethindrone (17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one), together with 0.06 mg of the estrogenic compound, mestranol (3-methoxy-19-nor-17 α -pregna-1,3,5 (10)-trien-20-yn-17-ol).

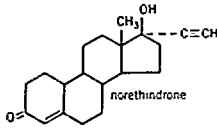


MODICON Tablets are a combination oral contraceptive. Each MODICON Tablet contains 0.5 mg of the progestational compound, norethindrone (17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one), together with 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17 α -pregna-1,3,5 (10)-trien-20-yne-3,17-diol).

MODICON 28 Tablets are a combination oral contraceptive. Each white MODICON 28 Tablet contains 0.5 mg of the progestational compound, norethindrone (17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one), together with 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17 α -pregna-1,3,5 (10)-trien-20-yne-3,17-diol). Each green tablet contains inert ingredients.



MICRONOR Tablets are a progestogen-only oral contraceptive. Each MICRONOR Tablet contains 0.35 mg of the purified crystalline compound, norethindrone (17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one), a synthetic progestogen.



CLINICAL PHARMACOLOGY FOR COMBINATION ORAL CONTRACEPTIVES ONLY

Combination oral contraceptives act primarily through the mechanism of gonadotropin suppression due to the estrogenic and progestational activity of the ingredients. Although the primary mechanism of action is inhibition of ovulation, alterations in the genital tract including changes in the cervical mucus (which increase the difficulty of sperm penetration) and the endometrium (which reduce the likelihood of implantation) may also contribute to contraceptive effectiveness.

CLINICAL PHARMACOLOGY PROGESTOGEN ORAL CONTRACEPTIVES

The primary mechanism through which MICRONOR prevents conception is not known, but progestogen-only contraceptives are known to alter the cervical mucus, exert a progestational effect on the endometrium, interfering with implantation, and, in some patients, suppress ovulation.

INDICATIONS AND USAGE

ORTHO-NOVUM 1/50 □ 21, ORTHO-NOVUM 1/50 □ 28, ORTHO-NOVUM 1/20 □ 21, ORTHO-NOVUM 1/20 □ 28, MODICON, MODICON 28 and MICRONOR are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

ORTHO-NOVUM 2 mg □ 21 is indicated for the treatment of hypermenorrhea. ORTHO-NOVUM 2 mg □ 21 is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception (See first paragraph immediately following the opening WARNINGS statement.)

ORTHO-NOVUM 10 mg is indicated for the treatment of endometriosis and hypermenorrhea. ORTHO-NOVUM 10 mg is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. (See second paragraph immediately following the opening WARNINGS statement.)

Oral contraceptives are highly effective. The pregnancy rate in women using conventional combination oral contraceptives (containing 35 mcg or more of ethinyl estradiol or 50 mcg or more of mestranol) is generally reported as less than one pregnancy per 100 woman-years of use. Slightly higher rates (somewhat more than one pregnancy per 100 woman-years of use) are reported for some combination products containing 35 mcg or less of ethinyl estradiol, and rates on the order of three pregnancies per 100 woman-years are reported for the progestogen-only oral contraceptives.

These rates are derived from separate studies conducted by different investigators in several population groups and cannot be compared precisely. Furthermore, pregnancy rates tend to be lower as clinical studies are continued, possibly due to selective retention in the longer studies of those patients who accept the treatment regimen and do not discontinue as a result of adverse reactions, pregnancy or other reasons.

In clinical trials with ORTHO-NOVUM 1/50 □ 21, 3,852 patients completed 45,937 cycles, and a total of 10 pregnancies was reported. This represents a pregnancy rate of 0.26 per 100 woman-years.

In clinical trials with ORTHO-NOVUM 1/50 □ 28, 1,590 patients completed 7,330 cycles, and a total of three pregnancies was reported. This represents a pregnancy rate of 0.5 per 100 woman-years.

In clinical trials with ORTHO-NOVUM 1/20 □ 21, and ORTHO-NOVUM 1/20 □ 28, 3,454 patients completed 34,068 cycles, and a total of five pregnancies was reported. This represents a pregnancy rate of 0.18 per 100 woman-years.

In clinical trials with ORTHO-NOVUM 2 mg □ 21, 6,097 patients completed 121,233 cycles, and a total of 13 pregnancies was reported. This represents a pregnancy rate of 0.13 per 100 woman-years. In clinical trials with ORTHO-NOVUM 2 mg □ 21, 965 patients completed 3,743 cycles, and no pregnancies were reported. This represents a pregnancy rate of 0.0 per 100 woman-years.

In clinical trials with ORTHO-NOVUM 10 mg, 1,185 patients completed 32,906 cycles, and a total of one pregnancy was reported. This represents a pregnancy rate of 0.03 per 100 woman-years.

The dropout rate for medical reasons, as observed in the clinical trials conducted with MODICON, appears to be somewhat higher than observed with higher dose combination products. The dropout rate due to menstrual disorders and irregularities was also somewhat higher, dropouts being equally split between menstrual disorders and irregularities and other medical reasons attributable to the drug.

In clinical trials with MODICON and MODICON 28, 1,103 patients completed 12,948 cycles of use, and a total of four pregnancies was reported. This represents a pregnancy rate of 0.37 per 100 woman-years.

In clinical trials with MICRONOR, 2,963 patients completed 25,901 cycles of therapy, and a total of 55 pregnancies was reported. This represents an average pregnancy rate of 2.54 per 100 woman-years.

A higher pregnancy rate of 3.72 was recorded in "fresh" patients (those who had never taken oral contraceptives prior to starting MICRONOR therapy) to a large extent because of incorrect tablet intake. This compares to the lower pregnancy rate of 1.95 recorded in "changeover" patients (those switched from other oral contraceptives).

This difference was found to be statistically significant. Furthermore, an even greater statistically significant difference in pregnancy rates between these two groups was found during the first six months of MICRONOR therapy. Therefore, it is especially important for "fresh" patients to strictly adhere to the regimen.

Table 1 gives ranges of pregnancy rates reported in the literature¹ for other means of contraception. The efficacy of these means of contraception (except the IUD) depends upon the degree of adherence to the method.

Table 1
Pregnancies Per 100 Women-Years

IUD, less than 1-6;
Diaphragm with spermicidal product (creams or jellies), 2-20;
Condom, 3-36; Aerosol foams, 2-29; Jellies and creams, 4-36;
Periodic abstinence (rhythm) all types, less than 1-47;
1. Calendar method, 14-47;
2. Temperature method, 1-20;
3. Temperature method—intercourse only in postovulatory phase, less than 1-7;
4. Mucus method, 1-25;
No contraception, 60-80.

DOSE-RELATED RISK OF THROMBOEMBOLISM FROM ORAL CONTRACEPTIVES

Two studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism.^{2,3} For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of oral contraceptives be started on preparations containing .05 mg or less of estrogen.

CONTRAINDICATIONS

Oral contraceptives should not be used in women with any of the following conditions:

1. Thrombophlebitis or thromboembolic disorders.
2. A past history of deep vein thrombophlebitis or thromboembolic disorders.
3. Cerebral vascular or coronary artery disease.
4. Known or suspected carcinoma of the breast.
5. Known or suspected estrogen-dependent neoplasia.
6. Undiagnosed, abnormal genital bleeding.
7. Known or suspected pregnancy (see WARNINGS, No. 5).

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

ORTHO-NOVUM 2 mg □ 21 should only be used for contraception when lower dose formulations prove unacceptable.

ORTHO-NOVUM 10 mg should be used for contraception only when formulations with lower progestogen doses prove unacceptable.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Four principal studies in Great Britain^{4,5,6} and three in the United States^{7,8} have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause (Tables 2, 4). Overall excess mortality due to pulmonary embolism or stroke is on the order of 1.0 to 3.5 deaths annually per 100,000 users and increases with age (Table 3).

