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TO Dr. Grinspoon

For your information.

August 22, 1985
Rick Cotton

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The FDA and Drug Uses: Reprise

To the Editor.—The recent editorial by Dr Archer' is a useful addition to the literature exploring the nature and significance of official Food and Drug Administration (FDA) drug labeling and the role of such information in drug selection and use by physicians. The editorial correctly notes that the FDA cannot approve or disapprove of how a physician uses lawfully marketed drugs. The FDA can and does, however, approve indications for a drug's use and approves what a drug manufacturer may say in labeling, advertising, or publications intended to acquaint physicians with a drug's properties and uses. Although FDA officials³ have over the years sought to clarify the status and role of approved drug labeling, we felt that a wider audience needed to have an authoritative policy statement on this issue. We chose the *FDA Drug Bulletin*,⁴ as Archer notes, as the most appropriate vehicle since it is sent to more than 1 million health professionals.

I believe it is helpful for the readers of *JAMA* to be reminded by Archer that the FDA does not approve or disapprove of how physicians use drugs. The agency's function in this area is, rather, to make certain that drug information provided to physicians by manufacturers conforms with the scientific data presented to the agency, including the results of controlled clinical trials, on which drug approval is based.

As I sought to clarify in an article¹ on this issue in 1983, unlabeled uses range from unstudied to carefully investigated—some salutary, others hazardous, some occurring very infrequently, others so common and so widespread as to constitute usual medical practice. The use of a drug for an unlabeled indication may be anything from appropriate to very unsound, even hazardous, medical practice. The latter occurs when a drug is found either ineffective or

unsafe for a particular indication—for example, the use of digitalis or drugs with thyroid hormone activity for weight control. In such cases, the official labeling may include a prominently displayed "box warning" advising physicians that such use of the drug is hazardous and in effect "disapproved." Such warnings are relatively rare and should be a deterrent to inappropriate prescribing.

Soffer² examines the unlabeled use issue with respect to edetate disodium (EDTA), a drug widely promoted by its proponents in "chelation therapy" for cardiac and peripheral vascular disease. He states that such use cannot be recommended because there are no data from controlled trials that demonstrate efficacy and there is great potential danger in such treatment. In fact, he states that physicians who recommend such use are abusing a precious freedom, the flexibility to prescribe for unlabeled indications. Edetate disodium is officially labeled for the emergency treatment of hypercalcemia and for the control of ventricular arrhythmia associated with digitalis toxicity. It is not labeled, and indeed has never been adequately studied, for the treatment of atherosclerosis. While the promoted but unlabeled use is not referred to in the "Indications" or "Warning" section of the official labeling, under "Contraindications" the labeling states: "It is not indicated for the treatment of generalized arteriosclerosis associated with advancing age."

Thus, while physicians are not prevented from using edetate disodium to treat patients for atherosclerosis simply because that indication is not included in the FDA-approved labeling, the labeling does warn against it. We believe that the absence of the atherosclerosis indication and the presence of the contraindication of this use in the FDA official labeling serve as a very important alert to the physician. Thus, as Archer correctly points out, physicians are not legally bound to abide by FDA official drug labeling, nor do the dictates of sound medical practice require that they invariably do so. But, we would emphasize, it behooves them to be familiar with it.

STUART L. NIGHTINGALE, MD
Food and Drug Administration
Rockville, Md

1. Archer JD: The FDA does not approve uses of drugs. *JAMA* 1984;252:1054-1055.
2. Crout JR: In praise of the lowly package insert. *Food Drug Cosmetic Law J* 1974;29:139-145.
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4. Use of approved drugs for unlabeled indications. *FDA Drug Bull* 1982;12:4-5.

Guidelines for Letters

Letters will be published at the discretion of the editor as space permits and subject to editing and abridgment. They should be typewritten double-spaced and submitted in duplicate. They should not exceed 500 words of text. References, if any, should be held to a minimum, preferably five or fewer. Letters discussing a recent *JAMA* article should be received within one month of the article's publication. Letters must not duplicate other material published or submitted for publication. An assignment of copyright is essential for publication. It is not feasible routinely to return unpublished letters unless such is requested. Letters not meeting these guidelines are generally not acknowledged. Also see "Instructions for Authors."

5. Nightingale SL: The FDA's role in appropriate drug use. In Morgan JP, Kagan DV (eds): *Society and Medication: Conflicting Signals for Prescribers and Patients*. Lexington, Mass, DC Heath & Co, 1983, pp 63-71.
6. Soffer A: Chelation clinics: An abuse of the physician's freedom of choice. *Arch Intern Med* 1984;144:1741-1742.

In Reply.—I appreciate Dr Nightingale's letter and agree with everything he has stated. The letter does much to clarify and expand on what I said in my editorial. Although I was thinking in a somewhat different context about FDA disapproval of uses of drugs, Dr Nightingale's explanation of how the agency does sometimes validly express disapproval of some uses of some drugs should prove valuable to readers. As noted in the editorial, however, on some occasions labeling has, in a sense, expressed "disapproval" of valid uses of drugs as I specified.

