LAETRILE: THE SCIENCE

Although Laetrile may possibly be safe, at least if used in small doses, scientific results do not support its effectiveness

BY JOAN AREHART-TREICHEL

Laetrile (the chemical amygdalin) is found in the kernels of many fruits, notably apricots, peaches, plums and bitter almonds. It is also found in cassava, lima beans and numerous other plants in a slightly different chemical form. The notion of using Laetrile as a cancer drug got its first major impetus in the United States in 1920 when Ernst T. Krebs Sr., a California physician, tried apricot pits as a cancer treatment. Laetrile received another big shove in 1952 when Ernst T. Krebs Jr., a biochemist, developed a purified form of Laetrile for injection. Yet only in recent years, and especially during the past few months, have thousands of Americans been clamoring for Laetrile, largely through the promotion of organizations such as the Committee for Freedom of Choice in Cancer Therapy and the National Health Foundation.

Some Laetrile proponents have been pushing the U.S. Food and Drug Administration to approve it. The FDA has resisted on the grounds that Laetrile is worthless against cancer. Other Laetrile supporters have tried to get around FDA prohibition of interstate commerce of Laetrile by smuggling it into the United States from Mexico or by legalizing its manufacture and use on a state-by-state basis. So far they have made headway, particularly in the latter direction. Seven states have approved Laetrile use.

The Laetrile controversy seems to keep growing. Should Americans be allowed to use the drug or not? Not enough attention, however, has been devoted to the science behind Laetrile. What evidence is there for the safety of Laetrile and for its effectiveness against cancer? Is the evidence sufficient to pass judgment on Laetrile as a cancer drug?

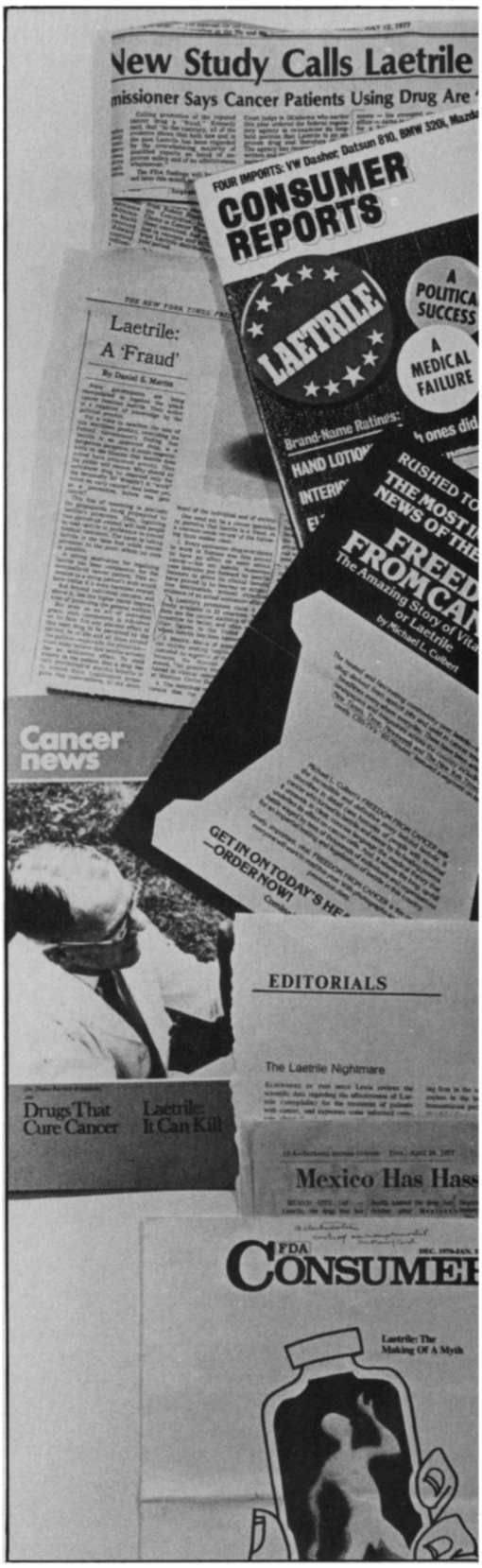
The first and somewhat easier question is that of Laetrile's safety. Extensive animal experiments on the safety and effectiveness of Laetrile were conducted by a team of researchers at the Memorial Sloan-Kettering Cancer Center in New York City and at the Catholic Medical Center in Woodhaven, N.Y., from 1972 to 1976, and the results will be published early next year in the *Journal of Surgical Oncology*. These experiments showed no harmful effects of Laetrile in mice except when very large doses were used. Nor when Laetrile was given along with accepted cancer drugs did it alter their benefits or toxicity.

