

A CLINICAL TRIAL OF AMYGDALIN (LAETRILE) IN THE TREATMENT OF HUMAN CANCER

CHARLES G. MOERTEL, M.D., THOMAS R. FLEMING, PH.D., JOSEPH RUBIN, M.D., LARRY K. KVOLS, M.D., GREGORY SARNA, M.D., ROBERT KOCH, M.D., VIOLANTE E. CURRIE, M.D., CHARLES W. YOUNG, M.D., STEPHEN E. JONES, M.D., AND J. PAUL DAVIGNON, PH.D.

Abstract One hundred seventy-eight patients with cancer were treated with amygdalin (Laetrile) plus a "metabolic therapy" program consisting of diet, enzymes, and vitamins. The great majority of these patients were in good general condition before treatment. None was totally disabled or in preterminal condition. One third had not received any previous chemotherapy. The pharmaceutical preparations of amygdalin, the dosage, and the schedule were representative of past and present Laetrile practice. No substantive benefit was observed in terms of cure, im-

provement, or stabilization of cancer, improvement of symptoms related to cancer, or extension of life span. The hazards of amygdalin therapy were evidenced in several patients by symptoms of cyanide toxicity or by blood cyanide levels approaching the lethal range. Patients exposed to this agent should be instructed about the danger of cyanide poisoning, and their blood cyanide levels should be carefully monitored. Amygdalin (Laetrile) is a toxic drug that is not effective as a cancer treatment. (N Engl J Med. 1982; 306:201-6.)

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AMYGDALIN has had many centuries of use for medical purposes, perhaps first documented by Dioscorides of Anazarbos shortly after the birth of Christ.¹ Usually administered in the form of bitter almonds, it was a common ingredient of herbal prescriptions for a variety of illnesses, and by liberal interpretation of ancient pharmacopeias one might conclude that it was used for the treatment of cancer.² With the advent of the science of medicine, amygdalin, along with most other herbal agents, was abandoned for clinical therapy. In 1952, however, it was revived by Ernest Krebs, Jr., who registered it with the United States Patent Office under the trade name of Laetrile, to be used for the treatment of "disorders from intestinal fermentation" — i.e., cancer. In the ensuing years, Laetrile completely eclipsed any other unorthodox therapy ever used for any disease in our time. It has been legalized by 27 of our 50 states, and it is also legal for use nationwide under a federal court order, which, although it has been reviewed by the United States Supreme Court, has not been reversed. That these phenomena were not just responses to vocal minorities was evidenced by a nationwide Harris poll showing that the American public favored legalization by an amazing 30 per cent margin.

In response to these public pressures, the National Cancer Institute elected to evaluate amygdalin by soliciting practitioners who use Laetrile to mail in their best results. Sixty-eight case reports were received and reviewed by several cancer experts, who concluded, "The panel judged six Laetrile courses to have produced a response. . . ."³ Whereas such evidence can be challenged, of greater concern is the fact that Laetrile has remained a major and unresolved public-health problem for over a quarter of a century, involving many thousands of cancer patients in direct

treatment and causing serious doubts and concerns in many more. In addition, a valid scientific question could be raised if this widespread and continued public acceptance possibly reflected true therapeutic activity, animal-model data notwithstanding. These humanitarian and scientific issues were the primary considerations that led to National Cancer Institute sponsorship and Food and Drug Administration approval of a clinical trial of amygdalin for the treatment of advanced cancer. This report provides a documentation of that trial.

METHODS

Patient Selection

All patients selected had histologically proved cancer for which no standard treatment was known to be curative or to extend life expectancy. All patients had had no surgery, radiation therapy, or chemotherapy for at least one month. Special emphasis was placed on selecting patients in good general condition and particularly on selecting a substantial proportion of patients who had had no previous exposure to cytotoxic drugs. All patients were ambulatory and able to maintain oral nutrition. Patients who were totally disabled and bedridden were ineligible for study. Each patient had either a tumor area that could be measured in two dimensions or malignant hepatomegaly with a clearly defined liver edge extending at least 5 cm below the costal margin. Lesions demonstrable by radioisotope liver scan or by computerized tomographic scan were accepted if they measured at least 5 cm in diameter. Patients in whom the tumor size could only be estimated (e.g., those with extrarectal or pelvic masses) and patients with only osseous lesions were not eligible for study. Laboratory abnormalities, effusions, or other secondary physiologic effects of malignant disease were also not accepted as indicators of an objective response.

