There are also, of course, questions about when a patient is eligible for the palliative mode of treatment as opposed to the rescue mode of hospital medicine. Should another chemotherapeutic agent be tried in a failing patient with a "treatable" tumor, such as breast cancer? Should an episode of hypercalcemia be vigorously treated, or should the patient be allowed to progressively lapse into coma? Indeed, is the vigorous treatment of dehydration with intravenous fluids appropriate, and should such treatment be considered outside the terrain of palliative care? And should the patient be involved in these decisions? There are no rigid rules. Palliative care still requires considerable physician judgment and skilled medical management. Perhaps the attention to communication and psychosocial issues can be made available to patients and families in any setting, and appropriate judgment for symptom control, without excessive technology, applied to meet any patient's problems, without the need for a special treatment unit. That remains to be seen. For the interim, it appears that the hospice movement will provide either a "separatist" or an "integrationist" motif of medical care for the dying, depending on community needs and resources.

And, of course, there is the question of finances. Who is to pay for these services, especially at home, but also in the inpatient unit? Will third-party payers acknowledge the validity of home care, especially for the professionals giving service outside of the hospital, as well as the special character of inpatient facilities? Although some communities do provide third-party coverage contracts for visiting nurses and home-health aides, families frequently have considerable out-of-pocket costs. Free-standing inpatient facilities are struggling with this fiscal question at present. Overall, there is a belief that hospice-type care will prove money saving when compared to usual hospital costs for the care of terminal patients. But that is yet to be fully worked through.

University of Massachusetts
Medical Center
Worcester, MA 01605

MELVIN J. KRANT, M.D.

REFERENCES

1. Woodward KL, Gosnell M, Reese M, et al: Living with dying. Newsweek 91(18):52-63, May 1, 1978
2. A better way of dying. Time 111(23):66, June 5, 1978
3. Dying at home. J R Coll Gen Pract 28:3-4, 1978
4. Wilkes E: Some problems in cancer management. Proc R Soc Med 67:1001-1005, 1974
5. Ward AWM: Terminal care in malignant disease. Soc Sci Med 8:413-420, 1974
6. Parkes CM: Home or hospital?: terminal care as seen by surviving spouses. J R Coll Gen Pract 28:19-30, 1978
7. Sternbach RA: Psychophysiology of pain. Int J Psychiatry Med 6:63-73, 1975
8. Fordyce WE, Fowler RS Jr, Lehmann JF, et al: Some implications of learning in problems of chronic pain. J Chronic Dis 21:179-190, 1968
9. Twycross RG: Studies on the use of diamorphine in advanced malignant disease (DM Thesis). Oxford, 1976
10. Hampe SO: Needs of the grieving spouse in a hospital setting. Nurs Res 24:113-120, 1975

SPECIAL REPORT ON LAETRILE: THE NCI LAETRILE REVIEW

Results of the National Cancer Institute's Retrospective Laetrile Analysis

NEIL M. ELLISON, M.D., DAVID P. BYAR, M.D., AND GUY R. NEWELL, M.D.

Abstract The National Cancer Institute, in response to widespread public interest, undertook a retrospective analysis of Laetrile treatment. Only 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 is estimated that at least 70,000 Americans have used Laetrile, only 93 cases were submitted for evaluation. Twenty-six of these Laetrile cases had to be eliminated because of insufficient documentation, and an equal number of conventionally treated cases selected from the Institute's files were added to the records to be analyzed. A panel of 12 oncologists, who had no knowledge of the actual treatments given, was then asked to evaluate the results of 160 courses of treatment (68 Laetrile, 68 chemotherapy, 24 "no treatment") in the abstracted records from 93 patients. The panel judged six Laetrile courses to have produced a response (two complete and four partial). These results allow no definite conclusions supporting the anti-cancer activity of Laetrile. The National Cancer Institute will use the data in deciding if further study is needed.