Table 2
Hospitalization Rates Due to Venous Thromboembolic Disease*
Admissions annually per 100,000 women, age 20-44

Users of oral contraceptives	45
Nonusers	5

Table 3
Death Rates Due to Pulmonary Embolism or Cerebral Thrombosis*
—Deaths Annually Per 100,000 Nonpregnant Women

	Age 20 to 34	Age 35 to 44
Users of oral contraceptives	1.5	3.9
Nonusers2	.5

CEREBROVASCULAR DISORDERS

In a collaborative American study¹⁰ of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than in nonusers and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than in nonusers (Table 4).

Table 4
Summary of Relative Risk of Thromboembolic Disorders
and Other Vascular Problems in Oral Contraceptive Users
Compared to Nonusers

	Relative risk, times greater
Idiopathic thromboembolic disease	4-11
Post surgery thromboembolic complications	4-6
Thrombotic stroke	4-9.5
Hemorrhagic stroke	2
Myocardial infarction	2-12

MYOCARDIAL INFARCTION

An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported^{11,12} confirming a previously suspected association (Tables 5 & 6). These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia), the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

The annual excess case rate (increased risk) of myocardial infarction (fatal and nonfatal) in oral contraceptive users was estimated to be approximately 7 cases per 100,000 women users in the 30-39 age group and 67 cases per 100,000 women users in the 40-44 age group.

In terms of relative risk, it has been estimated¹³ that oral contraceptive users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the amount of smoking is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups, as shown in Table 5, must be given serious consideration. The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; it is quite likely that the same synergistic action exists, but perhaps to a lesser extent.

Table 5
Estimated Annual Mortality Rate Per 100,000 Women
From Myocardial Infarction By Use Of
Oral Contraceptives, Smoking Habits, And Age (in years)

Smoking habits	Myocardial Infarction			
	Women aged 30-39		Women aged 40-44	
	Users	Non-users	Users	Non-users
All smokers	10.2	2.6	62.0	15.9
'Heavy'	13.0	5.1	78.7	31.3
'Light'	4.7	.9	28.6	5.7
Nonusers	1.8	1.2	10.7	7.4
Smokers and nonusers	5.4	1.9	32.8	11.7

*Heavy smoker: 15 or more cigarettes per day. From Jain, A.K., Studies in Family Planning, 8:50, 1977.

Table 6
Myocardial Infarction Rates in Users And Nonusers Of
Oral Contraceptives In Britain^{11,12}—Cases Annually
Per 100,000 Women

	Nonfatal		Fatal	
	Age 30 to 39	Age 40 to 44	Age 30 to 39	Age 40 to 44
Users of oral contraceptives	5.6	56.9	5.4	32.0
Nonusers of oral contraceptives	2.1	9.9	1.9	12.0
Relative risk	2.7	5.7	2.8	2.8

Risk of Dose

In an analysis of data derived from several national adverse reaction reporting systems¹, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptive preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States.⁴ Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only oral contraceptives have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk.

The risk of thromboembolic and thrombotic disorders, in both users and nonusers of oral contraceptives, increases with age. Oral contraceptives are, however, an independent risk factor for these events.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES

A large prospective study¹⁴ carried out in the United Kingdom estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of oral contraceptives according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—23/100,000; ages 45-49—140/100,000), the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous versus intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for five or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for five or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group.

This study reports that the increased risk of circulatory diseases may persist after the pill is discontinued.

Another study published at the same time confirms a previously reported increase of mortality in pill users from cardiovascular disease.¹⁴

The available data from a variety of sources have been analyzed¹⁴ to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of oral contraceptives) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Figure 1 below.¹⁴ The study concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke. (The rates given for pill only smokers for each age group are for smokers as a class. For "heavy" smokers [more than 15 cigarettes a day], the rates given would be about double; for "light" smokers [less than 15 cigarettes a day], about 50 percent.)

The mortality associated with oral contraceptive use in nonsmokers over 40 is higher than with any other method of contraception in that age group.

The lowest mortality is associated with the condom or diaphragm backed up by early abortion.

The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia and especially by cigarette smoking. The risk of myocardial infarction in oral contraceptive users is substantially increased in women age 40 and over, especially those with other risk factors. The use of oral contraceptives in women in this age group is not recommended.

Based on the data currently available, the following chart gives a gross estimate of the risk of death from circulatory disorders associated with the use of oral contraceptives:

**SMOKING HABITS AND OTHER PREDISPOSING CONDITIONS—
RISK ASSOCIATED WITH USE OF ORAL CONTRACEPTIVES**

Age	Below		
	30	30-39	40+
Heavy smokers	C	B	A
Light smokers	D	C	B
Nonsmokers (no predisposing conditions)	D	C,D	C
Nonsmokers (other predisposing conditions)	C	C,B	B,A

- A—Use associated with very high risk.
- B—Use associated with high risk.
- C—Use associated with moderate risk.
- D—Use associated with low risk.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

A four- to six-fold increased risk of post surgery thromboembolic complications has been reported in oral contraceptive users.¹¹⁻¹³ If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. OCULAR LESIONS. There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives. Discontinue oral contraceptive medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions and institute appropriate diagnostic and therapeutic measures.

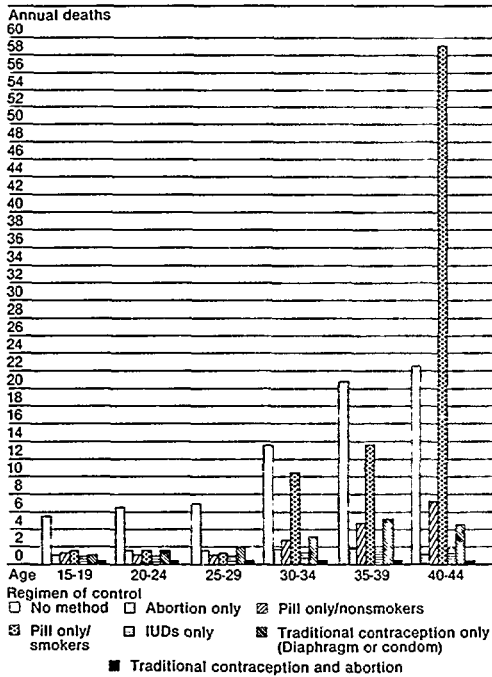
3. CARCINOMA. Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in oral contraceptives, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs.

In humans, three case control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women.¹⁴⁻¹⁶ One publication¹⁴ reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on oral contraceptives. Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time oral contraceptives were first given, polycystic ovaries), nearly all occurred in women who had used a sequential oral contraceptive. These products are no longer marketed. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Several studies¹⁷⁻²¹ have found no increases in breast cancer in women taking oral contraceptives or estrogens. One study²¹, however, while also noting no overall increased risk of breast cancer in women treated with oral contraceptives, found an excess risk in the subgroups of oral contraceptive users with documented benign breast disease. A reduced occurrence of benign breast tumors in users of oral contraceptives has been well-documented.²²⁻²⁴

In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of all women taking oral contraceptives is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception.

Figure 1. Estimated annual number of deaths associated with control of fertility and no control per 100,000 nonsterile women, by regimen of control and age of woman.



4. HEPATIC TUMORS. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives.²⁵⁻²⁹ One study²⁵ showed that oral contraceptive formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users of oral contraceptives. Two studies relate risk with duration of use of the contraceptive, the risk being much greater after four or more years of oral contraceptive use.^{26,27} While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. USE IN OR IMMEDIATELY PRECEDING PREGNANCY, BIRTH DEFECTS IN OFFSPRING, AND MALIGNANCY IN FEMALE OFFSPRING. The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.^{30,31} This risk has been estimated to be of the order of 1 to 4 in 1000 exposures.^{32,33} Although there is no evidence at the present time that oral contraceptives further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix.^{34,35} Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract.^{36,37} Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including oral contraceptives, in pregnancy.³⁸⁻⁴² One case control study³⁸ has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction

defects in exposed fetuses is somewhat less than one in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses.