JOHN ARCHER, MD

Medication Similarities

To the Editor.—The recent letter by Brennan et al¹ reminded me of a patient referred to our general medical clinic for hypertension. According to the patient, her blood pressure had been well controlled for several years while taking 5 mg/day of methyclothiazide (Enduron). She had recently seen her physician and had her prescription refilled. Her blood pressure had been noted to be well controlled at that visit. The medication bottle brought by her to our clinic contained 10-mg tablets of propranolol hydrochloride (Inderal), not 5-mg tablets of methyclothiazide. She had been taking them once daily as directed on the label.

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Staphylococcus epidermidis Septicemia in Children: An Emerging and Difficult Problem

Bacteria thought to be innocuous are a hazard to children whose immunologic capability is reduced by disease or by immunosuppressive therapy. Among bacteria responsible for severe infections is *Staphylococcus epidermidis*, a common surface inhabitant, ordinarily of no consequence to a healthy host. In the August issue of the *American Journal of Diseases of Children (AJDC)*, Louise Friedman and her colleagues at Memorial Sloan-Kettering and Cornell University Medical College in New York City detail the role of *S epidermidis* as a cause of septicemia among 92 children with leukemia.¹ They report that 12.7% of all septicemic episodes are caused by *S epidermidis* and explore the factors that have allowed this organism to become the fourth most frequent pathogen in their experience. The severity of *S epidermidis* septicemia is underscored by two deaths among the 19 patients affected.

Primary care physicians are now responsible for the ongoing care of children who are immunodeficient because of disease and/or therapy that compromises the immune response. It is critical that they recognize the important role *S epidermidis* now plays in illness among their patients in this category. Among the factors that enhance *S epidermidis*' pathogenicity are (1) the administration of immunosuppressive therapy, (2) the use of broad-spectrum antibiotics, (3) the presence of neutropenia, and (4) the need for indwelling catheters and drains. Skin and soft-tissue infections with *S epidermidis*, alone or with other organisms, also predispose one to septicemia. Given such factors, the physician should obtain blood cultures if fever or other signs of systemic infection occur and should not ignore or dismiss the isolation of *S epidermidis* from such specimens.

A further consideration is the antibiotic resistance pattern of these isolates. The Friedman et al report and a previous study reported in *AJDC* demonstrate the high frequency of resistance of these bacteria to penicillin, methicillin sodium, erythromycin, and other commonly employed antibiotics.¹² These findings and others have suggested that vancomycin hydrochloride be administered as the first-line antibiotic in children with presumed or proved *S epidermidis* septicemia. Earlier this year several reports and an editorial were published in *AJDC* that emphasized the role of vancomycin, some problems in its use, and the data needed for adequate dosage.¹³ The physician who cares for such children must familiarize (or refamiliarize) himself with vancomycin, an antibiotic more widely used in the

late 1950s and early 1960s, but only recently reutilized.

Several themes emerge from the most recent *AJDC* report and from those that preceded it: (1) *S epidermidis* is an emerging and potentially lethal pathogen in immunocompromised children; (2) it should be sought and, if found in clinical specimens, should not be ignored; and (3) modern therapy includes the initial administration of vancomycin to patients suspected or proved to have *S epidermidis* septicemia.

VINCENT A. FULGINITI, MD
Editor, *AJDC*

1. Friedman LE, Brown AE, Miller DR, et al: *Staphylococcus epidermidis* septicemia in children with leukemia and lymphoma. *AJDC* 1984;138:715-719.
2. Baumgart S, Hall SE, Campos JM, et al: Sepsis with coagulase-negative staphylococci in critically ill newborns. *AJDC* 1983;137:461-463.
3. Odio C, Mohs E, Sklar F, et al: Adverse reactions to vancomycin used as prophylaxis for CSF shunt procedures. *AJDC* 1984;138:17-19.
4. Alpert G, Campos JM, Harris MC, et al: Vancomycin dosage in pediatrics reconsidered. *AJDC* 1984;138:20-22.
5. Banner W Jr, Ray CG: Vancomycin in perspective. *AJDC* 1984;138:11-16.

The FDA Does Not Approve Uses of Drugs

As a reviewer of medical manuscripts and reader of published articles, I find it frustrating to continue to find reference to "Food and Drug Administration (FDA)-approved uses of drugs"—or worse, allegations that certain uses are "not approved." For nearly two decades, through published articles, speeches, and personal communications, I have cautioned the medical profession against such diction. Perhaps the most definitive article was "Instrument or Impediment? The Regulatory Monograph in Medical Communications." The FDA cannot approve or disapprove of how a legally marketed drug is used by a physician in his practice. The agency approves of what the manufacturer may recommend about uses in its labeling (package insert) and advertising.

