Laetrile: The Regulatory Challenge of an Unproven Remedy

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Synopsis

The controversy over Laetrile is nearly at an end, the worthlessness of the drug having been demonstrated beyond reasonable doubt. But the Laetrile experience raised important questions of public policy, some of which remain unresolved and all of which are worthy of examination. Could the Laetrile phenomenon have been prevented? Did the regulatory system perform as intended? Could there be another Laetrile?

The drug regulatory system administered under law by the Food and Drug Administration, like any other system carried out by Government in a free society, functions only so long and so far as the public will allow. Survey after survey shows that there is overwhelming support by the American people for the consumer health protection activities of the FDA. But, as the case of Laetrile proves, that support is neither absolute nor permanent. It can be selectively or totally withdrawn.

In those circumstances, it would seem that the best, perhaps the only, recourse in a free society is for those institutions and groups that have a responsibility for protection of the public health—institutions outside Government as well as within it—to identify, expose, and halt quackery that threatens the public health and welfare. Their weapons in such a struggle are facts as well as laws, credibility as well as confidence, compassion as well as the scientific method.

While the role of a drug regulatory agency may be limited, submission of scientific data as part of application for an investigational permit should be encouraged. If a promoter of an unproven remedy does not follow the usual channels to demonstrate safety and efficacy, consideration must be given by others to sponsoring such studies; however, concurrent regulatory (enforcement) and public education activities are to be encouraged and should not be seen as conflicting.

FEW SUBSTANCES IN THE HISTORY of drug regulation or of cancer quackery rival Laetrile in terms of the public clamor that accompanied its promotion and the public policy issues surrounding its appearance on the stage of unorthodox therapy. The controversy over Laetrile itself is nearly at an end, the worthlessness of the drug having been demonstrated beyond any reasonable doubt. Yet the Laetrile experience raised important public policy questions concerning the roles of medicine and science, of regulatory and research agencies, of lawmakers and courts of law, and of the drug regulatory system embodied in the Federal Food, Drug, and Cosmetic Act and carried out by the Food and Drug Administration. Some of those questions remain unresolved, and all are worthy of examination.

Background

Laetrile is one of a long and sad roster of substances purported to cure or alleviate cancer (*1*). The cancer "cure" developed by Harry Hoxsey before World War II victimized countless patients until State and Federal action brought about the end of this obvious fraud. By the 1950s, another unproven, secret cancer remedy, Krebiozen, achieved wide acclaim, partly because of the support of Dr. Andrew C. Ivy, who had been a distinguished teacher and investigator. Krebiozen was never approved for use in the United States, and by the beginning of the decade of the 1970s this substance, too, had faded from the scene. Its place was taken by Laetrile, quietly in the 1960s and early 1970s and then with great fanfare and public acclaim in the mid-to-late 1970s.

Laetrile is probably the most economically successful, and certainly the most controversial, cancer remedy promoted to the American public in this century or any other. While it is agreed that Laetrile is obtained from apricot kernels, there have been conflicting statements from the drug's proponents and others about precisely what it is. Proponents claim that Laetrile is l-mandelonitrile beta glucuronide, from which the name "Laetrile" is derived. Analysis of confiscated samples

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generally revealed amygdalin. Laetrile has been promoted to the public as amygdalin, vitamin B-17, a drug, and a food.

Nor is there uncertainty only about what Laetrile is; claims for its value in treating cancer (and for other medical uses) are equally varied and obscure. In the approximately 25 years that Laetrile has commanded more or less attention in this country, its advocates have claimed variously that the substance is effective in the cure or mitigation of cancer, that it prevents cancer, that it promotes the action of other cancer therapies, that it is an analgesic, and that it has value in the treatment of sickle cell anemia, parasitic disease, and hypertension. None of these properties of Laetrile has ever been demonstrated in a controlled investigation.

The spectacular "success" of Laetrile in the mid-to-late 1970s can probably be attributed to a variety of factors—some psychological, some political, and some undoubtedly reflecting the skill and, mostly, resourcefulness of its promoters. Like most other "quack" remedies for cancer, Laetrile benefited from the fears and anxieties of patients and their families, which are most intense immediately following the diagnosis of a highly fatal and often severely painful disease.