There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.⁴¹ Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks.

(See indications for use of ORTHO-NOVUM 10 mg in the treatment of endometriosis.)

It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend three months although no precise information is available on which to base this recommendation.

The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. GALLBLADDER DISEASE. Studies^{42,43} report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives and estrogens. In one study, an increased risk appeared after two years of use and doubled after four or five years of use. In one of the other studies, an increased risk was apparent between six and twelve months of use.

7. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives. An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives.⁴⁴

8. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in patients receiving oral contraceptives.⁴⁵ In some women hypertension may occur within a few months of beginning oral contraceptive use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives. Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug.

9. HEADACHE. The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause.

10. BLEEDING IRREGULARITIES. Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

An alteration in menstrual patterns is likely to occur in women using progestogen-only oral contraceptives. The amount and duration of flow, cycle length, breakthrough bleeding, spotting and amenorrhea will probably be quite variable. Bleeding irregularities occur more frequently with the use of progestogen-only oral contraceptives than with the combinations and the dropout rate due to such conditions is higher.

Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. Postuse anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. However, in progestogen-only oral contraceptive failures, the ratio of ectopic to intrauterine pregnancies is higher than in women who are not receiving oral contraceptives, since the drugs are more effective in preventing intrauterine than ectopic pregnancies.

12. BREAST FEEDING. Oral contraceptives given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs.⁴⁶ The effects, if any, on the breast-fed child have not been determined. If feasible, the use of oral contraceptives should be deferred until the infant has been weaned.

PRECAUTIONS

General

1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical examination being performed.
2. Under the influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.
3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related.
4. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.
5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued.
6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients.
7. Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency.
8. Serum folate levels may be depressed by oral contraceptive therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping oral contraceptives, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.
9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.
10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives:
 - a. Increased sulfobromophthalein retention.
 - b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
 - c. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T₄ by column, or T₄ by radioimmunoassay. Free T₃ resin uptake is decreased, reflecting the elevated TBG, free T₄ concentration is unaltered.
 - d. Decreased pregnanediol excretion.
 - e. Reduced response to metyrapone test.

INFORMATION FOR THE PATIENT

(See Patient Labeling printed below.)

DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin.

CARCINOGENESIS

See WARNINGS section for information on the carcinogenic potential of oral contraceptives.

PREGNANCY

Pregnancy category X. See CONTRAINDICATIONS and WARNINGS.

NURSING MOTHERS

See WARNINGS.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS):

- | | |
|----------------------|----------------------|
| Thrombophlebitis. | Hypertension. |
| Pulmonary embolism. | Gallbladder disease. |
| Coronary thrombosis. | Liver Tumors. |
| Cerebral thrombosis. | Congenital Anomalies |
| Cerebral hemorrhage. | |

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

Mezenteric thrombosis.
Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally.

Gastrointestinal symptoms (such as abdominal cramps and bloating).
Breakthrough bleeding.

Spotting.
Change in menstrual flow.
Dysmenorrhea.
Amenorrhea during and after treatment.

Temporary infertility after discontinuance of treatment.
Edema.

Chloasma or melasma which may persist.
Breast changes: tenderness, enlargement, and secretion.
Change in weight (increase or decrease).

Change in cervical erosion and cervical secretion.
Possible diminution in lactation when given immediately postpartum.
Cholestatic jaundice.

Migraine.
Increase in size of uterine leiomyomata.
Rash (allergic).

Mental depression.
Reduced tolerance to carbohydrates.
Vaginal candidiasis.

Change in corneal curvature (steepening).
Intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted:

Premenstrual-like syndrome. Hirsutism.
Cataracts. Loss of scalp hair.

Changes in libido. Erythema multiforme.

Chorea. Erythema nodosum.

Changes in appetite. Hemorrhagic eruption.

Cystitis-like syndrome. Vaginitis.

Headache. Porphyria.

Nervousness. Impaired renal function.

Dizziness.

ORTHO-NOVUM 1/50 □ 21 and ORTHO-NOVUM 1/50 □ 28 contain tartrazine. Allergic reactions have been reported with the ingestion of this dye in some patients.

ACUTE OVERDOSE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, ORTHO-NOVUM Tablets, MODICON Tablets, and MICRONOR must be taken exactly as directed and at intervals not exceeding 24 hours.

21-DAY REGIMEN (21 days on, 7 days off)

The dosage of ORTHO-NOVUM 1/50 □ 21, ORTHO-NOVUM 1/80 □ 21, ORTHO-NOVUM 1/2 mg □ 21 and MODICON for the initial cycle of therapy is one tablet administered daily from the 5th day through the 25th day of the menstrual cycle, counting the first day of menstrual flow as "Day 1."

The use of these products for contraception may be initiated postpartum. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS concerning thromboembolic disease.) If ORTHO-NOVUM 1/50 □ 21, ORTHO-NOVUM 1/80 □ 21, ORTHO-NOVUM 2 mg □ 21 and MODICON Tablets are first taken later than the fifth day of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on these products until after the first seven consecutive days of administration. For subsequent cycles, no tablets are taken for 7 days, then a new course is started of one tablet a day for 21 days.

The dosage regimen then continues with 7 days of no medication, followed by 21 days of medication, instituting a three-weeks-on, one-week-off dosage regimen. The possibility of ovulation and conception prior to initiation of medication should be considered. If the patient misses more than one tablet, the patient should begin taking tablets again as soon as remembered and another method of contraception used for the balance of that tablet cycle.

ORTHO-NOVUM 2 mg □ 21: Following three months of treatment of hypermenorrhea, medication may be discontinued to determine the need for further therapy.

28-DAY REGIMEN (Sunday Start)

When taking ORTHO-NOVUM 1/50 □ 28, the first yellow tablet should be

taken on the first Sunday after menstruation begins. When taking ORTHO-NOVUM 1/80 □ 28 or MODICON 28, the first white tablet should be taken on the first Sunday after menstruation begins. If period begins on Sunday, the first yellow tablet or white tablet is taken on that day. Tablets are taken without interruption as follows: One yellow or white tablet daily for 21 days, then one green tablet daily for 7 days. After 28 tablets have been taken, a yellow or white tablet is then taken the next day (Sunday) etc. Contraceptive reliance should not be placed on these products until after the first 7 consecutive days of administration. The use of ORTHO-NOVUM 1/50 □ 28, ORTHO-NOVUM 1/80 □ 28, and MODICON 28 for contraception may be initiated postpartum. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS concerning thromboembolic disease.) The possibility of ovulation and conception prior to initiation of medication should be considered. If the patient misses more than one tablet, the patient should begin taking tablets again as soon as remembered and another method of contraception used for the balance of that tablet cycle.

MICRONOR (Continuous Regimen)

MICRONOR (norethindrone) is administered on a continuous daily dosage regimen starting on the first day of menstruation, i.e., one tablet each day, every day of the year. Tablets should be taken at the same time each day and continued daily. The patient should be advised that if prolonged bleeding occurs, she should consult her physician.

The use of MICRONOR for contraception may be initiated postpartum (see WARNINGS section). When MICRONOR is administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS concerning thromboembolic disease.)

If the patient misses one tablet, MICRONOR should be discontinued immediately and a method of nonhormonal contraception should be used until menses has appeared or pregnancy has been excluded.

Alternatively, if the patient has taken the tablets correctly, and if menses does not appear when expected, a nonhormonal method of contraception should be substituted until an appropriate diagnostic procedure is performed to rule out pregnancy.