LAETRILE, a cyanogenic glycoside, has been estimated to have been used for over two decades by at least 70,000 patients for palliation, prevention or cure of cancer. Many physicians view this treatment as quackery or, at best, a placebo. The history of Laetrile has been reviewed in both lay[1,2] and medical publications.[3,4] Laetrile has shown no reproducible antitumor activity in extensive animal experiments[5-9]; its safety has been questioned[10-13]; and review of data for patients treated with Laetrile has not provided convincing evidence of efficacy.[4]

In response to public demand some prominent physicians called for a prospective clinical trial of Laetrile.[14] Others were opposed,[15] primarily on ethical grounds and because they did not wish to establish a precedent for clinical tests of drugs that showed no promise in preclinical studies, especially when other therapies with preclinical promise are constantly becoming available. For these reasons,

From the Office of the Director and the Biometry Branch, National Cancer Institute (address reprint requests to Dr. Ellison at the National Cancer Institute, Building 31, Room 11A52, Bethesda, MD 20014).

after a period of planning with other governmental agencies,* the National Cancer Institute initiated a nationwide search for documented responses to Laetrile.[16]

Materials and Methods

Case Solicitation

Patients thought to have shown an objective beneficial antitumor response to Laetrile were sought through national publicity, including a press conference, articles in the medical and lay press, contact with known pro-Laetrile groups, and the distribution of 455,000 letters (385,000 to physicians as well as 70,000 to other health professionals, such as pharmacists, hospital administrators and officials in health departments). No attempt was made to seek nonresponders or to establish the total number of patients treated with Laetrile. Eligibility required consent of the patient or next of kin (if deceased), confirmatory histologic material, measurable disease, adequately documented history, use of Laetrile with or without "metabolic therapy" (special diet, vitamins, minerals, enzymes and chelating agents) for a period of at least 30 days with a preceding interval of at least 30 days in which no conventional therapy was given, and records written in English. Assurances were given that the Food and Drug Administration would not be involved with review or collection of the data and that no legal proceedings would be instituted on the basis of data accumulated.

Extensive and complete information was requested concerning diagnosis, therapy, and progress of each patient from physicians, clinics, hospitals and laboratories known to have been involved in the care of the patient. Scans and x-ray studies, laboratory reports, admission or outpatient history and physical examinations, sequential office or outpatient records, operative or procedural summaries, medication records, pathology reports, discharge or death summaries, radiation-therapy summaries, autopsy reports and death certificates were sought. All pathological material received was reviewed at the Armed Forces Institute of Pathology to confirm the diagnosis of cancer.

Review Mechanism

Summaries of Laetrile-treated cases containing all pertinent objective and subjective data were presented to a review panel consisting of 12 experienced clinical oncologists not on the staff of the National Cancer Institute.† Summaries taken from the Institute's files of an undisclosed number of cases treated by conventional therapy were also presented. Some of these patients had intervals of no treatment. For NCI cases, data were often deleted so that they would more closely resemble the Laetrile-treated cases for which we usually had less information. Some Laetrile-treated cases had intervals of "no treatment," as well as treatment with "conventional therapy." In each summary, one to three "interventions" were to be evaluated and these were designated simply by the letters X, Y and Z. Radiation or surgical therapies were always explicitly mentioned. The panel was, of course, kept unaware of which intervention ("no therapy," Laetrile treatment or "conventional therapy" consisting of chemotherapy or hormones) was being evaluated in each instance. It was first asked to decide for each blinded treatment course whether data were sufficient for any analysis. If so, the response was then classifed as "non-evaluable" (see Table 1 for definitions) or as "complete response," "partial response," "stable disease" or "progressive disease." In addition, the panel was asked to decide whether increased disease-free interval, increased length of life, decreased complications or other benefits could be attributed to that treatment course. Finally, the reviewers were asked to state whether they believed the intervention given was "no treatment," conventional therapy, or Laetrile. Every reviewer evaluated each summary independently, after which there was a group discussion in which a majority consensus was obtained for each treatment course of each case. After group evaluation the panelists had the option of reviewing all available information on any case, an option taken only once.

Table 1. Evaluation of Laetrile-Treatment Courses by Panel Consensus.

Panel Consensus	No. of Laetrile-Treatment Courses					
No. of dissenting panelists →	*0*	*1*	*2*	*3*	*4*	*5*
Insufficient data	11	2	2	1	4	1	1
Non-evaluable (NE)*	35	17	8	3	3	3	1
Complete response (CR)	2	0	0	0	1	0	1
Partial response (PR)	4	0	1	0	3	0	0
Stable disease (ST)	9	0	1	2	1	2	3
Progressive disease	7	1	2	2	1	0	1
Total	68†	20	14	8	13	6	7

*21 patients with no followable disease, 12 with concomitant conventional antitumor treatment, 1 with non-malignant disease on review, & 1 with more than 1 of the preceding reasons.