Treatment Methods

The amygdalin (n-mandelonitrile- β -D-glucosido-6- β -D-glucoside) was supplied by the Pharmaceutical Resources Branch of the National Cancer Institute as a naturally derived substance prepared from apricot pits. So that the preparations would correspond with the products distributed by the major Mexican supplier, an RS-epimer racemic mixture (labeled RS-amygdalin) was used for intravenous therapy, and the R epimer (labeled R-amygdalin) was used for oral treatment.⁴ Amygdalin was supplied for intravenous use in vials containing 3 g of lyophilized RS-amygdalin and for oral use in tablets containing 0.5 g of R-amygdalin. The identity and labeled strength of the oral and intravenous preparations of amygdalin supplied by the National Cancer Institute were established by a variety of analytic techniques, including infrared spectroscopy, nu-

From the Department of Oncology, Mayo Clinic; the UCLA Johnson Comprehensive Cancer Center, Los Angeles; the Memorial Sloan-Kettering Cancer Center, New York; the University of Arizona Cancer Center, Tucson; and the Pharmaceutical Resources Branch, National Cancer Institute, Bethesda, Md. Address reprint requests to Dr. Moertel at the Mayo Comprehensive Cancer Center, Rochester, MN 55905.

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clear magnetic resonance, high-pressure liquid chromatography, thin-layer chromatography, gas chromatography, and optical rotation. The parenteral product was evaluated for sterility and absence of pyrogens in two laboratories. The tablet and parenteral formulations of amygdalin were found to be of high purity and to contain the appropriate concentrations compatible with the labeling statements. In addition to these quality-control measures taken by the National Cancer Institute as it supplied the drug, the Mayo Clinic also studied each drug lot independently as it arrived for clinical use. By multiple means of analysis, it was determined that the material was indeed pure amygdalin at essentially 100 per cent of labeled strength and that on enzyme breakdown it yielded the expected quantities of both benzaldehyde and cyanide.

The routes, dosage, and schedule of amygdalin administration were chosen to be representative of current Laetrile practice. This information was determined from the writings of some leading practitioners of Laetrile therapy^{8,9} and from direct consultation with others. Amygdalin was administered in 21 daily intravenous injections at a daily dose of 4.5 g per square meter of body-surface area. The intravenous course was administered either on consecutive days (121 eligible patients) or during weekdays only (57 patients). Afterward, oral maintenance therapy was initiated at a dose of 0.5 g given three times a day. We had some difficulty in obtaining consensus among the major proponents of Laetrile on the accompanying so-called "metabolic therapy" program. Some objected to any efforts in this regard, saying that they were unnecessary and might distort the effects of amygdalin itself. Others, however, urged us to include megadoses of numerous vitamins as well as an array of unusual ancillary treatments. We elected to compromise between these extremes, using very high but not massive doses of vitamins. We also added the usual pancreatic enzymes. To meet the anticipated objections of some Laetrile practitioners that we had not used high enough doses of amygdalin or of vitamins, we also treated a smaller group of patients with an extremely high-dose program. The details of both our standard program and our high-dose program are listed in Table 1.

In addition, all patients in both dosage groups were placed on a diet identical to the one currently recommended by most Laetrile practitioners. This involved restriction of eggs, dairy products, meats, refined-flour products, refined white sugar, common table salt, sugar-coated cereals, coffee, tea, colas, and all alcoholic beverages. Foods that were encouraged included fresh fruits and vegetables, whole-grain breads, whole-grain cereals, seeds, nuts, raisins, dates, and figs.

Clinical Methods

All patients were fully informed about the experimental and unorthodox nature of the treatment program as well as any possible alternative treatment available to them. A signed form giving informed consent, approved by the Human Subjects Committee at each of the four participating centers, was obtained from each patient. Before therapy, patients gave a pertinent medical history and had a complete physical examination as well as a chest x-ray film, blood counts, and blood-chemistry determinations. This evaluation was repeated after the intravenous course, after the first two weeks of oral treatment, and every five weeks thereafter. In addition,

whole-blood cyanide levels were determined at the completion of intravenous treatment, 48 hours after the initiation of oral treatment, and at every subsequent reevaluation. These determinations were made two hours after the first morning dose of oral amygdalin, when the maximum elevation in cyanide was anticipated.¹⁰ If the morning blood cyanide level was greater than 2 µg per milliliter but less than 3 µg per milliliter 48 hours after the initiation of oral amygdalin therapy, daily blood levels of cyanide were measured until they had stabilized without symptoms suggestive of toxicity. If the blood cyanide level was found to be 3 µg per milliliter or greater at any time, amygdalin therapy was permanently discontinued.