Exactly how much Laetrile is safe for humans, however, has really not been determined, and certainly it can be harmful if taken in sufficient doses. For instance, two cancer patients were treated for serious adverse reactions to Laetrile last month at the Georgetown University Medical Center in Washington. One of the patients developed fever, rash and gastrointestinal symptoms that promptly disappeared after discontinuation of Laetrile, only to recur after she resumed taking the compound. The other patient experienced a weakening of the eye muscles and eyelids. Within 48 hours of being taken off Laetrile, his condition improved dramatically and resolved itself completely within six days. Then in June, a Buffalo, N.Y., infant died from accidental ingestion of an unknown number of Laetrile pills her father was taking. (Laetrile ultimately breaks down in the body into the poison cyanide.) Several Californians who ate apricot pits as a health food suffered cyanide poisoning from them. A three-year-old girl who ate 15 apricot kernels experienced cyanide poisoning as well. Both acute and chronic cyanide poisoning have been reported among Nigerians, Jamaicans and Malasians who ate a lot of cassava.

As for Laetrile's effectiveness, or lack thereof, the evidence is more extensive and complex. First the test-tube evidence:

Unlike many cancer remedies of questionable value, Laetrile is a well-known and identifiable chemical substance, amygdalin. Amygdalin is broken down in the body by enzymes known as beta-glucosidases to yield dextrose and mandelonitrile, which is benzyaldehyde plus a molecule of hydrogen cyanide. Laetrile proponents offer several different arguments for how Laetrile's pharmacological actions can kill cancer tissues in the body.

One of their arguments, initiated by Ernst Krebs Jr., is that cancer tissues are selectively killed by Laetrile because they contain more of the beta-glucosidase enzymes than healthy tissues do. Is there any scientific basis to this claim? Apparently not. As Joseph R. DiPalma, professor of pharmacology at Hahnemann Medical College in Philadelphia, told SCIENCE NEWS, "Cancer cells which have been analyzed many, many times have very little contents of this type of enzymes." Thomas H. Jukes, a nutrition scientist at the University of California at Berkeley, agreed in the Sept. 13, 1976, JOURNAL OF THE AMERICAN MEDICAL



BEHIND THE CONTROVERSY

Volker Zinser/Science News

ASSOCIATION: "There are only traces of beta-glucosidase in animal tissues and even less in experimental tumors."

Another Laetrilist claim is that rhodanese, an enzyme that converts toxic hydrogen cyanide to nontoxic thiocyanate, is present in tumors in lower amounts than it is present in normal tissues, and hence tumors cannot protect themselves against hydrogen cyanide. Any basis to this argument? It doesn't look like it. According to Daniel S. Martin, a cancer-therapy scientist at the Catholic Medical Center and one of the investigators in the recent Laetrile studies at that complex, assays of this enzyme have shown no such differences between cancerous and healthy tissues.

Still a third assertion by Laetrile proponents is that Laetrile is a vitamin—

The Laetrile controversy: Not just a science issue

The dispute over whether Laetrile should be legalized or not extends far beyond scientific evidence regarding its safety and efficacy. The best way to understand the issues is to examine the positions of Laetrile proponents and opponents.

One group of Laetrile supporters, members of the Committee for Freedom of Choice in Cancer Therapy, believes that cancer patients should have access to any drug they choose regardless of what the FDA rules. A similar position is taken by members of the National Health Federation who advocate, along with Laetrile, other "natural" methods of healing such as health foods, chiropractory and acupuncture. In his book *Health Purifiers and Their Enemies* (Prodist 1977), Julius A. Roth writes: "Health freedom is essential to all these organizations. Its ideological essence is the ready possibility, open to us all, to choose whatever form of health maintenance or health care we wish."