†1 patient had 2 separate courses of Laetrile separated by a 12-month interval.

In addition to the cases studied in the manner described above, the panel was presented in an unblinded fashion with 11 translated case histories and supporting laboratory data submitted by the director of a Mexican clinic who believed these cases showed beneficial antitumor effects from Laetrile.

Statistical Analysis

The design of this review does not permit statistical analysis of the results except with respect to the efficacy of the blinding procedure. No direct comparison of the three types of intervention (Laetrile, conventional chemotherapy, "no treatment") is possible because neither the Laetrile cases nor those taken from the Institute's files were randomly chosen. The only Laetrile cases solicited were those believed to have responded favorably, whereas the NCI cases were deliberately selected and abstracted to be similar to the Laetrile cases. The courses of conventional treatment and "no treatment" were included not for statistical comparison with the Laetrile treatment but simply in an attempt to "blind" the panel and thus minimize any pro- or anti-Laetrile biases that may have existed. The kappa statistic[17] was used for assessing agreement between reviewers' guesses and actual treatment.

*Charles Anello, Sc.D., Food and Drug Administration; David Byar, M.D., National Cancer Institute; Neil Ellison, M.D., National Cancer Institute; Henry Falk, M.D., M.P.H., Center for Disease Control; Nelson Irey, M.D., Armed Forces Institute of Pathology; Lorraine Kershner, M.A., National Cancer Institute; William McGuire, M.D., National Cancer Institute; Bayard Morrison, M.D., National Cancer Institute; Guy Newell, M.D., National Cancer Institute; Stuart Nightingale, M.D., Food and Drug Administration; James Stratton, M.D., Center for Disease Control; Robert Young, M.D., Food and Drug Administration; and John Ziegler, M.D., National Cancer Institute.

†Irwin H. Krakoff, M.D., Vermont Regional Cancer Center (chairman); Laurence Baker, D.O., Wayne State University School of Medicine; Lawrence W. Davis, M.D., Jefferson Medical College, Thomas Jefferson University; Rose Ruth Ellison, M.D., Columbia University, College of Physicians and Surgeons; George C. Escher, M.D., Albert Einstein College of Medicine, Yeshiva University; Robert B. Golbey, M.D., Memorial Sloan-Kettering Hospital; Rita M. Kelley, M.D., Massachusetts General Hospital; Louis Leone, M.D., Rhode Island Hospital; Virgil Loeb, Jr., M.D., Washington University School of Medicine; Gerald P. Murphy, M.D., D.Sc., Roswell Park Memorial Institute; Kenneth B. Olson, M.D., New Smyrna Beach, Florida; and Manuel Valdivieso, M.D., M.D. Anderson Hospital and Tumor Institute.

Results

Case Solicitation

Although only beneficial antitumor responses were solicited, we received replies from 220 physicians who, as a group, claimed knowledge of more than 1000 patients showing no beneficial response to Laetrile. Nineteen physicians said that they had followed patients showing only subjective responses to Laetrile. Two-hundred thirty patients or their next of kin were asked to release their records for study. The names of some were obtained in response to the nationwide mailing and the others were publicly on record as having benefited from Laetrile. In only 93 of these 230 cases were authorizations for release of medical records received, permitting us to seek further information. Twenty-six of these 93 patients were not presented to the panel because it was obvious that data were insufficient for evaluation according to the criteria for review. Information was obtained for the 67 remaining Laetrile-treated cases by contacting 393 physicians, clinics, hospitals or laboratories either once or repeatedly. Information was received from 81 per cent of those contacted (from 35 of 49 physicians who treated patients with Laetrile and from 283 of 344 for all other contacts).

Evaluation of Therapies

Altogether, 22 tumor types were represented: 15 types for 26 patients who did not receive Laetrile, ranging from one to four patients for each tumor type; and 22 tumor types for the 67 Laetrile-treated patients, with a range of 1 to 11 patients per tumor type.

The panel was asked to evaluate 160 treatment courses for 93 patients. Forty-one patients received only one course, 37 received two courses, and 15 received three courses of treatment. The actual interventions for these 160 courses were 24 "no treatment," 68 Laetrile (with or without metabolic therapy) and 68 chemotherapy.