Therapy was continued in all patients at least until they had definite evidence of progressive malignant disease or until severe clinical deterioration precluded further treatment and observation.

To assess the effects of therapy, we performed tumor measurements in each patient before treatment and at every evaluation thereafter. Body weight, performance status, and symptomatic status were also determined. Objective results of therapy were recorded according to the following classifications. For an objective response, three criteria had to be met: (1) a 50 per cent decrease in the product of the longest perpendicular diameters of the most clearly measurable area of malignant disease chosen before treatment as a primary indicator lesion (or, if malignant hepatomegaly was employed as a primary indicator, a decrease of at least 30 per cent in the sum of measurements below the xiphoid process and both costal margins at the midclavicular lines); (2) no increase in the size of other areas of malignant disease; and (3) no appearance of new areas of malignant disease. For an objectively stable condition, two criteria had to be met: (1) insufficient regression of indicator lesions to meet the criteria for objective response or an increase of less than 25 per cent in the size of indicator lesions, and (2) no appearance of new areas of malignant disease. For objective progression, any one of three criteria had to be met: (1) an increase of more than 25 per cent in any indicator lesion relative to the baseline measurement of that lesion; (2) the appearance of new areas of malignant disease; or (3) severe clinical deterioration precluding further therapy and observation.

In short, the methods of this trial were entirely comparable with those employed in studies of any new agent being developed and tested for cancer treatment through more traditional channels. They were designed to provide the maximum opportunity for amygdalin to display therapeutic activity if such potential existed.

RESULTS

A total of 179 patients were entered into the study. These included six patients described earlier in our study of the pharmacology and toxicology of amygdalin.¹⁰ One hundred sixty-five patients were treated with the standard-dose regimen, and 14 with the high-dose regimen. One patient was declared ineligible because of inadequate histologic confirmation of malignant disease before therapy. A total of 178 eligible patients were therefore given therapy and could be followed for survival. Three patients were considered completely unevaluable for objective response: two because they died suddenly of causes not directly related to cancer within three days of the beginning of therapy, and one because he left the program after only six intravenous injections, claiming that his pain had not been relieved. Four patients who had objectively stable conditions on early evaluations could not be evaluated up to the time of progression: two refused to continue therapy at five and six weeks because they had had no improvement in pretreatment symptoms, one withdrew from the program at three weeks because of family problems, and one had

Table 1. Amygdalin and "Metabolic Therapy" Regimens.

AGENT	STANDARD DOSE	HIGH DOSE
Amygdalin		
Intravenous course	4.5 g/m ² of body-surface area/day × 21 days	7 g/m ² /day × 21 days
Oral maintenance	0.5 g 3 times daily	0.5 g 4 times daily
Vitamins		
A	25,000 U/day	100,000 U/day
C	2 g/day	10 g/day
E	400 U/day	1200 U/day
B complex and minerals	1 capsule/day	1 capsule/day
Pancreatic enzymes (Vinkase)	12 tablets/day	12 tablets/day

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therapy discontinued at five weeks according to the protocol because blood cyanide levels during the oral regimen exceeded 3.0 µg per milliliter. At least partial therapeutic observations could therefore be made in 175 patients, and the clinical courses of 171 patients were fully documented to the time of measurable progression of disease.

The characteristics of all eligible patients are listed in Table 2. Tumor types included a preponderance of colorectal, lung, and breast cancers with the standard-dose regimen. All patients chosen for the high-dose regimen had colorectal cancer. It is particularly noteworthy that over one third of all patients had received no prior chemotherapy. In addition, 71 per cent of the patients had good performance status — that is, they were capable of working full or part time.

Toxicity

Data on the possible toxicity of intravenous and oral amygdalin are shown in Table 3. Most of these reactions were either mild and transient or accompanied by advancing cancer and possibly not drug-related. Four patients had dermatitis, which was probably related to the treatment. In addition, a few patients receiving oral amygdalin had a syndrome of headache, dizziness, mental obtundation, nausea, and vomiting. These symptoms subsided promptly when

Table 2. Characteristics of Eligible Patients.