Other Regimens

In the initial cycle, the dosage of ORTHO-NOVUM 10 mg for contraception and hypermenorrhea is one tablet administered daily from the 5th through the 24th day of the menstrual cycle, counting the first day of menstrual flow as "Day 1." The use of ORTHO-NOVUM 10 mg for contraception may be initiated postpartum. When ORTHO-NOVUM 10 mg is administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS concerning thromboembolic disease.) If ORTHO-NOVUM 10 mg is first taken later than the fifth day of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on ORTHO-NOVUM 10 mg until after the first seven consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered. If the patient misses more than one tablet, the patient should begin taking tablets again as soon as remembered and another method of contraception used for the balance of that tablet cycle. In all subsequent cycles the first tablet is taken on the 7th day following completion of the previous 20-day course, i.e., 6 days without medication. Following three months of treatment of hypermenorrhea, medication may be discontinued to determine the need for further therapy.

Clinical experience indicates that the use of ORTHO-NOVUM 10 mg indefinitely postpones menses and controls ovulation, resulting in symptomatic and clinical improvement in cases of endometriosis. (a) Suppressive therapy—ORTHONOVUM 10 mg daily for 3 to 9 months is suggested with an increase in dose to 20 or 30 mg daily when indicated by the occurrence of breakthrough bleeding. Duration of treatment is determined on the basis of clinical findings. (b) Cyclic therapy—Some cases of endometriosis apparently respond to cyclic therapy with ORTHONOVUM 10 mg, which suppresses ovulation. Administer one tablet daily for 20 days (as described above for contraception).

(See discussion of Dose-Related Risk of Thromboembolism from Oral Contraceptives.)

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

HOW SUPPLIED

ORTHO-NOVUM 1/50□21 Tablets (as yellow unscored tablets with "Ortho" and "1" debossed on each side) are available in a DIALPAK Tablet Dispenser containing 21 tablets and a dispensing unit which contains one DIALPAK and two refills of 21 tablets each. Each yellow ORTHO-NOVUM 1/50□21 Tablet contains 1 mg of the progestational compound, norethindrone, together with 0.05 mg of the estrogenic compound, mestranol.

ORTHO-NOVUM 1/50□21 is available for clinic usage in a VERIDATE Tablet Dispenser (unfilled) and VERIDATE Refills.

ORTHO-NOVUM 1/50□28 Tablets (as yellow unscored tablets with "Ortho" and "1" debossed on each side) are available in a DIALPAK Tablet Dispenser containing 28 tablets, 21 yellow norethindrone with mestranol tablets and 7 green tablets containing inert ingredients. Each yellow ORTHO-NOVUM 1/50□28 Tablet contains 1 mg of the progestational compound, norethindrone, together with 0.05 mg of the estrogenic compound, mestranol.

ORTHO-NOVUM 1/50□28 is available for clinic usage in a VERIDATE Tablet Dispenser (unfilled) and VERIDATE Refills.

ORTHO-NOVUM 1/80□21 Tablets (as white unscored tablets with "Ortho" and "1" debossed on each side) are available in a DIALPAK Tablet Dispenser containing 21 tablets and a dispensing unit which contains one DIALPAK and two refills of 21 tablets each. Each white ORTHO-NOVUM 1/80□21 Tablet contains 1 mg of the progestational compound, norethindrone, together with 0.08 mg of the estrogenic compound, mestranol.

ORTHO-NOVUM 1/80□21 is available for clinic usage in a VERIDATE Tablet Dispenser (unfilled) and VERIDATE Refills.

ORTHO-NOVUM 1/80□28 Tablets (as white unscored tablets with "Ortho" and "1" debossed on each side) are available in a DIALPAK Tablet Dispenser containing 28 tablets, 21 white norethindrone with mestranol tablets and 7 green tablets containing inert ingredients. Each white ORTHO-NOVUM 1/80□28 Tablet contains 1 mg of the progestational compound, norethindrone, together with 0.08 mg of the estrogenic compound, mestranol.

ORTHO-NOVUM 1/80□28 is available for clinic usage in a VERIDATE Tablet Dispenser (unfilled) and VERIDATE Refills.

ORTHO-NOVUM 2 mg□21 Tablets (as white unscored tablets with "Ortho" and "2" debossed on each side) are available in a DIALPAK Tablet Dispenser containing 21 tablets. Each white ORTHO-NOVUM 2 mg□21 Tablet contains 2 mg of the progestational compound, norethindrone, together with 0.10 mg of the estrogenic compound, mestranol.

ORTHO-NOVUM 2 mg□21 is available for clinic usage in a VERIDATE Tablet Dispenser (unfilled) and VERIDATE Refills.

ORTHO-NOVUM 10 mg Tablets (as white unscored tablets with "Ortho" and "10" debossed on each side) are available in a DIALPAK Tablet Dispenser containing 20 tablets. Each white ORTHO-NOVUM 10 mg Tablet contains 10 mg of the progestational compound, norethindrone, together with 0.06 mg of the estrogenic compound, mestranol.

MODICON Tablets (as white unscored tablets with "Ortho" appearing on each side) are available in a DIALPAK Tablet Dispenser containing 21 tablets. Each white tablet contains 0.5 mg of the progestational compound, norethindrone, together with 0.035 mg of the estrogenic compound, ethinyl estradiol.

MODICON is available for clinic usage in a VERIDATE Tablet Dispenser (unfilled) and VERIDATE Refills.

MODICON 28 Tablets (as white unscored tablets with "Ortho" appearing on each side) are available in a DIALPAK Tablet Dispenser containing 28 tablets, 21 white norethindrone with ethinyl estradiol tablets and 7 green tablets containing inert ingredients. Each white MODICON 28 Tablet contains 0.5 mg of the progestational compound, norethindrone, together with 0.035 mg of the estrogenic compound, ethinyl estradiol.

MODICON 28 is available for clinic usage in a VERIDATE Tablet Dispenser (unfilled) and VERIDATE Refills.

MICRONOR Tablets (as lime unscored tablets with "Ortho" and "0.35" debossed on each side) are available in a DIALPAK Tablet Dispenser containing 35 tablets. Each lime MICRONOR Tablet contains 0.35 mg of the progestational substance norethindrone.