The results of the panel consensus for the 68 Laetrile treatment courses appear in Table 1 along with information as to how the panel voted. Details concerning the two patients judged to have complete responses and the four judged to have partial responses appear in Table 2. Three additional patients were judged to show increased disease-free interval, although Laetrile was used when there was no definite followable cancer. The diagnoses in these three cases were Stage III testicular embryonal-cell carcinoma, Stage III ovarian adenocarcinoma, and a malignant tumor in an axillary lymph node, probably metastatic. The panel also judged that one "no treatment" intervention for a Ewing's sarcoma showed a partial response.

Overall, the judges would have been expected to guess the intervention correctly in about 41 per cent of treatment courses. In fact, they guessed correctly in about 65 per cent ($P<<0.001$) despite our efforts at blinding the treatments. However, a consensus of the panel believed that the treatment was chemotherapy for the six Laetrile-treatment courses judged as partial or complete responses and the three Laetrile-treatment courses judged to show increased disease-free interval.

In reviewing the 11 Mexican cases, one was judged as having insufficient information, nine as nonevaluable (either due to concurrent therapy with conventional antitumor agents or inevaluable disease) and one as showing progressive disease.

Table 2. Laetrile-Treated Patients Judged by Panel Consensus to Have Complete or Partial Responses.

Case No.	Tumor Type	Individual Opinions*				Treatment Guesses†			Comment
		NE	CR	PR	ST	N	L	C	
34	Nodular well differentiated lymphoma (IIIA)	1	9	2	0	0	1	11	Regression of palpable lymph nodes
73	Squamous-cell carcinoma of the lung	1	7	4	0	0	0	12	Bronchoscopic & radiographic improvement
79	Metastatic carcinoid	0	0	11	1	0	0	12	Reduction of palpable abdominal mass & decreased 5-HIAA
33	Intraperitoneal papillary adenocarcinoma, primary unknown	2	0	9	1	0	0	12	Reduction of palpable abdominal mass
93	Nodular sclerosing Hodgkin's (IVB)	2	0	9	1	0	3	9	Radiographic improvement of biopsy-proved pulmonary nodule
68	Hilar node adenocarcinoma, probable lung primary	3	0	9	0	2	2	8	Radiographic resolution of an unbiopsied pulmonary nodule

*See Table 1 for abbreviations.
†N denotes no treatment, L Laetrile, & C chemotherapy.

Discussion

Despite widespread publicity and intensive efforts, the 67 Laetrile-treated cases presented to the review panel were far fewer than the 200 to 300 that we had hoped to obtain.[16] We have no way of knowing whether reluctance to submit cases, paucity of objective antitumor responses to Laetrile, or other reasons explain our difficulty in collecting cases. Since only

81 per cent of those approached supplied information, our findings should be interpreted with caution.

The judgment that many cases had insufficient information or were not evaluable should in no way be taken as criticism of the management of these patients, since in treating patients, one often uses several treatments together in the desire to help the patient rather than to evaluate the effects of a single therapy. Also, it should not be deduced that these patients showed neither improvement nor progression of disease — they were simply not evaluable for our specific purposes. The lack of unanimous agreement in judging responses is not surprising. Universal agreement about criteria for response does not exist, especially when a variety of tumor types are considered and clinical experience varies.

The objective of this retrospective analysis was to see if it would be possible to document beneficial objective anticancer responses to Laetrile. We cannot dismiss the possibility that the six patients in Table 2 responded to Laetrile, but the design of this study in no way allows us to draw this conclusion. Submission of incorrect clinical interpretations, falsified data, intentional or unintentional omission of data (for example, concurrent conventional therapy), the possibility that we were unaware of some physicians treating these patients or non-response to our inquiries must all be considered in interpreting these findings. It should be emphasized that the 67 Laetrile-treated cases analyzed in this report cannot be identified as the denominator for the six Laetrile-treated patients who were judged to be responders. These 67 cases were submitted for review because they were thought to demonstrate Laetrile's anticancer effects. Only patients showing a beneficial response were solicited, and no attempt was made to review the effects of Laetrile in all the other 70,000 or more patients in whom this agent has been used.