CHARACTERISTIC	no. of patients		
	STANDARD-DOSE REGIMEN	HIGH-DOSE REGIMEN	ALL PATIENTS
Sex			
Male	92	8	100
Female	72	6	78
Age (yr)			
Median	57	60	57
Range	18-84	39-73	18-84
Primary tumor			
Colorectal*	44	14	58
Lung†	30	—	30
Breast*	21	—	21
Melanoma	15	—	15
Sarcoma	10	—	10
Pancreas*	8	—	8
Stomach*	7	—	7
Kidney*	6	—	6
Lymphoma	5	—	5
Ovary*	4	—	4
Other (1 or 2 each)	14	—	14
Prior radiation therapy ‡			
Yes	72	0	72
No	92	14	106 (60)
Prior chemotherapy ‡			
Yes	109	9	118
No	55	5	60 (34)
Performance status §§			
0-1	116	11	127 (71)
2-3	48	3	51
Institution			
University of Arizona	19	—	19
UCLA	40	—	40
Mayo Clinic	82	14	96
New York Memorial	23	—	23

*Adenocarcinoma. †Non-small-cell carcinoma.
 ‡Figures in parentheses denote percentages.
 §§Eastern Cooperative Oncology Group score: 0, fully active; to 4, totally disabled.

Table 3. Toxicity of Amygdalin Therapy.

TOXIC REACTION	ROUTE	
	INTRAVENOUS % of 178 patients	ORAL % of 137 p
Nausea	31	30
Vomiting	25	17
Headache	7	8
Dizziness	7	10
Mental obtundation	4	5
Dermatitis	2	2

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oral amygdalin was discontinued. They were sometimes (but not always) associated with relatively high levels of blood cyanide. One patient receiving high-dose regimen had bouts of tachycardia and dyspnea two hours after her morning dose of amygdalin. Her blood cyanide level during one of these episodes was 2.9 µg per milliliter. The symptoms stopped when amygdalin was discontinued. Her dose was then reduced from four to three tablets daily. Her symptoms did not recur, and morning blood cyanide levels remained lower than 2 µg per milliliter.

Figure 1 shows the mean and the spread between the fifth and the 95th percentiles of blood cyanide levels. After intravenous therapy, these levels were either negligible or not detectable. There was a definite elevation after oral administration. Consistent with our earlier pharmacologic study, these levels tended to increase over the first 48 hours and then to stabilize. Table 4 shows the maximum cyanide levels observed in any patient receiving either the standard-dose regimen or the high-dose regimen. Eleven patients had levels exceeding 2 µg per milliliter, and it is noteworthy that three of these 11 were receiving the high-dose program. The highest level observed was just under 4 µg per milliliter.

Five patients had evidence of the narrow range of safety of this therapy with regard to cyanide intoxication. One patient, described earlier in our pharmacologic study,¹⁰ had typical symptoms of cyanide toxicity associated with rapidly rising blood cyanide when she took large amounts of raw almonds in association with the amygdalin. Almonds are known to be a rich source of β-glucosidase, which causes breakdown of amygdalin and release of cyanide. A second patient took two amygdalin tablets in the morning to make up for one that she had forgotten the night before. This patient had transient and mild mental obtundation in association with a peak cyanide level of 3.5 µg per milliliter, as compared with 0.6 µg per milliliter when she was taking amygdalin in the prescribed single-tablet doses. She recovered from this episode rapidly and had no recurrence on resuming amygdalin therapy. A third patient took two amygdalin tablets half an hour apart because she slept late one morning. This patient also had symptoms suggestive of cyanide poisoning, with nausea, vomiting, headache, and mental obtundation. These symptoms subsided spon-

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sponse was real, a response rate of less than 1 per cent certainly can not be regarded as salutary. The fact that amygdalin therapy did not slow the advance of malignant disease or induce "stabilization" is clearly evidenced by the facts that more than half these patients had measurable tumor progression when they terminated the intravenous induction therapy and that over 90 per cent had progression by three months. The minimal rates of improvement in symptoms, performance status, and body weight are within the range that could be anticipated with placebo treatment. Patients died rapidly, with a median survival of only 4.8 months. It must be concluded that amygdalin (Laetrile) in combination with high doses of vitamins, pancreatic enzymes, and a diet of the type commonly employed by "metabolic therapists" is of no substantive value in the treatment of cancer. Further investigation or clinical use of such therapy is not justified.