Failure to recognize this distinction can have various harmful results. Many valid uses of drugs become recognized long before they are included in manufacturers' literature—provided they ever are. Such uses may range from the unstudied (but reasonable) to the thoroughly investigated. Yet, references to

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"approved uses" may lead physicians into the mistaken notion that they are somehow prohibited from medically sound prescribing merely because a manufacturer and the FDA, for whatever reason, have not concluded a transaction between themselves to include a use in the labeling.

A third-party provider may refuse to furnish or pay for a drug based on the absence of some recommendation in the manufacturer's FDA-approved literature. If that is the only reason for refusal, it is a deplorable administrative mistake. The FDA has no legal authority to impose such action.

If a malpractice suit should arise from real or alleged injury by a drug, the plaintiff's lawyer would probably attempt to strengthen his case if he could point to lack of recommendation in the manufacturer's literature for the use involved. Injustice might result if the defense failed to point out that the FDA does not regulate the practice of medicine. The labeling might be given some consideration in how well it reflects proper practice, but it should not be allowed to establish what is proper. Other medical literature or expert testimony can quite validly support correct use of a drug.

The fact that, based on adequate clinical trials, the FDA often approves additions to labeling recommendations for uses that have been employed for years gives mute testimony that the uses were proper all along. Some examples among many are worth repeating: propranolol for angina pectoris and hypertension, metronidazole for amebiasis, amantadine for parkinsonism, diazepam for status epilepticus, imipramine for childhood enuresis, colestyramine resin for hyperlipidemia, lidocaine for arrhythmias. Thus, physicians, not the FDA, still determine how drugs are used in the practice of medicine.

For anyone who might continue to consider package inserts as dogma, the preceding list involves some remarkable incongruities. Long before propranolol was labeled for angina pectoris, many cardiologists considered it a form of malpractice to perform a coronary bypass operation unless a patient had had a therapeutic trial with the drug.

For years after injectable diazepam was recognized as the drug of choice for status epilepticus, its labeling bore warnings against its use in patients with epilepsy. After that absurdity was corrected regarding a largely pediatric disorder, the labeling long continued to advise that "The safety and efficacy of [the drug] in children under age 12 have not been established." [!]

For about a decade after imipramine was used successfully for childhood enuresis, the labeling contained warnings against giving the drug to children. Before labeling for amantadine disclosed that the drug could be useful in treatment of early A, influenza (as contrasted with mere prophylaxis), it actually denied, contrary to fact, that such evidence existed. Almost amusingly, for years after colestyramine resin was used successfully for hyperlipidemia, manufacturers listed this property of the drug as an "adverse reaction" or "side effect."

Some other valid uses of marketed drugs may never reach the status of being an addition to the existing labeling. A manufacturer may never see any financial incentive for pursuing the approval to advertise a drug for an uncommon need.

Another negative motive could be even more persuasive. As

an example, certain urinary tract infections may be cured by a single dose of an appropriate drug. If a manufacturer's approved labeling recommended, say, a ten-day regimen, that manufacturer might not choose to supplicate the government for the privilege of reducing sales.

Fortunately, the myth about the authoritarian status of the package insert is disappearing. An honorable and welcomed statement by the FDA has confirmed what I have said for two decades about "approved uses" of drugs: there is no such thing. The FDA statement even endorsed the same alternate and correct phrasing that I coined: An "unapproved use" should not connote a disapproved use, but merely an "unlabeled use." Uses in the labeling are merely that: "labeled uses."

The House of Delegates of the American Medical Association, at its 1982 Interim Meeting, adopted a report that quoted in full the FDA statement on this subject. The report called for the publisher of the *Physician's Desk Reference (PDR)* (Medical Economics Company, Oradell, NJ) to include this statement in future editions. Accordingly, in the 1983 and 1984 editions of the *PDR*, a summary of the FDA statement regarding the use of approved drugs for purposes not in the labeling appears in the FOREWORD.

Yet, habit is tenacious. Every edition of the *AMA Drug Evaluations* (American Medical Association, Chicago), beginning in 1971, has contained a discussion noting that the FDA has no authority to approve (or disapprove) how a physician may use a marketed drug in his practice. Ironically, however, the fifth edition organizes its discussion of at least one drug in terms of "approved" and "unapproved uses." (That will be avoided in future editions—John C. Ballin, PhD, oral communication, 1984.)

Perhaps the year 1984 will see one reversal of George Orwell's prediction. I have often read well-meaning statements that something was the "drug of choice" or "well established" or "fully recognized" for treatment of a disease—combined with the caveat that such use was "not approved." Such reasoning is Orwellian doublethink: the process of considering two opposite concepts at the same time and believing both.

The doublethink under discussion resulted in part from my own naiveté 22 years ago, when I contributed some unfortunate language to a federal statute. That, however, is another matter: I apologized to the world as best I could in a previous publication.

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American Medical Association
Chicago

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