The promise of a cure, or even of a palliation not available from so-called orthodox or traditional medicine, obviously is enormously attractive to cancer patients. Their fears and anxieties were capitalized on by Laetrile promoters, who alleged that organized medicine, in collusion with the pharmaceutical industry, the American Cancer Society, and the Government, was engaged in a conspiracy to prevent Laetrile from occupying its rightful place in health care. Thus, cancer patients were encouraged to feel that, by using Laetrile, not only were they availing themselves of a safe and effective remedy, but also they were somehow collaborating in an effort to "show up" the establishment—a powerful incentive, especially for those who philosophically distrust any Government regulation or those with special credentials. This was particularly true for patients who felt they were "cured" by Laetrile after being told by their personal physicians that they only had weeks or, at most, a few months to live. Also, promoters and patients to varying extents cherished the "illicit" nature of their actions and viewed them as acts of defiance.

Another rallying cry on which the advocates of Laetrile capitalized was "freedom of choice," the notion that cancer patients and those who care for them should be free to obtain and use Laetrile whether or not it had received official sanction by the Food and Drug Administration or approval by the medical and scientific community. As the argument ran, if a patient had not been helped by conventional treatment or elected not to have it, that patient and the physician should be free to use Laetrile because the drug *might* prove beneficial and, in any case, was *harmless*. Even though there was no evidence for these assertions, they were widely reported and—surprisingly to government officials, medical leaders, and practitioners—not infrequently championed in the public press (*2*). These arguments powerfully influenced public opinion in general and State legislative bodies in particular. They proved most difficult to deal with, since many members of the public were, if not in agreement with, at least sympathetic to, these views.

At the height of Laetrile's popularity, "black market" traffic was the most common source of the drug. A cancer patient (Rutherford) brought suit against the United States over access to Laetrile. The U.S. District Court for the Western District of Oklahoma, in a ruling handed down in spring 1977 (*3*), enjoined the Food and Drug Administration from impeding or preventing the importation and interstate transportation of Laetrile for use by a "terminally ill" cancer patient, providing a practicing physician submitted an affidavit attesting to, among other things, the "terminal" nature of the person's illness.

On appeal, the Tenth Circuit Court narrowed the ruling somewhat. The circuit court ruled that Laetrile, in the injectable form only, could enter the country and move in interstate commerce for the personal use of patients certified by a physician, in an affidavit, to be "terminally ill." Affidavits signed by a physician were widely used in the late 1970s.

On March 2, 1984, District Court Judge Luther Bohanan dismissed the complaint in this case and dissolved all injunctions against the United States. The "affidavit" system authorized in 1977 is no longer in effect. The Government may once again enforce the statute against Laetrile as an unapproved new drug.

The judicially sanctioned distribution system and the black market (conducted in violation of the court order) together provided a "safety valve" that allowed easy availability of Laetrile and facilitated its widespread use and popularization.

At the height of the Laetrile controversy, legislation of one kind or another was introduced in the majority of

States to permit and protect use of Laetrile by licensed physicians, despite the fact that it remained a federally unapproved drug. By October 1982, 24 States had enacted pro-Laetrile legislation. The laws, adopted mostly between 1977 and 1979, varied in their specific provisions. Some prohibited disciplinary action against physicians who prescribe, dispense, or administer Laetrile. Others contained provisions authorizing the manufacture of Laetrile, limiting its use to cancer patients only, requiring informed consent, or ruling that Laetrile is not a drug and thus is not subject to drug regulations (*4*).

The extent of this legislative activity is testimony to the effectiveness of the campaign to promote Laetrile. "Model legislation," developed by proponents, was disseminated to each State, and lobbying at the State level was intensive. Teams of Laetrile proponent "experts," including at least one "scientist," were dispatched to State legislatures to testify on behalf of the bills.

Laetrile and the FDA Regulatory Process

Under the American system of drug regulation, a drug may not be marketed in interstate commerce (or imported for marketing in the United States) until it has been approved by the Food and Drug Administration. FDA approval is predicated on proof of safety and effectiveness established through adequate and well-controlled double-blind clinical trials conducted by qualified experts.

Clinical trials of an investigational drug cannot begin until FDA has granted a Notice of Claimed Exemption for an Investigational New Drug (IND). Such an application for Laetrile was submitted in 1970. It was not approved, however, because uncertainty about the identity of the drug made questionable the results that might be obtained in clinical trials.