In the design and performance of this study, we considered it important to ensure that our methods were representative of those by which amygdalin has been employed, and that the maximum opportunity to allow these methods to produce a favorable therapeutic effect was provided. Particular attention was paid to the nature of the amygdalin tested, the dose and schedule of amygdalin, the concurrent "metabolic therapy," and the selection of patients. With regard to the type of amygdalin, Laetrile as originally de-

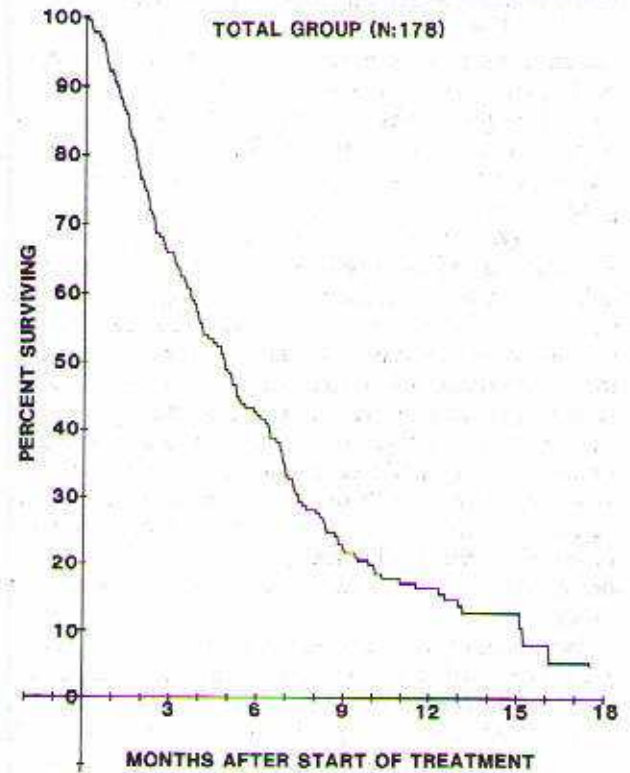


Figure 3. Patients' Survival Measured from the Start of Amygdalin Treatment.

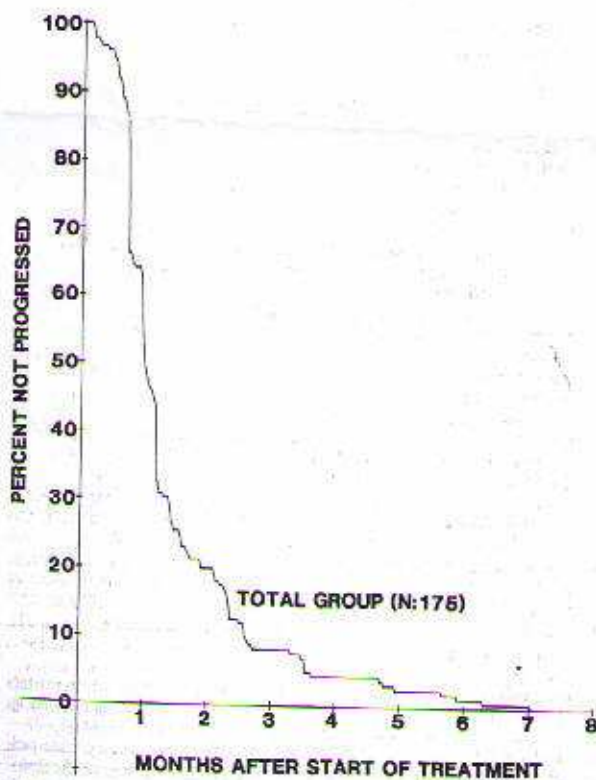


Figure 2. Interval from the Start of Amygdalin Treatment to Measured Objective Progression of Malignant Disease.

veloped and as used over the past three decades has been the natural substance derived from apricot pits. Amygdalin has been a known chemical entity for well over 100 years, and its extraction from natural sources is not technically challenging. The amygdalin used in this study was a natural product structurally identical to that made and distributed by the major Mexican manufacturer and distributor of Laetrile.