REFERENCES

1. "Population Reports," Series H, Number 2, May 1974; Series I, Number 1, June 1974; Series B, Number 2, January 1975; Series H, Number 3, 1975; Series H, Number 4, January 1976 (published by the Population Information Program, The George Washington University Medical Center, 2001 S St. NW, Washington, D.C.). 2. Inman, W.H.W., M.P. Vessey, B. Westerholm, and A. Engelund, "Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs," *Brit Med J* 2:203-209, 1970. 3. Stolley, P.D., J.A. Tonascia, M.S. Tockman, P.E. Sartwell, A.H. Rutledge, and M.P. Jacobs, "Thrombosis with low-estrogen oral contraceptives," *Am J Epidemiol* 102:197-208, 1975. 4. Royal College of General Practitioners, "Oral contraception and thromboembolic disease," *J Coll Gen Pract* 12:287-273, 1967. 5. Inman, W.H.W. and M.P. Vessey, "Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of childbearing age," *Brit Med J* 2:193-199, 1969. 6. Vessey, M.P. and R. Doll, "Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report," *Brit Med J* 2:651-657, 1969. 7. Sartwell, P.E., A.T. Masl, F.G. Arthes, G.R. Greene, and H.E. Smith, "Thromboembolism and oral contraceptives, an epidemiological case control study," *Am J Epidemiol* 92:325-330, 1969. 8. Boston Collaborative Drug Surveillance Program, "Oral contraceptives and venous thromboembolic disease, surgically confirmed gall bladder disease and breast tumors," *Lancet* 1:1339-1404, 1973. 9. Collaborative Group for the Study of Stroke in Young Women, "Oral contraception and increased risk of cerebral ischemia or thrombosis," *N Engl J Med* 289:871-878, 1973. 10. Collaborative Group for the Study of Stroke in Young Women, "Oral contraceptives and strokes in young women: associated risk factors," *JAMA* 231:718-722, 1975. 11. Mann, J.I. and W.H.W. Inman, "Oral contraceptives and death from myocardial infarction," *Brit Med J* 2:245-248, 1975. 12. Mann, J.I., W.H.W. Inman, and M. Thorogood, "Oral contraceptive use in older women and fatal myocardial infarction," *Brit Med J* 2:445-447, 1976. 13. Mann, J.I., M.P. Vessey, M. Thorogood, and R. Doll, "Myocardial infarction in young women with special reference to oral contraceptive practice," *Brit Med J* 2:241-245, 1975. 14. Tietze, C., "Now Estimate of Mortality Associated with Fertility Control," *Family Planning Perspectives* Vol. 9, No. 2, 74-76, 1977. 15. Vessey, M.P., R. Doll, A.S. Fairbairn, and G. Glover, "Post-operative thromboembolism and the use of oral contraceptives," *Brit Med J* 3:123-126, 1970. 16. Greene, G.R., and P.E. Sartwell, "Oral contraceptive use in patients with thromboembolism following surgery, trauma, or infection," *Am J Pub Health* 62:680-685, 1972. 17. Smith, D.C., R. Prentice, D.J. Thompson, and W.L. Herrmann, "Association of exogenous estrogen and endometrial carcinoma," *N Engl J Med* 293:1164-1167, 1975. 18. Zlot, H.K. and W.D. Finkle, "Increased risk of endometrial carcinoma among users of conjugated estrogens," *N Engl J Med* 293:1167-1170, 1975. 19. Mack, T.N., J.G. Pike, B.E. Henderson, R.I. Pfeiffer, V.R. Garkins, M. Arthur, and S.E. Brown, "Estrogens and endometrial cancer in a retirement community," *N Engl J Med* 294:1262-1267, 1976. 20. Silverberg, S.G., and E.L. Hakowski, "Endometrial carcinoma in young women taking oral contraceptive agents," *Obstet Gynecol* 46:503-506, 1975. 21. Vessey, M.P., R. Doll, and P.M. Sulton, "Oral contraceptives and breast neoplasia, a retrospective study," *Brit Med J* 2:719-724, 1972. 22. Vessey, M.P., R. Doll, and K. Jones, "Oral contraceptives and breast cancer. Progress report of an epidemiological study," *Lancet* 1:941-943, 1975. 23. Boston Collaborative Drug Surveillance Program, "Surgically confirmed gall bladder disease, venous thromboembolism and breast tumors in relation to postmenopausal estrogen therapy," *N Engl J Med* 290:15-19, 1974. 24. Arthes, F.G., P.E. Sartwell, and E.F. Lewison, "The pill, estrogens, and the breast. Epidemiological aspects," *Cancer* 28:1331-1334, 1971. 25. Fascal, E., and R.S. Paffenbarger, "Oral contraceptives as related to cancer and benign lesions of the breast," *J Natl Cancer Inst* 55:767-773, 1975. 26. Royal College of General Practitioners, "Oral Contraceptives and Health," London, Pitman, 1974. 27. Ory, H. P. Colo, B. MacMahon and R. Hoover, "Oral contraceptives and reduced risk of benign breast diseases," *N Engl J Med* 294:419-422, 1976. 28. Baum, J., F. Holtz, J. Bookstein, and E.W. Klein, "Possible association between benign hepatomas and oral contraceptives," *Lancet* 2:926-928, 1973. 29. Mays, E.T., W.M. Christopherson, M.M. Mahr, and H.C. Williams, "Hepatic changes in young women ingesting contraceptive steroids. Hepatic hemorrhage and primary hepatic tumors," *JAMA* 235:730-732, 1970. 30. Edmonsden, H.A., B. Henderson, and B. Bonton, "Liver-cell adenomas associated with the use of oral contraceptives," *N Engl J Med* 294:470-472, 1976. 31. Herbst, A.L., H. Ulfelder, and D.C. Poskanzer, "Adenocarcinoma of the vagina," *N Engl J Med* 294:878-881, 1971. 32. Greenwald, P., J.J. Barlow, P.C. Nasca, and W. Burnett, "Vaginal cancer after maternal treatment with synthetic estrogens," *N Engl J Med* 285:390-392, 1971. 33. Lanier, A.P., K.L. Noller, D.G. Decker, L. Elvback, and L.T. Kurland, "Cancer and stilbestrol. A follow-up of 1719 persons exposed to estrogen in utero and born 1943-1959," *Mayo Clinic Proc* 48:793-799, 1973. 34. Herbst, A.L., R.J. Kurman, and R.E. Scully, "Vaginal and cervical abnormalities after exposure to stilbestrol in utero," *Obstet Gynecol* 40:287-298, 1972. 35. Herbst, A.L., S.J. Robboy, G.J. Macdonald, and R.E. Scully, "The effects of local progesterone on stilbestrol-associated vaginal adenosis," *Am J Obstet Gynecol* 118:607-615, 1974. 36. Herbst, A.L., D.C. Poskanzer, S.J. Robboy, L. Friedlander, and R.E. Scully, "Prenatal exposure to stilbestrol: a prospective comparison of exposed female offspring with unexposed controls," *N Engl J Med* 292:334-339, 1975. 37. Staff, A., R.F. Mattingly, D.V. Foley, W. Featherston, "Clinical diagnosis of vaginal adenosis," *Obstet Gynecol* 43:118-128, 1974. 38. Sherman, A.I., M. Goldrath, A. Berlin, V. Vakhariya, F. Banconi, V. Michaels, P. Goodman, and S. Brown, "Cervical-vaginal adenosis after in utero exposure to synthetic estrogens," *Obstet Gynecol* 44:531-545, 1974. 39. Gal, I., B. Kirman, and J. Stern, "Hormone pregnancy tests and congenital malformation," *Nature* 216:83, 1967. 40. Levy, E.P., A. Cohen, and F.C. Fraser, "Hormone treatment during pregnancy and congenital heart defects," *Lancet* 7:611, 1973. 41. Nora, J.J. and A.H. Nora, "Birth defects and oral contraceptives," *Lancet* 1:941-942, 1973. 42. Janerich, D.T., J.M. Piper, and D.M. Gibaltis, "Oral contraceptives and congenital limb-reduction defects," *N Engl J Med* 291:697-700, 1974. 43. Carr, D.H., "Chromosome studies in selected spontaneous abortions I. Conception after oral contraceptives," *Canad Med Assoc J* 109:343-348, 1970. 44. Wynn, V., J.W.H. Doar, and G.L. Mills, "Some effects of oral contraceptives on serum-lipid and lipoprotein levels," *Lancet* 2:720-723, 1968. 45. Laumas, K.R., P.K. Malkani, S. Bhatnagar, and V. Laumas, "Radio-

actively in the breast milk of lactating women after oral administration of 3 H-norethynodrel." *Amer J Obstet Gynecol* 98:411-413, 1967. 46. Center for Disease Control, "Increased Risk of Hepatocellular Adenoma in Women with Long-term use of Oral Contraceptives," *Morbidity and Mortality Weekly Report*, 26:293-294, 1977. 47. Herbst, A.L., P. Cole, T. Colton, S. J. Robboy, R. E. Scully, "Age-incidence and Risk of Diethylstilbestrol-related Clear Cell Adenocarcinoma of the Vagina and Cervix," *Am. J. Obstet Gynecol*, 128:43-50, 1977. 48. Bibbo, M., M. Al-Nageeb, J. Bac-cann, W. Gill, M. Newton, K.M. Sleeper, M. Sonok, G.L. Wied, "Follow-up Study of Male and Female Offspring of DES-treated Mothers. A Preliminary Report," *Jour. of Repro Med.*, 15:29-32, 1975. 49. Gill, W.B., G.F.B. Schumacher, M. Bibbo, "Structural and Functional Abnormalities in the Sex Organs of Male Offspring of Mothers Treated with Diethylstilbestrol (DES)," *Jour of Repro Med.*, 16:147-153, 1976. 50. Henderson, B.E., B. Senton, M. Cosgrove, J. Baptista, J. Aldrich, D. Townsend, W. Hart, T. Mack, "Urogenital Tract Abnormalities in Sons of Women Treated with Diethylstilbestrol" *Pediatrics*, 58:505-507, 1976. 51. Heinenon, O.P., D. Stone, R.R. Nonson, E.B. Hook, S. Shapiro, "Cardiovascular Birth Defects and Antenatal Exposure to Female Sex Hormones," *N Engl. J. Med.*, 296:67-70, 1977. 52. Jain, A.K., "Mortality Risk Associated with the Use of Oral Contraceptives," *Studies in Family Planning*, 8:50-54, 1977. 53. Beral, V., "Mortality Among Oral Contraceptive Users," *Lancet*, 2:727-731, 1977. 54. Vessey, M.P., McPherson, K., and Johnson, B., "Mortality Among Women Participating in the Oxford/Family Planning Association Contraceptive Study," *Lancet* 2:731-733, 1977.