Even earlier (1962), when a New Drug Application (NDA)—that is, an application for approval to market Laetrile—was submitted to FDA, the claims for efficacy in the application were in conflict with those made by promoters of Laetrile. The NDA referred to Laetrile as a cancer palliative; however, literature promoting Laetrile at the time stated that "Laetrile does not palliate. It acts chemically to kill the cancer cell selectively."

During the period of intense public and legislative interest in Laetrile, organizations whose members include experts in cancer drug evaluation—the American Cancer Society, the American Medical Association, and the Committee on Neoplastic Diseases of the American Academy of Pediatrics—as well as an overwhelming majority of the nation's most eminent and well-qualified experts in the field did not recognize Laetrile as effective. Proponents of Laetrile insisted that these organizations were part of an industry-Government-orthodox medicine conspiracy. In response, they identified their own medical and scientific "experts" and had them "testify" before State legislatures.

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There was little objective scientific evidence available to convince State legislators and the public that the drug was ineffective. No results of rigorous, controlled studies had been published. Furthermore, because of variability in the prescribed treatment and questions (noted earlier) about the identity of the administered drug itself, there was little opportunity for scientific critique of uncontrolled clinical experience.

Unfortunately, the lack of scientific evidence about the drug and the views of responsible, orthodox spokespersons on Laetrile issues were viewed as of no consequence by State legislators and the public. Consumer groups were notably and surprisingly silent on this major public health issue.

The other Federal agency most directly involved in the Laetrile controversy was the National Cancer Institute of the National Institutes of Health. As the principal cancer research organization of the Federal Government, NCI was, like FDA, under considerable public pressure, generated by Laetrile's promoters, to sanction the drug and affirm the claims made for it. The Institute was also under pressure from other quarters (for example, State legislators and segments of orthodox medicine) to agree to undertake clinical studies to establish whether or not the substance was effective.

Laetrile had been repeatedly screened by NCI against a broad spectrum of animal-tumor systems. Most of these tests were completely negative. Others showed only marginal levels of activity that could not be reproduced. The lack of a positive effect in test animals was considered to be of major importance, since a clear showing of success in animals traditionally served as a precursor to clinical testing.

Questions were also raised about the drug's safety, particularly with regard to the oral dosage form. Amygdalin, taken by mouth, is broken down in the gastrointestinal tract, releasing cyanide. Studies had demonstrated that, in sufficiently large doses, oral amygdalin

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would kill experimental animals by cyanide poisoning. Human deaths due to amygdalin overdose had been documented, involving persons who had ingested ground apricot pits. Oral amygdalin in the form of Laetrile was alleged by its promoters to be safe, but during the height of the controversy two patients died—an infant who had taken Laetrile tablets and a young woman who drank the parenteral formulation manufactured in Mexico. All evidence of safety and effectiveness of the drug in humans was testimonial or anecdotal and usually had been provided either directly or indirectly by Laetrile promoters.

Although it was generally believed at the time that a clinical trial was at least feasible, there were strong ethical objections in some quarters to the prospect of offering cancer patients a drug for which no anticancer activity had been demonstrated, either in animals or in man. In addition, many persons in and out of government objected to spending public funds on what they believed to be a worthless nostrum. The use of Laetrile, however, continued to be widespread and was a public issue with strong emotional overtones. To perform a clinical trial without objective preclinical evidence of efficacy would be unusual, but FDA regulations did not preclude such a trial.

Retrospective case review. After much discussion, the NCI in 1978 determined that before a decision was made to conduct a clinical trial, a retrospective review of case records should seek to establish whether bona fide responses to Laetrile had occurred. On the recommendation of a task force of government epidemiologists, oncologists, and regulatory officials, reports of cases thought to have shown objective benefit from Laetrile were solicited by mail request to 385,000 physicians and 70,000 other health professionals, and by direct contact with pro-Laetrile groups.