The dosage and schedules of amygdalin used by practitioners of Laetrile therapy over the years have varied considerably. It would be impossible to duplicate and study each of these regimens, and there is no scientific rationale for choosing among them. For the purpose of this trial, however, we did consider it necessary to use methods that were fully representative of those employed, recommended, and described in published articles by leading proponents of Laetrile. Our doses of both intravenous and oral amygdalin were entirely typical of Laetrile practice today,⁵ and they were substantially higher than those originally employed, for which favorable results were claimed.⁶ From a comparative standpoint, the doses that we administered probably matched the higher ranges of actual doses administered by Laetrile practitioners, since assays of the product that they used have consistently shown an amygdalin content well below the amount indicated on the label.⁴

The schedule of 21 intravenous treatments followed by oral maintenance is one that has been employed for

many years by American Laetrile practitioners and by Mexican Laetrile clinics. It is based on the published recommendations of Ernest Krebs, Jr., the developer of Laetrile, who stated that intravenous treatment should be given over periods ranging from 10 to 31 days.⁵ The precise dosage schedule that we employed was that advocated by two of the foremost Laetrile practitioners.^{7,8}

Although the primary purpose of this study was to evaluate amygdalin itself, we did consider it appropriate to incorporate the diet, vitamins, and enzymes that have become part of recent Laetrile regimens. It should be pointed out, however, that the initial claims for effectiveness of Laetrile were made when the substance was used without any accompanying "metabolic therapy" program. To answer possible objections of megavitamin enthusiasts, we also treated a group of patients with one of the most common malignant diseases, colorectal cancer, using massive doses of vitamins. This group of patients did not fare better than those treated with the more moderate program.

With regard to patient selection, we did not think it would be justifiable to enter patients for whom standard therapy is known to hold a curative potential or to extend life expectancy. Excluding such patients seemed entirely appropriate, since the overwhelming majority of patients who have sought Laetrile therapy in the past, and for whom claims of effectiveness have been made, were patients in whom standard treatment had failed.⁹ We did believe, however, that amygdalin should be tested in patients with good general and nutritional status. Certainly, with regard to testing any antineoplastic drug, the excellent performance status of our patients and the large proportion with no previous exposure to chemotherapy must be considered very favorable.

An important point that must be made concerns the hazards of amygdalin therapy. Laetrile has been advertised to the public, the state legislatures, and the courts as nontoxic. The evidence for this lack of toxicity, however, was no better than the evidence for a favorable therapeutic effect. Although there were no drug-related fatalities under the conditions of this trial, our results demonstrate that oral Laetrile is a toxic drug. Several patients had symptomatic toxicity or high levels of blood cyanide or both; the cyanide approached levels known to kill animals¹¹ and reached levels that have been reported in fatal cases in poisoning in human beings.¹² Relatively minor alterations in the treatment program or infractions of the instructions on drug intake, which patients are prone to commit, elevated blood cyanide to dangerous concentrations. Simultaneous consumption of food with a high β -glucosidase content produced symptomatic cyanide toxicity. Many Laetrile practitioners today are encouraging patients to reproduce these hazardous conditions, e.g., to take two tablets of Laetrile in a single dose or to eat large amounts of raw almonds concurrently with therapy. Special precautions to avoid fatal

drug reactions were a vital component of this study. These included meticulous instruction to the patient, monitoring of blood cyanide levels as the patient was first being given oral therapy and periodically thereafter, education of the patient about the symptoms of cyanide toxicity, and instruction of the patient's family physician about the symptoms and treatment of cyanide toxicity. Such precautions have not been incorporated into the practices of Laetrile therapists, and it is doubtful that any have had access to the technically demanding laboratory assay for blood cyanide. To the danger of cyanide toxicity must also be added the hazards associated with intravenous and oral administration of drug products imported from questionable sources with no enforced standards of quality or purity. Samples of amygdalin from the major Mexican manufacturer have been found to have a high frequency of microbial and endotoxic contamination.¹³ Physicians using such products must accept the associated liabilities. Certainly, the now established toxicity of Laetrile must be considered by persons in state legislatures and the federal courts who are charged with protecting the public safety. If, for any reason, the legalized dispensing of Laetrile is allowed to continue, the quality-control standards and clinical safety measures employed in this study should be made mandatory.

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