Other Laetrile backers are political extremists of both left and right who deeply distrust the "establishment," whether it is political, medical or whatever. They suspect that cancer researchers have covered up results that support Laetrile because the scientists have sold out to drug companies which cannot make money off of natural substances such as Laetrile and which hence do not want to see it marketed. They are convinced that physicians oppose Laetrile because it would cure cancer patients and hence deprive them of doctor fees. For instance, at an FDA Laetrile hearing in May, John Yarbro, a physician at the University of Missouri School of Medicine, asked, "Do you really believe that a quarter-million physicians across this country could let people die so that they can make a profit?" Laetrile advocates clapped and jeered, "You said it! You said it! You said it!"

Yet some Laetrile champions appear to be out for a quick buck themselves. Some 7,000 cancer patients will undergo Laetrile treatments at two Tijuana, Mexico, clinics this year at an average weekly cost of $350. Customs officials on the Mexican border are seizing 40,000 vials of Laetrile monthly, making it the second biggest American smuggling problem after narcotics. Laetrile now has a higher markup than heroin. Whether Laetrile legalization would benefit such profiteers is doubtful. However it would unquestionably fill the coffers of American Laetrile manufacturers and dispensers.

As for the Laetrile antagonists, such as the FDA, the American Cancer Society and most cancer scientists, they largely oppose the legalization of Laetrile on the grounds that it has not been shown effective against cancer and that the FDA requires that a drug must be shown not only safe but effective before it can be marketed. They claim that if an exception is made for Laetrile, it would erode the FDA's jurisdiction over other drugs. They also argue that if Laetrile were made available to cancer patients, the patients would probably forego lifesaving cancer treatments and take Laetrile instead.

Given the radically different stances and motives of various Laetrile supporters and detractors, then, and particularly the antiscience, antiestablishment bias of many backers, it is highly unlikely that the present scientific evidence on Laetrile or even a clinical study of the drug will resolve the question of whether Laetrile should be legalized or not. Rather, the issue will probably be decided by which group garners the most influence with Congress.

It is difficult to disagree with Daniel Martin, one of the cancer scientists who has been studying Laetrile of late: "It is rather appalling that scientific knowledge has been negated by the political process, but that is what is happening here."

—Joan Arehart-Treichel

vitamin B_{17}—and thus a nutritional substance rather than a drug. Is there any evidence to support this claim? Dean Burk, a former National Cancer Institute scientist, believes that there might be. He asserts that it is "almost impossible ... ever to declare scientifically that a given compound is not a vitamin" and that "meats, milk, cheese, eggs and other proteins may similarly produce cyanide when decomposed by suitable enzymes or catalysts." In contrast, Jukes declares that Laetrile has "not the slightest resemblance to a vitamin. The crucial property of a vitamin is that its absence from the diet produces a specific deficiency disease in vertebrate animals. The cyanogenetic glycosides do not have this property." Yet when SCIENCE NEWS asked DiPalma whether tests had ever been conducted to determine whether Laetrile's absence from the diet might cause a deficiency disease, he replied: "I believe it is very easy to fall into the trap of trying to disprove something which has not enough merit to be disproven in the first place .... Obviously the great majority of the world's population does not consume amygdalin in any form, and it is ridiculous to even suggest that Laetrile is a vitamin."

So Laetrile has really not been adequately tested to determine whether it is a vitamin or not. Even if Laetrile were found to be a vitamin, of course, its vitamin properties would not demonstrate that it is also effective against tumors. Only one other vitamin has shown any anticancer properties to date, and that is vitamin A (SN: 3/13/76, p. 165).

Taking all of the above test-tube evidence into consideration, then, the conclusion is that none of it supports the ability of Laetrile to kill tumors.