Although it was estimated at the time that 70,000 Americans had used Laetrile, only 93 cases were submitted for evaluation, of which 68 included histologic proof of preexisting cancer and objective evidence of tumor reduction not attributable to any known cancer treatment other than Laetrile. A panel of 12 oncologists conducted the blind review of 160 courses of treatment: 68 Laetrile, 68 chemotherapy, and 24 "no treatment." The panel judged six Laetrile courses to have produced responses, two complete and four partial (*5*). These results, however, allowed no definitive conclusion supporting the anticancer activity of Laetrile. The public remained unsatisfied and confused.

Clinical trial. Laetrile continued to be a dominant unresolved problem for American medicine and the drug regulatory system. Pressure on State legislatures to approve the drug continued to mount. Shortly after the results of the retrospective review were published, NCI decided to sponsor a clinical trial of Laetrile.

Reasons for pursuing a clinical trial varied. A compelling reason for many was that while the Laetrile issue was fraught with ethical and legal concerns, basic humanitarian considerations required a resolution of the issue. Thousands of cancer patients were being exposed to a drug of no known effectiveness, dubious safety, and poor manufacturing quality. It was hoped that such a scientific trial would be convincing to the great majority of thoughtful Americans, to the mass media, and to State legislators and others who, in order to make Laetrile available, were willing to accept on faith the word of Laetrile promoters. Moreover, the legalization of Laetrile on a State-by-State basis was undermining the entire drug approval process.

The clinical trial was conducted with NCI support by a multi-institutional team led by a distinguished cancer researcher at the Mayo Clinic. Although the study could be neither controlled and randomized nor blinded, the lack of concurrent controls was partially offset by the fact that all patients were in the advanced stages of a disease known to be almost uniformly and rapidly fatal. Ethical objectives were minimized by requiring fully informed consent from all patients.

In anticipation of criticism by Laetrile advocates, only patients in otherwise good general condition were selected. Fully a third had never received chemotherapy or radiotherapy and therefore would be considered good candidates for Laetrile treatment. (Laetrile "failures" had been ascribed by proponents of the drug to the fact that cancer patients had been weakened by prior orthodox therapy—"cutting," "burning," and "poisoning.")

"Metabolic" therapy, using Laetrile combined with vitamins and a natural diet—a regimen advocated by many Laetrile proponents—was incorporated in the study. As a safety precaution, blood levels of cyanide were monitored to ensure that potentially toxic levels were not reached.

The final report of the clinical trial (*6*) made clear that in the group of 178 patients with a variety of types of advanced cancer, Laetrile produced no discernible bene-

fit, as measured by decreased tumor size or prolongation of survival, compared with historical controls. More than three-quarters of the patients had died of their disease by the end of the study, and their survival times seemed fully consistent with those of patients receiving no treatment. Moreover, several patients had symptoms suggestive of cyanide toxicity or blood cyanide levels that approached the toxic range (or both). Thus, the study demonstrated that Laetrile could not be considered either safe or effective.

The study results received widespread publicity, and those who had pressed for a scientific study as a means of dealing with public concern and with pressure from various responsible, and not-so-responsible, quarters were pleased. However, concurrently with these results, Laetrile as a "fad" already seemed to be fading.

FDA educational activities. In addition to a variety of enforcement actions, including seizures and prosecutions, FDA took a number of steps to educate and warn the public, health professionals, and State legislators about the direct and indirect health hazards of Laetrile use. The vehicles included specially prepared leaflets for consumers; articles in the FDA Drug Bulletin (*7–9*), which is sent to more than 1 million health professionals; testimony presented at State legislatures; and a special, widely disseminated Public Warning—only the second time in FDA's history that such a warning was issued.

Policy Issues

As a medical and scientific controversy, the case of Laetrile has pretty much been closed for several years. It is no longer in the news or a major subject of debate in State or Federal legislatures. As a public policy issue, however, the Laetrile affair raised questions that continue to command attention. Could the flagrant promotion of this unproven remedy have been avoided? Did the regulatory system perform as it was intended to, or did it bend nearly to the breaking point in the face of powerfully effective promotion and intense public pressure? And perhaps the most salient policy question: Can the same thing happen again?

1. Could the Laetrile phenomenon have been prevented?

Laetrile, an unapproved drug, was moving illegally in interstate commerce (and being imported) in direct violation of the Federal Food, Drug, and Cosmetic Act. Those associated with this traffic at its inception, when Laetrile was a relatively local issue, could have been prosecuted vigorously. We can only speculate whether convictions would have been obtained and upheld.