Other explanations for the six apparent responses to Laetrile are, of course, possible. Spontaneous regressions of tumors, although rare, have been documented in at least 176 cases, with frequency varying according to tumor type.[18] Even in the absence of true spontaneous regression, the well documented variability in the natural history of some tumors may confuse interpretation[19] and, in fact, the panel judged by consensus that a partial response occurred in one patient receiving no treatment during the course evaluated. The patients treated with Laetrile were almost always given concomitant metabolic therapy, including substances that might be regarded as immune stimulants, as well as general supportive-care measures such as improved diet, psychologic support and the unmeasurable ingredient of hope. This fact makes it difficult to attribute any tumor responses to Laetrile alone.

Despite the fact that the panel identified the correct treatment more often than would have been predicted by chance, a consensus guessed chemotherapy for the Laetrile treatment courses judged as complete or partial responses and those judged as showing increased disease-free interval. This finding can be interpreted as demonstrating that these treatment courses were in fact given a fair review. Although a more thorough evaluation might have been possible by allowing the panel to examine the records submitted to us, we thought that blinding was more important to avoid charges of anti-Laetrile bias by the review panel.

This retrospective analysis illustrates the difficulty of drawing inferences about therapeutic efficacy in the absence of properly designed randomized trials. The results of this analysis and other information on Laetrile will be used by the National Cancer Institute to determine whether further study is justified.

We are indebted to Ms. Lorraine Kershner for assistance in case solicitation, to Dr. Patrick Bradley-Moore for reviewing scans, to Dr. Gordon Head for reviewing x-rays, to Dr. Sylvan Green and Ms. Janis Beach for assistance with data processing and computer analysis and to Dr. Nelson Irey for co-ordinating pathological review.

References

1. Culbert ML: Freedom from Cancer. The amazing story of vitamin B-17, or Laetrile. New York, Pocket Books, 1977
2. Kittler GD: Laetrile: Control for cancer, New York, Warner Paperback Library, 1973
3. Laetrile Background Information. New York, American Cancer Society, August, 1977
4. United States Department of Health, Education, and Welfare. Laetrile: The commissioner's decision. (DHEW Publication No. 77-3056). Washington, DC, Government Printing Office, 1977
5. Laster WR Jr, Schabel FM Jr: Experimental studies of the antitumor activity of amygdalin MF (NSC-15780) alone and in combination with β glucosidase (NSC-128056). Cancer Chemother Rep 59:951-965, 1975
6. Wodinsky I, Swiniarski J: Antitumor activity of amygdalin MF (NSC-15780) as a single agent and with β-glucosidase (NSC-128056) on a spectrum of transplantable rodent tumors. Cancer Chemother Rep 59:939-950, 1975
7. Stock CC, Tarnowski GS, Schmid FA, et al: Antitumor tests of Amygdalin in transplantable animal tumor systems. J Surg Oncol 10:81-88, 1978
8. Stock CC, Martin DS, Sugiura K, et al: Antitumor tests of amygdalin in spontaneous animal tumor systems. J Surg Oncol 10:89-123, 1978
9. Ovejera AA, Houchens DP, Barker AD, et al: Inactivity of DL-Amygdalin against human breast and colon tumor xenografts in athymic (nude) mice. Cancer Treat Rep 62:576-578, 1978
10. Smith FP, Butler TP, Cohan S, et al: Laetrile toxicity: a report of two cases. JAMA 238:1361, 1977
11. Davignon JP: Contaminated Laetrile: a health hazard. N Engl J Med 297:1355-1356, 1977
12. Humbert JR, Tress JH, Braico KT: Fatal cyanide poisoning: accidental ingestion of Amygdalin. JAMA 238:482, 1977
13. Schmidt ES, Newton GW, Sanders SM, et al: Laetrile toxicity studies in dogs. JAMA 239:943-947, 1978
14. Moertel CG: A trial of Laetrile now. N Engl J Med 298:218-219, 1978
15. Lipsett MB, Fletcher JC: Ethics of Laetrile clinical trials. N Engl J Med 297:1183-1184, 1977
16. Newell GR: Why the National Cancer Institute chooses a case-record review of Laetrile. N Engl J Med 298:216-218, 1978
17. Fleiss JL: Statistical Methods for Rates and Proportions. New York, Wiley, 1973, pp 143-147
18. Cole WH: Opening address: spontaneous regression of cancer and the importance of finding its cause. Natl Cancer Inst Monogr 44:5-9, 1976
19. Conference on Spontaneous Regression of Cancer. Natl Cancer Inst Monogr 44:1-148, 1976