The patient labeling for oral contraceptive drug products is set forth below:

BRIEF SUMMARY PATIENT PACKAGE INSERT

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Oral contraceptives taken as directed are about 99% effective in preventing pregnancy (The mini-pill, however, is somewhat less effective.) Forgetting to take your pills increases the chance of pregnancy.

Women who have or have had clotting disorders, cancer of the breast or sex organs, unexplained vaginal bleeding, a stroke, heart attack, angina pectoris, or who suspect they may be pregnant should not use oral contraceptives.

Because many risks increase with age, birth control pills are not recommended for women past the age of 40.

Most side effects of the pill are not serious. The most common side effects are nausea, vomiting, bleeding between menstrual periods, weight gain, and breast tenderness. However, proper use of oral contraceptives requires that they be taken under your doctor's continuous supervision, because they can be associated with serious side effects which may be fatal. Fortunately, these occur very infrequently. The serious side effects are:

1. Blood clots in the legs, lungs, brain, heart or other organs and hemorrhage into the brain due to bursting of a blood vessel.
2. Liver tumors, which may rupture and cause severe bleeding.
3. Birth defects if the pill is taken while you are pregnant.
4. High blood pressure
5. Gallbladder disease

Some of the symptoms associated with these serious side effects are discussed in the detailed leaflet given you with your supply of pills. Notify your doctor if you notice any unusual physical disturbance while taking the pill.

The estrogen in oral contraceptives has been found to cause breast cancer and other cancers in certain animals. These findings suggest that oral contraceptives may also cause cancer in humans. However, studies to date in women taking currently marketed oral contraceptives have not confirmed that oral contraceptives cause cancer in humans.

The detailed leaflet describes more completely the benefits and risks of oral contraceptives. It also provides information on other forms of contraception. Read it carefully if you have any questions, consult your doctor.

Caution: Oral contraceptives are of no value in the prevention or treatment of venereal disease.

DETAILED PATIENT LABELING

WHAT YOU SHOULD KNOW ABOUT ORAL CONTRACEPTIVES

Oral contraceptives (the pill) are the most effective way (except for sterilization) to prevent pregnancy. They are also convenient and, for most women, free of serious or unpleasant side effects. Oral contraceptives must always be taken under the continuous supervision of a physician. The information in this leaflet under the headings "Who Should Not Use Oral Contraceptives," "The Dangers of Oral Contraceptives," and "How to Use Oral Contraceptives as Effectively as Possible, Once You Have Decided to Use Them" is also applicable when these drugs are used for other indications.

ORTHO NOVUM 2 mg may be prescribed for you for the treatment of hypermenorrhea.

ORTHO NOVUM 10 mg may be prescribed for you for the treatment of hypermenorrhea and endometriosis.

It is important that any woman who considers using an oral contraceptive understand the risks involved. Although the oral contraceptives have important advantages over other methods of contraception, they have certain risks that no other method has. Only you can decide whether the advantages are worth these risks. This leaflet will tell you about the most important risks. It will explain how you can help your doctor prescribe the pill as safely as possible by telling him about yourself and being alert for the earliest signs of trouble. And it will tell you how to use the pill properly, so that it will be as effective as possible. There is more detailed information available in the leaflet prepared for doctors. Your pharmacist can show you a copy; you may need your doctor's help in understanding parts of it.

WHO SHOULD NOT USE ORAL CONTRACEPTIVES

- A. If you have now, or have had in the past, any of the following conditions you should not use the pill:
 1. Heart attack or stroke.
 2. Clots in the legs or lungs.
 3. Angina pectoris.
 4. Known or suspected cancer of the breast or sex organs.
 5. Unusual vaginal bleeding that has not yet been diagnosed.
- B. If you are pregnant or suspect that you are pregnant, do not use the pill.

C. Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

- D. If you have scanty or irregular periods or are a young woman without a regular cycle, you should use another method of contraception because, if you use the pill, you may have difficulty becoming pregnant or may fail to have menstrual periods after discontinuing the pill.
- E. Although it is your decision, since many risks increase with age, birth control pills are not recommended for women past the age of 40.

DECIDING TO USE ORAL CONTRACEPTIVES

If you do not have any of the conditions listed above and are thinking about using oral contraceptives, to help you decide, you need information about the advantages and risks of oral contraceptives and of other contraceptive methods as well. This leaflet describes the advantages and risks of oral contraceptives. Except for sterilization, the IUD and abortion, which have their own exclusive risks, the only risks of other methods of contraception are those due to pregnancy should the method fail. Your doctor can answer questions you may have with respect to other methods of contraception. He can also answer any questions you may have after reading this leaflet on oral contraceptives.

1. What Oral Contraceptives Are and How They Work. Oral Contraceptives are of two types. The most common, often simply called "the pill," is a combination of an estrogen and a progestogen, the two kinds of female hormones. The amount of estrogen and progestogen can vary, but the amount of estrogen is most important because both the effectiveness and some of the dangers of oral contraceptives are related to the amount of estrogen. This kind of oral contraceptive works principally by preventing release of an egg from the ovary. When the amount of estrogen is 50 micrograms or more, and the pill is taken as directed, oral contraceptives are more than 99% effective (i.e., there would be less than one pregnancy if 100 women used the pill for one year). Pills that contain 20 to 35 micrograms of estrogen vary slightly in effectiveness, ranging from 98% to more than 99% effective.

The second type of oral contraceptive, often called the "mini-pill," contains only a progestogen. It works in part by preventing release of an egg from the ovary but also by keeping sperm from reaching the egg and by making the uterus (womb) less receptive to any fertilized egg that reaches it. The mini-pill is less effective than the combination oral contraceptive, about 97% effective. In addition, the progestogen-only pill has a tendency to cause irregular bleeding which may be quite inconvenient, or cessation of bleeding entirely. The progestogen-only pill is used despite its lower effectiveness in the hope that it will prove not to have some of the serious side effects of the estrogen-containing pill (see below) but it is not yet certain that the mini-pill does in fact have fewer serious side effects. The discussion below, while based mainly on information about the combination pills, should be considered to apply as well to the mini-pill.

2. Other Nonsurgical Ways to Prevent Pregnancy. As this leaflet will explain, oral contraceptives have several serious risks. Other methods of contraception have lesser risks or none at all. They are also less effective than oral contraceptives, but, used properly, may be effective enough for many women. The following table gives reported pregnancy rates (the number of women out of 100 who would become pregnant in one year) for these methods:

Pregnancies Per 100 Women Per Year

- Intrauterine device (IUD), less than 1-6;
- Diaphragm with spermicidal products (creams or jellies), 2-20;
- Condom (rubber), 3-36; Aerosol foams, 2-29; Jellies and creams, 4-36;
- Periodic abstinence (rhythm) all types, less than 1-47;
- 1. Calendar method, 14-47;
- 2. Temperature method, 1-20;
- 3. Temperature method—Intercourse only in postovulatory phase, less than 1-7;

4. Mucus method, 1-25;

No contraception, 60-80.