State licensing bodies had the authority to punish physicians who prescribed or administered Laetrile and pharmacists who dispensed it. Only after State laws were enacted and a Federal district court established the "affidavit system" for Laetrile was the use of this substance by health professionals able to don the cloak of "legality."

Leaving aside the major question of the availability of manpower and other resources to pursue vigorous enforcement action against Laetrile and its proponents, there is no doubt that U.S. law provided a means to attempt to halt traffic in Laetrile soon after it began.

2. Did the regulatory system perform as intended?

FDA initially did not approve an application to conduct clinical investigations of Laetrile because the sponsors were unable to supply the kind and quality of data required under FDA regulations. Not only was this appropriate, but for FDA to have done otherwise would have been illegal.

Laetrile promoters then followed an extralegal course rather than attempting to supply the additional requisite information. The fact that Laetrile continued to be traded and promoted without approval is evidence that the system did indeed bend, if not break, in the presence of public pressure fanned by skillful promotion. Because sufficiently early and vigorous enforcement action was not carried out, such action at a later date was more difficult and could not in itself effectively deal with public policy concerns.

The passage of State laws and the establishment, by the court, of the "affidavit system" would seem to imply that dissatisfaction with the regulatory system was sufficiently great to override that system, in effect, when it was felt to be in conflict with the public will. However, the collection of preclinical and clinical information by a nonregulatory agency (the National Cancer Institute) and its subsequent funding of clinical trials meant that the regulatory procedures for clinical testing were eventually followed. Without NCI's retrospective case review, developed by epidemiologists, the definitive trial would not have been performed.

Publication of the report of the NCI study satisfied the general public, the press, and, by inference, State legislatures, which have enacted no new laws permitting the use of Laetrile.

3. Could there be another Laetrile?

As one who was deeply involved in FDA's role in the Laetrile matter, who testified before State legislative bodies that were considering pro-Laetrile legislation, and who helped orchestrate public and professional education

efforts to warn of the hazard of Laetrile use, I would prefer to be able to say that we will never again see a medical fraud of this magnitude perpetrated on the American public. Unfortunately, I cannot.

The drug regulatory system administered under law by the FDA, like any other system carried out by Government in a free society, functions only so long and so far as the public will allow. Survey after survey shows that there is overwhelming support by the American people for the consumer health protection activities of the FDA. But, as the case of Laetrile proves, that support is neither absolute nor permanent. It can be selectively or totally withdrawn.

In those circumstances, it would seem that the best, perhaps the only, recourse in a free society is for those institutions and groups that have a responsibility for protection of the public health—institutions outside Government as well as within it—to identify, expose, and halt quackery that threatens the public health and welfare. Their weapons in such a struggle are facts as well as laws, credibility as well as confidence, compassion as well as the scientific method. Arrayed against them are cunning deception on the part of the promoters of quackery and the fear and ignorance of desperate people, coupled often with a conviction that the "establishment" is bent on crushing those who oppose it.

While the role of a drug regulatory agency may be limited, submission of scientific data (as part of an application for an investigational permit) should be encouraged. If a promoter of an unproven remedy does not follow the usual channels to demonstrate safety and efficacy, consideration must be given by others to sponsoring such studies; however, concurrent regulatory (enforcement) and public education activities are to be encouraged and should not be seen as conflicting. It is noteworthy that at the same time FDA was permitting a clinical trial of Laetrile, it issued a nationwide Public Warning about the use of Laetrile. Both actions were viewed as responsible, salutary, and not inconsistent.

The challenge of quackery is formidable and seemingly unending. Experience tells us that a successor to Laetrile is almost surely on the horizon, if not in our midst. It is to be hoped that those of us in medicine and science, in and out of Government, will be better able to meet the next challenge of quackery.

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The Story of 'Joseph M.'—Mass Media Against 'Medical Bureaucracy'

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THE PHENOMENON OF QUACK MEDICINE in Western culture presents a special problem for medical authorities because of its increasing popularity among the public. Although legal procedures provide appropriate mechanisms to enforce routines for the regulation of new drugs, major difficulties are repeatedly encountered by the authorities in suppressing the promotion of quack medicine and calming public dissent against such action by the