Do animal experiments with Laetrile indicate any effectiveness against cancer? Take those conducted at the National Cancer Institute or under NCI contract at other institutions. The first was conducted at the Warf Institute in Madison, Wis., under NCI contract, in 1957. Laetrile was given to mice that had had tumors transplanted onto them—a common system for screening compounds for anticancer activity. Although the results of this experiment were not published, they showed that Laetrile produced no significant inhibition of tumor growth nor a significant increase in lifespan in the mice that had been given cancer. In 1960, a second experiment was run, under NCI contract, at Microbiological Associates, Inc. This time Laetrile from a different source was tested against the same mouse tumors. Again no antitumor activity was found. The results were not published. Then in 1969, a third Laetrile test was conducted at Microbiological Associates. This time Laetrile was tested alone or in combination with the enzyme that helps break it down in the body, beta-glucosidase, against leukemia in mice. The results, which were not published, showed that Laetrile was ineffective against cancer, either alone or in combination with the enzyme.

A fourth Laetrile experiment was carried out in 1973, under NCI contract, by Isidore Wodinsky and Joseph K. Swinarski of Arthur D. Little, Inc. of Cambridge, Mass. Laetrile, in daily injections of 3,200 milligrams per kilogram of body weight down to 6.25 mg/kg, was tested alone or in combination with beta-glucosidase against four kinds of tumors in rodents. It was found ineffective alone or in combination with the enzyme. These results were published in the September/October 1975 CANCER CHEMOTHERAPY REPORTS. A fifth experiment was conducted, under NCI contract, by W.R. Laster Jr. and F.M. Schabel Jr. of the Southern Research Institute in Birmingham, Ala. Laetrile, in injections of 500 mg/kg of body weight down to 23 mg/kg was tested alone or in combination with beta-glucosidase against three transplanted mouse tumors. No antitumor activity was found. These results were also published in the September/October 1975 CANCER CHEMOTHERAPY REPORTS.

Finally a sixth experiment has just been completed, under NCI contract, at the Battelle Memorial Institute in Columbus, Ohio, by David P. Houchens and Artemio A. Ovejera. In one phase, mice with breast cancer or colon cancer were injected every four days with three doses of 400, 800 or 1,600 mg/kg body weight of Laetrile. In another phase, mice with colon cancer were divided into separate groups and treated for nine days with either Laetrile alone; beta-glucosidase, the enzyme that breaks Laetrile down in the body into cyanide; or Laetrile and beta-glucosidase. The scientists report that they found no difference in the growth of the tumors that they followed for 42 days in the mice that did and did not receive Laetrile.

Thus NCI or NCI-sponsored Laetrile animal experiments concur with the test-tube evidence to date that Laetrile has no anticancer activity.

The most extensive animal tests ever conducted on the substance in the United States were done at Sloan-Kettering and the Catholic Medical Center. The Sloan-Kettering investigators included C. Chester Stock, George S. Tarnowski, Franz A. Schmid, Dorris J. Hutchison, Morris H. Teller, Kanematsu Sugiura, Isabel M. Mountain and Elisabeth Stockert. The Catholic Medical Center investigators were Daniel S. Martin and Ruth A. Fugman.

Eleven series of experiments, 23 experiments all told, were conducted to determine whether Laetrile has any ability to counter spontaneous breast cancer or leukemia in mice. The CD_8F_1 strain of mice was used in most of the breast-cancer research, the Swiss Webster albino mouse strain from one breast-cancer study and the AKR mice for the leukemia studies. Nineteen of the studies were performed with Laetrile obtained from Mexico, the other four with Laetrile from Germany. The doses of Laetrile used in all but two of the experiments varied from 1,000 to 3,000 mg/kg of body weight, considerably more than Laetrile patients usually take. In one experiment, 40 mg/kg of Laetrile was employed, which more closely approximated the 3 grams a day taken by many Laetrile patients. In the other experiment, doses as high as 4,000 and 5,000 mg/kg were used. Results from all the studies suggested that neither the source of Laetrile nor the dose level used produce any great differences in outcome. However, there were some discrepancies among the study results, apparently due to another cause.

In the initial set of six experiments, for instance, Suguira gave Laetrile to 60 mice and saline injections to 60 control mice. He found that while 90 percent of the control mice experienced lung metastases due to spreading breast tumors, only 21 percent of the treated mice did. Thus the investigators at Sloan-Kettering and the Catholic Medical Center conducted the subsequent experiments to see whether they could confirm these initial promising results and perhaps even expand them.