The figures (except for the IUD) vary widely because people differ in how well they use each method. Very faithful users of the various methods obtain very good results, except for users of the calendar method of periodic abstinence (rhythm). Except for the IUD, effective use of these methods requires somewhat more effort than simply taking a single pill every morning, but it is an effort that many couples undertake successfully. Your doctor can tell you a great deal more about these methods of contraception.

3. The Dangers of Oral Contraceptives.

a. *Circulatory disorders (abnormal blood clotting, heart attack, and stroke due to hemorrhage).* Blood clots (in various blood vessels of the body) are the most common of the serious side effects of oral contraceptives. A clot can result in a stroke (if the clot is in the brain), a heart attack (if the clot is in a blood vessel of the heart), or a pulmonary embolus (a clot which forms in the legs or pelvis, then breaks off and travels to the lungs). Any of these can be fatal. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impairment of vision in that eye. There is evidence that the risk of clotting increases with higher estrogen doses. It is therefore important to keep the dose of estrogen as low as possible, so long as the oral contraceptive used has an acceptable pregnancy rate and doesn't cause unacceptable changes in the menstrual pattern. Furthermore, cigarette smoking by oral contraceptive users increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and begins to become quite marked in women over 35 years of age. For this reason, women who use oral contraceptives should not smoke.

The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

Even without the pill the risk of having a heart attack increases with age and is also increased by such heart attack risk factors as high blood pressure, high cholesterol, obesity, diabetes, and cigarette smoking. Without any risk factors present, the use of oral contraceptives alone may double the risk of heart attack. However, the combination of cigarette smoking, especially heavy smoking, and oral contraceptive use greatly increases the risk of heart attack. Oral contraceptive users who smoke are about five times more likely to have a heart attack than users who do not smoke and about ten times more likely to have a heart attack than nonusers who do not smoke. It has been estimated that users between the ages of 30 and 39 who smoke have about a 1-in-10,000 chance each year of having a fatal heart attack compared to about a 1-in-50,000 chance in users who do not smoke, and about a 1-in-100,000 chance in nonusers who do not smoke. In the age group 40 to 44, the risk is about 1 in 1,700 per year for users who smoke compared to about 1 in 10,000 for users who do not smoke and to about one in 14,000 per year for nonusers who do not smoke. Heavy smoking (about 15 cigarettes or more a day) further increases the risk. If you do not smoke and have none of the other heart attack risk factors described above, you will have a smaller risk than listed. If you have several heart attack risk factors, the risk may be considerably greater than listed.

In addition to blood-clotting disorders, it has been estimated that women taking oral contraceptives are twice as likely as nonusers to have a stroke due to rupture of a blood vessel in the brain.

One report suggests that the risk of circulatory diseases appears to increase the longer you are on the pill and may continue after you stop.

b. *Formation of tumors* Studies have found that when certain animals are given the female sex hormone estrogen, which is an ingredient of oral contraceptives, continuously for long periods, cancers may develop in the breast, cervix, vagina, and liver.

These findings suggest that oral contraceptives may cause cancer in humans. However, studies to date in women taking currently marketed oral contraceptives have not confirmed that oral contraceptives cause cancer in humans. Several studies have found no increase in breast cancer in users, although one study suggested oral contraceptives might cause an increase in breast cancer in women who already have benign breast disease (e.g., cysts).

Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms or who were exposed to DES (diethylstilbestrol), an estrogen, during their mother's pregnancy must be followed very closely by their doctors if they choose to use oral contraceptives instead of another method of contraception. Many studies have shown that women taking oral contraceptives have less risk of getting benign breast disease than those who have not used oral contraceptives. Recently, strong evidence has emerged that estrogens (one component of oral contraceptives), when given for periods of more than one year to women after the menopause, increase the risk of cancer of the uterus (womb). There is also some evidence that a kind of oral contraceptive which is no longer marketed, the sequential oral contraceptive, may

increase the risk of cancer of the uterus. There remains no evidence, however, that the oral contraceptives now available increase the risk of this cancer.

Oral contraceptives do cause, although rarely, a benign (non-malignant) tumor of the liver. These tumors do not spread, but they may rupture and cause internal bleeding, which may be fatal. A few cases of cancer of the liver have been reported in women using oral contraceptives, but it is not yet known whether the drug caused them.

c. *Dangers to a developing child if oral contraceptives are used in or immediately preceding pregnancy.* Oral contraceptives should not be taken by pregnant women because they may damage the developing child. An increased risk of birth defects, including heart defects and limb defects, has been associated with the use of sex hormones, including oral contraceptives, in pregnancy. In addition, the developing female child whose mother has received DES (diethylstilbestrol), an estrogen, during pregnancy has a risk of getting cancer of the vagina or cervix in her teens or young adulthood. This risk is estimated to be about 1 to 4 in 1000 exposures. Abnormalities of the urinary and sex organs have been reported in male offspring so exposed. It is possible that other estrogens, such as the estrogens in oral contraceptives, could have the same effect in the child if the mother takes them during pregnancy.

If you stop taking oral contraceptives to become pregnant, your doctor may recommend that you use another method of contraception for a short while, for example three months. The reason for this is that there is evidence from studies in women who have had "miscarriages" soon after stopping the pill, that the lost fetuses are more likely to be abnormal. Whether there is an overall increase in "miscarriage" in women who become pregnant soon after stopping the pill as compared with women who do not use the pill is not known, but it is possible that there may be. If, however, you do become pregnant soon after stopping oral contraceptives, and do not have a miscarriage, there does not appear to be evidence that the baby has an increased risk of being abnormal.

d. *Gallbladder disease.* Women who use oral contraceptives have a greater risk than nonusers of having gallbladder disease requiring surgery. The increased risk may first appear within one year of use and may double after four or five years of use.

e. *Other side effects of oral contraceptives.* Some women using oral contraceptives experience unpleasant side effects. Some of these may be temporary. Your breasts may feel tender, nausea and vomiting may occur, you may gain or lose weight, and your ankles may swell. A spotty darkening of the skin, particularly of the face, is possible and may persist. You may notice unexpected vaginal bleeding or changes in your menstrual period. Irregular bleeding is frequently seen when using the mini-pill or combination oral contraceptives containing less than 50 micrograms of estrogen.

More serious side effects include worsening of migraine, asthma, epilepsy, and kidney or heart disease because of a tendency for water to be retained in the body when oral contraceptives are used. Other side effects are growth of preexisting fibroid tumors of the uterus; mental depression; and liver problems with jaundice (yellowing of the skin). Your doctor may find that levels of sugar and fatty substances in your blood are elevated; the long-term effects of these changes are not known. Some women develop high blood pressure while taking oral contraceptives, which ordinarily returns to the original levels when the oral contraceptive is stopped.

Other reactions, although not proved to be caused by oral contraceptives, are occasionally reported. These include more frequent urination and some discomfort when urinating, kidney disease, nervousness, dizziness, some loss of scalp hair, an increase in body hair, an increase of decrease in sex drive, appetite changes, cataracts, and a need for a change in contact lens prescription or inability to use contact lenses.

After you stop using oral contraceptives there may be a delay before you are able to become pregnant or before you resume having menstrual periods. This is especially true of women who had irregular menstrual cycles prior to the use of oral contraceptives. As discussed previously, your doctor may recommend that you wait a short while after stopping the pill before you try to become pregnant. During this time, use another form of contraception. You should consult your physician before resuming use of oral contraceptives after childbirth, especially if you plan to nurse your baby. Drugs in oral contraceptives are known to appear in the milk, and the long-range effect on infants is not known at this time. Furthermore, oral contraceptives may cause a decrease in your milk supply as well as in the quality of the milk.