Partial confirmation was achieved in a joint experiment conducted by Suguira and Schmid. Whereas Suguira noted lung metastases among 100 percent of control mice, he noted only 38 percent among treated mice. Whereas Schmid identified 80 percent of control mice with metastases, he identified only 44 percent of treated mice with them. In fact, Suguira confirmed his initial results with two other experiments he conducted alone. In one, 91 percent of control mice showed metastases, versus 22 percent of the treated mice. In the other, 81 percent of controls showed metastases, versus only 17 percent of treated mice.

However, in the numerous other experiments conducted with or without Suguira, the investigators were not able to approach these promising results and in several instances even came up with better results for controls than for treated animals. For example, in an experiment on mice with spontaneous breast cancer that he conducted alone, Schmid found lung metastases among 70 percent of treated mice versus only 58 percent for controls. In a joint experiment on mice with spontaneous breast tumors, Martin, Fugman, Tarnowski and Suguira found lung metastases in 42 percent of the treated mice versus 21 percent of the controls.

Why such a discrepancy in results? Apparently it is because not all of the experiments were evaluated by the same method. Results favorable to Laetrile nearly all resulted from macrovision or microscopic examination and mostly from Suguira's visual observation at that. The results most unfavorable to Laetrile came from bioassay, where lungs from the test animals were shredded and injected into other mice. If the lung tissue injections made tumors form, then one

could conclude that the lungs had contained metastases.

A prime example of how these two methods of evaluation produced discrepant results came from a blind experiment on spontaneous breast cancers in mice conducted by Suguira. In this arrangement, he did not know which of the mice had received Laetrile and which had not. Suguira's visual evaluation showed that 54 percent of the treated mice experienced lung metastases compared with 63 percent of control mice. Bioassay, in contrast, demonstrated that 85 percent of the treated mice, compared with 83 percent of control mice, were positive for them. In still another blind experiment conducted by Suguira, visual evaluation produced somewhat favorable results for Laetrile; bioassay did not.

Which type of evaluation is one to believe, then? The bioassay results must be considered the stronger of the two since they are totally objective. There is no need to rely on an observer's eyesight or unintentional visual bias, which is the case with macrovision or microscopic examination. In other words, Suguira's positive results for Laetrile, dependent entirely on visual observation, could be pitted against the less favorable visual results obtained by the other investigators, but they simply cannot stack up against the negative results procured by bioassay.

When all these results are taken together, then, they, like the NCI animal tests and test-tube research, rule out anticancer activity for Laetrile. What's more, the Sloan-Kettering investigators tested Laetrile against various kinds of transplanted tumors in mice. These results were totally negative.

Finally, how about clinical evidence for Laetrile's effectiveness against tumors? Some 50,000 Americans have so far taken Laetrile for cancer. A number of them have not been helped by it or even have died. Yet other attest to Laetrile's curative powers or at least to its palliative effects—pain relief or feeling better. Do such testimonials constitute clinical evidence for Laetrile's efficacy? No, most cancer scientists reply. For instance, in many cases where patients have claimed that Laetrile has brought about a cancer remission, pathology reports have not been available to document the before and after effects or even that a patient had cancer in the first place. As for Laetrile's palliative effects, scientists tend to point out that they are probably psychologically induced and that such a placebo effect could be achieved with any drug in which a patient believes. Yet, even if Laetrile's pain-relieving impact were physiologically rather than psychologically induced, it would not be the same as antitumor activity.

So should a scientifically controlled clinical trial be conducted to test Laetrile's effectiveness against cancer? From a scientific viewpoint, no. All of the 40 anticancer drugs on the American market were shown to be active against tumors in animals before they were shown effective against human cancers. In contrast, animal studies to date do not demonstrate antitumor activity for Laetrile. So it is highly unlikely that Laetrile would show any anticancer efficacy in a clinical trial. However, because of strong political pressure on the scientific community to conduct such a trial, the NCI may break precedence and do so.

Whether even a well-conducted clinical study would quell the Laetrile controversy, of course, is questionable in view of the antiscience, antiestablishment bias of many Laetrile proponents (see accompanying box). But then medical science would at least have done all that it could in order to arrive at a fair conclusion. □