4. *Comparison of the Risks of Oral Contraceptives and Other Contraceptive Methods.* The many studies on the risks and effectiveness of oral contraceptives and other methods of contraception have been analyzed to estimate the risk of death associated with various methods of contraception. This risk has two parts: (a) the risk of the method itself (e.g., the risk that oral contraceptives will cause death due to abnormal clotting), and (b) the risk of death due to pregnancy or abortion in the event the method fails. The results of this analysis are shown in the bar graph (Figure 1). The height of the bars is the number of deaths per 100,000 women each year. There are six sets of bars, each set referring to a specific age group of women. Within each set of bars there is a single bar for each of the different contraceptive methods. For oral contraceptives, there are two bars—one for smokers and the other for nonsmokers. The analysis is based on present knowledge and new information could, of course, alter it. The analysis shows that the risk of death from all methods of birth control is low and below that associated with childbirth, except for oral con-

traceptives in women over 40 who smoke. It shows that the lowest risk of death is associated with the condom or diaphragm (traditional contraception) backed up by early abortion in case of failure of the condom or diaphragm to prevent pregnancy. Also, at any age the risk of death (due to unexpected pregnancy) from the use of traditional contraception, even without a backup of abortion, is generally the same as or less than that from use of oral contraceptives.

HOW TO USE ORAL CONTRACEPTIVES AS EFFECTIVELY AS POSSIBLE, ONCE YOU HAVE DECIDED TO USE THEM

1. What to Tell your Doctor.

You can make use of the pill as effectively as possible by telling your doctor if you have any of the following:

a. Conditions that mean you should not use oral contraceptives:

Clots in the legs or lungs.
Clots in the legs or lungs in the past.
A stroke, heart attack, or angina pectoris.
Known or suspected cancer of the breast or sex organs.
Unusual vaginal bleeding that has not yet been diagnosed.
Known or suspected pregnancy.

b. Conditions that your doctor will want to watch closely or which might cause him to suggest another method of contraception:

A family history of breast cancer.
Breast nodules, fibrocystic disease of the breast, or an abnormal mammogram.
Heart and kidney disease.
Diabetes.
Epilepsy.
High blood pressure.
Mental depression.
High cholesterol.
Fibroid tumors of the uterus.
Cigarette smoking.
Gallbladder disease.
Migraine headaches.

c. Once you are using oral contraceptives, you should be alert for signs of a serious adverse effect and call your doctor if they occur:

Sharp pain in the chest, coughing blood, or sudden shortness of breath (indicating possible clots in the lungs).
Pain in the calf (possible clot in the leg).
Crushing chest pain or heaviness (indicating possible heart attack).
Sudden severe headache or vomiting, dizziness or fainting, disturbance of vision or speech or weakness or numbness in an arm or leg (indicating a possible stroke).
Sudden partial or complete loss of vision (indicating a possible clot in the eye).
Breast lumps (you should ask your doctor to show you how to examine your own breasts).
Severe pain in the abdomen (indicating a possible ruptured tumor of the liver).
Severe depression.
Yellowing of the skin (jaundice).

2. How to Take the Pill So That It Is Most Effective.

To achieve maximum contraceptive effectiveness, ORTHO-NOVUM, MODICON and MICRONOR must be taken exactly as directed and at intervals not exceeding 24 hours.

21-Day Regimen: Counting the first day of menstrual flow as "Day 1," take one tablet daily from the 5th through the 25th day of the menstrual cycle. If the first tablet is taken later than the 5th day of the menstrual cycle or postpartum, contraceptive reliance should not be placed on ORTHO-NOVUM or MODICON until after the first seven consecutive days of administration. Take a tablet the same time each day, preferably at bedtime, for 21 days, then wait for 7 days during which time a menstrual period usually occurs. Following this 7-day waiting period, start taking a tablet each day for the next 21 days, thus using a three-weeks-on, one-week-off dosage regimen.

28-Day Regimen: The first white or yellow tablet should be taken on the first Sunday after the menstrual period begins. If period begins on Sunday, begin taking tablets that day. Take one white or yellow tablet at the same time each day for 21 consecutive days, then take one green tablet daily for 7 days during which time your menstrual period usually occurs. During the FIRST cycle, it is important that you use another method of birth control until you have taken a white or yellow tablet daily for seven consecutive days. After 28 tablets have been taken, (last green tablet will always be taken on a Saturday) take the first tablet (white or yellow) from your next package the following day (Sunday) whether or not you are still menstruating. With the 28-day regimen, pills are taken every day of the year.

20-Day Regimen: In the initial cycle, the dosage of ORTHO-NOVUM 10 mg for contraception is one tablet administered daily from the 5th through the 24th day of the menstrual cycle, counting the first day of the menstrual flow as "Day 1". If ORTHO-NOVUM 10 mg is first taken later than the fifth day of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on ORTHO-NOVUM 10 mg until after the first seven consecutive days of administration. In all subsequent cycles the first tablet is taken on the 7th day following completion of the previous 20-day course, i.e., 6 days without medication.

In the treatment of hypermenorrhea and endometriosis, your physician will discuss the regimen with you.

Continuous Regimen (MICRONOR): The first MICRONOR Tablet should be taken on the first day of the menstrual period.

Take one tablet at the same time each day without interruption for as long as contraceptive protection is desired.

The effectiveness of progestogen-only oral contraceptives, such as MICRONOR, is lower than that of the combination oral contraceptives containing both estrogen and progestogen. If 100 women utilized an estrogen-containing oral contraceptive for a period of one year, generally less than one pregnancy would be expected to occur; however, if MICRONOR had been utilized, approximately three pregnancies might occur.

Women who participated in the clinical studies with MICRONOR and who had not taken other oral contraceptives before starting MICRONOR had a higher pregnancy rate (four women out of 100), particularly during the first six months of therapy, and to a large extent because they did not take their tablets correctly.

Of course, if you don't take your tablets as directed, or forget to take them every day, the chance you may become pregnant is naturally greater.

MICRONOR (norethindrone) will probably cause some changes in your menstrual pattern. Your cycle, that is the time between menstrual periods, will vary. For example, you might have a 28-day cycle, followed by a 17-day cycle, followed by a 35-day cycle, etc. This is common with MICRONOR.

While using MICRONOR, your period may be longer or shorter than before. If bleeding lasts more than eight days, be sure to let your doctor know.

Occasionally women who are not taking the pill miss a period. This is also true for women taking the pill and it has been reported to occur as frequently as several times each year in some women, depending on various factors, such as age and prior history. Therefore, if you miss a period, or if you are taking mini-pills and it is 45 days or more from the start of your last menstrual period you may be pregnant and you should consult your physician before continuing to take the pill. (Your doctor is the best source of information about this.) The pill should not be used when you are pregnant because of some reports of the possibility of adverse effects on the developing child. Very rarely, women who are using the pill as directed become pregnant. The likelihood of becoming pregnant if you occasionally miss one or two pills is naturally higher. If you miss a period, especially if you have not taken the pill regularly, you should use an alternative method of contraception until pregnancy has been ruled out. If you have missed more than one tablet at any time, you should immediately start using an additional method of contraception and complete your pill cycle.

3. Periodic Examination.

Your doctor will take a complete medical and family history before prescribing oral contraceptives. At that time and about once a year thereafter, he will generally examine your blood pressure, breasts, abdomen, and pelvic organs (including a Papanicolaou smear, i.e., test for cancer).

Summary

Oral contraceptives are the most effective method, except sterilization, for preventing pregnancy. Other methods, when used conscientiously, are also very effective and have fewer risks.

Women who use oral contraceptives should not smoke.

In addition, if you have certain conditions or have had these conditions in the past, you should not use oral contraceptives because the risk is too great. These conditions are listed in the booklet. If you do not have these conditions and decide to use the "pill," please read the booklet carefully so that you can use the "pill."

Based on his or her assessment of your medical needs, your doctor has prescribed this drug for you. Do not give the drug to anyone else.

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